KJO
pISSN: 1011-8942 eISSN: 2092-9382

Korean J Ophthalmol 2017;31(2):123-131
https://doi.org/10.3341/kjo.2017.31.2.123

Original Article

Oral Administration of Cilostazol Increases Ocular Blood Flow in Patients with Diabetic Retinopathy

Duck Jin Hwang[1,2], Joo Young Shin[1], Hyeong Gon Yu[1]

[1]*Department of Ophthalmology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea*
[2]*HanGil Eye Hospital, Incheon, Korea*

Purpose: To investigate the effect of cilostazol on ocular hemodynamics and to determine whether the administration of cilostazol increases the ocular blood flow in patients with diabetic retinopathy.

Methods: This prospective observational study investigated the effect of orally administered cilostazol on diabetic retinopathy. Before and after administration for 1 week, pulsatile ocular blood flow (POBF) and retrobulbar hemodynamics were measured using a POBF analyzer and transcranial Doppler imaging, respectively. Visual acuity, intraocular pressure, and blood pressure were also evaluated before and after treatment.

Results: Twenty-five eyes of 25 patients were included in this study. POBF increased significantly (16.8 ± 4.6 μL/sec vs. 19.6 ± 6.2 μL/sec, $p < 0.001$) after administration of cilostazol, while no significant change was identified in visual acuity, intraocular pressure, and blood pressure. Mean flow velocity in the ophthalmic artery as measured with transcranial Doppler imaging also increased significantly after medication (23.5 ± 5.6 cm/sec vs. 26.0 ± 6.9 cm/sec, $p = 0.001$). The change in POBF directly correlated with the change in mean flow velocity ($r = 0.419$, $p = 0.007$).

Conclusions: Cilostazol was effective in increasing ocular blood flow in patients with diabetic retinopathy, possibly by modulating retrobulbar circulation.

Key Words: Blood flow velocity, Cilostazol, Diabetic retinopathy, Pulsatile flow

Medications that modulate blood flow are widely used in the treatment of cerebrovascular and cardiovascular diseases. These systemic medications may also affect ocular blood flow, as retinal circulation is similar to cerebral circulation [1-4]. Cilostazol, an antiplatelet agent, has been used for the prevention of ischemic stroke in Japan and other Asian countries [5]. Cilostazol acts as a direct and indirect antiplatelet agent by inhibiting platelet activation and improving overall vascular endothelial function [5,6]. This antiplatelet effect is mediated by cyclic guanosine monophosphate, which inhibits phosphodiesterase-3 and also induces vasodilation [7,8]. Cilostazol also reportedly enhances cerebral blood flow in patients with chronic cerebral infarction. However, few studies have examined the

Received: January 6, 2016 *Accepted*: February 17, 2016

Corresponding Author: Hyeong Gon Yu, MD, PhD. Department of Ophthalmology, Seoul National University College of Medicine, #103 Daehak-ro, Jongno-gu, Seoul 03080, Korea. Tel: 82-2-2072-2438, Fax: 82-2-741-3187, E-mail: hgonyu@snu.ac.kr

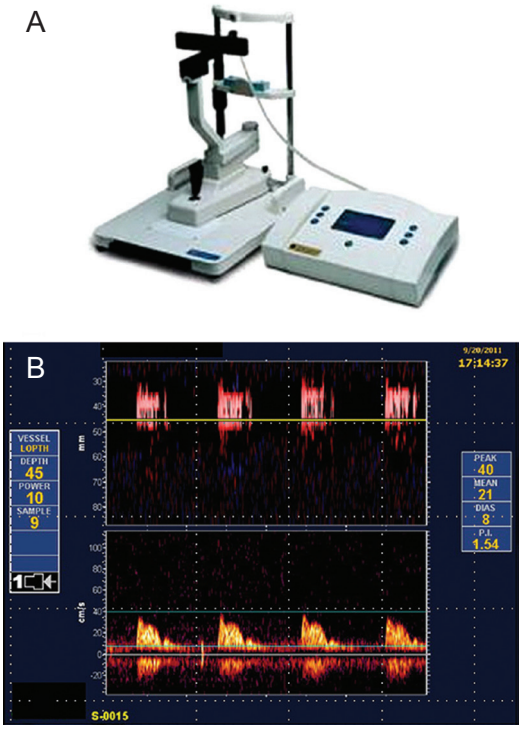

Fig. 1. (A) The pulsatile ocular blood flow analyzer (Paradigm Medical Instruments, Salt Lake City, UT, USA), (B) the transcranial Doppler image using a TCD150M device (Spencer Technologies, Seattle, WA, USA). This case shows a peak systolic velocity (PEAK), mean flow velocity (MEAN), end diastolic velocity (DIAS) and pulsatility index (PI) of the left ophthalmic artery at 1 week after the administration of cilostazol.

effects of systemic medications on ocular blood flow.

The pulsatile ocular blood flow (POBF) analyzer (Paradigm Medical Instruments, Salt Lake City, UT, USA) **(**Fig. 1A) is a device that noninvasively measures ocular blood flow by measuring changes in intraocular pressure (IOP) caused by pulsatile rhythmic filling of the intraocular vessels with a pneumatic applanation tonometer [9-11]. The device's design is based on the assumption that venous outflow from the eye is non-pulsatile. Moreover, ocular rigidity, which is used to derive changes in ocular volume from changes in IOP, is assumed to be the same in all subjects. The calculation of POBF is automatically derived from the beat-to-beat IOP variation as measured using the five pulses that are closest to each other. POBF is calculated on a "per-minute" or "per-second basis" as beat-to-beat variation in IOP, which provides an indirect assessment of total ocular blood flow.

Changes in ocular blood flow have been known to correlate with the development and progression of diabetic retinopathy, leading to macular edema and retinal neovascularization [12-14]. Although the exact nature of ocular blood flow abnormalities in diabetic retinopathy has not yet been established, the effect of pathogenic mechanisms such as vascular and rheological abnormalities and long-term hyperglycemia on the microvasculature seem to alter the blood flow in patients with diabetic retinopathy [15-19]. In addition, ocular ischemia caused by this dysregulated blood flow induces the expression of cytokines such as vascular endothelial growth factor, which also may affect retinal blood flow [20-22]. Thus, there is a possibility that eyes with diabetic retinopathy may potentially benefit from medications altering ocular blood flow. While previous studies have mainly focused on retinal blood flow in diabetic retinopathy, interest in investigating the hemodynamics of the entire ocular circulation has been prompted by the development of the POBF analyzer, which is a clinically feasible technique for the measurement of POBF [9-11]. It has been suggested that the pulsatile component of ocular blood flow is a reliable parameter for the evaluation of the choroidal circulation.

Therefore, in this study, we investigated the effect of cilostazol on ocular hemodynamics and evaluated whether the administration of cilostazol increases ocular blood flow in patients with diabetic retinopathy.

Materials and Methods

Participants

Patients over 30 years of age with type 2 diabetes, diabetic retinopathy, and a visual acuity of 20 / 50 or better were enrolled in this prospective observational study. All participants were seen at Seoul National University Hospital from October 2011 to March 2012. The baseline POBF analyses were performed in conjunction with a transcranial Doppler (TCD) examination and blood pressure (BP) measurements. Ophthalmic evaluations of best-corrected visual acuity (BCVA), IOP, and Cirrus HD optical coherence tomography (OCT; Carl Zeiss Meditec, Dublin, CA, USA) measurements were performed. One week after the administration of cilostazol (Pletal; Otsuka Pharmaceutical, Tokyo, Japan), all examinations were repeated. All POBF examinations were performed by a single trained examiner (DJH) to reduce inter-examiner bias. The central

foveal thickness (CFT, the mean retinal thickness of the central 1 mm circle), the macular cube volume, and the macular cube average thickness were measured using a Cirrus HD OCT unit. When both eyes were eligible for the study, each eye was individually evaluated; however, a computer algorithm randomly selected only one eye for use in the statistical analysis. The type of diabetic retinopathy was also classified into two subgroups: a non-proliferative diabetic retinopathy (NPDR) group and a panretinal photocoagulation (PRP)-treated proliferative diabetic retinopathy (PDR) group.

Upon enrollment, the clinical history of each patient was thoroughly evaluated. After screening, patients were administered cilostazol twice daily at a dose of 100 mg for 1 week (200 mg per day). Patients who were taking aspirin at the time of enrollment in this study were asked to stop aspirin treatment for 2 weeks before beginning the cilostazol regimen. The 200-mg cilostazol dose was continued for 1 week if no complication or severe event was observed. The administration of any other anti-platelet drugs that could strongly influence the effect of cilostazol was prohibited during the study period. However, pre-existing prescription drugs for chronic diseases such as hypertension and diabetic mellitus were continued throughout the study period.

Patients with the following conditions were excluded from the study: a history of retinal surgery; ocular diseases, excluding diabetic retinopathy; new retinal vessels observed with fluorescein angiography; macular edema with a CFT exceeding 300 μm; severe hypertension (defined as having a systolic BP greater than 180 mmHg or a diastolic BP greater than 110 mmHg); hypersensitivity to the cilostazol treatment; pregnancy or the possibility of pregnancy; uncontrolled diabetes (hemoglobin A1c >8%); angina pectoris, myocardial infarction, or heart failure.

POBF measurement

A POBF analyzer was used to assess blood flow according to methods previously described [9-11]. This noninvasive technique assessing ocular blood flow is based on the IOP pulse. A modified applanation prism with distensible film at the contact surface is used to measure blood velocity. A pneumotonometer is used to create a waveform representing the ocular pulse. The amplitude and pulse rate (PR) of this waveform are then used to calculate POBF. The POBF analyzer has been found to be reliable and reproducible in measuring ocular pulse amplitude (PA), pulse volume (PV), PR, and POBF [9,10,23,24].

Retrobulbar vessel (ophthalmic artery) blood velocity

The TCD studies were performed using a TCD150M device (Spencer Technologies, Seattle, WA, USA) (Fig. 1B), which calculates a power M-mode Doppler image and provides a single-gate spectrogram. TCD has shown good reproducibility and repeatability in the assessment of the ophthalmic artery [25]. The peak systolic velocity (PSV), mean flow velocity (MFV), end diastolic velocity (EDV), and pulsatility index (PI) of the ophthalmic artery were evaluated at baseline and 1 week after the administration of cilostazol. The ophthalmic artery can be situated above or below the optic nerve in the posterior orbit and passes forward into the nasal orbit in a horizontal plane slightly superior to that of the optic nerve. These vessels were examined at a point approximately 25 mm behind the globe in the nasal orbit. At this point, the vessels lie in a straight position that facilitates accurate measurements. The PI was calculated using the following formula (PSV – EDV) / (MFV), which was used to characterize the peripheral vascular resistance.

Statistical analyses

Statistical analyses were performed using a commercially available software package PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA). Changes between values measured at baseline and those measured 1 week after the administration of cilostazol were evaluated using the paired *t*-test and Wilcoxon signed-rank test for normally distributed data and data that were not normally distributed, respectively. Significant differences in the POBF analyzer and TCD values between the subgroups (NPDR group vs. PRP-treated PDR group) were evaluated using the Mann-Whitney test for nonparametric data. Analysis of covariance was performed to adjust for age, gender, and the duration of diabetes mellitus in the subgroup analysis. Spearman's nonparametric regression analysis was used to determine the correlation between POBF and TCD at the ophthalmic artery. A *p*-value less than 0.05 was considered to be statistically significant.

Ethics statement

The study was approved by the institutional review board of Seoul National University Hospital (no. 0620113380) and followed the guidelines of Good Clinical Practice. Written informed consent for participation was obtained from all patients after they had been given a thorough explanation of this study. The study was carried out in accordance with the tenets of the Declaration of Helsinki.

Results

We enrolled 25 eyes from 25 patients with diabetic retinopathy. The mean age was 62.5 ± 12.0 years and 16 patients (64%) were male. The mean duration of diabetes mellitus was 14.6 ± 7.0 years. The PDR group (18.4 ± 6.4 years) had a longer duration of diabetes mellitus than the NPDR group (11.6 ± 6.0 years) (p = 0.001). Cilostazol was well tolerated by all of the patients, and no complications or severe adverse events were observed during the 1 week of administration. There were no significant changes in vi-

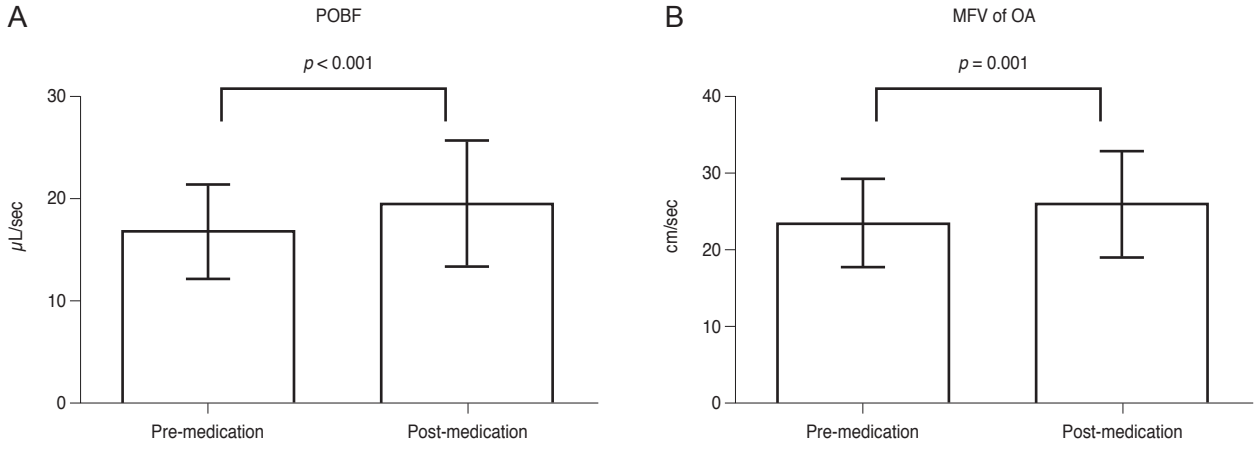

Fig. 2. One week after cilostazol administration, (A) pulsatile ocular blood flow (POBF) had increased by 17.1% (p < 0.001) and (B) mean flow velocity (MFV) of ophthalmic artery (OA) had increased by 11.7% (p = 0.001). Values are means with error bars representing standard deviation.

Table 1. Changes in POBF analyzer and transcranial Doppler parameters after cilostazol administration

	Pre-medication	Post-medication	p-value*
POBF			
IOP (mmHg)	14.0 ± 3.3	13.7 ± 3.2	0.273
PA (mmHg)	2.8 ± 1.3	2.3 ± 0.9	<0.001
PV (μL)	6.3 ± 3.0	5.7 ± 2.9	0.276
PR (times/min)	72.8 ± 14.3	91.2 ± 21.6	<0.001
POBF (μL/sec)	16.8 ± 4.6	19.6 ± 6.2	<0.001
Transcranial Doppler			
MFV (cm/sec)	23.5 ± 5.6	26.0 ± 6.9	0.001
PSV (cm/sec)	43.9 ± 12.5	49.4 ± 15.1	0.001
EDV (cm/sec)	9.9 ± 2.0	10.3 ± 2.0	0.154
PI†	1.4 ± 0.2	1.5 ± 0.2	0.056

Values are presented as mean ± standard deviation.
POBF = pulsatile ocular blood flow; IOP = intraocular pressure; PA = pulse amplitude; PV = pulse volume; PR = pulse rate; MFV = mean flow velocity in the ophthalmic artery; PSV = peak systolic velocity in the ophthalmic artery; EDV = end diastolic velocity in the ophthalmic artery; PI = pulsatility index.
*Wilcoxon signed-rank test; †(PSV – EDV) / (MFV).

sual acuity, IOP, or BP after medication. Among the OCT parameters, there were no significant changes in the CFT (255.9 ± 26.4 μm vs. 254.0 ± 27.4 μm, $p = 0.111$), macular cube volume (10.32 ± 1.0 mm^3 vs. 10.3 ± 1.0 mm^3, $p = 0.845$), or macular cube average thickness (286.7 ± 29.0 μm vs. 287.3 ± 28.2 μm, $p = 0.111$), respectively.

POBF analysis

The PA, PR, and POBF measurements exhibited significant changes after cilostazol administration, as shown in Table 1. At 1 week after cilostazol administration, PA had decreased by 17.9% (2.8 ± 1.3 mmHg vs. 2.3 ± 0.9 mmHg, $p < 0.001$), and PR had increased by 25.3% (72.8 ± 14.3 times/min vs. 91.2 ± 21.6 times/min, $p < 0.001$). Mean POBF was 16.8 ± 4.6 μL/sec at baseline and increased by 17.1% to 19.6 ± 6.2 μL/sec after 1 week of cilostazol medication ($p < 0.001$) (Fig. 2A). PV remained relatively constant throughout the study period ($p > 0.05$).

Retrobulbar vessel (ophthalmic artery) blood velocities

Table 1 also shows the change in the TCD parameters induced by cilostazol. MFV was 23.5 ± 5.6 cm/sec at baseline and then increased significantly by 11.7% to 26.0 ± 6.9 cm/sec with medication administration ($p = 0.001$) (Fig. 2B). PSV also increased by 12.8% (43.9 ± 12.5 cm/sec vs. 49.5 ± 15.1 cm/sec, $p = 0.001$). EDV and PI remained relatively constant throughout the study.

Correlation between the POBF and TCD parameters

A moderate correlation between changes in POBF and TCD was observed. The changes in the POBF were found

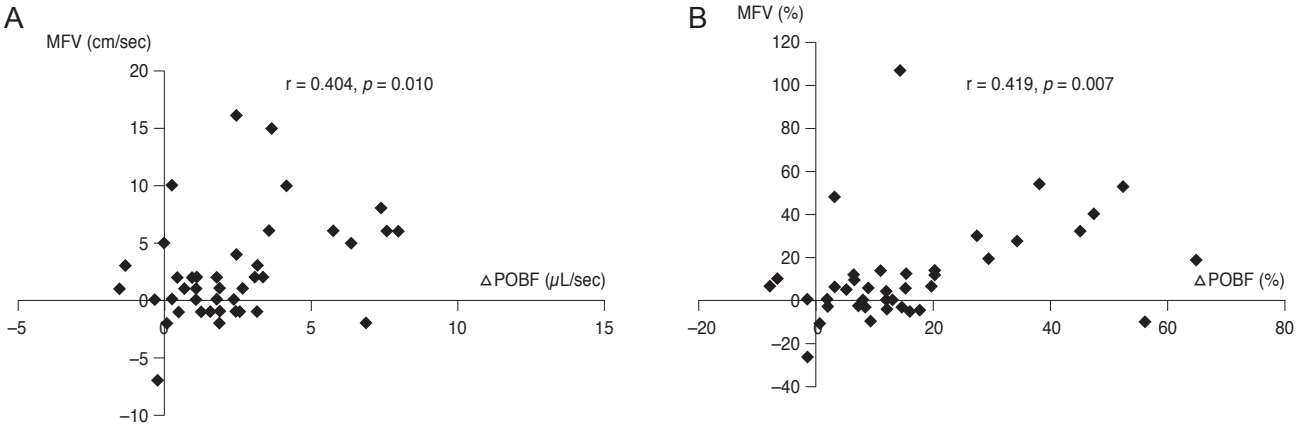

Fig. 3. Spearman's regression analysis showed that the change in pulsatile ocular blood flow (POBF) was found to correlate with the change in mean flow velocity (MFV) of the ophthalmic artery: (A) absolute change: r = 0.404, $p = 0.010$; (B) percentage change: r = 0.419, $p = 0.007$.

Table 2. Comparison of POBF and MFV in the NPDR and PDR groups

	NPDR (n = 12)	PDR (n = 13)	*p*-value*	*p*-value†
Pre-POBF	17.5 ± 4.6	15.9 ± 4.4	0.346	0.326
Post-POBF	20.2 ± 7.2	18.7 ± 4.6	0.868	0.272
ΔPOBF	2.8 ± 3.8	2.8 ± 2.6	0.431	0.728
Pre-MFV	22.9 ± 5.9	24.2 ± 5.4	0.352	0.243
Post-MFV	24.5 ± 6.5	27.6 ± 7.1	0.177	0.144
ΔMFV	1.6 ± 4.4	3.4 ± 4.6	0.211	0.675

Values are presented as mean ± standard deviation.
POBF = pulsatile ocular blood flow; MFV = mean flow velocity in the ophthalmic artery; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Pre-POBF = POBF at baseline; Post-POBF = POBF after medication; ΔPOBF = post-POBF – pre-POBF; Pre-MFV = MFV in the ophthalmic artery at baseline; Post-MFV = MFV in the ophthalmic artery after medication; ΔMFV = post-MFV – pre-MFV.
*Mann-Whitney *U*-test; †Age, gender, and duration of diabetes mellitus were adjusted by analysis of covariance.

to correlate with the changes in MFV (absolute change: r = 0.404, p = 0.010; percentage change: r = 0.419, p = 0.007, respectively), as shown in Fig. 3A and 3B, respectively. The changes in the POBF also correlated with the changes in PSV and EDV (r = 0.393, p = 0.012 and r = 0.337, p = 0.034, respectively).

Comparison of the NPDR and PDR groups

After dividing the 25 patients into two groups (a NPDR group and PRP-treated PDR group), subgroup analyses were performed for the POBF and TCD parameters. There was no significant difference in any of the POBF or TCD parameters between the two groups. A summary of the results can be seen in Table 2. The analysis of covariance revealed no significant inter-group differences after adjustment for age, sex, and duration of diabetes mellitus (p > 0.05). Neither age nor gender was found to be a significant predictor of changes in POBF or MFV (p = 0.275 and p = 0.114, respectively).

Discussion

In this study, ocular blood flow as assessed by the POBF analyzer increased with oral administration of cilostazol in patients with diabetic retinopathy patients. This increase in ocular blood flow was parallel to the increase in retrobulbar vessel blood flow velocity as measured with TCD. The same trend of increased ocular blood flow was observed irrespective of the degree of diabetic retinopathy.

The average increase in POBF observed in this study was 17.1%. This change in ocular blood flow was significant even after considering the previously proven test/retest variability [9,10,23,24]. Furthermore, to minimize the interobserver variability, all measurements were performed by a single experienced operator, which is very important in measuring POBF [26]. POBF values have a wide normal range and low discriminating power [27], so intra-individual comparisons with repeated examinations, as performed in this study, are more useful than inter-individual comparisons. POBF analysis also showed that cilostazol administration significantly decreased PA and increased PR, which have been reported to be negatively correlated with each other in healthy subjects [28], and PV did not change significantly. These trends may explain the increase in POBF, which is affected by PA, PR, and PV [9-11].

However, the outcomes of the present study should be discussed with an awareness of the associated instrumental limitations. Currently, there is no established gold standard for the assessment of ocular blood flow, and therefore validation of any given method is limited to comparison with other methods. Although the measurement of ocular blood flow with the POBF analyzer has empirical validity, it is necessary to consider the accuracy of our results. This is important because the measurement of blood flow from the ocular pulse is based on specific assumptions [11], hence no single method may provide a complete description of ocular blood flow. We therefore performed TCD to also evaluate retrobulbar vessel velocity, and found that the mean velocity in the ophthalmic artery had increased by 11.7 %. These changes in the TCD parameters of retrobulbar hemodynamics suggest that cilostazol treatment may modulate the velocity of blood in the retrobulbar vessels. Changes in POBF were found to moderately correlate with changes in MFV by TCD, although ocular blood flow accounts for only a small portion of blood flow through the ophthalmic artery [29]. Changes in POBF also correlated with changes in PSV and EDV as well as MFV. Despite the fact that the POBF and TCD measure different phenomena, the simultaneous increase in POBF and retrobulbar blood flow, as measured by the TCD, raises the possibility that the increase in POBF may reflect an actual increase in ocular blood flow, which may be affected by the increase in retrobulbar blood flow.

The exact mechanism of cilostazol in increasing ocular blood flow remains to be clarified. Although cilostazol reportedly enhances cerebral blood flow in cases of chronic cerebral infarction, its effect on ocular blood flow has not been investigated, and its ability to increase ocular blood flow remains unknown, especially in the diabetic state. To the best of our knowledge, this is the first study designed to elucidate the effect of systemic medication on ocular blood flow in patients with diabetic retinopathy. It may be speculated that the increased ocular blood flow observed in this study was due to the vasodilatory effect of cilostazol, as cilostazol is known to act as a platelet inhibitor and vasodilator. The PI calculated from the parameters measured by TCD, which reflects vascular resistance, showed no significant change. The blood flow velocity was observed to increase, thereby increasing the retrobulbar blood flow. Cilostazol may affect the autoregulatory func-

tion of ocular blood flow and cause the vascular resistance to remain constant despite increased cerebral blood flow, thereby allowing increased ocular blood flow.

No significant change was identified in the IOP, BP, BCVA, and OCT thickness parameters, such as the CFT and the macular cube volume at 1 week after the administration of cilostazol. With the increased ocular blood flow induced by cilostazol, autoregulatory mechanisms may have decreased ocular vascular resistance to maintain a constant IOP. Additionally, cilostazol may have a direct effect on inducing vasodilation in the ocular vasculature. However, the exact mechanism and the effect on retinal blood flow remain unclear. Spectral domain-OCT parameters do not represent retinal blood flow, and there are no reliable methods currently available to assess retinal blood flow. The challenge of evaluating the effects of cilostazol on retinal blood flow and its long-term clinical outcomes remains to be solved in future studies.

Previous studies on cilostazol reported a lower mean POBF in the PRP-treated PDR group as compared to the NPDR group. However, our results showed no significant difference in POBF values between the NPDR group and PDR groups. In addition, the POBF of the NPDR and PDR groups were higher than those reported in previous studies for patients with diabetic retinopathy. Perrott et al. [30] reported a mean value of 15.9 μL/sec for the NPDR group, which was lower than the values reported in this study. Savage et al. [19] reported mean values of 15.7 μL/sec for moderate to severe NPDR and 10.3 μL/sec for PRP-treated PDR, both of which were also lower than the values reported in this study (16.8 μL/sec for NPDR and 19.6 μL/sec for PDR). This may be due to variability in the conditions of the patients enrolled in these studies, as most related studies have reported a small sample size, and only patients with relatively good vision were enrolled in our study. In addition, the interpretation and comparison of the POBF values may be limited by differences in patient age, sex, and the classification of diabetic retinopathy.

The clinical significance of this increase in ocular blood flow with the administration of cilostazol in patients with diabetic retinopathy remains to be evaluated. Studies describing the role of altered ocular blood flow in patients with diabetic retinopathy report conflicting results. Increased ocular blood flow does not directly correlate with either improved visual acuity or delayed progression of diabetic retinopathy. Our understanding of the role of ocular blood flow in the pathophysiology of diabetic retinopathy is in its infancy, and attempts to pharmacologically modify the progression of diabetic retinopathy are also in their primitive stages. To the best of our knowledge, our study is the first to evaluate the effects of systemic medication on ocular blood flow in diabetic retinopathy. The results of this study suggest that cilostazol may have potential value in increasing ocular blood flow in patients with diabetic retinopathy, although the long-term benefits need to be elucidated. With regard to safety, none of the patients in this study showed any complications or severe adverse events during medication administration. Moreover, in a recent report [31], the addition of cilostazol to a regimen of aspirin therapy did not increase the bleeding tendency when compared with a regimen consisting of aspirin alone. Cilostazol treatment could therefore safely be added to an ongoing antiplatelet regimen without increasing the risk of bleeding in patients with diabetic retinopathy.

There are some limitations to this study that should be considered when interpreting the results. Most importantly, there was no control group of normal non-diabetic subjects. This is a major limitation in an interventional drug study. Second, the sample size was small, with a relatively brief study period. A large-scale long-term comparative study with a control group will be necessary to confirm these findings.

In this study, cilostazol increased ocular blood flow by more than 10% without any significant side effects in patients with diabetic retinopathy. This demonstrates its potential as a tool for increasing blood flow in diabetic retinopathy, although its long-term clinical benefit remains to be clarified. Further studies are required to investigate whether increased ocular blood flow due to cilostazol can slow the progression of diabetic retinopathy or improve visual outcome.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

The authors disclosed receipt of the following financial support for the research: Otsuka Pharmaceutical provided financial support for this investigator-initiated research. The sponsor or funding organization had no role in the design or conduct of this research.

Statistical analyses were aided by the consultation of Medical Research Collaborating Center of Seoul National University College of Medicine and Seoul National University Hospital.

References

1. Patton N, Aslam T, Macgillivray T, et al. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 2005;206:319-48.
2. Delaey C, Van De Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res* 2000;32:249-56.
3. Li G, Shih YY, Kiel JW, et al. MRI study of cerebral, retinal and choroidal blood flow responses to acute hypertension. *Exp Eye Res* 2013;112:118-24.
4. Yoshida Y, Sugiyama T, Utsunomiya K, et al. A pilot study for the effects of donepezil therapy on cerebral and optic nerve head blood flow, visual field defect in normal-tension glaucoma. *J Ocul Pharmacol Ther* 2010;26:187-92.
5. Uchiyama S, Demaerschalk BM, Goto S, et al. Stroke prevention by cilostazol in patients with atherothrombosis: meta-analysis of placebo-controlled randomized trials. *J Stroke Cerebrovasc Dis* 2009;18:482-90.
6. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005;6:3-11.
7. Tanaka T, Ishikawa T, Hagiwara M, et al. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. *Pharmacology* 1988;36:313-20.
8. Schror K. The pharmacology of cilostazol. *Diabetes Obes Metab* 2002;4 Suppl 2:S14-9.
9. Langham ME, Farrell RA, O'Brien V, et al. Blood flow in the human eye. *Acta Ophthalmol Suppl* 1989;191:9-13.
10. Silver DM, Farrell RA, Langham ME, et al. Estimation of pulsatile ocular blood flow from intraocular pressure. *Acta Ophthalmol Suppl* 1989;191:25-9.
11. Krakau CE. Calculation of the pulsatile ocular blood flow. *Invest Ophthalmol Vis Sci* 1992;33:2754-6.
12. Sakata K, Funatsu H, Harino S, et al. Relationship between macular microcirculation and progression of diabetic macular edema. *Ophthalmology* 2006;113:1385-91.
13. Mendivil A, Cuartero V, Mendivil MP. Ocular blood flow velocities in patients with proliferative diabetic retinopathy and healthy volunteers: a prospective study. *Br J Ophthalmol* 1995;79:413-6.
14. Cuypers MH, Kasanardjo JS, Polak BC. Retinal blood flow changes in diabetic retinopathy measured with the Heidelberg scanning laser Doppler flowmeter. *Graefes Arch Clin Exp Ophthalmol* 2000;238:935-41.
15. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care* 1998;21:143-56.
16. Bursell SE, Clermont AC, Kinsley BT, et al. Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabetic retinopathy. *Invest Ophthalmol Vis Sci* 1996;37:886-97.
17. Feke GT, Tagawa H, Yoshida A, et al. Retinal circulatory changes related to retinopathy progression in insulin-dependent diabetes mellitus. *Ophthalmology* 1985;92:1517-22.
18. Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. *Acta Ophthalmol Scand* 1999;77:522-5.
19. Savage HI, Hendrix JW, Peterson DC, et al. Differences in pulsatile ocular blood flow among three classifications of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2004;45:4504-9.
20. Campochiaro PA; C99-PKC412-003 Study Group. Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. *Invest Ophthalmol Vis Sci* 2004;45:922-31.
21. Aiello LP, Cahill MT, Cavallerano JD. Growth factors and protein kinase C inhibitors as novel therapies for the medical management diabetic retinopathy. *Eye (Lond)* 2004;18:117-25.
22. Yokota T, Ma RC, Park JY, et al. Role of protein kinase C on the expression of platelet-derived growth factor and endothelin-1 in the retina of diabetic rats and cultured retinal capillary pericytes. *Diabetes* 2003;52:838-45.
23. Butt Z, O'brien C. Reproducibility of pulsatile ocular blood flow measurements. *J Glaucoma* 1995;4:214-8.
24. Morgan A, Hosking S. Ocular blood flow tonometer reproducibility: the effect of operator experience and mode of application. *Ophthalmic Physiol Opt* 2001;21:401-6.
25. Baxter GM, Williamson TH. Color Doppler imaging of the

eye: normal ranges, reproducibility, and observer variation. *J Ultrasound Med* 1995;14:91-6.
26. Schmetterer L, Dallinger S, Findl O, et al. Noninvasive investigations of the normal ocular circulation in humans. *Invest Ophthalmol Vis Sci* 1998;39:1210-20.
27. Aydin A, Wollstein G, Price LL, Schuman JS. Evaluating pulsatile ocular blood flow analysis in normal and treated glaucomatous eyes. *Am J Ophthalmol* 2003;136:448-53.
28. Gekkieva M, Orgul S, Gherghel D, et al. The influence of sex difference in measurements with the Langham ocular blood flow system. *Jpn J Ophthalmol* 2001;45:528-32.
29. Hayreh SS. The ophthalmic artery: III. branches. *Br J Ophthalmol* 1962;46:212-47.
30. Perrott RL, Drasdo N, Owens DR, North RV. Can pulsatile ocular blood flow distinguish between patients with and without diabetic retinopathy? *Clin Exp Optom* 2007;90:445-50.
31. Kim SH, Chang HW, Choi TH, et al. Cilostazol effectively reduces the decrease of flow volume in a thrombotic anastomosis model in a rat: a novel application of ultrasonography for evaluation. *Ann Plast Surg* 2010;64:482-6.