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Choroidal Thickness Increase After Latanoprost Treatment

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***Abstract**: Latanoprost is the first prostaglandin analogue introduced for glaucoma treatment whose action is not fully understood until today. The purpose of this study is to evaluate the effect of latanorpost on choroidal thickness in a group of 16 eyes in patients newly diagnosed with glaucoma using last generation OCT (Optical Coherence Tomography). The IOP (intraocular pressure) and the subfoveal choroidal thickness were measured before and after one week, one month, 3 and 6 months of treatment with latanoprost. The subfoveal choroidal thickness was 219.2±63.8µm before treatment and 255.6±76.4µm after one week of treatment. Increased thickness of the choroid seven days post-intervention correlates with decreased intraocular pressure from 29.0±3.2mmHg pre-intervention to 17.6±3.1mmHg p<0.001 (p=0.018). The results of this study confirm the idea of latanoprost uveoscleral alternative drainage increase.*

***Keywords**: glaucoma, choroidal thickness, latanoprost*

1.Introduction

Glaucoma is the leading cause of irreversible blindness, affecting almost 50 million people worldwide. The purpose of antiglaucoma treatment is to decrease the IOP, which can be done either with medication that can decrease the production of aqueous humor or by increasing the uveoscleral outflow. There are 5 classes of ocular hypotensive agents that are used in common clinical practice for glaucoma treatment at the moment: ß-adrenergic antagonists, prostaglandin analogues, adrenergic agonists, carbonic anhydrase inhibitors and cholinergic agents. Among them, prostaglandin analogues and cholinergic agents have direct effects on the two drainage routes.

Prostaglandin analogue is the first-line glaucoma medication, due to a superior intra-ocular pressure (IOP) lowering effect, good safety profile, and once-daily dosage. Latanoprost is an f2a prostaglandin which decreases the IOP by increasing the uveoscleral outflow by stimulating matrix metalloproteinases (MMP), dissolving extracellular matrix with widening of connective tissue spaces among ciliary muscle bundles (1,2). Uveoscleral outflow is thought to be driven or changed by pressure gradients through the uvea, by movements of the ciliary muscle, and by cytoskeletal alterations or changes in the extracellular matrix within the drainage tissues. The term *uveoscleral outflow* refers to the drainage of ocular aqueous umor other than through the trabecular meshwork.

The choroid, which connects the ora serrata with the optic disc, provides > 70% of the circulating blood of the eye, is the most abundant blood-vessel layer, and is maintained by the highest blood flow in the body per unit tissue weight (3,4).

Quantitative analysis of the choroidal layer is necessary in order to understand the vascular role in the pathophysiology of glaucoma. The choroid plays a vital role in the pathophysiology of many diseases affecting the retina, but adequate visualization of the choroid using OCT has not been possible until recently. Choroidal thickness measurement in foveolar area is now possible using OCT. With advancements in OCT image processing software, more refined details of the posterior segment can be appreciated and characterized in vivo. Many authors recently reported the successful examination and measurement of choroidal thickness in normal and pathologic states using the OCT instrument (5-12).

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2.Materials and methods

This prospective study included 16 patients with newly diagnosed POAG (primary open-angle glaucoma) who received topical antiglaucoma treatment with latanoprost 1 drop at 9 o'clock AM. All the subjects were prospectively enrolled at the Retina Clinic of Ponderas Academic Hospital between May and September 2018. The study protocol was approved by the Institutional Review Board of Retina and adhered to the tenets of the Declaration of Helsinki. Each subject was required to sign an informed consent statement before enrollment and before any measurements.

All the participants had to meet the following criteria for inclusion: older than 18 years of age, open-angle status on gonioscopic examination, patients with newly diagnosed POAG who had no previous topical hypotensive therapy. Patients with a history of other ocular surgery were excluded. Participants with systemic hypertension and diabetes mellitus were included unless they had been diagnosed with diabetic or hypertensive retinopathy.Choroidal thickness measurements by optical coherence tomography were carried out on the first visit before latanoprost use and at intervals of 7 and 30 days 3 and 6 months of therapy.

The diagnosis of POAG was made on elevated intraocular pressure associated with changes in visual field and by decreased thickness of the retinal nerve fiber layer. (RNFL) measured by OCT. The glaucomatous visual field defects were defined as a cluster of ≥3 points with $P< 0.05$ on a pattern deviation map in at least one hemifield, including ≥ 1 point with $P< 0.05$, or a glaucoma hemifield test result outside the normal limits.

Each patient had the IOP measured using Goldmann tonometer and the subfoveol choroidal thickness using OCT TRITON PLUS before treatment and at one week, one month, three and six months after starting the treatment.

Macular choroidal thickness (mCT) was measured at the fove. The choroidal thickness was defined as the perpendicular distance between the outer border of the retinal pigment epithelium and the inner border of the sclera. To reduce manual measurement variability, our study used OCT software in the "automated segmentation" mode to determine the location of the retinal pigment epithelium layer and in the "Angio B-scan" mode to distinguish the choroidal layer from the scleral border based on choroidal vascularity.

One of the big advantage of 1050 nm wavelength is that it can easily pass through the retinal pigment epithelium (pigment within cells = melanin). The shorter 840 nm wavelength of SD OCT is scattered by the RPE and absorbed by melanin within the cells. Minimal light reaching the choroid means minimal light returning to the detector and that is why it is difficult to give high quality images of choroid or sclera with 840nm. However, 1050 nm wavelength passes through the RPE and can reach the choroid and even the sclera. Uncompromised choroidal imaging is impossible with SD OCT and is a big clinical benefit of SS OCT. The scattering of light is related to the wavelength of light. Shorter wavelights are scattered more and this is why the sky appears blue – the short blue wavelengths are scattered more than longer visible wavelengths by the earth's atmosphere. In the context of OCT, the longer 1050 nm is more resistant to scatter, not only at the level of the RPE but also when it passes through cataract and hemorrhage.

The swept source OCT will create uniform and high sensitivity images compared with SD OCT. It will allow visualization of the choroidal and scleral tissues.

Statistical analysis. The IOP and choroid thinness at different time points of follow- up were described using mean and standard deviation. In order to study the difference between baseline and different time points of follow-up, the mean and standard deviation were calculated, and the paired t-test was used to assess the difference. For the purpose of assessing the trend observed over the follow-up period, a repeated measure was used to evaluate the effect of latanoprost on IOP and choroid thinness, first globally, based on the records for all time points, and secondly on the records after treatment only. In order to assess the correlations between difference of IOP and difference of choroid thinness, the

Pearson correlation coefficient was used. Statistical analyses were carried out using SPSS 23.0. p values less 0.05 were considered to be significant.

3.Results and discussions

The patients' mean age was 64.4±3.7 years, 75% of them were from urban areas.

Table 1
Patient's characteristics - baseline

Characteristics	Mean ± SD
Age (years)	64.4±3.7
Residence area N (%) Urban Rural	 12 (75.0) 4 (25.0)
IOP (mmHg)	29.0±3.2
Choroid thinness (µm)	219.2±63.8

Baseline mean untreated intraocular pressure was 29.0±3.2 mmHg and the choroidal thickness 219.2±63.8 µm (Table 1).

Table 2
Evolution of IOP and choroid thinness during the 6 months follow-up

	Baseline	7 days	One month	3 months	6 months	Trend	
						p*	p**
IOP (mmHg) p value vs. baseline	29.0±3.2	17.6±3.1 <0.001	18.3±1.8 <0.001	18.4±2.1 <0.001	19.1±3.0 <0.001	<0.001	0.391
Choroid thinness (µm) p value vs. baseline	219.2±63.8	255.6±76.4 0.011	260.5±71.3 0.004	248.4±72.1 0.022	251.2±62.3 0.001	0.012	0.589

p* = p values of the trend including baseline values
p** = p values of the trend disregarding baseline values (among post intervention values)

Tabel 2 shows the evolution of IOP and the choroidal thickness from initiation of treatment to six months post-intervention. The decrease in IOP was maintained at 7 days post-intervention (from 29.0±3.2 mmHg pre-interventional to 17.6±3.1 mmHg; p<0.001) up to 6 months post-interventional evaluation (19.1±3.0 mmHg; p<0.001). Also, the choroidal thickness was significantly increased one-week post-intervention (from 219.2±63.8 µm to 255.6±76.4 µm, p=0.011) and it was maintained increased to 6 months after treatment (251.2±62.3 µm, p=0.001). Significant changes were observed in the evolution of IOP (p<0.001) and in choroidal thickness (p=0.012) over the entire period of the study. There were no significant differences post-intervention neither in evolution of IOP (p=0.391) nor in choroidal thickness (p=0.589). Therefore, the IOP decreased and the choroidal thickness significantly increased post-intervention regarding primary results. The results obtained did not suffer significant changes over the other three subsequent evaluations.

Table 3
Correlation between differences of IOP and difference of choroid thinness during the follow-up period

	Difference 7 days vs.baseline		Difference one month vs.baseline		Difference 3 months vs.baseline		Difference 6 months vs.baseline	
	Mean±SD	rho (p value)	Mean±SD	rho (p value)	Mean±SD	rho (p value)	Mean±SD	rho (p value)
IOP (mmHg)	-11.4±4.0		-10.7±4.0		-10.6±4.0		-9.9±4.1	

Choroid thinness (µm)	36.4±49.8	-0.582 (0.018)	41.3±48.5	-0.245 (0.360)	29.2±45.7	-0.316 (0.234)	32.0±31.7	-0.275 (0.302)

The decrease of IOP correlates significantly with choroidal thickness (p=0.018) (Table 3). The choroid is mainly composed of vascular tissue and choroidal perfusion plays a very important role in neuroprotection. The goal of modern glaucoma therapy is to have a controlled IOP and neuroprotection. Most studies focuse on the effect of antiglaucoma drugs on baseline ocular blood flow.

We found only one study that concludes that the increase in blood flow is indeed beneficial in terms of visual field preservation. Martinez et al. showed that an increase in blood flow is beneficial in terms of visual field preservation (15).

Boltz et al. tested the effect of latanoprost on choroidal blood flow regulation in the face of changes in ocular perfusion (16). In one of the Boltz et al. studies published in 2011 they showed that latanoprost improved choroidal blood flow regulation during both the increase and the decrease in ocular perfusion pressure. They concluded that the improvement in choroidal blood flow regulation might be a consequence of an ocular hypotensive effect of the drug. This result is important to understand the relationship between ocular blood flow and glaucoma, because any reduction in IOP is beneficial for slowing down the progression of the disease by improving choroidal blood flow.

Koz et al. found a statistically significant lower resistive index in the ophthalmic artery after 6 months of latanoprost therapy using color Doppler ultrasound (17).

Gherghel et al. showed an increment in the mean ocular perfusion pressure and an improvement in ocular perfusion at the optic nerve head and retina levels using the Heidelberg Retina Flowmeter system (18).

Our study was performed with a last generation ocular tomograph which allowed us a better visualization, delineation and measurement of the ocular layers with a great view of the choroid. Using OCT TRITON PLUS, we could measure the choroidal thickness which significantly increases one-week post-intervention (from 219.2±63.8 µm to 255.6±76.4 µm, p=0.011) and it was maintained increased at 6 months after treatment (251.2±62.3 µm, p=0.001). The decrease in IOP was maintained at 7 days post-intervention (from 29.0±3.2 mmHg pre-intervention to 17.6±3.1 mmHg; p<0.001) up to the 6 months post-interventional evaluation (19.1±3.0 mmHg; p<0.001).

Some authors have reported diurnal variation of choroidal thickness (13 14) which is why we did the measurements in our study at 9 o'clock in the morning, the time when the patient puts one drop of latanoprost in each eye. In this way we checked if the patients put the drop correctly and we eliminated the possible variation of hours in the measurement of the choroid. In conclusion, the results of this study confirm and demonstrate the increase of uveoscleral alternative drainage after latanoprost treatment.

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