• Clinical Research •

Quantifying latanoprost-induced conjunctival hyperemia by anterior segment optical coherence tomography angiography

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Abstract

• **AIM:** To evaluate the mid-term effects of topical latanoprost 0.005% on vessel density (VD) of the bulbar conjunctiva using anterior segment optical coherence tomography angiography (OCTA).

• **METHODS:** Thirty-four eyes of 21 patients and 18 eyes of 9 healthy subjects were recruited as the treatment and control groups, respectively. The treatment group was instructed to apply generic latanoprost 0.005% once daily at night, while the control group received no medication. Anterior segment OCTA was performed on all eyes at baseline, 3wk, and 12wk after initiation of latanoprost. The superficial bulbar conjunctival VD was measured in the superior, inferior, temporal, and nasal quadrants. A linear mixed model was used to compare the change in the VD between groups.

• **RESULTS:** The change in the VD was not different between groups in temporal, and nasal quadrants at 3-week and 12-week time points. The VD in the superior bulbar conjunctiva was significantly increased after 12wk (P=0.029) while the change from baseline after 3wk was not different between groups (P=0.218). After adjustment for age and gender superior hemi (P=0.006) and center (P=0.016) of the inferior quadrant of bulbar conjunctiva showed increased VD after 12wk.

• **CONCLUSION:** The trend of changes in the superior and inferior conjunctival VD is increased following topical latanoprost administration and these changes can be quantified using anterior segment OCTA.

• **KEYWORDS:** latanoprost; conjunctival hyperemia; conjunctival vessel density; anterior segment optical coherence tomography angiography

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INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide. It is estimated that 111.8 million people aged 40-80y will have glaucoma by 2040[1]. Intraocular pressure (IOP) is the only modifiable risk factor[2]. Several options are currently available for the medical therapy of glaucoma, including prostaglandin analogs (PGAs), beta-blockers, alpha agonists, carbonic anhydrase inhibitors, parasympathomimetic, rho-associated protein kinase inhibitors, and hyperosmotic agents. Latanoprost, a PGA, received Food and Drug Administration approval in 2000[3]. Since PGAs are potent IOP reducers, usually prescribed once daily, they are preferred as the first-line treatment option in patients with glaucoma[4].

Topical PGAs are associated with several side effects, including meibomian gland dysfunction, trichiasis, hypertrichosis, darkening of the eyelids and periocular skin, orbitopathy, and conjunctival hyperemia[5-6]. Latanoprost-induced conjunctival hyperemia has been shown to occur most frequently 1–2wk after initiation of the drug and declines thereafter[7]. Furthermore, different drops in this family can cause varying degrees of hyperemia. While some studies have reported that latanoprost causes less conjunctival hyperemia compared to bimatoprost, others have not identified a significant difference[8-9]. Optical coherence tomography angiography (OCTA) is a dye-free and noninvasive tool for the evaluation of ocular blood flow[10]. This technique allows for the assessment of the vasculature of the retina, choroid, and also scleroconjunctival

regions[11]. Studies evaluating latanoprost-induced conjunctival hyperemia often, rely on the patients' reports or standard photographs. OCTA, by providing quantitative measures of conjunctival vasculature, offers a more accurate and objective method for understanding conjunctival hyperemia.

In this study, we aimed to quantitatively evaluate the latanoprost-induced conjunctival hyperemia in medication-naïve eyes using OCTA.

PARTICIPANTS AND METHODS

Ethical Approval The institutional review board of the Tehran University of Medical Sciences approved the study (IR.TUMS.FARABIH.REC.1400.018) and the tenets of the declaration of the Helsinki and its later amendments have been adhered to. All patients signed the informed consent form.

In this prospective interventional case series, we enrolled 34 eyes of 21 patients in the treatment group and 18 eyes of 9 subjects in the control groups. The eyes in the treatment group were recruited from the referral cases at the glaucoma clinic of the Farabi Eye Hospital between April 2020 and January 2021. All eyes underwent a comprehensive and thorough ophthalmic examination, including corrected distance visual acuity (CDVA) assessment, slit-lamp biomicroscopy, IOP measurement using Goldmann applanation tonometry, indirect gonioscopy with a Zeiss 4-mirror goniolens, dilated funduscopy and measurement of the central corneal thickness measurement.

Medication naïve glaucomatous eyes that reached target IOP with latanoprost were enrolled as the treatment group in this investigation. These eyes had primary open angle glaucoma, primary angle-closure glaucoma, or pseudoexfoliation glaucoma. All eyes exhibited glaucomatous optic neuropathy—characterized by generalized cup enlargement, neuroretinal rim notching, optic nerve head hemorrhage, or retinal nerve fiber layer defects—accompanied by corresponding visual field loss. Primary angle-closure glaucoma was defined as having iridotrabecular contact exceeding 180 degrees without secondary causes of angle closure and eyes were enrolled 3mo after undergoing laser peripheral iridotomy. The eyes with primary open angle and pseudoexfoliation glaucoma demonstrated wide and open angle on gonioscopy. The eyes with pseudoexfoliation glaucoma showed deposition of the fibrillar material on the pupillary margin and/or the lens capsule. Patients in the treatment group were instructed to instill the latanoprost in the lower conjunctival sac once nightly and close the eyelids for 5min to ensure proper distribution and retention on the ocular surface. All the eyes in the treatment group used the latanoprost with the same generic brand. Healthy eyes not requiring topical medications during the study were recruited as the control group. Exclusion criteria included a history of laser peripheral iridotomy in the past 3mo, any intraocular surgery other than uncomplicated cataract surgery within six months, or the presence of any ocular surface disease, uveitis, cystoid macular edema, keratitis, blepharitis, ocular trauma, pterygium, symblepharon, and other types of glaucoma associated with conjunctival hyperemia (*e.g.*, neovascular glaucoma).

Anterior Segment Optical Coherence Tomography Angiography The OCT AngioVue system (Optovue Inc, Fremont, CA, USA), integrated into the Avanti spectral-domain OCT was used to image the scleroconjunctival vessels. The superficial vessel density (VD) of the bulbar conjunctiva was measured using a 3 mm×3 mm scan pattern in the superior, inferior, temporal, and nasal quadrants. To obtain clear images, patients were instructed to gaze in the desired directions and imaging was performed while allowing normal blinking.

The 3 mm×3 mm scan pattern comprises a central circle and a peripheral annulus. The central ring has a diameter of 1 mm while the peripheral annulus has inner and outer diameters of 1 and 3 mm, respectively. To ensure consistent imaging location at baseline and follow-up visits, the center of the measurement circle was aligned with the geographic center of the cornea. Additionally, the border of the central circle was positioned tangentially to the limbus in each imaging session (Figure 1). VD, defined as the ratio of the area occupied by vessels to the total area was automatically calculated as whole image VD (wiVD) as well as VD in superior and inferior hemi and within the central circle (Figure 1).

Eyes in the treatment group underwent imaging at baseline, 3, and 12wk after initiating latanoprost 0.005% (Sina Darou, Iran). Imaging of the control eyes was performed in the same manner. All eyes were imaged between 9 *a.m.* and 11 *a.m.* to minimize the potential effects of diurnal variation on the vasculature. Images with poor quality—defined as a signal quality less than 4, poor clarity, motion artifacts, localized weak signal, or segmentation errors—were excluded.

Statistical Analysis To calculate the sample size we considered the type 1 error of 0.05, a study power of 80%, and a minimum detectable difference of 6 between two groups. As no similar studies were available, we estimated the variance to be 0.2 based on a pilot study and assumed equal variance between the groups. The calculated sample size was 30 eyes in the treatment group and 20 eyes in the control group. To assess the normality of data we used the Shapiro-Wilks test as well as the Q-Q plot. Data were presented as mean, standard deviation, range, and frequency. The *t*-test and Chi-square test were used to compare the baseline characteristics. Given the possible correlation of measurements within the eyes of each subject, we used an interaction analysis of time and group within a linear mixed model to assess the differences between the groups based on baseline values. An adjusted *P*-value

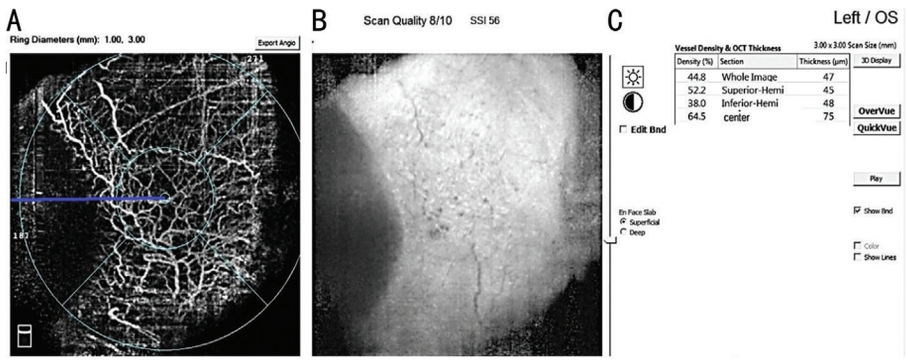

Figure 1 Anterior segment OCTA acquisition protocol for the bulbar conjunctiva OCTA of the bulbar conjunctiva in the temporal quadrant of a left eye (A) with the central measurement circle and peripheral annulus. As indicated by the blue line, the coordinates of the analyzed area are determined by aligning the center of the 3×3 measurement circle with the geographic center of the cornea. Additionally, the nasal border of the central circle is placed tangential to the limbus (B). The image of the 3 mm×3 mm scanned area (C), and the printout illustrates vessel density, which is automatically calculated for the whole image, as well as for the superior and inferior hemi, and the central circle. OCTA: Optical coherence tomography angiography.

for age and gender was also provided. All statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Thirty-four eyes of 21 patients were enrolled in the treatment group and 18 eyes of 9 healthy subjects were considered as the control group. The mean±SD age was 61±8y and 52±9y in the treatment and control groups, respectively (P=0.010). The female-to-male ratio was different between groups (P<0.001). As was expected, IOP was higher in the treatment group (19.8±4.5 mm Hg *vs* 14±2.4 mm Hg; P<0.001). The eyes in the treatment group had a higher cup-to-disc ratio (0.66±0.2 *vs* 0.41±0.19; P<0.001) and lower CDVA (0.22±0.31 *vs* 0.09±0.17 logMAR; P=0.009). Table 1 demonstrates the baseline clinical and demographic characteristics of the eyes.

Superficial VD of the superior, inferior, temporal, and nasal quadrants of the bulbar conjunctiva at baseline and follow-up visits are shown in Table 2. Compared to the control group, the treatment group showed a significant increase in VD of the superior quadrant of the bulbar conjunctiva after 12wk. After adjustment for age and gender, the VD in the superior hemi and center of the inferior quadrant of bulbar conjunctiva showed a significant increase in the treatment group after 12wk (P=0.006 and 0.016, respectively).

Figure 2 shows the trend of VD in the superior quadrant of the treatment and control groups during the 12-week follow-up. There was an increasing trend in VD of the eyes in the treatment group while such a condition was not observed in the control group.

DISCUSSION

This investigation revealed a significant increase in the VD of the superior and inferior (after adjustment for age and gender) quadrants of the superficial bulbar conjunctiva after initiation of latanoprost. These changes in VD were measured quantitatively using anterior segment OCTA and a unique analytical approach.

PGAs are frequently used for the management of glaucoma and ocular hypertension due to their once-daily instillation (except for unoprostone) and potent IOP reduction properties. The IOP reduction is achieved by increasing the uveoscleral outflow through the activation of prostaglandin F2α receptors. Several side effects have been described for PGAs which may arise from different mechanisms. For instance, ocular irritation may result from the activation of the prostaglandin E_2 receptors[12]. As glaucoma typically requires lifelong medications, careful consideration of side effects is crucial in

Table 1 Baseline demographic and clinical characteristics of the study eyes

Parameters	Treatment group	Control group	*P*
No. of eyes/subjects	34/21	18/9	
Age (y, mean±SD)	61±8	52±9	0.010[a]
Gender			<0.001[b]
Female	9 (42.9%)	3 (33.3%)	
Male	12 (57.1%)	6 (66.7%)	
Diagnosis			
POAG	21 (61.7%)		
PACG	8 (23.5%)		
PXG	5 (14.7%)		
IOP (mm Hg, mean±SD)	19.8±4.5	14±2.4	<0.001[a]
CCT (µm, mean±SD)	530.1±38.9	539.1±15.5	0.563[a]
CDR (mean±SD)	0.66±0.2	0.41±0.19	<0.001[a]
CDVA (logMAR, mean±SD)	0.22±0.31	0.09±0.17	0.009[a]

[a]Based on the *t*-test; [b]Based on the Chi-square test. SD: Stardard deviation; POAG: Primary open angle glaucoma; PACG: Primary angle-closure glaucoma; PXG: Pseudoexfoliation glaucoma; IOP: Intraocular pressure; CCT: Central corneal thickness; CDR: Cup-to-disc ratio; CDVA: Corrected distance visual acuity.

Table 2 The vessel densities in different quadrants of the bulbar conjunctiva at baseline and follow-up visits

Location	Time	Treatment group	Control group	P^3	Adjusted $P^{3,a}$
Superior quadrant					
Whole image	Baseline	39.2±7.3	43.2±4.5		
	Week 3	42.2±6.5	42.8±5.3	0.218	0.210
	Week 12	43.7±5.9	41.9±5	0.029	0.110
	P^1	0.334	0.971		
	P^2	0.054	0.999		
Superior hemi	Baseline	44±11.1	50.3±9.4		
	Week 3	48.9±11.9	47.9±10.8	0.126	0.806
	Week 12	50.1±10.6	48.2±9.2	0.065	0.443
	P^1	0.329	0.957		
	P^2	0.124	0.981		
Inferior hemi	Baseline	34.6±11.6	36.2±6.3		
	Week 3	35.7±11.1	37.4±6.7	0.993	0.364
	Week 12	36.9±9.7	35.4±5.1	0.421	0.353
	P^1	0.977	0.986		
	P^2	0.815	0.912		
Center	Baseline	55.5±17.7	69.1±66.7		
	Week 3	60.9±13.6	54.4±12.3	0.169	0.531
	Week 12	59±10.9	53.2±11.2	0.180	0.205
	P^1	0.514	0.998		
	P^2	0.773	0.890		
Inferior quadrant					
Whole Image	Baseline	34.7±6.4	38.3±6.5		
	Week 3	37.1±6.7	38.9±6.8	0.531	0.900
	Week 12	37.9±6.4	37.6±4.6	0.141	0.298
	P^1	0.457	0.473		
	P^2	0.200	0.552		
Superior hemi	Baseline	45.1±7.5	43.1±8		
	Week 3	46.8±9.1	45.9±7	0.751	0.442
	Week 12	47.6±8.3	42.9±7.8	0.438	0.006
	P^1	0.832	0.688		
	P^2	0.584	>0.999		
Inferior hemi	Baseline	24.7±8.9	33.4±10.6		
	Week 3	27.5±8.9	32±11.5	0.317	0.451
	Week 12	28.2±10.7	32.4±8.9	0.278	0.684
	P^1	0.567	0.463		
	P^2	0.471	0.298		
Center	Baseline	56.1±12.1	54.5±15.6		
	Week 3	60.7±11	57.5±10.2	0.756	0.299
	Week 12	62.4±10.9	56.6±8.9	0.415	0.016
	P^1	0.349	0.861		
	P^2	0.133	0.997		
Temporal quadrant					
Whole image	Baseline	39.5±7.1	42.1±6.2		
	Week 3	41.2±6.2	42.8±4.9	0.712	0.064
	Week 12	39.5±5.4	42.9±5.2	0.767	0.137
	P^1	0.733	0.941		
	P^2	>0.999	0.638		
Superior	Baseline	43.6±10.1	45.1±9.1		
	Week 3	44.6±9.3	46±7.2	0.984	0.321
	Week 12	40.4±7.6	40.5±9	0.720	0.472
	P^1	0.970	0.926		
	P^2	0.490	0.751		
Inferior hemi	Baseline	35.6±11.2	39.2±8.3		
	Week 3	38.1±8.2	39.5±7.5	0.584	0.178
	Week 12	38.7±7.9	45.2±6.5	0.444	0.128
	P^1	0.721	0.970		
	P^2	0.592	0.630		
Center	Baseline	55.0±15.4	60.2±8.6		
	Week 3	61.9±10	57.4±9	0.058	0.249
	Week 12	59.9±14.9	60.3±9.9	0.418	0.344
	P^1	0.154	0.997		
	P^2	0.553	0.952		
Nasal quadrant					
Whole image	Baseline	39.4±8.1	44±10.9		
	Week 3	41.7±6.8	46.8±9.3	0.906	0.506
	Week 12	41.3±7.8	46.5±9.9	0.900	0.843
	P^1	0.593	0.900		
	P^2	0.761	0.380		
Superior	Baseline	43.8±10.5	46.4±11.5		
	Week 3	56.1±74	48.9±11.4	0.586	0.795
	Week 12	39.4±9.1	46.4±10.4	0.325	0.076
	P^1	0.755	0.732		
	P^2	0.303	0.915		
Inferior hemi	Baseline	34.9±13	41.6±14.7		
	Week 3	39.3±12.2	44.8±10.6	0.833	0.678
	Week 12	43.1±13	45.6±10.6	0.464	0.135
	P^1	0.514	>0.999		
	P^2	0.085	0.927		
Center	Baseline	57.6±18.9	61.4±10.8		
	Week 3	64.3±14.2	63.6±8.7	0.481	0.364
	Week 12	65.8±12.4	62.3±11	0.237	0.502
	P^1	0.404	0.792		
	P^2	0.212	0.851		

P^1: Comparison of vessel density at week 3 to the baseline within groups; P^2: Comparison of vessel density at week 12 to the baseline within groups; P^3: Comparison of vessel density at each time point between groups. [a]Adjusted for age and gender based on a linear mixed model.

medical therapy. Some studies have identified conjunctival hyperemia as a leading factor in reduced patient compliance with topical PGA treatment[4,13].

Most studies comparing latanoprost and timolol have shown more extensive hyperemia in favor of latanoprost[14]. Albeit, the exact mechanism of PGA-induced conjunctival hyperemia is unknown. It has been postulated that conjunctival hyperemia results from vasodilation rather than inflammatory responses[14-15]. The same mechanism has been suggested for eyelash changes[16]. Furthermore, the incidence of hyperemia varies among different PGAs. A study by Honrubia *et al*[17] demonstrated that latanoprost causes less hyperemia than bimatoprost and travoprost. Additionally, the discontinuation rate of drops in patients using topical PGAs was lower with latanoprost[4].

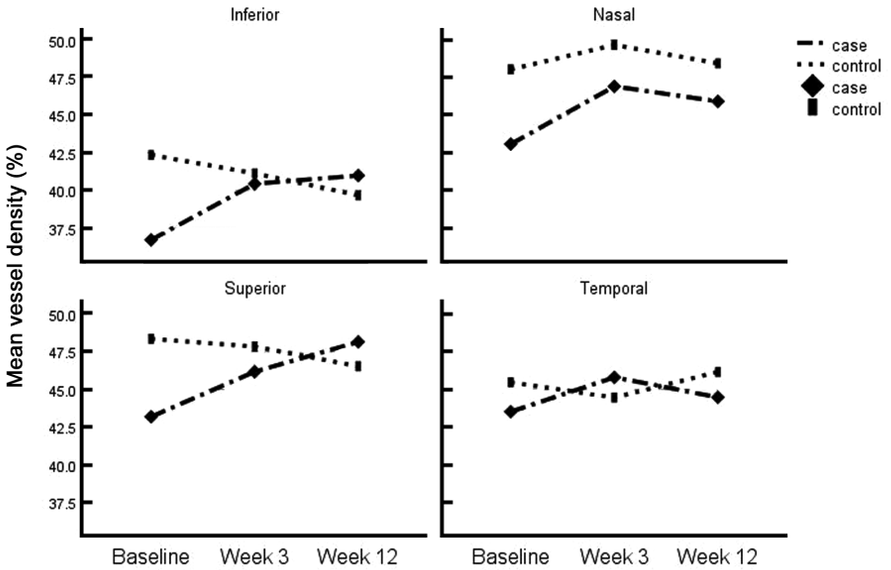

Figure 2 The trend of whole image vessel density in different quadrants The whole image vessel density was increasing in the treatment group in superior and inferior quadrants and the maximum density was observed at 12wk of follow-up. This trend was not seen in the control group.

It should be noted that both latanoprost and preservatives have a role in hyperemia. In the current investigation, we used generic latanoprost preserved with benzalkonium chloride (BAK). The epithelial tissue shows the highest concentration of BAK 48h after application[18]. Also, it can remain in ocular tissues for a long time and cause dose-dependent ocular surface toxicity and redness[19-20]. Tear film instability, direct damage to the conjunctival epithelium, and immunologic reactions have been proposed as mechanisms for the toxic effects of BAK[20]. Some studies have evaluated the role of BAK in ocular surface problems by comparing preserved and nonpreserved latanoprost. Fewer ocular surface problems including redness were observed in eyes taking preservative-free latanoprost[21-23]. Almost all studies that have evaluated the extent of hyperemia following the use of PGAs have assessed the hyperemia based on patient reports or standard photographs. In a study, where latanoprost-induced conjunctival hyperemia was evaluated using standard photographs, it was found that the hyperemia peaks at 1–2wk after initiation of the drop and declines thereafter[7]. We detected an increase in the VD only 12wk after prescribing latanoprost which can be explained by the inherent limitations of subjective and qualitative studies. The difference in VD was significant in the superior quadrant of the superficial conjunctiva. After adjustment for age and gender, VD in the superior hemifield and center of the inferior quadrant was also higher in the treatment group. This finding highlights the higher magnitude of conjunctival hyperemia in the perilimbal area. Additionally, we found increased VD only in the superior and inferior quadrants of the bulbar conjunctiva. This might be explained by the timing of latanoprost application which was once at night, while VD was measured in the morning. Other quadrants of bulbar conjunctiva may reveal hyperemia earlier after administration of the drop. Furthermore, we measured the VD in the superficial layer. Other quadrants may show increased VD in the deeper layers.

In a study by Akagi *et al*[24] the short-term effects of topical bimatoprost were evaluated using anterior segment OCTA. They showed an increase in the conjunctival VD two hours after the instillation of bimatoprost while the intrascleral VD did not change. In the current investigation, we used a novel method for the registration of the bulbar conjunctival. By applying this method, we ensured that the same location would be evaluated at both the baseline and follow-up. Additionally, this is the first study that prospectively evaluated the latanoprost-induced conjunctival hyperemia in the mid-term, quantitatively.

This study had several limitations. First, the eyes in the treatment and control groups were not completely matched. There were significant differences in age and gender between groups. Second, we only evaluated the superficial VD. The change in the VD may occur in the deeper and intrascleral vessels which were not assessed in the current investigation. Third, the latanoprost was ordered to be instilled at night. The imaging was done between 9 *a.m.* and 11 *a.m.* So, the possible immediate effects of latanoprost on VD were missing. Also, the conjunctival hyperemia may be variable during 24h. Fourth, our results would be more accurate by recruiting a control group using preservative-free latanoprost or BAK-containing eye drops formulated by pharmaceutical companies which should be considered in future studies. Fifth, we did not evaluate the conjunctival VD in the first two weeks after administration of the latanaprost. As mentioned earlier, one study showed that conjunctival hyperemia is at its highest level during one to two weeks after initiation off

the latanoprost[7]. Sixth, we evaluated the ocular surface of the subjects subjectively and qualitatively upon entry into the study. As mild ocular surface abnormalities might affect the results it should be considered as another limitation. Seventh, our sample size was relatively small. Subtle differences can be detected by gathering a bigger sample size. Lastly, we enrolled different types of glaucoma. The ocular surface side effects of latanoprost might be different in different types of glaucoma.

In conclusion, our study showed that anterior segment OCTA can be applied for quantifying the latanoprost-induced changes in the VD of the conjunctiva. We detected an increase in the superior and inferior quadrants of the bulbar conjunctiva 12wk after the initiation of latanoprost.

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Conflicts of Interest: Vahedian Z, None; **Azimi A,** None; **Tabatabaei SM,** None; **Fakhraie G,** None.

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