Effect of Prostaglandin Analogue Medications on Thickness of Corneal Epithelium and Stroma

Prostaglandin Analoglarının Korneal Epitel ve Stroma Kalınlığı Üzerine Etkisi

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ÖZ

Amaç: Tek bir göz damlasında veya diğer antiglokom göz damaları ile kombine olarak kullanılan prostaglandin analoglarının (PGA) korneal epitelyum ve stroma kalınlığı üzerine etkisini değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya 59 hastanın toplam 82 gözü dahil edildi. Tıbbi kayıtlarında anterior segment optik koherens tomografi (AS-OKT) ile ölçülmüş korneal kalınlık değerleri olan glokom hastaları ve glokom şüpheli bireyler üç gruba ayrılmıştır. Grup 1, üç PGA (latanaprost %0.005, travoprost %0.004, veya bimatoprost %0.03)'dan gerek tek birisini, gerekse de bunlardan birisinin timolol ile kombinasyonunu içeren sadece bir antiglokom göz damlasını kullanmakta olan hastaları içermektedir. Grup 2, PGA'lardan herhangi birisini içermek kaydıyla, birden fazla antiglokom göz damlası kullanmakta olan glokom hastalarını içermektedir. Grup 3, herhangi bir antiglokom göz damlası kullanmayan, glokom şüpheli bireyleri içermektedir.

Bulgular: Korneal epitelin ortalama kalınlığı Grup 1ve Grup 2'de belirgin olarak ince idi.[(Grup 1'de 56±3.1 μm iken, Grup 3'de 61.2±2.1 μm, p<0.001), (Grup 2'de 56.3±2.8 μm iken, Grup 3'de 61.2±2.1 μm, p<0.001)]. Bununla birlikte, korneal stromanın ortalama kalınlığı sadece Grup 2'de belirgin olarak ince idi. [(Grup 2'de 448±4 μm iken, Grup 3'de 496±40 μm, p<0.001), (Grup 2'de 448±40 μm iken, Grup 1'de 486±30 μm, p=0.001)].

Sonuç: Prostaglandin analogları tek bir göz damlası şeklinde veya diğer antiglokom göz damlaları ile kombine olarak kullanıldıklarında korneal epitelyal kalınlığı azaltabilmektedirler. Ancak, korneal stromal incelme PGA'lar diğer antiglokom göz damlaları ile kombinasyon halinde kullanıldıklarında ortaya çıkabilir.

Anahtar Kelimeler: AS-OCT; Korneal epitel; Kornea stroması; Prostaglandin analogları.

ABSTRACT

Purpose: To evaluate the effect of prostaglandin analogues (PGAs) used in one eye drop, or in combination with other anti-glaucoma eye drops on the thickness of corneal epithelium and stroma.

Materials and Methods: A total 82 eyes of 59 patients were included into this retrospective study. The glaucoma patients and glaucoma-suspected individuals, who had the values of corneal thickness measured by anterior segment optical coherence tomography (AS-OCT) in their medical records, were assigned to three groups. Group 1 involved the glaucoma patients who were receiving only one anti-glaucoma eye drop which contains either only one of the three PGAs (latanoprost 0.005%, travoprost 0.004%, or bimatoprost 0.03%), or a combination of one of those with timolol. Group 2 involved the glaucoma patients who were receiving more than one anti-glaucoma eye drop, provided that one of them should contain any of the PGAs. Group 3 involved the glaucoma-suspected individuals who were not receiving any anti-glaucoma eye drop.

Results: The mean thickness of the corneal epithelium was significantly thinner in Group 1 and Group 2 [(56±3.1 μm in Group 1 vs. 61.2±2.1 μm in Group 3, p<0.001), (56.3±2.8 μm in Group 2 vs. 61.2±2.1 μm in Group 3, p<0.001)]. On the other hand, the mean thickness of corneal stroma was only significantly thinner in Group 2 [(448±40 μm in Group 2 vs.496±40 μm in Group 3, p<0.001), (448±40 μm in Group 2 vs. 486±30 μm in Group 1, p=0.001)].

Conclusions: The PGAs can reduce corneal epithelial thickness when they are used in one eye drop, or in combination with the other anti-glaucoma eye drops. However, corneal stromal thinning may appear in case of PGAs are used in combination with other anti-glaucoma eye drops.

Key Words: AS-OCT; corneal epithelium; corneal stroma; prostaglandin analogues.

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INTRODUCTION

Glaucoma that can be defined as a raised intraocular pressure (IOP) related optic neuropathy is one of the important cause of blindness worldwide.[1] Raised IOP was shown to be one of the most important factors for optic nerve head damage in glaucoma patients.[2] So that, anti-glaucoma medications, of which mechanism of action depend on either enhancing the outflow of the aqueous humor, or decreasing the secretion of aqueous humor are used to maintain IOP level at target range, customized for glaucoma patients. In clinical practice, among the various anti-glaucoma eye drops, prostaglandin analogues (PGAs) (latanoprost 0.005% and travoprost 0.004%) or prostamids (bimatoprost 0.03%) are usually chosen to manage the IOP level of glaucoma patients as a first step therapy. The high ratio of preference of PGAs can be attributed to their easy usage and efficacy, because they are used only one time per a day, and they have been suggested to achieve about 30% reduction in the elevated IOP level by increasing the aqueous humor outflow through the uveoscleral pathway.[3] Despite obtaining favorable IOP reduction with the application of PGAs, these drugs have been charged with some ocular surface alterations such as conjunctival inflammation[4] and corneal thinning.[5]

The exact mechanism by which PGAs lead to decrease in the corneal thickness remains unknown, but evidences from several clinical and experimental studies can point out the relevance of PGAs with the expression of various extracellular matrix protein degrading enzymes called matrix metalloproteinases (MMPs).[6] Apart from the possible detrimental effect of PGAs themselves on ocular surface structures, in vitro and in vivo studies have demonstrated the corneal epithelial toxicity of benzalkonium chloride (BAC)[7] that is a preservative agent, usually included in PGAs, as well as in other anti-glaucoma medications for preventing microbial proliferation.[8] The cytotoxic effect of BAC on corneal epithelium has been suggested to occur in its concentration ranging between 0.005% and 0.01%.[9] The concentration of BAC involved in commercially available PGAs such as latanoprost, travoprost, and bimatoprost is 0.02%, 0.015%, and 0.005% respectively. Therefore, PGAs containing a concentration of BAC which is higher than 0.001 % may give rise to corneal epithelial changes, even they are applied as monotherapy. Besides leading to corneal epithelial toxicity, because of its high penetrance to deep structures of cornea,[10] we believe that exposure of cornea to PGAs with extremely increased concentration of BAC may also result in corneal stromal alteration.

In this study, for the purpose of getting insight about the toxicity degree of PGAs, we aimed to compare both corneal epithelial and stromal thickness of glaucoma patients who were receiving mono or combined therapy of PGAs.

MATERIALS AND METHODS:

Materials:

This observational and retrospective study was conducted at the Ophthalmology Department of Canakkale Onsekiz Mart University, after local ethics committee approved the study protocol in accordance with the Declaration of Helsinki for research involving human subjects. The glaucoma patients who had the values of corneal thickness measured by anterior segment optical coherence tomography (AS-OCT) in their medical records, were assigned to two study groups (Group 1 and Group 2) according to the number of use of anti-glaucoma eye drop. On the other hand, the glaucoma-suspected individuals who had the values of corneal thickness measured by anterior segment optical coherence tomography (AS-OCT) in their medical records were assigned to control group (Group 3). Group 1 involved the glaucoma patients who were receiving only one anti-glaucoma eye drop which contains either only one of the three PGAs (latanoprost 0.005%, travoprost 0.004%, or bimatoprost 0.03%), or a combination of one of the three PGAs with timolol. Group 2 involved the glaucoma patients who were receiving more than one anti-glaucoma eye drop, provided that one of them should contain any of the PGAs. Group 3 involved the glaucoma-suspected individuals who were not receiving any anti-glaucoma eye drop.

The participants with active ocular inflammation such as uveitis, scleritis, and episcleritis, participants with corneal and/or conjunctival diseases such as corneal scars, keratoconus, corneal dystrophies, infectious or noninfectious keratitis eg. peripheral ulcerative keratitis, conjunctivitis, conjunctivochalazis, conjunctival dystrophies, pterygium, pinguecula, participants with any rheumatic diseases, and also participants who had one or more of those histories; previous ocular surgery, ocular trauma, contact lens wear, treatment with retinoic acids, and diabetes mellitus were not included in this study.

Corneal Image Acquisition using AS-OCT:

Both eyes of each patient in Group 1 and Group 2, and right eye of each individual in Group 3, who met the inclusion criteria of this study was selected for the measurement of thickness of corneal epithelium and stroma that had been obtained through an Anterior Segment 5 Line Raster scanning protocol of Cirrus HD-OCT 4000 (Carl Zeiss Meditec Inc., Dublin, CA). This scanning protocol produces five horizontal scan lines 3 mm long separated by 250 micrometer, and each scan line is comprised of 4096 A scans. We had preferred to use this device in order to get high resolution images of the corneal epithelium and stroma for evaluating the ocular surface of participants since this spectral-domain OCT takes 27,000 axial scans per second with using 5 micrometer axial resolution. Additionally, it enables us to properly measure the thickness of the anterior and posterior ocular structures by placing the caliper tool manually.

After selecting proper corneal images, the thicknesses of corneal epithelium and stroma were manually measured with the help of the caliper tool of AS-OCT. The thickness of the corneal epithelium was measured by placing the caliper tool between the first line and the second line of the corneal image which respectively represents the tear film layer and Bowman's layer of the cornea. The second line can be obviously visible below the corneal apex. The thickness of corneal stroma was measured by placing the caliper tool between the second line and the third line of the corneal image which respectively represents the Bowman's layer and Descement's membrane (Figure1).

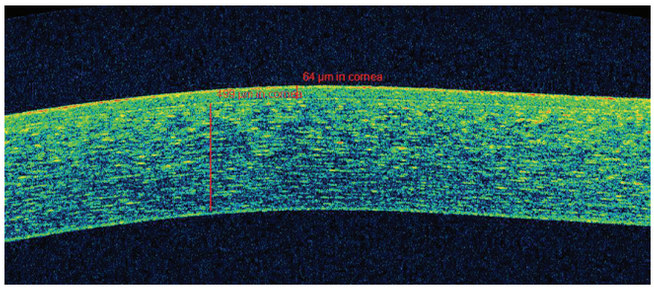

Figure 1: *OCT image (Cirrus HD- OCT; Carl Zeiss Meditec Inc.) of the cornea. The 64 µm vertical distance which is between the corneal apex and second line represents the thickness of the corneal epithelium. On the other hand, the 499 µm vertical distance which is between the second and third line represents the thickness of the corneal stroma.*

Statistical Analysis:

Statistical analysis were performed using the SPSS software version 15 (Statistical Package for Social Science, Chicago, Illinois, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations (SD) for all variables. Since the thickness of corneal epithelium and stroma, as well as age of patients and duration of anti-glaucoma eye drop usage were not normally distributed; the Kruskal-Wallis test was conducted to compare these parameters between three groups. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. An overall %5 type-1 error level was used to infer statistical significance.

RESULTS

A total 82 eyes of 59 patients were included into this retrospective study. The number of evaluated eyes in Group 1 (n=12), Group 2 (n=14), and Group 3 (n=33) was respectively as 23, 26, and 33. In Group 1, since one patient had a pterygium in one eye, in Group 2 since two patients had an unilateral glaucoma, AS-OCT findings of these eyes were not included in this study. There was no statistically significant difference between three groups in terms of age [The mean±SD of age in Group 1, Group 2, and Group 3 was 65.5±5.6, 66.8±8.5, and 61.2±11.9 respectively. The p value of age between Group 1 and Group 2 was 0.8, between Group 2 and Group 3 was 0.2, and between Group 1 and Group 3 was 0.25]. There was also no statistically significant difference between Group 1 and Group 2, according to the mean duration of anti-glaucoma eye drop usage [4.87±3.5 (min:1-max:10) years in Group 1 vs. 5.81±5.5 (min:1-max:20) years in Group 2, p=0.9)]. In Group 1, six glaucoma patients received treatment with latanoprost (Xalatan®), four with fixed combination of bimatoprost and timolol maleate (Ganfort®), and two with fixed combination of latanoprost and timolol maleate (Xalacom®).

In Group 2, five glaucoma patients received treatment with fixed combination of dorzolamide and timolol maleate, in addition to latanoprost (Cosopt®+Xalatan®), two with fixed combination of bimatoprost and timolol maleate, in addition to brimonidine (Ganfort® + Alphagan®), one with fixed combination of brinzolamide and timolol maleate, in addition to brimonidine and latanoprost (Azarga®+Alphagan®+Xalatan®), one with fixed combination of bimatoprost and timolol maleate, in addition to brinzolamide (Ganfort®+Azopt®), one with fixed combination of brinzolamide and timolol maleate, in addition to travoprost (Azarga®+Travatan®), one with fixed combination of brinzolamide and timolol maleate, in addition to bimatoprost (Azarga®+Lumigan®), one with fixed combination of dorzolamide and timolol maleate, in addition to brimonidine and travoprost (Cosopt®+Alphagan®+Travatan®), one with combinations of brinzolamide, brimonidine and latanoprost (Azopt®+Alphagan®+Xalatan®), and one with fixed combination of latanoprost and timolol maleate, in addition to brinzolamide (Xalacom®+Azopt®).

With regarding the mean thickness of corneal epithelium, there was a statistically significant decrease in both Group 1 and Group 2 in comparison with Group 3 [(56±3.1 µm in Group 1 vs. 61.2±2.1 μm in Group 3, p<0.001), and (56.3±2.8 µm in Group 2 vs. 61.1±2.4 µm in Group 3, p<0.001)]. On the other hand, no statistically significant difference was found between Group 1 and Group 2 in mean thickness of corneal epithelium [(56±3.1 µm in Group 1 vs. 56.3±2.8 µm in Group 2, p=0.6)]. With regarding the mean thickness of corneal stroma, it was determined to be statistically significantly thinner in Group 2, in comparison with Group 3 and Group 1[(448±40 µm in Group 2 vs. 496±40 µm in Group 3, p<0.001), (448±40 µm in Group 2 vs.486±30 µm in Group 1, p=0.001)]. There was no statistically significant difference between Group 1 and Group 3 in terms of mean thickness of corneal stroma [(486±30μm in Group 1 vs. 496±40μm in Group 3, p=0.2)]. (Table 1 depicts statistical comparisons of the corneal epithelium and stroma among all groups).

Table 1: *The statistical comparisons of corneal epithelium and stroma between Group 1, Group 2 and Group 3.*

Thickness (μm) (mean±SD)	**Group 1(*)**	**Group 2(**)**	**Group 3 (***)**	**p (1-2)**	**p (1-3)**	**p (2-3)**
Corneal Epithelium	55.9±3.1	56.5±2.8	61.1.±2.4	0.5	<0.001	<0.001
Corneal Stroma	485±29	450±43	499±39	0.001	0.15	<0.001

*Glaucoma patients who were receiving only one antiglaucoma eyedrop which contains either only of the three PGAs, or a combination of one of those with timolol.

**Glaucoma patients who were receiving more than one antiglaucoma eyedrop, provided that one of them should contain any of the PGAs.

***Glaucoma-suspected individuals who were not receiving any antiglaucoma eyedrop.

DISCUSSION

The measurement of central corneal thickness (CCT) has been reported to form a substantial part of the ocular examination in the assessment of individuals for the suitability of refractive surgery, and in the correct calculation of IOP value in glaucoma patients.[11,12] The importance of CCT for these mentioned ophthalmological conditions may arise from its relevance with the biomechanical profile of the cornea that is the composition of viscous and elastic property of the cornea, and indicates the degree of corneal rigidity. In ophthalmological practice, ocular response analyzer (ORA) is usually used to evaluate the biomechanical property of the cornea after refractive surgery,[13] in the diagnosis of keratoconus,[14] and in the follow up of glaucoma progression.[15] Corneal hysteresis (CH) and corneal resistance factor (CRF) are two parameters of ORA that respectively represent viscous dampening and elastic ability of the cornea.[16] In several clinical studies, decreased CH value has been related with the development and progression of glaucoma.[15] A moderate positive correlation was previously demonstrated between CCT and CH in healthy individuals,[16] as well as in glaucoma patients.[17]

Because corneal stroma forms the significant portion of the CCT, and it can provide much more viscoelastic ability to entire cornea, it is reasonable to consider that the changes particularly in the thickness of corneal stroma may affect the biomechanical property of cornea. This proposal may be consistent with the finding of the study conducted by Congdon et al. in which they reported the increased risk of optic nerve head damage in glaucoma patients with thinner CCT, as well as with decreased CH.[18] Therefore, measurement of corneal stromal thickness may be more important than the measurement of entire thickness of cornea, or thickness of corneal epithelium when CCT is taken into account as a parameter of corneal biomechanics. Since glaucoma patients can be under risk of corneal toxicity owing to use of long-termed anti-glaucomatous drugs, the separately measurement of thicknesses of corneal layers may yield to give opinion about the deepness of corneal damage in these individuals. The report of keratoconus progression, or development of increased corneal curvature after refractive surgery in patients under treatment with a PGA can be a good example for demonstrating the possible side effect of an anti-glaucomatous drug to the corneal stroma.[19,20]

However, besides the active compound of anti-glaucomatous drugs, their preservative substance, i.e BAC may also contribute to corneal stromal toxicity apart from influencing corneal epithelium. The ocular surface toxicity of BAC has been previously introduced by several experimental trials.[21-23] Kim et al.,[24] revealed corneal epithelial desquamation, as well as stromal shrinkage in mice exposed to either 0.02% BAC, or PGAs containing different concentrations of BAC, and they attributed these pathological changes detected in corneal layers to increased inflammation and apoptotic cell death. Pauly et al. reported apoptotic cell death in superficial corneal epithelium after the exposure of human reconstituted corneal cells to a concentration of 0.001% BAC.[25] The similar result was also reported by Pellinen et al. who demonstrated in rabbits that corneal epithelial toxicity of PGAs depends on the concentration of BAC existing in these drugs, and it can occur when concentration of BAC exceeds 0.001%.[26] Among anti-glaucoma eye drops that contain BAC, only tafluprost was reported to contain 0.001% BAC which is the lowest concentration of this preservative.[27]

In the current study, tafluprost was absent among the anti-glaucoma eye drops that were being used by glaucoma patients. We determined a significant corneal epithelial thinning in glaucoma patients who were receiving either only one anti-glaucoma eye drop (Group 1), or more than one anti-glaucoma eye drop (Group 2). We consider that corneas of patients in Group 1 and Group 2 might have been exposed to BAC, of which minimum concentration is higher than 0.001%. Because, anti-glaucoma eye drop containing the minimum concentration of BAC (0.005%) in Group 1 and Group 2 was bimatoprost, and the use of this eye drop alone even lead to exposure of BAC exceeding 0.001%. Thus, decrease in the thickness of corneal epithelium may have arisen from the corneal epithelial toxicity of increased concentration of BAC. Differently from Group 1, significant decrease in corneal stromal thickness was observed in Group 2. This result may be attributable to exposure of corneal stroma to extremely higher concentration of BAC, because of its deep corneal penetrance. Since BAC is a quaternary ammonium compound, it can result in protein denaturation and subsequently give rise to loss of corneal epithelial barrier by disrupting tight junction-related proteins like zonula occludin.[28] Increased penetrance of PGAs to corneal stroma, owing to impaired epithelial barrier may have also contributed to corneal stromal thinning in the present study, because inhibitory effect of latanoprost on cultured porcine corneal stromal cells was previously demonstrated by Wu et al.,[29] Interestingly, in the present study, 85% of patients in Group 2 were also receiving one of the carbonic anhydrase inhibitors (CAI) which may be related with the increase in the corneal thickness through influencing the corneal endothelial pump function. Nevertheless, it has been previously revealed that dorzolamide, a topical form of CAI had a slight effect on corneal thickness, as well as the number of corneal endothelial cells for only one day, and no significant alterations on corneal thickness had been determined in the following examinations.[30]

Although, many studies investigating the effect of PGAs on CCT can be found in the literature, measurement of CCT was obtained by using ultrasound pachymetry or confocal biomicroscopy in most of them.[31-33] In the current study, different from these previous studies, we used AS-OCT findings of the patients in order to evaluate the thickness of corneal epithelium and stroma separately. The confocal biomicroscopic evaluation of the cornea can also serve this purpose, but its contact with the cornea and technical difficulties while acquisition of corneal image may limit its usage. The present study may be of valuable in terms of clinically indicating the possible deleterious effect of long-termed usage of PGAs as a monotherapy and combined therapy on corneal epithelium and stroma respectively.

If the current study is supported with further prospective investigations, involving the biomechanical assessment of cornea using ORA, the efficacy of PGAs in combination with other anti-glaucoma medications in the management of glaucoma may become more understandable.

In conclusion, we propose that in addition to corneal epithelial thinning, decrease in corneal stromal thickness may appear as a result of long-termed use of multiple anti-glaucoma medications. However, different from corneal epithelium, PGAs may likely display adverse effect on corneal stroma in case of their combination with the other anti-glaucoma eye drops which can lead to increase in cumulative concentration of BAC. Therefore, glaucoma patients who are already under risk of corneal thinning should be closely followed for both corneal epithelial and stromal toxicity of anti-glaucoma eyedrops. The measurement of CCT using AS-OCT may be beneficial for obtaining insight about the effect of anti-glaucoma eye drops on both corneal epithelial and stromal thickness.

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