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Short term effects of latanoprost on intraocular pressure, central corneal thickness and anterior chamber depth in open angle glaucoma

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Received: 2015-01-18 Accepted: 2015-06-23

拉坦前列素滴眼液对开角型青光眼患者眼压、角膜中央厚度和前房深度的影响

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摘要

目的:探讨开角型青光眼患者局部应用拉坦前列素滴眼液 6mo 后(0.005%,一日一次),眼压(IOP)、角膜中央厚度(CCT)和前房深度(ACD)的变化。

方法:本研究包含初诊为原发性开角型青光眼(POAG)或剥脱性青光眼(PXG)患者 24 例 37 眼。采用 Goldmann 压平眼压计测量 IOP,超声测厚仪测量 CCT,超声生物测量仪测量 ACD 和 ACD/轴长(AL)。比较治疗前,记录治疗后 3mo 和 6mo 的 IOP,CCT,ACD 和 ACD/AL 测量值。

结果:IOP 于治疗前,治疗后 3mo、6mo 平均值分别为 25.0±4.2、17.5±2.0、16.9±1.7,可见治疗后显著降低。CCT 于治疗前,治疗后 3mo、6mo 平均值分别为 546.6±31.5,541.0±29.4、542.2±29.3,可见治疗后显著降低。ACD 于治疗前,治疗后 3mo、6mo 平均值分别为 3.00±0.43,2.95±0.42、2.97±0.41,可见治疗后 3mo 显著降低,6mo 无显著改变。ACD/AL 治疗后改变与 ACD 情况相似。CCT 和 ACD 的测量值在 POAG 中有显著变化,而在 PXG 中则没有。

结论:开角型青光眼患者应用拉坦前列素滴眼液治疗后,除 IOP 大幅降低外,角膜厚度及 ACD 亦出现短期内降低。

关键词:拉坦前列素滴眼液;开角型青光眼;中央角膜厚度;前房深度;眼压

引用:Cavdarli C, Yarangumeli A, Akil H, Kural G. 拉坦前列素滴眼液对开角型青光眼患者眼压、角膜中央厚度和前房深度的影响. 国际眼科杂志 2015;15(12):2040-2044

Abstract

• AIM: To investigate the changes in intraocular pressure (IOP), central corneal thickness (CCT) and anterior chamber depth (ACD) in eyes with open angle glaucoma treated with topical latanoprost (0.005%, once a day) for 6mo.

• METHODS: Thirty seven eyes of 24 newly diagnosed patients with primary open-angle glaucoma (POAG) or pseudoexfoliation glaucoma (PXG) were included. IOP was measured with Goldmann applanation tonometry, CCT was measured with ultrasound pachymeter, while ACD and ACD/axial length (AL) values were obtained by ultrasound biometry. IOP, CCT, ACD and ACD/AL measurements before treatment were compared with the recordings at the 3mo and the 6mo of treatment.

• RESULTS: Mean IOP values at baseline, and at 3mo and 6mo were, 25.0±4.2, 17.5±2.0 and 16.9±1.7, respectively, showing a significant reduction after treatment. Mean CCT values at baseline, and at 3mo and 6mo were, 546.6±31.5, 541.0±29.4 and 542.2±29.3, respectively, showing a significant reduction after treatment. Mean ACD values at baseline, and at 3mo and 6mo were, 3.00±0.43, 2.95±0.42 and 2.97±0.41, respectively, showing a significant reduction at 3mo, but not at 6mo. ACD/AL changes after treatment were similar to the ACD course. The significant changes in CCT and ACD measurements were found to be related with the POAG eyes, not with the PXG eyes, when evaluated separately.

• CONCLUSION: Apart from a substantial reduction in IOP, latanoprost induces corneal thinning and ACD reduction at the short term of treatment in eyes with open angle glaucoma.

• KEYWORDS: latanoprost; open angle glaucoma; central corneal thickness; anterior chamber depth; intraocular pressure
DOI:10.3980/j.issn.1672-5123.2015.12.04

Citation: Cavdarli C, Yarangumeli A, Akil H, Kural G. Short term effects of latanoprost on intraocular pressure, central corneal thickness and anterior chamber depth in open angle glaucoma. *Guoji Yanke Zazhi*(*Int Eye Sci*) 2015;15(12):2040-2044

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by intraocular pressure (IOP) associated optic disc cupping and specific visual field defects. IOP is important in

the diagnosis, in determining of the progression and in evaluation of the response to the treatment of glaucoma. There is evidence indicating that reduction of IOP slows the progression of glaucomatous optic neuropathy[1].

Central corneal thickness (CCT) was found to be a predictor for the development of glaucoma in the Ocular Hypertension Treatment Study (OHTS) according to which the risk of glaucoma was inversely correlated with CCT[2]. However, measurements of CCT taken within a clinical setting by a trained observer may show significant variability, therefore more than one reading may be required[3,4]. Corneal thickness influence the measurement of IOP and factors affecting CCT such as topical antiglaucoma agents require further investigation.

Topical prostaglandin (PG) analogues are widely used in glaucoma treatment since they are quite effective in reducing IOP and latanoprost has one of the best efficacy-tolerability profiles of the PG analogues available for glaucoma treatment with good patient compliance and persistence[5]. PGs lead to structural and functional remodeling in the connective tissue by inducing matrix metalloproteinases (MMPs) which cause reduction in extracellular matrix elements of the ciliary muscle and widen the spaces between the muscle fibers, resulting in an increase in uveoscleral outfiow and a decrease in IOP[6,7]. This group of agents has been reported to decrease anterior chamber depth (ACD) shortly after the initiation of the treatment[8]. Collagen type IV and fibrillin are the main construction elements of the ciliary zonules, and analogous structural and functional changes such as an anterior displacement of the crystalline lens might as well be induced by activated MMPs[9,10]. This issue is important for the follow up of the narrow angle glaucoma patients, while ACD and CCT should be taken into account before anterior segment interventions, such as cataract extraction, or refractive surgeries.

The aim of this prospective study was to investigate the alterations in IOP, CCT, ACD and ACD/axial length (AL) ratio in eyes with open angle glaucoma during the first 6mo follow-up of latanoprost 0.005% therapy.

SUBJECTS AND METHODS

In this prospective study we evaluated 37 eyes of 24 newly diagnosed open angle glaucoma patients [primary open-angle glaucoma (POAG) or pseudoexfoliation glaucoma (PXG)] who were treated with latanoprost 0.005% (Xalatan, Pfizer Inc., New York, USA) between September 2011 and June 2013 in the Glaucoma Unit of the Ankara Numune Training and Research Hospital, Turkey. Mean patient age was 58.5±12.6, 7 patients were male and 17 were female. The study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional review board of our hospital. The treatment and adverse effects were fully explained to the patients, as were other therapeutic options. All patients provided informed consent.

All patients underwent a complete ophthalmic examination which included visual acuity testing with Snellen chart, anterior segment examination with slit-lamp biomicroscopy, gonioscopy with the Goldmann three mirror lens, IOP measurements with Goldmann applanation tonometer at 8, 10, 12 a. m. and 2 p. m., CCT measurements by ultrasound pachymetry, visual field test with Humphrey automated perimetry, and fundus examination with pupil dilation.

The study evaluated the changes in IOP, CCT, ACD, ACD/AL with latanoprost 0.005% treatment after 3mo, and after 6mo from the initiation. The patients were asked to instill latanoprost 0.005% once daily at 9 p. m. to the conjonctival sac. In 3mo of the study protocol patients were questioned for compliance. Patients missing to instill their drops in two consecutive days or in more than two nonconsecutive days per month were excluded for poor or doubtful compliance. Measurements of refractive status, best corrected visual acuity, IOP and biomicroscopic anterior and posterior segment examination were performed at each visit.

Inclusion Criteria for the Primary Open-angle Glaucoma Subjects Age more than 30y, IOP measurement 22 mm Hg or higher, no anterior chamber angle pathology in gonioscopy, open anterior chamber angle (grade 3 or more) according to the Shaffer grading system, C/D ratio more than 0.4, and a visual field defect indicating glaucomatous optic neuropathy.

Inclusion Criteria for the Pseudoexfoliation Glaucoma Subjects Age more than 30y, IOP measurement 22 mm Hg or higher, open anterior chamber angle (grade 3 or more) according to the Shaffer grading system, presence of the pseudoexfoliation material at the angle, pupillary tuft or lens capsule, and a visual field defect indicating glaucomatous optic neuropathy.

Subjects with a previous history of any ocular surgery, significant refractive error (myopia, hyperopia, or astigmatism over 3D), contact lens usage, retinopathy and related photocoagulation therapy, trauma, keratitis or uveitis were excluded. Patients with chronic obstructive pulmonary disease, ischemic heart disease, history of a hypersensitivity reaction to latanoprost, as well as pregnancy or breastfeeding were also excluded from the study.

The same examiner recorded IOP measurements with the Goldmann applanation tonometer, CCT measurements by ultrasonic pachymetry (IOPAC Advanced. Heidelberg Engineering, Portable Ophthalmic Devices Inc. Victoria, BC, Canada), ACD and ACD/AL measurements by ultrasonic biometry (OPTIKON 2000 S. p. A. Via del Casale di Settebagni, Roma, Italy) between 9 and 10 a. m. in each visit. Ultrasonic pachymetry was set to take the mean of 5 measurements of CCT within 5 μm standard deviation.

During the biometry measurement the patient was asked togaze at the level of the 2/10 line on the Snellen chart, at a distance of 6 m with the study eye: the contralateral eye was occluded to avoid convergence movements during the measurement. The examiner tried to touch the probe perpendicularly to the centre apex of the cornea without applying pressure. The ultrasound device was set to take the mean of 5 consecutive measurements of ACD and AL automatically than ACD/AL was calculated.

RESULTS

The study was initiated with 46 eyes of 30 patients and concluded with 37 eyes of 24 patients. Nine eyes of 6 patients excluded from the study because of newly diagnose of diabetes mellitus, cataract surgery and latanoprost incompliance. Treatment was recommended to 11 of the eyes due to the PXG and 26 of the eyes due to the POAG.

The mean IOP courses in POAG and PXG groups and in total are presented in Table 1. The reductions of IOP at the 3mo and the 6mo were statistically significant ($P<0.001$). The mean IOP at the 6mo appeared to be lower than the mean IOP at the 3mo, however, the differences were not statistically significant ($P=0.399$, $P=0.049$, $P=0.039$, for PXG and POAG groups, and for overall respectively).

The mean CCT of all patients was 546.6±31.5 μm before the treatment, 541.0±29.4 μm at 3mo of the treatment, 542.2±29.3 μm at 6mo. Reductions in CCT at the 3mo and the 6mo compared to the baseline were statistically significant ($P<0.001$). CCT values at the 3mo and the 6mo showed no statistically significant difference ($P=0.175$).

The CCT changes, in eyes with POAG and PXG are presented in Table 2. There seemed to be a reduction in CCT in the PXG group after the treatment but a statistically significant difference was not confirmed ($P=0.345$). There was a significant reduction in the mean CCT of the POAG group both at 3mo and at 6mo. The slight increase in CCT in the POAG group from 3mo to 6mo was not found to be statistically significant ($P=0.314$).

The mean ACD of all patients was 3.00±0.43 mm before latanoprost treatment, was 2.95±0.42 mm at 3mo, and was 2.97±0.41 mm at 6mo (Table 2). Reduction was significant for the 3mo but not for the 6mo.

The ACD changes in the two groups are presented in Table 2. The difference in ACD after the treatment was not significant in the PXG group ($P=0.039$), but there was a significant decrease in ACD in the POAG group at 3mo ($P=0.006$).

The mean ACD/AL ratio was 0.128±0.016 before the latanoprost treatment, was 0.126±0.016 at 3mo, and was 0.127±0.016 at 6mo of latanoprost therapy. There was a statistically significant decrease in ACD/AL ratio at the 3mo of latanoprost treatment ($P=0.001$), but not at 6mo.

The ACD/AL ratio changes, in eyes with POAG and PXG are presented in Table 2. In the PXG group the difference between baseline and the 3 mo and the 6mo of latanoprost therapy was not significant ($P=0.059$). In the POAG group there was a statistically significant decrease in ACD/AL ratio at the 3mo of the therapy ($P=0.021$), but not at 6mo.

Table 1 The mean IOP (mm Hg) course

Groups	Baseline	3mo	6mo	[1]P
PXG ($n=11$)	27.0±3.8[a,b]	16.6±1.8[a]	16.1±1.4[b]	<0.001
POAG ($n=26$)	24.1±4.1[a,b]	17.8±2.0[a]	17.2±1.7[b]	<0.001
Overall ($n=37$)	25.0±4.2[c,d]	17.5±2.0[c]	16.9±1.7[d]	<0.001

[1]Friedman test; According to the Bonferroni Correction if $P<0.025$, the difference is statistically significant. [a]Statistically significant difference between baseline and 3mo in IOP values according to Bonferroni Correction ($P<0.0083$); [b]Statistically significant difference between baseline and 6mo in IOP values according to Bonferroni Correction ($P<0.0083$); [c]Statistically significant difference between baseline and 3mo ($P<0.001$); [d]Statistically significant difference between baseline and 6mo ($P<0.001$).

DISCUSSION

Despite the developments in the field ofglaucoma surgery and laser modalities, use of topical agents is still the initial and the major treatment option in most cases. Latanoprost, a PG $F_{2\alpha}$ analogue, is an effective ocular antihypertensive agent for the management of high IOP. The drug is probably one of the most potent IOP-lowering agents available today[5,11].

In this prospective study, latanoprost was found to decrease the mean IOP between 30.4% (3mo) to 32.4% (6mo) as a whole. The IOP decrease in the PXG group was more relevant than in the POAG group. That might be related with the higher baseline IOP or relatively small number of patients in the PXG group.

Latanoprost 0.005% has been shown to reduce IOP during the day and night[12] as a result of increasing the aqueous outflow through the uveoscleral pathway by remodeling the connective tissue. Activation of the PG receptors (mainly EP2 and FP receptors) within the ciliary body stimulates secondary messenger cascade for MMP synthesis. PG induced remodeling effect of MMPs lead to reductions in extracellular matrix elements of the ciliary muscles, widens the spaces between the muscle fibers and decreases the resistance against aqueous humour. Another mechanism by which latanoprost could modify IOP is the stimulation of the FP receptors in the trabecular cells. It has been suggested that aqueous outflow also could be increased by the PG induced remodeling changes of the extracellular matrix within the trabeculum[13].

In patients with ocular hypertension or open-angle glaucoma, a single drop of latanoprost 0.005% solution administered topically once daily reduces diurnal IOP by 22% to 39% over 1 to 12mo treatment[14]. Mean IOP reductions from baseline were reported to be between 28% to 31% with latanoprost in a meta-analysis by van der Valk *et al*[15]. Our results for IOP reduction in POAG group were consistent with the findings in these studies.

In our study there were statistically significant reductions in the mean CCT values at 3mo and 6mo of the treatment compared to the baseline, and the CCT at the 3 mo and the 6mo did differ significantly. However, when the groups were evaluated separately, a significant reduction in CCT was only found in the POAG group.

Sen *et al*[16] compared the effects of latanoprost and bimatoprost on CCT of the patients diagnosed as POAG, PXG, ocular hypertension and normal tension glaucoma. A significant reduction in CCT was observed at the 6, 12, and 24mo with latanoprost and bimatoprost. Moreover, Lass *et al*[17] compared the long-term effects of latanoprost alone, the fixed combination of latanoprost-timolol, and timolol alone on

Table 2 CCT, ACD, ACD/AL course in PXG and POAG groups, and overall

Parameters	Baseline	3mo	6mo	[1]*P*
CCT				
PXG (*n*=11)	542.7±39.9	540.1±37.7	539.5±36.2	0.345
POAG (*n*=26)	548.2±28.0[a,b]	541.5±26.0[a]	543.3±26.5[b]	<0.001
Overall (*n*=37)	546.6±31.5[c,d]	541.0±29.4[c]	542.2±29.3[d]	<0.001
ACD				
PXG (*n*=11)	3.07±0.49	3.02±0.46	3.03±0.47	0.039
POAG (*n*=26)	2.97±0.41[a]	2.92±0.40[a]	2.95±0.39	0.006
Overall (*n*=37)	3.00±0.43[c]	2.95±0.42[c]	2.97±0.41	<0.001
ACD/AL				
PXG (*n*=11)	0.130±0.017	0.127±0.016	0.128±0.016	0.059
POAG (*n*=26)	0.127±0.016[a]	0.125±0.016[a]	0.126±0.016	0.021
Overall (*n*=37)	0.128±0.016[c]	0.126±0.016[c]	0.127±0.016	<0.001

[1]Variance analysis in the repeated measurements, according to the Bonferroni Correction if $P<0.025$, the difference is statistically significant. [a]Statistically significant difference between baseline and 3mo according to Bonferroni Correction ($P<0.025$); [b]Statistically significant difference between baseline and 6mo according to Bonferroni Correction ($P<0.025$); [c]Statistically significant difference between the baseline and 3mo measurements ($P<0.001$); [d]Statistically significant difference between baseline and 6mo measurements ($P=0.004$).

corneal thickness after 12mo of treatment and reported an overall CCT reduction about 1.1% ± 2.5%, with no significant difference between the three groups.

Viestenz *et al*[18] also pointed out that the topical application of $PGF_{2\alpha}$ analogues reduced the CCT. They attributed this issue to the effects of $PGF_{2\alpha}$ analogues on the extracellular matrix of the corneal stroma *via* upregulation of MMPs. Moreover, Liu *et al*[19] reported that among the antiglaucoma drugs examined, only latanoprost stimulated collagen gel contraction mediated by human corneal fibroblasts. They interpreted this finding as this action of latanoprost might affect corneal shape and thereby influence measurement of IOP, but another long term study with latanoprost shows that latanoprost eye drops significantly reduce CCT during the initial stage of use, however, CCT reduction does not clinically affect IOP values[20] and latanoprost, travoprost, and bimatoprost have a similar effect on CCT[21]. Brandt *et al*[22] reported a slightly higher rate of thinning in patients treated with topical PG analogues as one of the results of the OHTS, and concluded that the observed drug related thinning was unlikely to influence tonometry or clinical decision-making substantially in most clinical situations. This conclusion is also applicable to the results of our study in which an overall CCT reduction of about 5 microns was demonstrated. Nevertheless the use of topical PG analogues might better be avoided in patients with keratoconus or after procedures such as laser-assisted *in situ* keratomileusis[6].

The present study revealed a significant decrease in ACD with latanoprost therapy at 3mo compared to the baseline, but no significant ACD difference from baseline was found at the 6mo when all eyes were considered. However, when we evaluated the PXG and the POAG groups separately, ACD reduction at the 3mo was significant in the POAG group only. A similar pattern of reduction was also found in ACD/AL ratios. ACD/AL reduction was only significant in the POAG group at 3mo. Gutierrez-Ortiz *et al*[11] evaluated the short term effect of latanoprost 0.005% in patients with glaucoma or ocular hypertension and reported significant reduction in ACD but did not identify any change in the visual acuity and lens thickness. Simsek *et al*[23] evaluated the effect of long-term application of bimatoprost and latanoprost on the ACD of POAG patients. The ACD and ACD/AL values of the patient group treated with PG analogues was reported to be lower than those of the control group. They also suggested that interpreting ACD/AL ratio could be more convenient than ACD value due to the effect of the individual differences on the outcomes when comparing different patient groups.

Latanoprost induced narrowing in the anterior chamber might be the result of relaxation of the ciliary zonules. Some components of the ciliary zonules such as fibrillin-1 and collagen IV can be modified by PGs and MMPs. Fibrillin has an important role in the strength and elasticity of ocular connective tissues and it is the principal component of the ciliary zonules[24]. Latanoprost causes disruption of the fibrillin rich microfibers and zonular bundles which changes zonular ultrastructure and characteristics[25]. Collagen IV within the uveoscleral outflow pathway is also degraded by PG analogues, and a similar degradation in zonular fibres might result in further weakening[7,9]. These changes might explain the decrease in ACD after treatment with latanoprost as we found in the present study.

Although it is possible that latanoprost induced reduction in ACD might lead to a narrowing of the anterior chamber angle to some extent[26], the clinical evidence derived from the prolonged widespread use of the drug suggests that it is a safe and effective option even for the treatment of patients with closed angle glaucoma[27,28].

The change in the ACD with latanoprost usage has been

proposed to be an issue in terms of cataract surgery[11]. Some formulas take ACD into account when calculating intraocular lens (IOL) power. However, a 0.05 mm decrease in ACD as in our study would only result in a negligible change of less than 0.1 D in IOL power with the Haigis Formula[29]. On the other hand zonular weakening might deserve consideration in some candidates for cataract surgery.

In conclusion, apart from a substantial reduction in IOP, latanoprost induces corneal thinning and ACD reduction at the short term of treatment, especially in eyes with POAG, however, clinical significance of these structural changes appears to be minor. More studies related with the long-term effects of latanoprost and other PG analogues are needed to elucidate the further effects of this drug on ocular structures and their possible clinical relevance.

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