The Effects of Latanoprost on Corneal Thickness, Endothelial Cell Density, Topography; Anterior Chamber Depth and Axial Length

Latanoprostun Kornea Kalınlığı, Endotel Sayısı, Topografi, Ön Kamara Derinliği ve Aksiyel Uzunluğa Etkileri*

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ABSTRACT

Purpose: Latanoprost has effects on extracellular matrix and collagen metabolism in the ciliary body. The same mechanisms probably act in cornea, zonula fibers and sclera. The aim of the current study was to analyze the clinical visible effects latanoprost on axial length (AL), anterior chamber depth (ACD), corneal topography, endothelial cell density (ECD) and central corneal thickness (CCT).

Materials and Methods: Fifty-four eyes of 54 patients with newly diagnosed primary open angle glaucoma, normotensive glaucoma or ocular hypertension were included. Patients were examined before treatment and at the first, third and sixth month after latanoprost treatment. Visual acuity (VA), spheric equıvalent (SE), intraocular pressure (IOP), AL, ACD, corneal topography, ECD, and CCT were measured at each examination.

Results: Twenty-one males and 33 females with a mean age of 59.2±12.6 years were included in the study. The mean IOP which was 21.4±7.2 mmHg before therapy significantly decreased to 14.6±4.6 mmHg at the first month, 14.9±3.6 mmHg at the third month and 14.7±3.5 mmHg at the sixth month ($p<0.001$). A significant positive correlation was found between baseline IOP and IOP-lowering effect and a negative correlation was present between IOP-lowering effect and AL ($p<0.05$). No significant change in VA and SE was found after treatment. No significant change was observed in AL, ACD, ECD, and corneal topography parameters ($p>0.05$). A statistically significant reduction in CCT was observed within 6 months ($p=0.03$).

Conclusion: Although latanoprost 0.005% does not cause clinically detectable changes in corneal topography, ECD, ACD and AL, it only causes statistically significant reduction in central corneal thickness within 6 months of the treatment period. Further large-scale studies with longer follow-ups are needed to elucidate effects of latanoprost on ocular structures.

Key Words: Latanoprost, axial length, anterior chamber depth, corneal topography, endothelial cell density and central corneal thickness.

ÖZ

Amaç: Latanoprost siliyer cisimde ekstrasellüler matriks ve kollajen metabolizması üzerine etkilidir. Aynı mekanizma kornea, zonüller ve sklera için de geçerli olabilir. Çalışmanın amacı latanoprostun aksiyel uzunluk (AU), ön kamara derinliği (ÖKD), korneal topografi, endotel hücre yoğunluğu (EHY) ve merkezi kornea kalınlığı (MKK) üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya yeni tanı konmuş primer açık açılı, normotansif glokomlu veya oküler hipertansiyonlu 54 hastanın 54 gözü alındı. Hastalar, tedavi öncesi ve latanoprost tedavisi sonrası 1., 3. ve 6. ayda muayene edildi ve göz içi basınçları (GİB), AU, ÖKD, korneal topografi, EHY ve MKK'ları değerlendirildi.

Bulgular: Yirmi bir erkek, 33 kadın hastanın ortalama yaşı 59.2±12.6 idi. GİB tedavi öncesi 21.4±7.2 mmHg iken tedavi sonrası 1. ayda 14.6±4.6, 3. ayda 14.9±3.6 ve 6. ayda 14.7±3.5 mmHg'ya düştü ($p<0.001$). GİB düşürücü etki ile başlangıç GİB arasında pozitif korelasyon, AU ile negatif korelasyon saptandı ($p<0.05$). Takiplerde AU, ÖKD, EHY ve korneal topografi parametrelerinde anlamlı değişim görülmedi ($p>0.05$). MKK'nda istatistiksel olarak anlamlı incelme saptandı ($p=0.03$).

Sonuç: Latanoprost %0.005, 6 aylık tedavi süresinde AU, ÖKD, EHY ve korneal topografi parametrelerinde klinik olarak tespit edilebilen değişikliğe neden olmazken MKK'nda anlamlı incelmeye yol açmaktadır. Latanoprostun öküler etkilerinin aydınlatılması için daha geniş-uzun takipli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Latanoprost, aksiyel uzunluk, ön kamara derinliği, kornea.

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INTRODUCTION

Latanoprost 0.005% (13,14-dihydro-17 phenyl -18,19,20 -trinor -PGF2α-1 -isopropyl ester, Xalatan, Pharmacia&Upjohn Company, Peapack, NJ, USA) is a prostaglandin analogue which is currently prescribed as a first-line drug for glaucoma therapy. It lowers intraocular pressure (IOP) by increasing uveoscreral outflow.[1-6] The uveoscleral outflow pathway largely consists of ciliary muscle, as well as iris root and sclera. The ciliary body is made of an extracellular matrix (ECM) and muscle bundles surrounded by basement membrane. Latanoprost seems to have direct effect on these structures, in particular on the ciliary muscle.[1] Uveoscleral outflow passes through extracellular spaces within the ciliary muscle and then through the suprachoroidal space to the posterior pole of the eye. Ciliary muscle contains several different prostaglandin (PG) receptors. Activation of these receptors (FP and EP_2 receptors) stimulates several linked responses, including CAMP formation and induction of nuclear regulatory proteins, including c-Fos and c-Jun.

These signals lead to increased biosynthesis of matrix metalloproteinases (MMPS), a family of secreted proteases that can cleave collagens and other extracellular structural proteins. In addition, it reduces the amount of the ECM molecules such as collagen type I, type III and type IV in the ciliary muscle. These responses increase the space between ciliary muscle fibres and reduce the resistance in the uveoscleral outflow pathway.[1-3]

The same mechanisms probably act in other ocular structures (eg, zonula fibers, cornea, sclera) and may lead to a range of subclinical and clinical visible changes. Considering the fact that latanoprost has effects on ECM and collagen (components of cornea and sclera) metabolism, this study was performed to evaluate the clinical effects of this drug on axial length (AL), anterior chamber depth (ACD), corneal topography, endothelial cell density (ECD) and central corneal thickness (CCT).

MATERIALS AND METHODS

Fifty-four eyes of 54 concecutive patients with newly diagnosed primary open angle glaucoma (POAG), normotensive glaucoma (NTG) or ocular hypertension (OHT) without any previous antiglaucoma therapy between December 2007-March 2009 were included into this prospective trial.

Exclusion criteria were glaucoma types other than POAG, OHT, NTG (pseudoexfoliation glaucoma, angle-closure glaucoma, secondary glaucomas), age less than 40 years; presence of diabetes mellitus, collagen-vascular disease, presence of any other ophthalmic disease such as uveitis, thyroid ophthalmopathy, inflammatory orbital disease, allergic conjunctivitis, dry eye syndrome. Other ocular or systemic conditions which caused exclusion from the study were as follows: Any condition which prevents reliable applanation tonometry, history of ocular trauma, intraocular surgery or laser, contact lens use and topical or systemic steroid administration; high myopia (axial length longer than 26 mm), and any local or systemic medication that might affect IOP.

When both eyes of the same patient fulfilled the inclusion criteria only the right eye was included in the study. The procedure was fully explained to the patients. Informed consent was obtained from all patients in accordance with the Helsinki Declaration.

We assessed the following variables at baseline: Patient age, gender, type of glaucoma, manifest refraction (spheric equıvalent, SE), best corrected visual acuity (BCVA), biomicroscopy, fundus examination, IOP, AL, ACD, corneal topography, ECD and CCT measurements. All examinations were performed by the same physician. Experienced technicians masked to the treatment performed each measurements.

Treatment was started with latanoprost 0.005% once daily. Patients were examined before treatment and at the first, third and sixth month after treatment. Best corrected visual acuity, IOP, AL, ACD, corneal topography, ECD, and CCT measurements were recorded in each examination and compared statistically. Visual acuity was assessed with Snellen chart. Intraocular pressure was measured by Goldmann applanation tonometer. Two consecutive readings were taken of each eye and the average was recorded.

Axial length and ACD were measured by IOL Master optical biometry (Carl Zeiss Meditec AG, Germany). Corneal topography was performed with Orbscan (Baush&Lomb, Rochester, New York, USA). We examined corneal shape with Orbscan and the following parameters were evaluated: Sim K, mean power and astigmatic power in 5 mm zone, and CCT. Corneal endothelial cell density was obtained by Konan cell check CC7000 non-contact specular microscope. The correlation between IOP-lowering effect and age, baseline IOP, AL, ACD and CCT were analysed.

Statistical analysis was performed SPSS for Windows. Repeated measures ANOVA was used for each parameter to evaluate the changes before and after treatment. The correlation between parameters was evaluated by Pearson's correlation coefficient and linear regression analysis. A P value of less than 0.05 was considered statistically significant.

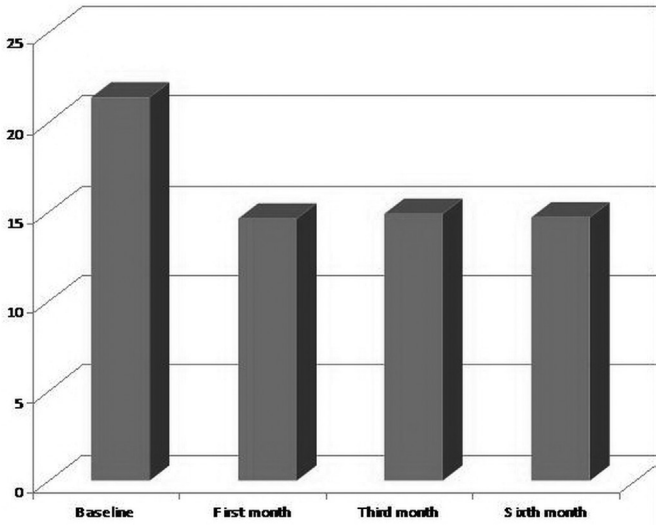
RESULTS

A total of 54 eyes of 54 patients with a mean age of 59.2±12.6 years were included in the study. There were 21 males and 33 females. The diagnosis was POAG in 74% of the eyes (40), OHT in 3.7% of the eyes (2) and NTG in 22.2% of eyes (12). Table 1 shows baseline values of patients before using latanoprost. The baseline mean BCVA was 0.84±0.23 and after initiation of the treatment it was 0.88±0.21 at first month, 0.88±0.22 at third month and 0.84±0.24 at sixth month (p=0.13).

Table 1: Patients age and baseline values.

	Mean	Range
Age	59.2±12.6	40-79
Baseline IOP (mmHg)	21.4±7.2	12-36
Baseline BCVA	0.8±0.2	0.2-1.0
Baseline SE	0.2±1.8	(-5.25)-(+2.0)
Baseline AL (mm)	23.4±1.2	20.9-25.9
Baseline ACD (mm)	2.6±0.6	1.78-3.95
Baseline ECD (cells/mm^2)	2502.3±413.1	1577-3257
Baseline corneal thickness (μ)	549.4±39.7	418-607

IOP: Intraocular Pressure, BCVA: Best Corrected Visual Acuity, SE: Spheric Equivalent, AL: Axial Length, ACD: Anterior Chamber Depth, ECD: Endothelial Cell Dencity, mm: Milimeter, mmHg: Milimeter mercury, μ: Micrometer, ±: mean and standart deviation.



Graphic: Changes in IOP.

Table 2: Effects of latanoprost 0.005% on axial length.

	Baseline	First month	Third month	Sixth month	p
AL (mm)	23.4±1.2	23.5±1.1	23.4±1.1	23.4±1.1	0.10
ACD (mm)	2.6±0.6	2.6±0.4	2.5±0.3	2.5±0.3	0.51
ECD (cells/mm^2)	2502.3±413.1	2423.0±399.8	2458.9±282.7	2441.7±352.2	0.17
Corneal thickness (μ)	549.4±39.6	544.7±64.6	540.1±50.5	542.8±45.8	0.03

AL: Anterior Chamber Depth, ACD: Endothelial Cell Dencity, ECD: And Central Corneal Thickness, mm: Milimeter, μ: Micrometer, ±: mean and standard deviation.

The baseline mean SE was 0.2±1.8 and at sixth month after treatment it was 0.2±2.1 (p=0.33). No significant change in BCVA was found throughout the treatment period. Spherical equivalent also remained unchanged after treatment with latanoprost 0.005%. The mean IOP which was 21.4±7.2 mmHg before therapy significantly decreased to 14.6±4.6 mmHg at the first month (27.0%), 14.9±3.6 mmHg (22.0%) at the third month and 14.7±3.5 mmHg (24.6%) at the sixth month of treatment with latanoprost 0.005% (p<0.001, graphic).

Table 2 shows changes of AL, ACD, ECD and CCT. A statistically significant reduction in CCT was observed within 6 months of the treatment period (p=0.03). No significant change was observed in other parameters with topical latanoprost 0.005% (p>0.05).

Table 3 gives details of Orbscan parameters. No significant change was observed in these parameters (p>0.05). A significant positive correlation was found between baseline IOP and IOP-lowering effect and a negative correlation was present between IOP-lowering effect and AL (p<0.001 and p=0.04 respectively, Pearson correlation analysis). Linear regression analysis showed significant relation between baseline IOP and IOP-lowering effect (p<0.001).

Table 3: Effects of 0.005% latanoprost on orbscan parameters.

	Baseline	First month	Third month	Sixth month	p
Sim K	0.79±0.52	0.74±0.54	0.78±0.59	0.71±0.50	0.58
Mean power	43.3±1.9	43.5±1.8	43.4±1.7	43.4±1.9	0.90
Mean astigmatism	0.8±0.8	0.8±0.6	0.7±0.6	0.7±0.4	0.91

±: mean and standard deviation.

DISCUSSION

Biological effects of latanoprost on ECM and collagen metabolism which components of cornea and sclera have been reported.[1-3,7] In view of this observation, we investigated any clinically detectable influence of latanoprost on ocular structures.

Our study showed that although latanoprost did not cause clinically detectable changes in corneal topography, ECD, ACD, AL and BCVA, it was assosiated with a decrease of CCT over a period of 6 months. We were unable to find another study which evaluates the effect of latanoprost on multiple parameters in the literature (Pubmed search). Latanoprost is absorbed through the cornea, where it is hydrolyzed to its active form.[6] Gagnon et al found a statistically lower endothelial cell density in POAG subjects than age-matched without glaucoma.

Those subjects receiving greater number of glaucoma medications had lower cell counts.[8] The effects of other topical ocular hypotensive agents on corneal endothelium were also studied. Timolol was found to have no effect on the corneal endothelium in healthy eyes and ocular hypertensive subjects.[9,10]

Lass et al., reported that topical therapy with latanoprost had an effect on corneal thickness and corneal endothelial cell density equivalent to Timolol in subjects with OHT and POAG and in normal corneas at the end of a 12-month follow up. He found that the change in mean central corneal thickness was 1.1% decline and mean ECD demonstrated a marginal increase of 0.3%.[6]

Corneal edema was not reported in clinical trial with latanoprost.[6] Although corneal thickness and cell density are indirect measures of endothelial function, they are easily obtained, reproducible and reflects clinically important direct toxic effects on the endothelium by the determination of any compromise of endothelial functional reserve.[11] Latanoprost can be considered to have good long-term corneal safety in ocular hypertensive and POAG subjects.[6]

We detected no significant change in ECD and any corneal edema. We also thought that latanoprost is safe for in terms of corneal transparency.The possible effects of topical antiglaucomatous medications on CCT values during the follow up glaucoma patients were investigated in different studies.[4,6,7,11-16] Viestenz et al have compared 3 patient groups either receiving PGF2α analogues, carbonic anhydrase inhibitors or both of them with controls. They only found PG analogs to decrease CCT significantly, which might be attributed to the effects of PG on cornea stromal matrix metalloproteinases.[7]

Sen et al., observed a significant reduction 1.9$\pm$2.4% within 24 months with latanoprost and they suggested to measure CCT values in the follow up of glaucoma patients more than once because of the thinning effects of PG analogues.[12] Arcieri et al., compared CCT values of the patients who were on latanoprost, bimatoprost or travoprost monotheraphy and they observed a significant reduction of 0.6% only with bimatoprost.[13] Hatanaka et al., showed that latanoprost, travoprost and bimatoprost are assosiated with CCT reduction over a period of 8 weeks.[14] A recent study reported that 24-months use of latanoprost may decrease the CCT in patients with NTG.[15]

We also found that latanoprost is accompanied by statistically significant decrease of CCT within 6 months of treatment. Whereas Bafa et al a slight but significant increase in CCT was recorded in the latanoprost group. This could be an explained with an increase in intracellular free calcium concentration and activation of the protein kinase C with latanoprost instillation and a change in the shape of the cells according to this study.[16] The corneal stroma consists of corneal fibroblasts and ECM (mostly type 1 collagen) and is responsible for the shape and thickness of the cornea.[4]

Liu et al., cultured human corneal fibroblasts in a 3-dimensional gel of type 1 collagen and in latanoprost. In that study latanoprost stimulated collagen gel contraction mediated by human corneal fibroblasts suggesting that latanoprost increased the contractility of these cells. This action of latanoprost might have affected corneal shape and thickness and thereby influenced the measurement of IOP.[4] We found no significant change in corneal topography parameters with latanoprost in our study.

Marchini et al., found that latanoprost 0.005% caused a marked IOP-lowering effect in 30 patients with untreated OHT or POAG but did not alter the conformation of the anterior segment or angle structures which was measured by ultrasound biomicroscopy and did not induce any refractive and visual acuity change.[1] In addition the increase of ciliary body thickness indirectly supported the mechanism of uveoscleral outflow enhancement induced by latanoprost in that study.[1] Spherical equivalent and BCVA remained unchanged after treatment with latanoprost in our study.Latanoprost may cause a decrease in the extracellular matrix, such as collagen and fibrilin-1, which are components of the ciliary zonules, Thus it makes sense that the structure and perhaps the strength and elasticity of the ciliary zonules could be altered by treatment with latanoprost.[17] Gutierrez-Ortiz et al., reported that latanoprost decreased ACD in patients with glaucoma or OHT after 1 month of treatment.[17] In the same study no significant correlation was found between the magnitude of the latanoprost-induced IOP decrease and the latanoprost-induced ACD decrease. Simsek et al showed that the ACD of patients on prolonged therapy with prostaglandin analogues seems to be lower than control group.[18]

Cankaya et al., also reported that latanoprost was found to have a decreasing effect on ACD in eyes both with and without cycloplegia during the 3-month study period. Although that decrease was statistically significant, no effect on the clinical status of patients and no correlation with the degree of IOP reduction were found.[19] We could not detect any change in ACD from baseline related to latanoprost use during 6 month.Marquez et al., studied the effect of AL on the hypotensive effect of latanoprost in POAG and they found that both at third and sixth months IOP levels was significantly lower in eyes with a shorter AL compared with the eyes with a longer AL and no association between ACD and latanoprost-induced IOP reduction.[20]

Although there was no association with ACD, we also found negative correlation between IOP-lowering effect of latanoprost and AL. In addition no significant change was found in AL from baseline with latanoprost treatment. The limitations of study are small sample size, limited follow up and lack of control group. It is clear that further prospective, large-scale studies with longer follow-ups comparing with a control group are needed to elucidate long term effects of latanoprost 0.005% on ocular structures which may be relevant clinically.

Latanoprost 0.005% is widely prescribed as a first-line drug for glaucoma therapy. It is found to be effective in lowering IOP. We hypothesized that biological effects of latanoprost might cause clinical visible changes. Although we found no clinically detectable changes in visual acuity, spherical equivalent, corneal topography, endothelial cell density, anterior chamber depth and axiel length; latanoprost caused statistically significant reduction in central corneal thickness within 6 months of the treatment period. In our opinion, CCT evaluation at all follow-up visits may be beneficial for setting the target IOP levels in glaucoma practice.

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