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# Exploring the impact of latanoprostene bunod versus latanoprost on optic disc, macular, and choroidal vasculature: A comparative analysis

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## Abstract

**Purpose:** This study aims to compare the effect of latanoprostene bunod and latanoprost on the vasculature of the posterior segment of the eye.

**Methods:** The study included 34 eyes of 17 patients diagnosed with primary open-angle glaucoma or ocular hypertension. Of these, 14 eyes of 7 patients were administered latanoprost 0.005% (Latafree, VEM ilaç, Türkiye) once daily (defined as the LAT group), while 20 eyes of 10 patients were administered latanoprostene bunod 0.024% (Vyzulta, Bausch+Lomb, Rochester, NY, USA) once daily (defined as the VYZ group). Intraocular pressure (IOP), macular and optic disc vascular density (VD), as well as submacular and subfoveal choroidal vascular parameters, were assessed for changes within each group over time and compared between groups at all time points (at baseline, month 1, month 3, and month 6).

**Result:** Latanoprost demonstrated superiority in reducing IOP compared to latanoprostene bunod ( $p < 0.001$ ). Nevertheless, a substantial decrease in IOP was observed in both agents by the conclusion of the 6th month, in comparison with the initial baseline level (all  $p < 0.001$ ). At the 6th month, peripapillary VD was observed to be higher in the VYZ group ( $p = 0.001$ ), whereas the majority of macular VD or choroidal vascular parameters exhibited higher values in the LAT group.

**Conclusion:** Latanoprostene bunod may protect the optic nerve head from hypoperfusion-related damage by improving peripapillary vascular perfusion. IOP-lowering effect may be more pronounced with latanoprost, but both drugs can effectively lower IOP. In addition, the utilization of latanoprost may increase macular and choroidal vasculature.

**Keywords:** Choroidal vascularity index; Latanoprost; Latanoprostene bunod; Macular vascular density.

**G**laucoma represents a significant global public health concern, with a prevalence that is among the leading causes of blindness worldwide.<sup>[1]</sup> It is characterized by optic nerve damage and progressive vision loss. The principal objective of glaucoma therapy is to achieve a reduction in intraocular pressure (IOP) in order to mitigate the stress placed on the optic nerve head and thereby safeguard visual function.

Among the most frequently prescribed pharmaceutical agents for this indication are prostaglandin analogues, with latanoprost being one of the most commonly utilized agents within this pharmacological class.<sup>[2]</sup> This therapeutic approach is recommended as the initial treatment for glaucoma by the European Glaucoma Society guidelines.<sup>[3]</sup>



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However, more recently, new pharmaceutical agents have been developed for the management of glaucoma. One such agent is latanoprostene bunod, which combines the effects of nitric oxide and prostaglandin analogs.<sup>[4]</sup> In addition to their effect on IOP, prostaglandin analogs have been demonstrated to exert a modulating influence on the vascular structures of the choroid.<sup>[5]</sup> It is still of particular interest to examine changes in choroidal and retinal blood flow, as this may elucidate the pathophysiology of optic nerve damage and vision loss in glaucoma patients. Nevertheless, the precise impact of latanoprostene bunod and latanoprost on choroidal and retinal microcirculation remains a subject of ongoing investigation.

The central objective of the study is to undertake a comparative analysis of the choroidal vascular structures as well as the optic disc, macular, and foveal vascular densities (VD), in patients diagnosed with primary open-angle glaucoma or ocular hypertension, utilizing latanoprostene bunod and latanoprost.

## Materials and Methods

The study was conducted at the University of Erciyes, Department of Ophthalmology, Division of Glaucoma. The research was undertaken in accordance with the tenets set forth in the Helsinki Declaration, and this study was approved by the Institutional Review Board of the University (no:2024/251 and date: November 06, 2025). A written informed consent form was signed by all patients following the provision of a comprehensive explanation of the processes involved.

This prospective study included 34 eyes of 17 patients who had not previously received glaucoma treatment. The diagnosis of primary open-angle glaucoma or ocular hypertension was made by D.G.S. Patients who received latanoprost 0.005% (Latafree, VEM ilaç, Türkiye) were assigned to the LAT group (14 eyes of 7 patients), while those who received latanoprostene bunod 0.024% (Vyzulta, Bausch+Lomb, Rochester, NY, USA) were assigned to the VYZ group (20 eyes of the 10 patients). Both latanoprost and latanoprostene bunod were administered once daily (at 10:00 PM) to the respective group of patients.

Patients were excluded if they had any of the following conditions that could affect or disrupt the macula or choroid: diabetic retinopathy, ocular trauma, dense media opacities, age-related macular degeneration, uveitis or scleritis, +3D or more hyperopia, and -6D or more myopia. In addition, the exclusion criteria included any systemic disease, such as hypertension, diabetes mellitus, hyper-

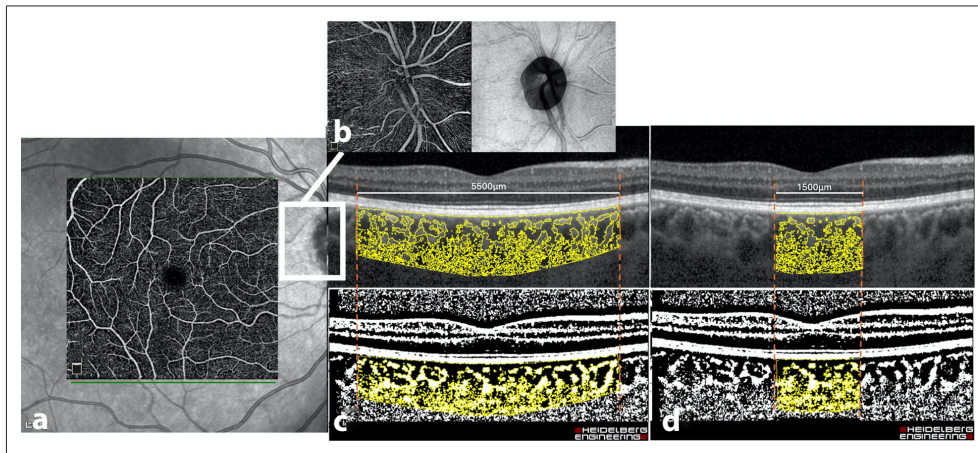
hypothyroidism, and connective tissue disorders.

A comprehensive ophthalmological examination was conducted for all subjects, which included IOP (using a Goldmann applanation tonometer), dilated fundus examination, and slit-lamp biomicroscopic examination. In addition, axial length (AxL) measurements were performed utilising the Nidek AL-Scan device (Nidek Co., Ltd., Gamagori, Japan), while central corneal thickness was determined through the use of the Sirius Scheimpflug tomographer and topographer (CSO, Costruzione Strumenti Oftalmici, Florence, Italy).

## ImageJ and Optical Coherence Tomography Angiography (OCTA) Imaging

Macular, foveal, peripapillary, and optic disc VD was obtained by OCTA using the RTVue XR Avanti (Optovue, Inc., Fremont, CA, USA). The device employs a split-spectrum amplitude-decorrelation angiography algorithm, which permits non-invasive imaging of the retinal vasculature. The instrument performs volumetric scans of  $304 \times 304$  A-scans at 70,000 A-scans per second, with an approximate acquisition time of 3.0 s. To assess the superficial capillary plexus and the deep capillary plexus in the macular region,  $3 \times 3$  mm and  $6 \times 6$  mm scan protocols were centered on the fovea. These two layers were accurately distinguished by the automatic segmentation function of the software. The percentage of the total area occupied by blood vessels in the parafoveal and perifoveal zones was calculated as macular vessel density (VD). The peripapillary and optic disc area were analyzed using the  $4.5 \times 4.5$  mm scan protocol, which was centered on the optic nerve head. One horizontal and one vertical scan were performed, with each scan centered on the optic disc.<sup>[6]</sup> The scans were conducted using 2- and 4-mm diameter rings, with a ring width of 1 mm, centered on the optic disc. Radial peripapillary VD was automatically measured using the device software. The VD within the whole disc, peripapillary area, and inner disc (specifically within the optic disc boundary) was automatically measured by the instrument software, and then calculated as the percentage of area occupied by blood vessels.

Images of macular optical coherence tomography (spectral-domain-OCT, version 1.9.17.0; manufactured by Heidelberg Engineering, Heidelberg, Germany) were captured through horizontal scanning, centered on the central/center foveal region, following pupil dilation. In addition, the enhanced depth imaging (EDI) protocol was employed to ensure accurate visualization of the choroid (Fig. 1). OCT images were used to evaluate choroidal parameters as reported in previous studies.<sup>[7-10]</sup> The subfoveal choroid



**Fig. 1.** (a) The macular scan image and (b) the optic disc scan image obtained by optical coherence tomography (OCT) angiography on the corresponding A-scan OCT image. (c) The submacular choroidal area (5500  $\mu\text{m}$ ) and the (d) subfoveal choroidal area (1500  $\mu\text{m}$ ) as presented in the corresponding B-scan OCT image. In the choroidal area, dark areas within the choroid represent the luminal area (vascular spaces), while the remaining lighter regions correspond to stromal tissue.

area (1500  $\mu\text{m}$  width) and the submacular choroid area (5500  $\mu\text{m}$  width) were manually segmented by O.E using the ImageJ software (version 1.54d, National Institutes of Health, Bethesda, MD, USA). The choroidal boundary was delineated from the Bruch's membrane to the choroid-sclera interface. The image was subsequently converted to an 8-bit binary format. The level of brightness was adjusted using the mean value obtained from the lumen of the three principal choroidal vessels within the region of interest (ROI), with the intention of considering the lumen of the choroidal vessels as the actual lumen area. The images were subjected to binarization using Niblack's auto-local thresholding method, to differentiate the luminal area (LA) from the stromal area (SA). The total choroidal area (TCA) was determined by adding together the LA and SA. The choroidal vascular index (CVI) was determined as the ratio of the LA to the TCA.<sup>[11,12]</sup>

OCTA images with a quality of 6/10 or higher (self-defined by the device) were selected for analysis. All OCT and OCTA imaging was conducted by the same experienced (and blinded) operator at a specific time between 08:30 and 10:30 AM. Furthermore, motion artifacts and segmentation errors were carefully excluded. When calculating the choroidal parameters, manual determination of the choroidal area, including demarcation of the sclerochoroidal border, was performed by one author (OE) and verified by another author (DGS).

All measurements were collected at the initial visit (defined as the baseline) before the commencement of latanoprost and latanoprostene bunod treatment. Subsequently, measurements were taken at the 1<sup>st</sup> month, 3<sup>rd</sup> month, and 6<sup>th</sup> month visits during the treatment period.

## Statistical Analysis

The statistical analyses were conducted using the IBM Statistical Package for the Social Sciences Statistics software, version 22 (IBM, Chicago, USA). Descriptive statistics (frequency, percentage, mean, median, minimum, and maximum values) were used for descriptive parameters. A Levene's test for homogeneity of variance was conducted. In addition, the Pearson Chi-square test was employed to assess nominal-ordinal data, while the Shapiro-Wilk test was utilized to assess the normality of the distribution of continuous variables. The Student's t-test was utilized for the analysis of data that exhibited a normal distribution, whereas data that did not conform to a normal distribution were evaluated using the Mann-Whitney U test and the Wilcoxon test. To perform a comparison of continuous parameters, a linear mixed model was utilized. A  $p < 0.05$  was deemed to represent a statistically significant result in all analyses.

## Results

The study included 34 eyes of 17 patients diagnosed with primary open-angle glaucoma (or ocular hypertension). Table 1 shows the demographic and clinical characteristics of the patients in this study, and there was no significant difference between the groups in these demographic or clinical characteristics (sex:  $p = 0.43$ , age:  $p = 0.502$ , eyes:  $p = 0.99$ , Axl:  $p = 0.735$ , and CCT:  $p = 0.580$ ).

No significant change was observed in macular or foveal choroidal vascular parameters, including CVI, LA, TCA, and SA, over time in each group (Table 2). However, at the 6<sup>th</sup> month, the submacular TCA, LA, and SA, as well as the subfoveal TCA and LA, were observed to be elevated in the

**Table 1.** Demographic and clinical characteristics

	VYZ	LAT	P
Sex (male/female)	4/6	2/5	0.43
Age (years)	56.85±21.0 (median: 65.5 [19–80])	52.86±7.4 (median: 53 [43–63])	0.502
Eyes (right/left)	10/10	7/7	0.99
Axl (mm)	22.80±0.71 (median: 23 [22–24])	22.89±0.82 (median: 23 [22–24])	0.735
Central corneal thickness (µm)	563.60±24.8 (median: 563 [515–607])	568.57±26.4 (median: 562 [544–631])	0.580

Axl: Axial length, VYZ: Vyzulta group, LAT latafreee group

LAT group relative to the VYZ group (all each  $p < 0.001$ ). In addition, the submacular and subfoveal CVI demonstrated an increase at the 3<sup>rd</sup> month in the LAT group when compared to the VYZ group (each  $p = 0.014$ ).

There was no significant difference over time in macular VD parameters in both groups (Table 3). Conversely,

certain macular VD parameters at the 3<sup>rd</sup> month, including superficial whole area, superficial hemi-superior, superficial hemi-inferior, superficial perifovea, deep whole area, deep hemi-inferior, deep parafovea, deep perifovea, demonstrated higher values in the LAT group in compared to the VYZ group ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.003$ ,  $p < 0.001$ ,  $p < 0.001$  and  $p = 0.001$ , respectively). In addition, all macular VD parameters, except for the deep whole area, were different between the VYZ and LAT groups at month 6 (Table 3). Among these parameters, superficial and deep foveal VD values were higher in the VYZ group, while the other variables were higher in the LAT group (superficial foveal VD [%]: VYZ=21.12±4.9, LAT=15.2±1.5,  $p < 0.001$ ; deep foveal VD [%]: VYZ=37.1±4.3, LAT=32±0.5,  $p < 0.001$ ) (Table 3).

Inside the optic disc, VD was not different between groups at all time points and did not change over time within each group (all  $p > 0.05$ ) (Table 4). In the VYZ group, whole disc VD and peripapillary VD increased at 1 and 6 months, but decreased at 3 months (whole disc VD [%]: baseline=46.7±4, at 1<sup>st</sup> month=49.9±3, at 3<sup>rd</sup> month=48.2±2.1 and 6<sup>th</sup> month=50.4±0.7; peripapillary VD [%]: baseline=51.8±3.2, at 1<sup>st</sup> month=53.3±3.1, at 3<sup>rd</sup> month=50.5±2.4 and at 6<sup>th</sup> month=54.6±1.3). In addition,

**Table 2.** Comparison of macular and foveal choroidal vascular parameters and IOP

Groups	Sub-macular (5500 µm)				Sub-foveal (1500 µm)			
	mTCA (mm <sup>2</sup> )	mLA (mm <sup>2</sup> )	mSA (mm <sup>2</sup> )	mCVI (%)	fTCA (mm <sup>2</sup> )	fLA (mm <sup>2</sup> )	fSA (mm <sup>2</sup> )	fCVI (%)
VYZ <sup>a</sup> (n=20)								
Baseline <sup>x</sup>	1.55±0.8	0.98±0.4	0.55±0.3	65.2±5.3	0.43±0.1	0.27±0.1	0.16±0.08	64±4.3
1 <sup>st</sup> month <sup>y</sup>	1.60±0.8	1.02±0.4	0.58±0.3	65.4±4.9	0.43±0.1	0.27±0.09	0.16±0.07	63.6±4.2
3 <sup>rd</sup> month <sup>z</sup>	1.60±0.9	1.02±0.5	0.57±0.4	65.6±4.5	0.43±0.2	0.27±0.1	0.16±0.08	63.9±3.9
6 <sup>th</sup> month <sup>t</sup>	1.38±0.2	0.87±0.1	0.51±0.04	62.8±1.8	0.40±0.04	0.24±0.02	0.16±0.03	61.3±2.3
<i>P</i> <sup>c</sup>	0.264	0.171	0.822	0.06	0.449	0.240	0.321	0,054
LAT <sup>b</sup> (n=14)								
Baseline <sup>x</sup>	1.88±0.5	1.15±0.2	0.72±0.2	62.0±4.1	0.49±0.1	0.29±0.06	0.19±0.07	61.5±4
1 <sup>st</sup> month <sup>y</sup>	1.78±0.3	1.11±0.2	0.67±0.1	62.5±3.2	0.47±0.1	0.29±0.05	0.18±0.04	61.7±2.2
3 <sup>rd</sup> month <sup>z</sup>	1.88±0.4	1.17±0.2	0.71±0.1	62.3±2	0.51±0.06	0.31±0.03	0.20±0.04	61±1.7
6 <sup>th</sup> month <sup>t</sup>	2.04±0.3	1.28±0.1	0.77±0.1	63.5±2.3	0.53±0.04	0.32±0.02	0.20±0.04	62.2±2.1
<i>P</i> <sup>c</sup>	0.076	0.057	0.451	0.444	0.172	0.077	0.310	0.621
<i>p</i> <sup>ab</sup>								
Baseline	0.183	0.21	0.162	0.074	0.276	0.395	0.184	0.105
1 <sup>st</sup> month	0.428	0.447	0.417	0.071	0.459	0.484	0.442	0.138
3 <sup>rd</sup> month	0.328	0.287	0.18	0.014*	0.128	0.187	0.078	0.014*
6 <sup>th</sup> month	<0.001*	<0.001*	<0.001*	0.319	<0.001*	<0.001*	0.535	0.276

LAT: Latafreee group, VYZ: Vyzulta group, CVI: Choroidal vascular index, LA: Luminal area, SA: Stromal area, TCA: Total choroidal area, m: Macular, f: Foveal, <sup>a</sup>*P*<sup>ab</sup>: Cross sectional *P*-value; <sup>c</sup>*P*: Longitudinal *P*-value; \*Statistically significant

**Table 3.** Comparison of macular and foveal vessel density parameters

Groups	Time	Macular VD (%)					
		Whole area	Hemi superior	Hemi inferior	Fovea	Parafovea	Perifovea
VYZ <sup>a</sup> (n=20)	Baseline						
	Superficial	44.9±4.7	44.9±4.7	45.1±4.8	19.02±7.5	47.05±5.4	45.05±4
	Deep	45.6±5.7	45.2±5.4	46±6.2	35±7.9	51.9±4.3	46.5±6.3
	1 <sup>st</sup> month						
	Superficial	46.7±4.3	46.8±4.2	46.6±3.9	19.81±7.6	48.5±4.3	47.4±3.9
	Deep	49.2±6.1	49.2±6.1	48.8±6.6	35.7±8.4	53.8±5.2	50.3±6.7
	3 <sup>rd</sup> month						
	Superficial	44.9±3.5	45±2.9	44.8±2.8	19.84±7.1	47.1±4.3	45.6±3.1
	Deep	44.6±5.7	44.5±5.2	44.2±5.7	35.6±7.1	49.7±4.6	45.4±6
	6 <sup>th</sup> month						
	Superficial	45.5±5.5	45.3±2.6	45.6±3	21.12±4.9	46.7±3.6	46.2±2.8
	Deep	46±4.2	43.9±4.6	46.1±4.1	37.1±4.3	52.3±3.9	47±4.4
	<i>p</i> <sup>c</sup>						
	Superficial	0.267	0.255	0.314	0.409	0.563	0.119
Deep	0.059	0.06	0.092	0.554	0.096	0.067	
LAT <sup>b</sup> (n=14)	Baseline						
	Superficial	47.8±3	47.6±2.4	47.7±3.2	14.3±5.6	47.7±4.1	48.1±4.2
	Deep	46.7±5.8	46.5±6.3	47.4±5.4	30±6.5	54.2±4.6	48.2±6.5
	1 <sup>st</sup> month						
	Superficial	48.4±6.3	46.6±5.8	47.1±5.7	15.2±5.9	49.5±5.3	48±6.6
	Deep	47.5±7.9	47.1±7.8	48.1±8.1	31.8±8.1	56.2±3.8	48.7±9.6
	3 <sup>rd</sup> month						
	Superficial	49.6±2	49.1±2.5	49.9±2.4	21.7±11.9	50.1±3.3	50.8±2
	Deep	50.3±4.2	49.6±5.3	51.1±3.7	36.5±10	56.3±2.2	52.4±4
	6 <sup>th</sup> month						
	Superficial	49±0.8	48.6±0.8	49.5±0.8	15.2±1.5	52.1±1.6	49.7±0.9
	Deep	48±3.3	47.1±3.3	49.2±3.4	32±0.5	54.4±2.2	50.1±3.5
	<i>p</i> <sup>c</sup>						
	Superficial	0.515	0.24	0.158	0.06	0.058	0.113
Deep	0.247	0.357	0.233	0.103	0.171	0.251	
<i>p</i> <sup>Ab</sup>	Baseline						
	Superficial	0.056	0.061	0.082	0.058	0.709	0.057
	Deep	0.587	0.606	0.502	0.061	0.148	0.461
	1 <sup>st</sup> month						
	Superficial	0.345	0.914	0.733	0.07	0.532	0.766
	Deep	0.473	0.396	0.779	0.192	0.153	0.566
	3 <sup>rd</sup> month						
	Superficial	<0.001*	<0.001	<0.001*	0.568	0.037	<0.001*
	Deep	0.003*	0.009	<0.001*	0.777	<0.001*	0.001*
	6 <sup>th</sup> month						
	Superficial	<0.001*	<0.001	<0.001	<0.001	<0.001	<0.001
	Deep	0.158	0.039	0.032	<0.001	0.081	0.041

LAT: Latafree group, VYZ: Vyzulta group, VD: Vessel density, *p*<sup>ab</sup>: Cross sectional *P*-value, *p*<sup>c</sup>: Longitudinal *P*-value, \*Statistically significant

**Table 4.** Comparison of papillary and peripapillary VD parameters

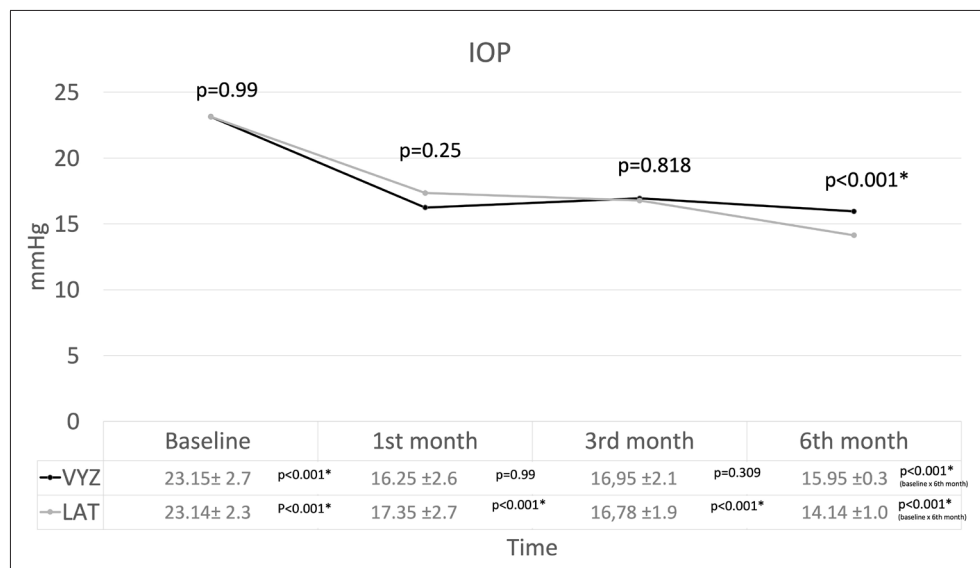
	Time	VYZ <sup>a</sup> (n=20)	LAT <sup>b</sup> (n=14)	<i>p</i> <sup>ab</sup>
Whole-Disc VD (%)	Baseline <sup>x</sup>	46.7±4	46.9±5.6	0.894
	1 <sup>st</sup> month <sup>y</sup>	49.9±3	51.1±2.4	0.227
	3 <sup>rd</sup> month <sup>z</sup>	48.2±2.1	47.6±6.6	0.698
	6 <sup>th</sup> month <sup>t</sup>	50.4±0.7	50±0.4	0.107
	<i>p</i> <sup>c</sup>	0.002*	0.112	-
	<i>p</i> <sup>xy</sup>	0.058	-	-
	<i>p</i> <sup>yz</sup>	0.037*	-	-
	<i>p</i> <sup>zt</sup>	0.005*	-	-
	<i>p</i> <sup>xt</sup>	0.006*	-	-
Disc-inside VD (%)	Baseline <sup>x</sup>	46.5±6.9	47.1±4.8	0.796
	1 <sup>st</sup> month <sup>y</sup>	48.3±7.6	49.3±7.6	0.69
	3 <sup>rd</sup> month <sup>z</sup>	50.3±8.8	45.6±10	0.159
	6 <sup>th</sup> month <sup>t</sup>	50.1±5.4	48.2±2.3	0.231
	<i>p</i> <sup>c</sup>	0.190	0.470	-
Disc-peripapillary VD (%)	Baseline <sup>x</sup>	51.8±3.2	53.8±4.1	0.123
	1 <sup>st</sup> month <sup>y</sup>	53.3±3.1	54.2±3.6	0.435
	3 <sup>rd</sup> month <sup>z</sup>	50.5±2.4	53.6±2.5	0.001*
	6 <sup>th</sup> month <sup>t</sup>	54.6±1.3	53±1.1	0.001*
	<i>p</i> <sup>c</sup>	<0.001*	0.560	-
	<i>p</i> <sup>xy</sup>	0.108	-	-
	<i>p</i> <sup>yz</sup>	0.025*	-	-
	<i>p</i> <sup>zt</sup>	<0.001*	-	-
	<i>p</i> <sup>xt</sup>	0.032*	-	-

LAT: Latafree group; VYZ: Vyzulta group, VD: Vessel density, *p*<sup>ab</sup>: Cross sectional *P*-value, *P*<sup>c</sup>: Longitudinal *P*-value. \*Statistically significant

when comparing the groups, it was lower in the VYZ group at month 3 and lower in the LAT group at month 6 (at 3<sup>rd</sup> month: *p*=0.001 and at 6<sup>th</sup> month: *p*=0.001).

Regarding IOP, the baseline, 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup> months in the VYZ group were 23.15±2.7 mmHg, 16.25±2.6 mmHg, 16.95±2.1

mmHg, and 15.95±0.3 mmHg (respectively), while in the LAT group were 23.14±2.3 mmHg, 17.35±2.7 mmHg, 16.78±1.9 mmHg, and 14.14±1.0 mmHg (respectively). IOP in the VYZ group was significantly decreased between baseline and 1<sup>st</sup> month (*p*<0.001) as well as between baseline and

**Fig. 2.** Changes in intraocular pressure over time in each group and comparison at all time points.

6<sup>th</sup> month ( $p<0.001$ ), while it was similar between 1<sup>st</sup> and 3<sup>rd</sup> month ( $p=0.99$ ) as well as 3<sup>rd</sup> and 6<sup>th</sup> month ( $p=0.309$ ). IOP in the LAT group was significantly reduced between baseline and 1<sup>st</sup> month ( $p<0.001$ ) as well as between baseline and 6<sup>th</sup> month ( $p<0.001$ ). This reduction was also observed between 3<sup>rd</sup> and 6<sup>th</sup> months ( $p<0.001$ ). However, there were comparable IOP values between the 1<sup>st</sup> and 3<sup>rd</sup> months in the LAT group. ( $p=0.99$ ) (Fig. 2). In addition, IOP was lower in the LAT group compared to the VYZ group at month 6 ( $p<0.001$ ) (Table 4).

The correlation of parameter changes (from baseline to month 6) in each group is shown in Table 5. In the VYZ group, whole disc VD was positively correlated with TCA, LA, and SA ( $\rho=0.596, p=0.006$ ;  $\rho=0.62, p=0.004$ ; and  $\rho=0.556, p=0.011$ , respectively), while superficial macular VD was negatively correlated with CVI ( $\rho=-0.541, p=0.014$ ). In the LAT group, there was a negative correlation between deep macular VD and CVI ( $\rho=-0.589, p=0.027$ ), while a positive correlation was found between deep macular VD and SA ( $\rho=0.69, p=0.006$ ).

**Table 5.** Correlations of parameter changes (from baseline to 6-month) in each group.

Parameters	Groups	IOP (mmHg)	w-Superficial macular VD (%)	w-Deep macular VD (%)	w-Optic disc VD (%)
CVI (%)	VYZ				
	Rho	-0.193	-0.541	-0.271	-0.269
	P	0.416	0.014*	0.249	0.251
	LAT				
	Rho	0.001	0.365	-0.589	-0.69
	P	0.997	0.199	0.027*	0.815
TCA (mm <sup>2</sup> )	VYZ				
	Rho	0.151	0.127	0.158	0.596
	P	0.526	0.593	0.506	0.006*
	LAT				
	Rho	-0.289	-0.142	0.516	0.413
	P	0.315	0.629	0.059	0.142
LA (mm <sup>2</sup> )	VYZ				
	Rho	0.167	0.08	0.124	0.62
	P	0.482	0.737	0.601	0.004*
	LAT				
	Rho	-0.318	-0.018	0.323	0.405
	P	0.268	0.95	0.26	0.151
SA (mm <sup>2</sup> )	VYZ				
	Rho	0.135	0.181	0.195	0.556
	P	0.57	0.445	0.409	0.011*
	LAT				
	Rho	-0.221	-0.275	0.69	0.351
	P	0.449	0.341	0.006*	0.218
IOP (mmHg)	VYZ				
	Rho	-	0.238	0.12	0.382
	P	-	0.313	0.613	0.096
	LAT				
	Rho	-	-0.386	-0.233	-0.10
	P	-	0.173	0.423	0.734

CVI: Choroidal vascular index, LA: Luminal area, SA: Stromal area, w: Whole, TCA: Total choroidal area, IOP: Intraocular pressure, LAT: Latafree group, VYZ: Vyzulta group, VD: Vascular density. \*Statistically significant

## Discussion

Prostaglandin analogs are frequently the preferred choice for the medical management of glaucoma due to their ability to decrease IOP by increasing uveoscleral outflow, a mechanism that has been demonstrated in numerous studies.<sup>[13,14]</sup> However, certain side effects, including serous retinal detachment and central serous chorioretinopathy, have prompted a noteworthy inquiry into its impact on the choroid and the posterior segment in recent years.<sup>[15]</sup> Moreover, a new drug, latanoprostene bunod 0.024%, has been shown to reduce IOP by increasing aqueous outflow through both the uveoscleral and trabecular pathways.<sup>[16]</sup> The effect of latanoprostene bunod on the posterior segment represents an intriguing and attention-grabbing research topic, particularly given that it is a nitric oxide-donating prostaglandin F2 $\alpha$  analog.

The present study examined the impact of both latanoprostene bunod and latanoprost on the optic disc vasculature, choroidal vascular structure, and macular vascular area. The findings of the present study indicated that the majority of choroidal vascular parameters exhibited a notable increase in the LAT group compared to the VYZ group at the 6<sup>th</sup> month. These results suggest that the choroidal vascular effect may be more pronounced in latanoprost than in latanoprostene bunod. Although latanoprostene bunod contains nitric oxide, which has the potential to induce vasodilation, the observed superiority of latanoprost in LA may indicate that nitric oxide does not exert a significant effect on the choroidal area. Furthermore, the results in the area of submacular TCA or SA may indicate that latanoprost has a greater capacity for uveoscleral outflow. This may prove beneficial in reducing IOP, as evidenced by the findings of the current study, which indicated that the LAT group exhibited superior efficacy in lowering IOP compared to the VYZ group. Nevertheless, both medications demonstrated successful IOP reduction by the conclusion of the 6-month trial period.

A number of studies in the literature have indicated that topical prostaglandin analogs can cause a breakdown of the retinal blood-aqueous barrier, resulting in disruption of the posterior lens capsule and subsequent access for inflammatory mediators to reach the macula.<sup>[17,18]</sup> This, in turn, leads to macular edema due to the breakdown of the blood-retinal barrier caused by the release of the inflammatory mediators.<sup>[19]</sup> Moreover, some studies have indicated a potential correlation between increased superficial and deep macular VD and macular edema.<sup>[20]</sup> After 6 months, the higher results on macular VD and submacular choroidal parameters with latanoprost

in the current study may be attributed to its vasodilator effect. However, this effect may be deleterious, as it may be a potential trigger for macular edema, serous retinal detachment, or central serous chorioidopathy, which may manifest as a side effect of latanoprost. In consideration of the aforementioned side effects, latanoprostene bunod may be regarded as a safer alternative to latanoprost. Nevertheless, as macular or choroidal thickness was not evaluated in the present study, no definitive conclusions can be drawn on this matter.

It is noteworthy that in the VYZ group, despite the absence of a statistically significant change at the various time points, the vast majority of superficial and deep macular VD parameters exhibited an increase at the 1<sup>st</sup> month, which then underwent a decrease at the 3<sup>rd</sup> month. Although the nitric oxide present in latanoprostene bunod has a relatively short half-life and a short-term effect on vasodilation, it may nevertheless exert an influence on this change.<sup>[21,22]</sup> Nevertheless, this effect seems to be transient or perhaps its vasodilatory effect was suppressed by another factor, such as desensitization or rebound. Somehow, it is also possible that vasoconstriction occurred, which could have resulted in a reduction of macular VD. Further investigation is required to gain a deeper understanding of this issue.

It has been demonstrated that the density of microvasculature in the optic disc can be diminished in patients diagnosed with glaucoma.<sup>[23,24]</sup> Furthermore, these changes can occur at the early stages or periods of glaucoma, which may indicate an early sign of glaucoma. The present study demonstrated that, at the 6<sup>th</sup> month, the VYZ group exhibited increased whole optic disc and peripapillary VD, which may indicate that the optic disc damage was prevented due to an improvement in optic disc or peripapillary area perfusion. Moreover, at the conclusion of the 6<sup>th</sup> month, peripapillary VD was observed to be higher in the VYZ group than in the LAT group, which lends support to the superiority of latanoprostene bunod over latanoprost on the peripapillary vasculature. In a comparative study, Liu *et al.*<sup>[25]</sup> investigated the efficacy of latanoprostene bunod (0.024%) and timolol (0.5%) in reducing IOP and increasing ocular perfusion pressure. Their findings revealed that latanoprostene bunod demonstrated a more pronounced reduction in IOP and an augmented increase in ocular perfusion pressure in comparison to timolol. The increased perfusion observed in their study was found to be associated with a decrease in IOP. However, our peripapillary VD results suggest that a different mechanism may be involved, as latanoprostene bunod demonstrated superior efficacy in increasing peripapillary VD, whereas

latanoprost showed superiority in reducing IOP at the end of the 6-month study period. It is possible that the nitric oxide contained in the latanoprostene bunod can induce selectively vasodilatation within the peripapillary area, thereby increasing perfusion and protecting the optic nerve head from hypoperfusion-related damage. In addition, our correlation results indicate that in patients treated with latanoprostene bunod, alterations in choroidal parameters correlated with changes in peripapillary VD, whereas in those treated with latanoprost, the changes in choroidal parameters correlated with changes in deep macular VD. These correlations may suggest that the efficacy of these drugs differs in the various anatomical structures, such as the choroid, macula, or papillary/peripapillary area. Furthermore, they underscore the importance of considering the relationships between these structures, despite their distinct vascular supply.

The study conducted by Weinreb *et al.*<sup>[26]</sup> indicated that latanoprostene bunod (0.024%) demonstrated a more pronounced IOP reduction and comparable adverse effects in comparison to latanoprost 0.005%. In addition, some other studies have demonstrated comparable IOP-lowering effects between these two pharmaceutical agents in both animal and human models.<sup>[27,28]</sup> However, the duration of these studies was limited by their relatively short follow-up periods. The findings of our study indicated that although both eye drops were effective in reducing IOP, the outcomes may vary over a prolonged follow-up period: although the IOP in the 1<sup>st</sup> month of the present study exhibited a lower value in the VYZ group (though not to a statistically significant), the IOP at the end of 6 months point demonstrated a lower value in the LAT group (which was statistically significant). In addition, the cumulative corneal toxicity caused by benzalkonium chloride (BAK) on the ocular surface may have contributed to this difference in IOP reduction observed at the 6<sup>th</sup> month between the BAK-containing and preservative-free formulations, possibly by affecting drug bioavailability. Since this study did not directly assess BAK-induced toxicity, further investigations are warranted to explore this potential mechanism.

The present study was subject to certain limitations. Primarily, the patient cohort was small, and the follow-up period was relatively brief. Second, the peripapillary choroidal vasculature was not assessed, which could have provided additional information about choroidal perfusion of the peripapillary area. A third limitation of the study is that the thickness of the choroid was not measured, which would have affected the macular choroidal parameters. Additionally, the lack of assessment of visual acuity

prevented the evaluation of the relationship between visual function and vascular changes. The final limitation is the difference in preservative content BAK between the two compared medications; comparing two formulations with similar BAK content would have provided a more balanced evaluation.

In conclusion, although latanoprost 0.005% demonstrated superiority in reducing IOP compared to latanoprostene bunod 0.024%, both agents exhibited a significant reduction in IOP by the end of the 6<sup>th</sup> month. Moreover, while latanoprost 0.005% may be more efficacious in increasing the vasculature of the submacular or foveal choroidal area and the superficial or deep macular capillary plexus, latanoprostene bunod 0.024% may be more effective in increasing peripapillary VD.

**Ethics Committee Approval:** This study was approved by The Erciyes University Local Ethics Committee (No:2024/251; date:06/11/2024).

**Informed Consent:** Written informed consents were obtained from patient and his family.

**Peer-review:** Externally peer-reviewed.

#### **Authorship Contributions:**

Concept: F.O., D.G.S. ; Design: F.O., D.G.S. ; Supervision: M.U., K.E. ; Resource: O.E. ; Materials: M.U., O.E. ; Data Collection and/or Processing: O.E. ; Analysis and/or Interpretation: F.O. ; Literature Search: O.E. ; Writing: F.O. ; Critical Reviews: D.G.S., M.U.

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