The Effect of β-Blocker Eye Drops on Pulse Rate, Ocular Blood Flow, and Glaucoma Progression: A Retrospective Longitudinal Study

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ABSTRACT

Introduction: Our study was conducted to determine factors associated with the effectiveness of a β-blocker eye drop add-on in altering pulse rate (PR) in glaucoma patients.
Methods: This retrospective study examined 236 eyes of 138 patients who received a β-blocker eye drop add-on during follow-up. Patients were included if at least one PR measurement was available both before and after

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the add-on was started. We collected data on ophthalmic parameters: longitudinal PR; longitudinal choroidal blood flow, represented by laser speckle flowgraphy-measured mean blur rate (MBR); and diacron-reactive oxygen metabolites (d-ROMs). We used a multivariable linear mixed-effects model to investigate the effectiveness of the β-blocker eye drop add-on in altering PR and examined factors contributing to a larger PR alteration after the add-on was started by analyzing the effect on PR of the interaction term between the add-on and clinical factors. We used the k-means method to classify the patients.
Results: The β-blocker eye drop add-on reduced PR (-7.61 bpm, $P < 0.001$). Female gender, higher PR when the add-on was started, lower central corneal thickness, and a higher d-ROM

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level were associated with greater reduction in PR ($P < 0.05$). In a cluster of patients with these clinical features, choroidal MBR increased by + 3.42% when we adjusted for change over time; MD slope, which represents the speed of glaucoma progression, improved by + 0.64 dB/year ($P < 0.05$).

Conclusions: We identified a glaucoma subgroup in which PR decreased, choroidal blood flow increased, and glaucoma progression slowed after a β-blocker eye drop add-on was started.

Keywords: β-Blocker; Pulse rate; Ocular blood flow; Open-angle glaucoma

Key Summary Points

Why carry out this study?

We have previously reported that tachycardia is a risk factor for a decrease in ocular blood flow preceding neurodegeneration in eyes with glaucoma, but there is currently no effective therapeutic intervention available for this risk factor.

β-Blocker eye drops are prescribed to glaucoma patients with the aim of reducing intraocular pressure, but their effects on pulse rate and ocular blood flow are unknown.

In this study, we hypothesized that there might be a specific glaucoma subgroup in which β-blocker eye drops protect ocular blood flow and prevent glaucoma progression through pulse rate control rather than as a side effect of the β-blocker.

What was learned from the study?

High pulse rate, female gender, elevated blood oxidative stress, and a thin cornea contribute to a greater β-blocker-induced pulse rate reduction, and in glaucoma patients with these characteristics, the addition of β-blocker eye drops improves ocular blood flow and slows the progression of glaucomatous visual field defects.

β-Blocker eye drops are known for their effects in reducing intraocular pressure and causing bradycardia as a side effect; however, they may have protective potential in specific patients, sparking renewed discussion about their applicability and new indications for their use.

INTRODUCTION

Elevated intraocular pressure (IOP) is the only treatable risk factor for glaucoma; however, IOP elevation alone does not explain the entire pathogenesis of the disease [1]. Therefore, we have previously performed investigations of the relationship between glaucomatous visual field (VF) defect progression and factors other than high IOP, such as ocular blood flow (BF) impairment and high oxidative stress [2–6]. Recently, we reported that high pulse rate (PR) is a risk factor for a primary reduction in ocular BF and secondary glaucomatous neural loss [7]. Thus, we hypothesized that lowering PR in glaucoma patients with a tendency toward tachycardia would ameliorate ocular BF impairment and thereby slow glaucoma progression.

β-Blockers are adrenergic receptor antagonists that reduce PR by acting on β1 receptors in the heart. In the eye, β-blockers are known to reduce IOP by decreasing aqueous humor production. Until the advent of prostaglandin analogs (PGs) in the 1990s, β-blockers were the first choice for IOP-lowering drug treatment, and they remain in frequent use today as either a primary treatment or as an add-on to other types of anti-glaucoma eye drops. β-Blocker eye drops are used topically but can be systemically absorbed, and they have the potential to produce serious side effects, including bradycardia [8, 9]. Thus, after β-blocker eye drops were introduced, many studies investigated their effect on PR. These studies are valuable, but the majority had small sample sizes, examined specific groups of subjects (e.g., those that are

healthy and young), were short term, or were case reports [10–14]. Thus, it is not simple to apply their findings to the real-world glaucoma population, which is relatively old and usually uses β-blocker eye drops for a long period of time. In addition, ophthalmologists usually avoid prescribing β-blocker eye drops for vulnerable patients (e.g., elderly patients with a history of heart disease [15–18]), explaining the lack of knowledge about clinical background factors affecting the outcome of β-blocker eye drop treatment on PR reduction in real-world glaucoma patients.

Against this background, we first determined whether β-blocker eye drops reduced PR in a real-world population of patients with glaucoma that we examined over a relatively long follow-up period. Next, we examined clinical factors affecting whether β-blocker eye drops reduced PR in eyes with glaucoma. Finally, we determined whether there was a subgroup of glaucoma patients in whom PR reduction, a change in ocular BF, and slowing of glaucoma progression could be observed.
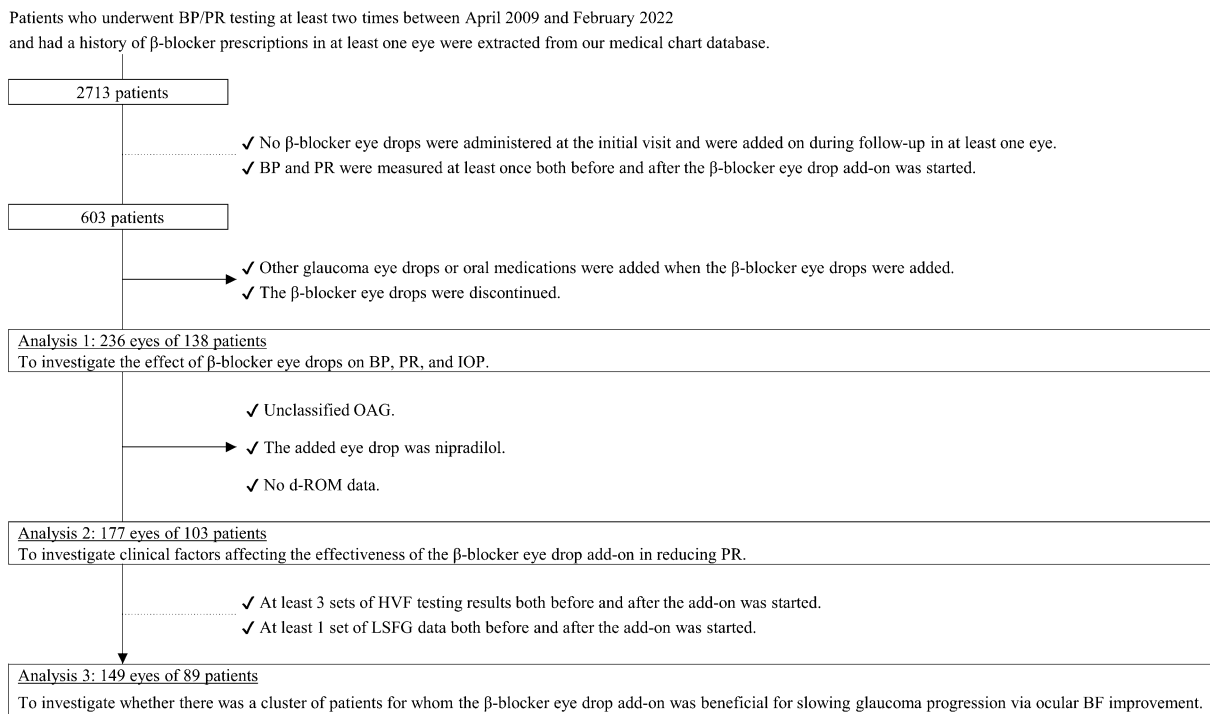
METHODS

Subjects

The initial diagnosis of glaucoma was made by a glaucoma specialist (TN), and follow-up was performed at Tohoku University Hospital, located in Miyagi, Japan. In this study, 2713 patients who underwent testing between April 2009 and February 2022 for blood pressure (BP) and PR at least two times and had a history of β-blocker eye drop use in at least one eye were drawn from our medical database. A flow chart of subject selection is shown in Fig. 1. A total of 236 eyes of 138 patients were selected to investigate the effects of β-blocker eye drops on BP, PR, and IOP (clinical characteristics are shown in Tables 1 and 2). As a reference, the same selection process was used for subjects who received other anti-glaucoma eye drops, including PGs, carbonic anhydrase inhibitors (CAIs), α2 stimulators, α1 blockers, and rho kinase inhibitors. The number of eyes that met the criteria for these other eye drops is shown in

Supplementary Table S1. We next investigated background factors affecting whether β-blocker eye drops reduced PR. For this investigation, we excluded patients who were diagnosed as having unclassified open-angle glaucoma (OAG) (i.e., if no baseline IOP data were available) and patients without diacron reactive oxygen metabolite (d-ROM) data. We also excluded patients who started the β-blocker eye drop add-on by changing an existing α1 blocker to nipradilol, because there were only two eyes of such patients. A total of 177 eyes of 103 patients met these criteria. Finally, we selected eyes for which reliable Humphrey visual field (HVF) testing was performed at least three times and for which laser speckle flowgraphy (LSFG) testing was performed at least once both before and after the add-on was started. A total of 149 eyes of 89 patients met these criteria, and we investigated changes in choroidal mean blur rate (MBR) and MD slope after the β-blocker add-on was started. The procedures in this study followed the tenets of the Declaration of Helsinki and were approved by the institutional review board of Tohoku University Graduate School of Medicine (no. 2021-1-265). All patients provided informed written consent to have data from their medical records used in research.

Measurement of Clinical Variables

Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was measured with spectral-domain OCT (3D OCT-2000, Topcon, Inc., Tokyo, Japan), axial length was measured with the IOL Master (Zeiss Meditec, Dublin, CA, USA), IOP was measured with Goldmann applanation tonometry, and VF was measured with the SITA standard 24-2 program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). Reliable results were obtained from all subjects for VF testing (fixation errors < 20%, false positives < 33%, and false negatives < 33%) [3, 7]. As we described previously [5], assays of oxidative stress in the plasma and blood serum were performed with the d-ROM test, which measures the total oxidant capacity of a sample, and total plasma antioxidant capacity was assayed using the biologic

Patients who underwent BP/PR testing at least two times between April 2009 and February 2022
and had a history of β-blocker prescriptions in at least one eye were extracted from our medical chart database.

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┌──────────────────┐
│  2713 patients   │
└──────────────────┘
        ✓ No β-blocker eye drops were administered at the initial visit and were added on during follow-up in at least one eye.
        ✓ BP and PR were measured at least once both before and after the β-blocker eye drop add-on was started.

┌──────────────────┐
│  603 patients    │
└──────────────────┘
        ✓ Other glaucoma eye drops or oral medications were added when the β-blocker eye drops were added.
        ✓ The β-blocker eye drops were discontinued.
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Analysis 1: 236 eyes of 138 patients
To investigate the effect of β-blocker eye drops on BP, PR, and IOP.

        ✓ Unclassified OAG.
        ✓ The added eye drop was nipradilol.
        ✓ No d-ROM data.

Analysis 2: 177 eyes of 103 patients
To investigate clinical factors affecting the effectiveness of the β-blocker eye drop add-on in reducing PR.

        ✓ At least 3 sets of HVF testing results both before and after the add-on was started.
        ✓ At least 1 set of LSFG data both before and after the add-on was started.

Analysis 3: 149 eyes of 89 patients
To investigate whether there was a cluster of patients for whom the β-blocker eye drop add-on was beneficial for slowing glaucoma progression via ocular BF improvement.

Fig. 1 Selection scheme for including eyes in analyses 1–3. The dotted lines indicate the inclusion criteria, and the horizontal arrows indicate the exclusion criteria. *BF* blood flow, *BP* blood pressure, *d-ROM* diacron reactive oxygen metabolite, *HVF* Humphrey visual field, *IOP* intraocular pressure, *LSFG* laser speckle flowgraphy, *OAG* open-angle glaucoma, *PR* pulse rate

antioxidant potential (BAP) test, which measures the capacity of a sample to reduce ferric ions to ferrous ions with a thiocyanate derivative as a chromogen. Ocular BF was assessed with the LSFG-NAVI device (Softcare Co., Ltd., Fukutsu, Japan), which measures MBR in arbitrary units (AU) [19]. We used parapapillary choroidal MBR as an indicator of choroidal BF to determine the effect of the β-blocker eye drop add-on on ocular BF, because choroidal BF is less affected secondarily to glaucoma severity and is less autoregulated than optic nerve head (ONH)-tissue BF, as we have shown previously [20, 21]. To guarantee image quality, only LSFG data with ONH vascular cloud ≥ 0.28 were used [22]. Before the LSFG measurements, the pupils of the patients were dilated with 0.4% tropicamide, a muscarinic antagonist (Mydrin M; Santen Pharmaceutical Co., Ltd, Osaka, Japan). After the Mydrin M instillation, the patients sat in a dark, quiet room for 15 min to stabilize pupil dilation, BP, and PR. Then, BP and PR were measured (HBP-1300; Omron, Kyoto, Japan) and LSFG was performed. Mean BP was calculated as follows: mean BP = diastolic BP (DBP) + 1/3 (systolic BP [SBP] − DBP). Longitudinal follow-up data were collected for IOP, MD, choroidal MBR, and BP/PR.

Statistical Analysis

Continuous variables are presented as means ± standard deviation and discrete variables as frequencies and percentages. The evaluation of the effects of "β-blocker add-on (after: 1, before: 0)" on IOP, BP, and PR was performed using linear mixed-effects models. Age at add-on start date, gender, time from add-on start date (after: +, before: −, years), cataract surgery (after: 1, before: 0), and glaucoma surgery (after: 1, before: 0) were adjusted as fixed effects and "eyes" was nested within the "subject" variable as a random intercept and random slope (Supplementary Table S1). We used another linear

Table 1 Systemic characteristics of glaucoma patients (β-blocker add-on)

Number of patients (n)	138
Age (years)	59.8 ± 14.7
Male:female (n)	70:68
BMI (kg/m^2)	22.9 ± 3.3
Average SBP before add-on (mmHg)	127.4 ± 18.0
Average DBP before add-on (mmHg)	75.0 ± 12.6
Average PR before add-on (bpm)	78.8 ± 13.4
Smoking habit (n, %)	58, 42.0
Hypertension (n, %)	42, 30.4
DM (n, %)	11, 8.0
Dyslipidemia (n, %)	36, 26.1
Heart disease (n, %)	24, 17.4
Sleep apnea syndrome (n, %)	11, 8.0

BMI body mass index, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *PR* pulse rate, *SBP* systolic blood pressure

Table 2 Ocular characteristics of glaucoma patients (β-blocker add-on)

Number of eyes (n)	236
Diagnosis (eyes)	NTG: 161; POAG: 38; unclassified OAG: 7; other: 30
Added β-blocker (n)	Timolol: 190; carteolol: 44; nipradilol: 2
Average IOP before the add-on (mmHg)	14.0 ± 4.0
CCT (μm)	518.3 ± 35.1
Axial length (mm)	25.4 ± 1.6
MD (dB)	− 9.4 ± 7.3
Overall cpRNFLT (μm)	74.6 ± 18.9
Average choroidal MBR before add-on (AU)	6.8 ± 2.1
From PG to PG/β-blocker (n, %)	129, 54.6
From none to β-blocker (n, %)	59, 25.0
From CAI to CAI/β-blocker (n, %)	46, 19.5
From α1-blocker to α1-blocker/β-blocker (n, %)	2, 0.8

Diagnoses of "other" included secondary glaucoma and primary angle-closure glaucoma

CAI carbonic anhydrase inhibitor, *CCT* central corneal thickness, *cpRNFLT* circumpapillary retinal nerve fiber layer thickness, *IOP* intraocular pressure, *MBR* mean blur rate, *MD* mean deviation, *NTG* normal-tension glaucoma, *OAG* open-angle glaucoma, *PG* prostaglandin analogue, *POAG* primary open-angle glaucoma

mixed-effects model to assess the effect of clinical factors on PR change after the β-blocker eye drop add-on was started, represented by the interaction term between "β-blocker add-on" and each clinical parameter (Supplementary Table S2). Age, gender, and other clinical factors for which the interaction term with "β-blocker add-on" reached $P < 0.05$ were chosen for the next multivariable linear mixed-effects model (Table 3). We performed k-means clustering to cluster the eyes based on age at the add-on start date, gender (female: 1, male: 0), a history of diabetes mellitus (DM) (yes: 1, no: 0), average PR before the add-on, percentage change in PR, average choroidal MBR before the add-on was started, percentage change in choroidal MBR, central corneal thickness (CCT), d-ROM level, mean deviation (MD) slope before the add-on was started, and change in MD slope. The percentage change in each parameter was calculated as follows: percentage change in X = (average X after the add-on − average X before the add-on) × 100/average X before the add-on. The best cluster number was

determined by the cubic clustering criterion. In each cluster, the effect of "β-blocker add-on" on the percentage change in choroidal MBR was analyzed using linear mixed-effects models setting age at add-on start date, gender, time from add-on start date (after: +, before: −, years), mean BP, IOP, choroidal MBR at add-on start

Table 3 Linear mixed-effects model assessing the effect of clinical factors on PR change after the β-blocker add-on was started

	β	P value
Intercept (bpm)	14.22	0.180
Age at add-on start date (1 year older)	− 0.05	0.315
Female (reference, male)	− 0.55	0.699
DM (yes: 1, no: 0)	− 0.71	0.823
CCT (10 μm higher)	− 0.19	0.214
d-ROM level (10 U. Carr higher)	0.30	0.006*
PR at add-on start date (1 bpm higher)	0.85	< 0.001*
After β-blocker add-on (reference, before add-on)	18.42	0.100
Time from add-on start date (1 year later)	0.26	0.323
Age at add-on start date × after β-blocker add-on (reference, before add-on)	− 0.03	0.566
Female × after β-blocker add-on (reference, before add-on)	− 3.11	0.028*
DM × after β-blocker add-on (reference, before add-on)	3.80	0.241
CCT × after β-blocker add-on (reference, before add-on)	0.04	0.024*
d-ROM level × after β-blocker add-on (reference, before add-on)	− 0.03	0.001*
PR at add-on date × after β-blocker add-on (reference, before add-on)	− 0.42	< 0.001*

×: the interaction with "after add-on (reference, before add-on)" corresponds to the effect of the predictive factor on PR change due to the β-blocker eye drop add-on. β Partial regression coefficient
CCT central corneal thickness, *DM* diabetes mellitus, *d-ROM* diacron reactive oxygen metabolite, *PR* pulse rate
*Statistical significance

date, cataract surgery (after: 1, before: 0), and glaucoma surgery (after: 1, before: 0) as fixed effects and "eyes" nested within the "subject" variable as a random intercept and random slope (Table 5). The effect of "β-blocker add-on" on MD slope was also analyzed in cluster 1 and cluster 2, setting age at add-on start date, gender, averaged IOP in each term (i.e., before and after the add-on was started), whether cataract/glaucoma surgery was performed or not in each term (yes: 1, no: 0), and MD at add-on start date as fixed effects and "eyes" nested within the "subject" variable as a random effect. All statistical analyses were performed with R software (version 3.2.5) [23].

RESULTS

Systemic and ocular characteristics of the patients included in analysis 1 (236 eyes of 138 patients) are shown in Tables 1 and 2, respectively. Average IOP and PR before the add-on was started were 14.0 ± 4.0 mmHg and 78.8 ± 13.4 bpm, respectively. PR was measured 7.7 ± 4.6 times over a follow-up period of 4.1 ± 2.1 years. MD was $- 9.4 \pm 7.3$ dB. The added β-blocker was timolol in 80.5% (190/236) of the eyes, carteolol in 18.6% (44/236) of the eyes, and nipradilol (as an addition to α1-blocker eye drops) in 0.8% (2/236) of the eyes. The addition of the β-blocker eye drop add-on was performed as follows: in 54.6% (129/236) of the eyes, PGs were changed to a PG/β-blocker compound; in 25.0% (59/236) of the eyes, no eye drops had been used, so β-blocker eye drops were started; in 19.5% (46/236) of the eyes, CAIs were changed to a CAI/β-blocker compound; in 0.8% (2/236) of the eyes, an α1-blocker was changed to an α1-blocker/β-blocker compound. The eyes had NTG in 68.2% (161/236) of cases, primary open-angle glaucoma (POAG) in 16.1% (38/236) of cases, unclassified OAG in 3.0% (7/236) of cases, and other types of glaucoma (primary angle-closure glaucoma or secondary glaucoma) in 12.7% (30/236) of cases.

In this study population, PR and IOP decreased in response to the β-blocker eye drop add-on ($- 7.61$ bpm, $P < 0.001$ and $- 0.90$ mmHg, $P < 0.001$, respectively). On the other hand, a PR reduction in response to the

Table 4 Differences in clinical characteristics between clusters

Variables	Clusters		P value
	Cluster 1	Cluster 2	
Number of patients (n)	44	45	
Number of eyes (n)	77	72	
Age at add-on start date (years)	59.9 ± 10.9	58.6 ± 14.4	0.635
Female (n, %)	41, 93.2%	8, 17.8%	< 0.001*
Hypertension (n, %)	9, 20.5%	12, 26.7%	0.496
DM (n, %)	0, 0.0%	5, 11.1%	0.023*
Dyslipidemia (n, %)	10, 22.7%	11, 24.4%	0.899
Heart disease (n, %)	5, 11.4%	7, 15.6%	0.540
Sleep apnea syndrome (n, %)	3, 7.3%	5, 11.1%	0.529
Smoking habit (n, %)	6, 13.6%	29, 64.4%	< 0.001*
BMI (kg/m^2)	21.6 ± 3.2	23.9 ± 3.1	0.001*
Average SBP before add-on (mmHg)	126.5 ± 16.3	128.1 ± 19.1	0.669
Average DBP before add-on (mmHg)	74.1 ± 10.6	75.8 ± 13.3	0.489
Average PR before add-on (bpm)	86.1 ± 13.7	74.0 ± 10.7	< 0.001*
Change in PR (%)	− 12.4 ± 10.0	− 3.8 ± 9.8	< 0.001*
d-ROM level (U. Carr)	391.8 ± 60.0	357.8 ± 58.6	0.008*
Average IOP before add-on (mmHg)	12.9 ± 1.8	14.1 ± 2.6	0.001*
Change in IOP (%)	− 2.3 ± 12.9	− 10.0 ± 13.2	0.001*
Average choroidal MBR before add-on (AU)	6.4 ± 1.9	7.4 ± 2.0	0.043*
MD (dB)	− 10.4 ± 6.8	− 8.3 ± 6.8	0.065
MD slope before add-on (dB/year)	− 0.9 ± 1.3	− 0.3 ± 1.3	0.027*
Axial length (mm)	25.6 ± 1.7	25.7 ± 1.6	0.536
CCT (μm)	500.2 ± 31.2	527.5 ± 34.8	< 0.001*

AU arbitrary units, *BMI* body mass index, *CCT* central corneal thickness, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *d-ROM* diacron reactive oxygen metabolite, *IOP* intraocular pressure, *MBR* mean blur rate, *MD* mean deviation, *PR* pulse rate, *SBP* systolic blood pressure
*Statistical significance

other anti-glaucoma eye drop add-ons was not evident (Supplementary Table S1).

The results of analysis 2 (177 eyes of 103 patients) were as follows: 1 bpm higher PR when the add-on was started was associated with 0.42 bpm lower PR, 10 μm lower CCT was associated with 0.45 bpm lower PR, a 10 U. Carr higher d-ROM level was associated with 0.40 bpm lower PR, and an absence of a history of DM was associated with 7.24 bpm lower PR

Table 5 The effect of the β-blocker eye drop add-on on the percentage change in choroidal MBR

Clusters	Explanatory variables	β	P value
Cluster 1	Intercept (%)	95.01	< 0.001*
	Mean BP (1 mmHg higher)	0.30	< 0.001*
	IOP (1 mmHg higher)	0.29	0.254
	Age at add-on start date (1 year older)	− 0.36	0.039*
	Choroidal MBR at add-on start date (1 AU higher)	− 1.20	0.152
	Female (reference, male)	3.30	0.612
	After β-blocker add-on (reference, before add-on)	3.42	0.042*
	After cataract surgery (reference, before)	5.50	0.124
	After glaucoma surgery (reference, before)	− 8.46	0.216
	Time from add-on start date (1 year later)	− 0.63	0.315
Cluster 2	Intercept (%)	101.06	< 0.001*
	Mean BP (1 mmHg higher)	0.25	0.001*
	IOP (1 mmHg higher)	− 0.67	0.015*
	Age at add-on start date (1 year older)	− 0.04	0.714
	Choroidal MBR at add-on start date (1 AU higher)	− 1.64	0.016*
	Female (reference, male)	4.50	0.312
	After β-blocker add-on (reference, before add-on)	− 3.09	0.081
	After cataract surgery (reference, before)	6.56	0.563
	After glaucoma surgery (reference, before)	− 3.62	0.739
	Time from add-on start date (1 year later)	− 0.37	0.527

β Partial regression coefficient

AU arbitrary units, BP blood pressure, IOP intraocular pressure, MBR mean blur rate

*Statistical significance

(Supplementary Table S2). Subsequent multivariable linear mixed-effects models (Table 3) showed that female gender ($P = 0.028$), higher PR when the add-on was started ($P < 0.001$), lower CCT ($P = 0.024$), and a higher d-ROM level ($P = 0.001$) were associated with lower PR after the add-on, while age ($P = 0.566$) and a history of DM ($P = 0.241$) were not associated with lower PR after the add-on.

The results of analysis 3 (149 eyes of 89 patients) were as follows: the cubic clustering criterion showed that 2 was the best cluster number; the difference in clinical characteristics between these 2 clusters is shown in Table 4.

The characteristics of cluster 1 (compared to cluster 2) were as follows: a greater proportion of female subjects, a smaller proportion of subjects with a history of DM, a smaller proportion of subjects with a smoking habit, lower body mass index (BMI), lower average IOP before the add-on was started, a smaller percentage reduction in IOP, higher average PR before the add-on was started, a greater percentage reduction in PR, lower CCT, higher d-ROM level, lower average choroidal MBR, and a lower MD slope before the add-on was started (linear regression analysis for systemic parameters and linear mixed-effects model for ocular

parameters: $P < 0.05$). A history of DM, a smoking habit, and BMI became statistically insignificant as differentiators of the 2 clusters after we adjusted for the gender variable (multiple name-logistic regression: $P = 0.598$–0.999).

HVF testing and LSFG measurements were performed 13.6 ± 8.5 times before and 10.1 ± 5.2 times after the add-on was started and 5.9 ± 3.9 times before and 5.8 ± 4.2 times after the add-on was started, respectively. In cluster 1, choroidal MBR increased by 3.42% ($P = 0.042$) after the β-blocker eye drop add-on was started, even after we adjusted for potential confounding factors, such as the time from when the add-on was started. On the other hand, we did not observe that the add-on had any significant effect in cluster 2 ($\beta = -3.09\%$, $P = 0.081$) (Table 5). The β-blocker eye drop add-on ameliorated MD slope in cluster 1 ($+ 0.64$ dB/year, $P = 0.005$), while it did not have any effect in cluster 2 ($+ 0.10$ dB/year, $P = 0.687$).

DISCUSSION

This retrospective, longitudinal study included patients who received β-blocker eye drops as an add-on treatment during follow-up care for glaucoma. We first confirmed that the β-blocker eye drop add-on significantly reduced PR and IOP. Next, we showed that female gender, higher PR when the add-on was started, lower CCT, and a higher d-ROM level were associated with greater reduction in PR after the add-on was started. An analysis with k-mean clustering revealed 2 clusters of patients: cluster 1 included a greater proportion of female subjects, had a higher average PR before the add-on was started, a greater percentage reduction in PR, lower CCT, and a higher d-ROM level. Choroidal MBR increased and the MD slope slowed after the β-blocker add-on was started only in cluster 1.

This study reconfirmed previous findings that β-blocker eye drops affect PR. The effect of β-blockers on PR has been studied previously, as have the side effects of this treatment, because β-blockers were the first-line treatment for glaucoma in the 1980s. Although it is difficult to directly compare our results with previous studies because of differences in study populations, our current results are reasonable, because the PR reduction we observed in this study was close to some previous reports (approximately 10%) [10, 24, 25]. The strength of this study is that our results are based on an analysis of longitudinal PR data from glaucoma patients over a relatively long period of time. Another strength is that we examined the effectiveness of other anti-glaucoma eye drop add-ons in altering PR as a reference. Although comparisons of these data are not simple, because of possible differences in patient backgrounds, our finding that there was no PR reduction in response to the non-β-blocker eye drops suggests that PR reduction is a specific effect of β-blocker eye drops.

Being elderly and having a history of cardiac disease have been widely accepted as risk factors for bradycardia induced by β-blocker eye drops [15–18]. Our study did not find that aging and a history of cardiac disease were risk factors for a greater reduction in PR, possibly because we used a retrospective analysis of data from a clinic where attending doctors avoid prescribing β-blocker eye drops to patients who are too old or have a history of cardiac disease, especially for conditions like sinus bradycardia or atrioventricular block, which are contraindications for topical β-blocker eye drops [26]. In fact, the present study did not include any cases with a known history of these bradycardia-causing heart diseases, at least based on the initial interview. Furthermore, patients over the age of 80 years are often seen in case reports of bradycardia because of β-blocker eye drops [27, 28], but in our study, only 7 of 138 patients were > 80 years old.

On the other hand, our use of real clinical data allowed us to identify novel background factors associated with a greater reduction in PR. A tendency toward tachycardia suggests a significantly activated sympathetic nervous system, and it is reasonable that β-blocker eye drops, which block adrenergic receptors, would decrease PR in patients with higher PR. D-ROMs are a biomarker of systemic oxidative stress levels, which have been reported to be associated with sympathetic excitation [29]. Patients with higher oxidative stress are likely to have an

activated sympathetic nervous system, which might make β-blocker eye drops more likely to be effective.

Interestingly, we found that β-blocker eye drops were more likely to reduce PR when CCT was lower. Eye drops reach the systemic circulation through the nasolacrimal ducts or conjunctival vessels [30, 31], so it is unlikely that a thinner cornea would have facilitated systemic absorption. Rather, we consider it possible that patients with thinner corneas may also have an active sympathetic nervous system. In patients with heart failure, significant sympathetic nervous system activation is known to elevate markers of cardiac collagen degradation in the blood, resulting in cardiac remodeling [32]. As the heart and cornea share the same main component, type 1 collagen [33, 34], the same mechanism might function in the cornea, that is, sympathetic activation may accelerate degradation of the corneal collagen, leading to a thinner cornea. Another report showed that unilateral Horner's syndrome, a condition characterized by the disruption of the sympathetic nerves leading to ptosis, miosis, and anhidrosis on the affected side of the face [35], is associated with a significant increase in CCT on the affected side [36]. This suggests that the sympathetic nerve supply to the eye is important for corneal hydration. Taken together, these findings suggest that a thin cornea might be the result of an activated systemic sympathetic nerve leading to excessive degradation of collagen and/or hydration in the cornea. Further investigation is needed to clarify the relationship between sympathetic nervous system activation and CCT to support this theory.

We also found that female gender contributed to lower PR after the β-blocker eye drop add-on was started. Bugiardini et al. reported that β-blockers may be an acute precipitant of heart failure in new-onset coronary heart disease in women, but not in men, indicating that women might be more vulnerable to the side effects of β-blockers [37]. This might be because women are often physically smaller than men, making it possible that they experience stronger effects of medication at a given dose. However, in our study, BMI was not associated with a greater reduction in PR after the β-blockers were

started, challenging this explanation, at least in our study population. Another possibility is that activation of the sympathetic nervous system was more significant in women. Narkiewicz et al. reported that aging is accompanied by a greater increase in sympathetic traffic in women than in men, independent of menopausal status [38]. In their study, they found that at around the age of 60 years (the average age of our study population), women appeared to have more significant sympathetic activity than men, supporting our hypothesis. We need to recruit patients with a wider range of ages to confirm this point in the future.

It is interesting to note that PR decreased by approximately 12.4%, choroidal MBR increased by approximately 3.4%, and MD slope improved by 0.64 dB/year in cluster 1. This cluster included patients with higher PR before the add-on was started, a higher d-ROM level, and lower CCT. The IOP reduction rate was also lower in cluster 1 than in cluster 2; thus, the change in choroidal BF and the improvement in VF defect progression were unlikely to have been the result of the IOP reduction. Rather, it is likely that it was the result of the PR reduction due to the β-blocker eye drops. Though the target organ is different, several reports have described the toxicity of tachycardia to local tissues and the benefits of reducing PR with β-blocker oral medication [39, 40]. As described above, we recently showed that high PR is a risk factor for a primary reduction in ocular BF in eyes with glaucoma [7]. Local tissue BF is likely to be reduced because tachycardia tends to overload the heart, which can lead to impaired cardiac function and ineffective pumping. In fact, an approximately 12.4% decrease in PR, from 86.1 to 75.4 bpm, would move PR from outside the 25th to 75th percentiles to inside the percentiles for PR for a typical 60-year-old woman [41], so it is possible that this PR normalization improved local circulation. As we recently showed, there is an association between lower choroidal MBR and faster MD slope [20]; thus, the link between improved choroidal MBR and an amelioration of VF defect progression in this study was reasonable.

There are several limitations to this study. First, because it was retrospective, there may

have been bias in the clinical backgrounds of the cases that received the add-on β-blocker eye drops. For example, patients who are elderly, asthmatic, or have severe cardiac disease were less likely to be enrolled in this study. This makes it difficult to determine any potential side effects that might have arisen in a more representative population and may therefore have biased our finding that the β-blocker add-on had a beneficial effect. In addition, it is still unclear whether we can apply our results to other patient populations with other diseases or of other ethnicities. A multi-center, prospective investigation will be needed in the future. Second, although our sample size was relatively large compared with previous studies that examined the effects of β-blocker eye drops, it may still have been insufficient, especially for the clustering analysis. Although the present study population was divided into 2 clusters, it is likely that a larger number of clusters would have been found with a larger population. Third, while choroidal MBR is reportedly not influenced by glaucoma severity, it may be affected by aging [20]. This makes it challenging to isolate the direct impact of β-blocker eye drops on PR over time. We attempted to mitigate the effect of aging by adjusting for time (Table 5). However, a prospective study with multiple choroidal MBR measurements over a brief period before and after starting the add-on treatment would provide a more accurate understanding of the actual improvement in choroidal BF attributable to the add-on. The fourth limitation worth acknowledging is the possibility that improved choroidal BF in the cluster 1 group was due to the reduction of IOP, even though this was statistically smaller than that in cluster 2. This possibility arises from the finding that cluster 1 had lower CCT, making it challenging to determine the effects of the eye drop add-on on IOP. Moreover, choroidal BF might have increased because postural and diurnal fluctuations in IOP were controlled by the β-blocker eye drop add-on. However, measurement conditions at our institute were precisely controlled—posture was consistently fixed in a sitting position after rest, and 83.2% of the LSFG measurements were conducted between the hours of 9:00 and 15:00, a period

with no diurnal variation in choroidal MBR [42]—so the aforementioned possibility appears less likely. In addition, the significant difference in the change in IOP (%) showcased in Table 4 remains unchanged even when average IOP before the add-on and CCT are accounted for as explanatory variables ($P = 0.003$; multivariable linear mixed-effects model). Even when incorporating CCT into the model presented in Table 5, the results showing the improvement of choroidal BF remain consistent ($\beta = +\ 3.39\%$; $P = 0.043$). As such, we posit that the results highlighted in Tables 4 and 5 are primarily unaffected by these factors.

CONCLUSION

In conclusion, our findings suggest that within a specific subgroup of glaucoma patients, β-blockers could potentially offer benefits in controlling PR, enhancing choroidal BF, and managing the progression of the disease. This insight paves the way for further research into the role of β-blockers in glaucoma treatment.

Declarations

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