Systemic Prostaglandin E1 to Treat Acute Central Retinal Artery Occlusion

Yasuyuki Takai, Masaki Tanito, Yotaro Matsuoka, Katsunori Hara, and Akihiro Ohira

Department of Ophthalmology, Shimane University Faculty of Medicine, Izumo, Japan

Correspondence: Yasuyuki Takai, Department of Ophthalmology, Shimane University Faculty of Medicine, Enya 89-1, Izumo, Shimane, 693-8501, Japan; takai611@med.shimane-u.ac.jp.

Submitted: December 6, 2012
Accepted: April 1, 2013

Citation: Takai Y, Tanito M, Matsuoka Y, Hara K, Ohira A. Systemic prostaglandin E1 to treat acute central retinal artery occlusion. *Invest Ophthalmol Vis Sci*. 2013;54:3065–3071. DOI:10.1167/iovs.12-11445

Purpose. To report the efficacy of systemic prostaglandin E1 (PGE1) monotherapy for treating acute central retinal artery occlusion (CRAO).

Methods. The best-corrected visual acuity (BCVA) and side effects were evaluated retrospectively in 10 consecutive eyes (nine patients; mean age, 61.3 years) with acute CRAO treated with PGE1 monotherapy. The protocol included intravenous injection of 40 μg PGE1 twice daily (80 μg per day) for 5 days then oral PGE1 three times daily (30 μg per day) for at least 1 month. In four eyes, the retinal vessel diameters were assessed on serial fundus photographs.

Results. The mean time to treatment was 7.1 hours (range, 1–18 hours). The mean ± SD logarithm of the minimum angle of resolution (logMAR) BCVAs at baseline and 1 month after initiation of therapy were 2.67 ± 0.54 (range, 3.00–1.70) and 0.52 ± 0.62 (range, 2.00 to −0.18), respectively ($P = 0.005$); the BCVA improved by 1.0 or more logMAR unit at 1 month in all eyes. The BCVA improvement was correlated negatively with the time to treatment ($\rho = -0.655$, $P = 0.0492$), but was not correlated with age ($\rho = -0.473$, $P = 0.156$) and did not differ between sexes ($P = 0.0871$). Compared with baseline, the mean changes in the vessel diameters in four cases were 151.1% (range, 115.1%–188.0%) in the arteries and 191.0% (range, 127.2%–246.4%) in the veins 1 day after initiation of therapy. Angialgia during injection was the only side effect.

Conclusions. Systemic administration of PGE1 for acute CRAO rapidly restores retinal blood flow by its vasodilatory effects, improves VA, is well tolerated with few side effects, and requires no special training.

Keywords: central retinal artery occlusion, prostaglandin E1, vasodilation

Central retinal artery occlusion (CRAO), a stroke that occurs in the retina as the result of a thrombus or embolus,[1,2] usually leads to sudden unilateral visual impairment and unfavorable visual outcomes. Because of its rarity (1 in 10,000 ophthalmic outpatient visits),[3] no consistent therapeutic recommendation has been established. The natural course of CRAO is devastating: 92% of patients with CRAO have a visual acuity (VA) of counting fingers (CF) or worse,[4] whereas up to 8% of patients have improved VA due to spontaneous remission of the occlusion.[5–7] Conventional therapies for acute CRAO include anterior chamber paracentesis, ocular digital massage, IOP-lowering drugs, antiplatelet or anticoagulant drugs, administration of a mixture of carbon dioxide and oxygen gas, and combinations of these therapies, which have limited efficacy.[5–18] Previous reports have suggested the possible effectiveness of intra-arterial or intravenous thrombolysis using recombinant tissue plasminogen activator (rtPA) to improve the VA in patients with acute CRAO.[19,20] The advantage of rtPA over another anticoagulant, urokinase, is its clot selectivity[21,22]; rtPA has a higher affinity for fibrin-bound plasminogen and a lower affinity for circulating plasminogen.[22,23] Theoretically, thrombolysis and reperfusion of blood flow using rtPA in the early phase of acute CRAO could restore VA; however, life-threatening complications, such as cerebral or systemic bleeding, are major concerns associated with systemic administration of rtPA for treating a vision-threatening disease.[24] The European Assessment Group for Lysis in the Eye (EAGLE) reported the first randomized controlled trial (RCT) on intra-arterial thrombolysis with rtPA via a catheter inserted into the ophthalmic artery and reported the same visual results as ocular massage and topical beta-blockers, but more complications developed.[9] Thus, the use of rtPA also is not ideal for treating acute CRAO.

Prostaglandin E1 (PGE1) is a potent vasodilator of the peripheral vascular system and inhibits platelet aggregation via stimulating adenylate cyclase to produce cyclic adenosine monophosphate (AMP).[25,26] PGE1, which acts directly on the smooth muscle of the vascular wall leading to vascular dilatation and increased blood flow,[27] is used to treat patients with peripheral vascular disease, such as intermittent claudication and peripheral diabetic ulcers, with fewer hypotensive adverse effects.[28,29] Since the mid-1990s, several clinicians in Japan have used systemic PGE1 to treat acute CRAO and reported its clinical usefulness, although there have been few reports in the literature about the outcomes of PGE1 used to treat acute CRAO. In addition, some clinicians use PGE1 alone and others use PGE1 in combination with other therapeutics; thus, no recommended protocol has yet been established. In our department, we started using protocol-based systemic PGE1 therapy to treat acute CRAO in 2007. The aim of this study was to report the treatment outcomes following systemic PGE1 monotherapy by retrospectively reviewing the patients

TABLE 1. Characteristics of Subjects and VA Before and 1 Month After the Start of PGE1 Treatment

Case No.	Age, y	Sex	Eye	Time to Treatment, h	Vascular Risk Factors	Ocular Disease	BCVA Before Treatment, Decimal/logMAR	BCVA at 1 mo, Decimal/logMAR
1-1	52	F	Right	6	HT, DM	Diabetic retinopathy	HM/3.00	0.5/0.30
1-2	53	F	Left	2	HT, DM	Diabetic retinopathy	0.02/1.70	0.6/0.22
2	48	M	Left	1	HT, CRA	None	HM/3.00	1.5/–0.18
3	51	M	Left	4	HT, CRA	None	HM/3.00	0.1/1.00
4	59	F	Left	17		None	CF/2.00	0.2/0.70
5	64	M	Right	3	HT	None	HM/3.00	0.4/0.40
6	56	M	Right	2	HT, CRA	None	HM/3.00	1.0/0.00
7	77	F	Right	18	HT, CRA	Glaucoma	HM/3.00	CF/2.00
8	74	F	Right	11	HT	None	HM/3.00	0.6/0.22
9	79	F	Right	7	HT, CRA	None	0.01/2.00	0.3/0.52

DM, diabetes mellitus; F, female; HT, systemic hypertension; M, male.

with acute CRAO in our hospital database. We also evaluated the possible vasodilatory effects of PGE1 and changes in diameters of main branch of central retinal artery and vein before and after PGE1 administration in four cases.

SUBJECTS AND METHODS

Subjects

This retrospective study was conducted as a part of the study protocol "Epidemiologic Study of Ocular Morphology and Function," that the Ethics Committee of Shimane University Hospital approved and that adhered with the tenets of the Declaration of Helsinki. In our department, we began routine use of systemic PGE1 according to a standard treatment protocol in 2007. We searched the patient records in our department between January 2007 and December 2010 and identified 10 eyes of nine consecutive subjects with acute CRAO during that period. Because all 10 eyes had been treated with the protocol-based PGE1 monotherapy, they were included in the study. All subjects provided written informed consent before receiving systemic PGE1 monotherapy. The requirement for patient informed consent for inclusion in the current study was waived based on the approval of the ethics committee of our hospital, because the study protocol met the informed consent–omittable criteria as defined by the Japanese Ethics Guideline for Epidemiologic Study. By reviewing the patients' medical records, we collected the age at the initial visit, sex, laterality of the affected eye, duration from the onset of CRAO to the start of PGE1 administration (time to treatment), presence of systemic and ocular diseases, best-corrected VA (BCVA), and possible ocular and systemic adverse events recorded.

Protocol of PGE1 Therapy

Acute CRAO was defined as a sudden decrease of vision within 24 hours of a visit to our hospital and diagnosed by typical funduscopic findings, such as narrowed retinal arteries in all four quadrants and ischemic retinal edema with a cherry-red spot at the center of the macula. Patients suspected of having arteritic CRAO were not candidates for PGE1 therapy. For all subjects who were diagnosed with acute CRAO, possible contraindications for PGE1 use, including uncontrolled systemic hypertension, heart failure, hemorrhagic status, and major visceral diseases, were assessed by blood pressure measurements, electrocardiography recordings, and blood biochemistry testing. After the exclusion of contraindications, the subjects received an intravenous drip injection of 40 μg PGE1 (Prostandin; Ono Pharmaceutical, Osaka, Japan), which is a conjugated agent with cyclodextrin to improve its stability and hydrophilicity, dissolved in 250 mL of physiologic saline solution at an injection speed of 100 to 125 mL per hour twice daily (80 μg PGE1 per day) for 5 days; after that, they received 10 μg of oral PGE1 (Opalmon; Ono Pharmaceutical) three times daily (30 μg PGE1 per day) for at least 1 month. Based on this protocol, other therapies, such as IOP-lowering, vasodilating, and thrombolytic drugs, were prohibited. The protocol required ophthalmic checkups that included slit-lamp biomicroscopy, IOP measurement by applanation tonometry, and indirect ophthalmoscopy at least once daily for the first 5 days of PGE1 therapy and then once every 1 to 4 weeks during the period of oral PGE1 administration.

Evaluation of Clinical Efficacy of PGE1 Therapy

The primary efficacy end point was the change in BCVA between before and 1 month after therapy. For statistical analysis, the BCVA values measured with a Landolt decimal acuity chart were converted into the logarithm of the minimal angle of resolution (logMAR) VA. In the conversion, CF was 0.01 and hand motion (HM) was 0.001, according to the proposal of Holladay.[30] Data were analyzed using StatView

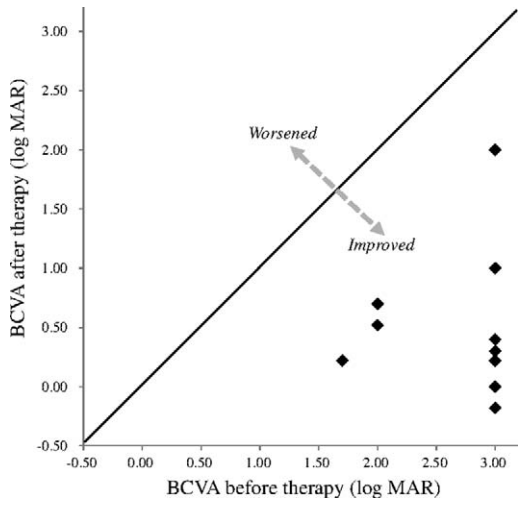

FIGURE 1. BCVA before and 1 month after initiation of PGE1 treatment.

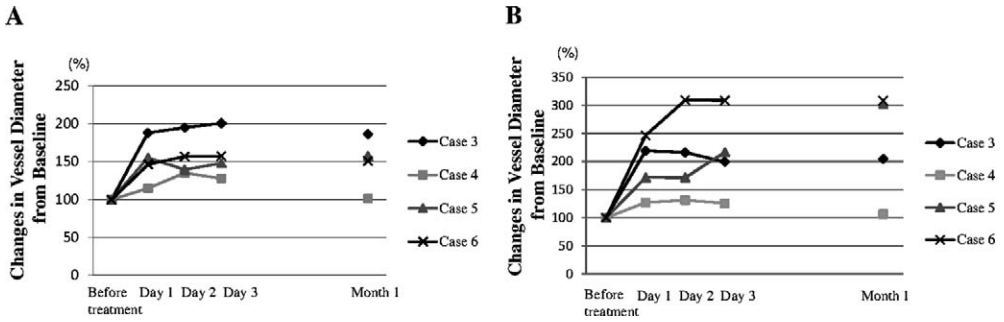

FIGURE 2. Quantification of (**A**) retinal arterial and (**B**) venous diameters during PGE1 treatment. The data are expressed as percent changes in diameter compared with the baseline values.

Version 5.01 statistical software (SAS Institute, Inc., Cary, NC). The difference between the logMAR BCVA before and 1 month after therapy was calculated using the Wilcoxon signed-ranks test. The correlations between the changes in the logMAR BCVA and age or the time to treatment were calculated using Spearman's correlation test; correlations between the changes in the logMAR BCVA and sex were calculated using the Mann-Whitney *U* test. *P* less than 0.05 was considered statistically significant.

Evaluation of Vasodilatory Effects of PGE1

Fundus photographs were continuously taken before and 1, 2, and 3 days and 1 month after the start of PGE1 therapy in cases 3, 4, 5, and 6. In these four cases, we quantified the retinal arterial and venous diameters on the fundus photographs to evaluate the possible vasodilatory effects of PGE1. All fundus photographs were obtained using a fundus camera model 50 IX (Topcon, Tokyo, Japan) with 50° fields and 2144 × 1424 pixel resolution. Measurement of vascular diameter was performed using the image analysis software Image J version 1.41 (available at http://rsb.info.nih.gov/ij/; developed by Wayne Rasband, MD, PhD, National Institutes of Health, Bethesda, MD) on a personal computer. Using the ruler tool, we measured in pixels the narrowest diameter of the first superotemporal branch of central retinal artery in the region between the optic disc and the second branch and the diameter of its parallel branch of central retinal vein side-by-side to the narrowest arterial points. The measurement was repeated three times on each photograph, and the mean of the three measurements was considered the diameter. Based on the data obtained from the measurements that were repeated three times, the coefficients of variation of the measurements ranged from 0.17% to 4.05%. The percent changes in the arterial and venous diameters from baseline (before the start of therapy) were calculated for each subject.

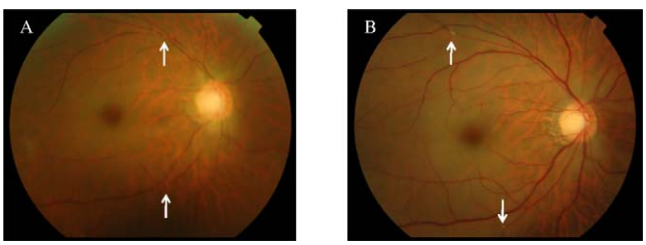

FIGURE 3. Fundus photographs from case 6. (**A**) Narrowing of the retinal arteries in all four quadrants and ischemic retinal edema with a cherry-red spot at the center of the macula are seen before PGE1 therapy. White plaques occlude the branch retinal artery (*arrows*). (**B**) Marked dilation of the retinal arteries and veins is seen in all four quadrants. Along with the arterial dilation, the white plaques have migrated to the periphery (*arrows*).

RESULTS

The subjects' characteristics and BCVA before (baseline) and 1 month after treatment are shown in Table 1 and Figure 1. The subjects included four men (four eyes) and five women (six eyes) (mean age, 61.3 years; range, 48–79 years). All subjects started PGE1 within 24 hours of the onset of visual symptoms (mean time to treatment, 7.1 hours; range, 1–18 hours). One subject (case 1-1) had developed CRAO earlier in the right eye and 18 months later in the left eye (case 1-2). As systemic vascular risk factors, eight patients (88.9%) had systemic hypertension, one patient (11.1%) had diabetes mellitus, and five patients (55.6%) had carotid artery stenosis. Other than CRAO, two eyes had diabetic retinopathy and one eye had glaucoma; no eyes had features of acute hypertensive retinopathy.

The mean ± SD logMAR BCVA was 2.67 ± 0.54 (range, 3.00–1.70) at baseline and significantly ($P = 0.005$) improved to 0.52 ± 0.62 (range, 2.00 to −0.18) 1 month after treatment; all eyes had a marked improvement (≥1.0 logMAR) in VA (Table 1), although one eye (case 7) with a BCVA of HM at baseline had CF vision after therapy. The BCVA improvement was correlated negatively with the time to treatment ($\rho = -0.655$, $P = 0.0492$); no correlation was found between the BCVA and age ($\rho = -0.473$, $P = 0.156$). The improvement in BCVA did not differ between men and women ($P = 0.0871$).

In cases 3, 4, 5, and 6, we quantified the retinal vessel diameters on the serial fundus photographs obtained during therapy. Compared with baseline, the vessel diameters increased in all four cases at 1 day after the start of therapy; the mean diameters in four cases were 151.1% (range, 115.1%–188.0%) in the arteries and 191.0% (range, 127.2%–246.4%) in the veins (Fig. 2). In cases 3, 5, and 6, the vasodilatory effect of PGE1 was sustained at 1 month after the start of therapy, whereas in case 4 it returned to the baseline value in the arteries and veins. Representative fundus photographs obtained from case 6 are shown in Figure 3. In this case, the dilated retinal arteries and veins were clearly observed on 1 day after the start of therapy. Some patients complained of angialgia during the intravenous injection of PGE1; no serious complications such as local and systemic bleeding or hypotensive shock were reported in any case during therapy.

Table 2. Results of Previous Trials in Central Retinal Artery Occlusion

Author, y	Study Design	Therapy	No. of Patients	Time to Treatment	VA Before Treatment	VA After Treatment	Predictors of Favorable Visual Outcome
Minton et al., 1937[17]	Retrospective case series	No comment	43	NA	CF or worse (98%)	Same or worse (94%)	NA
Lorentzen, 1969[5]	Retrospective case series	No comment	12	NA	CF or worse (92%)	Same or worse (100%)	NA
Karjalainen, 1971[18]	Retrospective case series	No comment	91	NA	NA	58% blind, 21% good or reduced VA	NA
Augsburger and Magargal, 1980[16]	Retrospective case series	Paracentasis, ocular massage, a 95% oxygen/5% carbon dioxide mixture, and oral acetazolamide	34	2.5 h–2 wk	CF or worse (97%)	Improvement more than 3 lines in 35% (12/34)	Time to treatment within 48 h
Duker et al., 1991[15]	Retrospective case series	Paracentasis, ocular massage, a 95% oxygen/5% carbon dioxide mixture, topical beta-blocker eye drop, and oral acetazolamide	33	NA	CF or worse (91%)	Improvement more than 3 lines in 9%, same or worse (91%)	NA
Schmidt et al., 1992[6]	Retrospective case-control study	Intra-arterial rtPA or urokinase vs. paracentasis, ocular massage, and pentoxifylline	14 vs. 41	4–60 h vs. within 12 h in 41% (17/41)	NA	Marked improvement in 28.6% (4/14) vs. VA improved from 20/700 to 20/50 in 1 patient, almost no change in the remaining patients	Time to treatment within 4 hours no continuous closure of macular arterioles
Atebara et al., 1994[7]	Retrospective case-control study	Paracentasis and a 95% oxygen/5% carbon dioxide mixture vs. no treatment	40 vs. 49	15 h vs. 7 d	CF or worse (85%) vs. CF or worse (90%)	Same or worse (90%) vs. same or worse (92.2%)	Presence of cilioretinal arteriolar sparing
Weber et al., 1998[14]	Retrospective case-control study	Intra-arterial urokinase vs. paracentasis and oral acetazolamide	17 vs. 15	4.2 h vs. 6 h	CF or worse (100%) vs. CF or worse (93%)	Slight or no improvement in 70% vs. slight or no improvement in 94%	No correlation between time to treatment
Schmidt et al., 2002[13]	Retrospective case-control study	Intra-arterial rtPA or urokinase vs. paracentasis, ocular massage, pentoxifylline, hemodilution, oral acetazolamide, heparin, and aspirin	62 vs. 116	9 h vs. 9 h	NA	Partial or no improvement in 83.9% vs. partial or no improvement in 94%	No correlation between time to treatment
Incandela et al., 2002[12]	Prospective case-control study	Pentoxifylline vs. placebo	5 vs. 5	NA	NA	Central retinal blood flow increase was 550% at 4 wk after treatment vs. central retinal blood flow increase was 288% at 4 wk after treatment	NA
Werner et al., 2004[11]	Prospective case-control study	Hemodilution and EECP vs. hemodilution	10 vs. 10	Within 120 h in all patients	CF or worse (80%) vs. CF or worse (80%)	Partial or no improvement in 90% vs. partial or no improvement in 90% significant increase in retinal blood flow was observed in EECP group at 3 h after treatment and no significant difference in both groups at 48 h later	NA

Investigative Ophthalmology & Visual Science

TABLE 2. Continued

Author, y	Study Design	Therapy	No. of Patients	Time to Treatment	VA Before Treatment	VA After Treatment	Predictors of Favorable Visual Outcome
Arnold et al., 2005[10]	Retrospective case-control study	Intra-arterial urokinase vs. paracentasis, oral acetazolamide, heparin, and aspirin	37 vs. 19	4 h vs. 4 h	0.006 vs. 0.008	Regained VA of >0.6 in 22% (8/37) vs. regained VA of >0.6 in 0% (0/19)	Young age time to treatment within 4 h
Schumacher et al., 2010[9]	Prospective case-control study	Intra-arterial rtPA vs. topical beta-blocker eye drop and intravenous acetazolamide	42 vs. 40	12.8 h vs. 11.0 h	2.18 (logMAR) vs. 2.11 (logMAR)	1.74 (logMAR), clinically significant visual improvement (>0.3 logMAR) in 57.1% (24/42) vs. 1.67 (logMAR), clinically significant visual improvement (>0.3 logMAR) in 60% (24/40)	Time to treatment within 12 h
Chen et al., 2011[8]	Prospective case-control study	Intravenous rtPA vs. placebo (intravenous saline)	8 vs. 8	14.4 h vs. 7.3 h	1.85 (logMAR) vs. 2.20 (logMAR)	Clinically significant visual improvement (>0.3 logMAR) in 25% (2/8) vs. clinically significant visual improvement (>0.3 logMAR) in 0% (0/8)	Time to treatment within 6 h

EECP, enhanced external counterpulsation.

DISCUSSION

We reported a series of 10 episodes of acute CRAOs in nine patients treated with systemic PGE1 monotherapy; clinically significant visual improvements (≥1.0 logMAR) occurred in all eyes, whereas one eye had a final VA of CF. The current study was the first to report a high rate of VA improvement resulting from administration of systemic PGE1 monotherapy to treat acute CRAO.

The EAGLE reported limited therapeutic efficacy of intra-arterial thrombolysis with rtPA administered via a catheter inserted into the ophthalmic artery to treat acute CRAO.[9] Previous investigators have reported that 74% of retinal emboli are composed of cholesterol, 10.5% of calcific material, and 15.5% of platelet-fibrin,[31] although fibrinolytic agents cannot dissolve cholesterol or calcified material but only platelet-fibrin thrombus. Substantial numbers of patients with acute RAO have hemodynamically relevant carotid artery stenosis,[32] and in the current study at least five (55.6%) of nine patients had carotid artery stenosis. Qualitative analysis of carotid artery stenotic plaques with light microscopy showed that the particles consisted primarily of soft acellular and amorphous material characterized by lipid-rich macrophages and cholesterol clefts.[33] Collectively, cholesterol particles are a major type of retinal emboli, which may explain why rtPA, the most widely advocated therapy of thrombolysis, has limited efficacy against acute CRAO.

PGE1, a potent endogenous vasodilator, is upregulated in its biosynthesis and release during hypoxia and ischemia.[34] It has a short time of onset of activity, and is rapidly eliminated from the local tissue and systemic circulation. The plasma concentration of endogenous PGE1 at steady state is approximately 0.25 ng/mL.[35] Analysis of fundus photographs showed that PGE1 substantially dilated the retinal vessels. Typically 10 to 20 minutes after the start of PGE1 administration, some patients reported brightening of their vision. Thus, rapid restoration of retinal blood flow due to prompt dilation of the retinal vessels is thought to occur with therapy. Theoretically, vasodilatory therapy using PGE1 is effective for all types of emboli and thus is more advantageous for treating CRAO than fibrin-selective thrombolysis therapy. The administered PGE1 dose may be an important factor after rapid inactivation of PGE1 in the lung[36] in achieving an effective vasodilation. Previous reports successfully treated one case of acute branch RAO with a daily dose of 140 μg of PGE1 for 2 days,[37] and two cases of arteritic anterior ischemic optic neuropathy with a daily dose of 80 μg of PGE1 for 2 days.[38] The current study suggested that, in cases with acute CRAO, a daily dose of 80 μg of PGE1 may be sufficient to dilate the retinal vessels, but this may depend on other factors, such as body weight. Regarding the side effects with venous injection of PGE1, based on the information provided by the postmarket product surveillance in Japan (the information found on the manufacturer's home page: http://www.ono.co.jp/eng/index.html), frequencies of angialgia, vomiting, and skin trouble are at 0.5% to 5.0% incidence, of systemic hypotension is rare at less than 0.5% incidence, and local or systemic bleeding is very rare at less than 0.05% incidence; the incidences of side effects are expected to be five times fewer with oral PGE1 than venous injection. In the current study, angialgia during venous injection was the only side effect observed.

Experimental studies have shown that irreversible necrotic cellular injury of the inner retina occurs as early as 4 hours after the onset of retinal ischemia.[4] Some studies have reported that thrombolysis during the early stage of acute CRAO can improve the clinical outcomes,[10,20] although another study reported no relationship between visual outcomes and the time to treatment.[19] In the current study, visual improvement

and the time to treatment tended to be correlated negatively with each other. Case 7, with the longest time to treatment of 18 hours, had a poor visual outcome of CF, and case 4, with a time to treatment of 17 hours, had less PGE1-mediated vasodilation than the other three cases (Fig. 2). Thus, the time to treatment could be a major contributor to the visual prognosis when using PGE1. In contrast to other therapies, such as catheterization and hyperbaric oxygen, PGE1 does not require special training or equipment, and, therefore, can be started in the emergency room or in a private clinic. Thus, easy access to treatment is a great clinical advantage for treating vision-threatening diseases such as CRAO.

The vasodilatory effect of PGE1 varies according to the anatomic location, can last for nearly 8 weeks, and is dose-dependent in severe intermittent claudication.[28] In the current protocol, to avoid a possible secondary stroke of the peripheral vessels, PGE1 was injected for 5 days and then administered orally for at least 1 month, although we did not determine if oral PGE1 was actually required to maintain the vasodilation after PGE1 was injected. Other than the vasodilatory effect, PGE1 had a cytoprotective activity against oxidative injury caused by retinal ischemia/reperfusion in a rat model through redox regulatory protein (thioredoxin) induction via the cyclic AMP–dependent pathway.[39,40] Thus, continuous use of oral PGE1 may contribute to a favorable prognosis, as seen in the current study by its cytoprotective effect, but that must be clarified in future studies.

In the literature, various drugs, procedures, and their combinations were tested for treating patients with CRAO (Table 2). Most studies included a small number of subjects, were conducted using a retrospective study design, and reported limited effectiveness of the tested treatments. As we also found, some studies found correlations between shorter time to treatment and favorable visual outcomes,[6,8–10,16] whereas others found no significant effects of time to treatment on visual outcomes.[13,14] Restoration of possible blood flow or vasodilation after treatments was examined in several studies. Schmidt et al.[6] found that continuous closure of macular arterioles was correlated with a poor prognosis after intra-arterial thrombolysis. Werner et al.[11] reported that a scanning laser Doppler-measured retinal blood flow, which was larger just after the enhanced external counterpulsation, did not differ between the treatment and the control groups 48 hours later. They discussed that a longer mean time to treatment of 2.5 days was a major reason for the poor prognosis of the treatment. On the other hand, Incandela et al.[2] reported a continuous 550% increase (from baseline) of retinal blood flow at 4 weeks after pentoxifylline treatment; however, the retinal blood flow immediately after the treatment and the visual outcome information were absent in the report. As few previous studies have shown, the current study supports the evidence that rapid, substantial, and continuous restoration of retinal blood flow by the therapeutic intervention likely contributes to the favorable visual outcome in acute CRAO. Because of the retrospective nature of the current study, the small number of cases, and the absence of a case-control design, the data require careful interpretation. A randomized, prospective trial can determine the true effectiveness of systemic PGE1 monotherapy; our experience provides motivation for conducting such a trial because PGE1 therapy reported in this study likely has an effect of VA improvement more favorable than previous studies.

In conclusion, use of systemic PGE1 to treat acute CRAO rapidly restores retinal blood flow by its vasodilatory effects, improves VA, is well tolerated with few side effects, and requires no special training.

Acknowledgments

Disclosure: **Y. Takai**, None; **M. Tanito**, None; **Y. Matsuoka**, None; **K. Hara**, None; **A. Ohira**, None

References

1. Rumelt S, Dorenboim Y, Rehany U. Aggressive systematic treatment for central retinal artery occlusion. *Am J Ophthalmol*. 1999;128:733–738.
2. Chen CS, Lee AW. Management of acute central retinal artery occlusion. *Nat Clin Pract Neurol*. 2008;4:376–383.
3. Schmidt D, Schumacher M, Feltgen N. Circadian incidence of non-inflammatory retinal artery occlusions. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:491–494.
4. Hayreh SS, Zimmerman MB, Kimura A, Sanon A. Central retinal artery occlusion. Retinal survival time. *Exp Eye Res*. 2004;78:723–736.
5. Lorentzen SE. Occlusion of the central retinal artery. A follow-up. *Acta Ophthalmol (Copenh)*. 1969;47:690–703.
6. Schmidt D, Schumacher M, Wakhloo AK. Microcatheter urokinase infusion in central retinal artery occlusion. *Am J Ophthalmol*. 1992;113:429–434.
7. Atebara NH, Brown GC, Cater J. Efficacy of anterior chamber paracentesis and Carbogen in treating acute nonarteritic central retinal artery occlusion. *Ophthalmology*. 1995;102:2029–2034; discussion 2034–2035.
8. Chen CS, Lee AW, Campbell B, et al. Efficacy of intravenous tissue-type plasminogen activator in central retinal artery occlusion: report from a randomized, controlled trial. *Stroke*. 2011;42:2229–2234.
9. Schumacher M, Schmidt D, Jurklies B, et al. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. *Ophthalmology*. 2010;117:1367–1375. e1.
10. Arnold M, Koerner U, Remonda L, et al. Comparison of intra-arterial thrombolysis with conventional treatment in patients with acute central retinal artery occlusion. *J Neurol Neurosurg Psychiatry*. 2005;76:196–199.
11. Werner D, Michalk F, Harazny J, Hugo C, Daniel WG, Michelson G. Accelerated reperfusion of poorly perfused retinal areas in central retinal artery occlusion and branch retinal artery occlusion after a short treatment with enhanced external counterpulsation. *Retina*. 2004;24:541–547.
12. Incandela L, Cesarone MR, Belcaro G, et al. Treatment of vascular retinal disease with pentoxifylline: a controlled, randomized trial. *Angiology*. 2002;53:S31–S34.
13. Schmidt DP, Schulte-Monting J, Schumacher M. Prognosis of central retinal artery occlusion: local intraarterial fibrinolysis versus conservative treatment. *AJNR Am J Neuroradiol*. 2002;23:1301–1307.
14. Weber J, Remonda L, Mattle HP, et al. Selective intra-arterial fibrinolysis of acute central retinal artery occlusion. *Stroke*. 1998;29:2076–2079.
15. Duker JS, Sivalingam A, Brown GC, Reber R. A prospective study of acute central retinal artery obstruction. The incidence of secondary ocular neovascularization. *Arch Ophthalmol*. 1991;109:339–342.
16. Augsburger JJ, Magargal LE. Visual prognosis following treatment of acute central retinal artery obstruction. *Br J Ophthalmol*. 1980;64:913–917.
17. Minton J. A clinical study of fifty-four cases of occlusion of the central artery of the retina and its branches: section of ophthalmology. *Proc R Soc Med*. 1937;30:285–300.
18. Karjalainen K. Occlusion of the central retinal artery and retinal branch arterioles. A clinical, tonographic and fluorescein angiographic study of 175 patients. *Acta Ophthalmol Suppl*. 1971;109:1–95.

19. Richard G, Lerche RC, Knospe V, Zeumer H. Treatment of retinal arterial occlusion with local fibrinolysis using recombinant tissue plasminogen activator. *Ophthalmology*. 1999; 106:768–773.
20. Hattenbach LO, Kuhli-Hattenbach C, Scharrer I, Baatz H. Intravenous thrombolysis with low-dose recombinant tissue plasminogen activator in central retinal artery occlusion. *Am J Ophthalmol*. 2008;146:700–706.
21. Agnelli G, Buchanan MR, Fernandez F, et al. A comparison of the thrombolytic and hemorrhagic effects of tissue-type plasminogen activator and streptokinase in rabbits. *Circulation*. 1985;72:178–182.
22. Sobel BE, Gross RW, Robison AK. Thrombolysis, clot selectivity, and kinetics. *Circulation*. 1984;70:160–164.
23. Hoylaerts M, Rijken DC, Lijnen HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem*. 1982;257:2912–2919.
24. Sloan MA, Gore JM. Ischemic stroke and intracranial hemorrhage following thrombolytic therapy for acute myocardial infarction: a risk-benefit analysis. *Am J Cardiol*. 1992;69:21A–38A.
25. Ruiz Rubio JL, Hernandez M, Rivera de los Arcos L, Martinez AC, Garcia-Sacristan A, Prieto D. Mechanisms of prostaglandin E1-induced relaxation in penile resistance arteries. *J Urol*. 2004;171:968–973.
26. Fox SC, Behan MW, Heptinstall S. Inhibition of ADP-induced intracellular Ca2+ responses and platelet aggregation by the P2Y12 receptor antagonists AR-C69931MX and clopidogrel is enhanced by prostaglandin E1. *Cell Calcium*. 2004;35:39–46.
27. Schror K, Weber AA. Roles of vasodilatory prostaglandins in mitogenesis of vascular smooth muscle cells. *Agents Actions Suppl*. 1997;48:63–91.
28. Belcaro G, Laurora G, Nicolaides AN, et al. Treatment of severe intermittent claudication with PGE1—a short-term vs a long-term infusion plan—a 20 week, European randomized trial—analysis of efficacy and costs. *Angiology*. 1998;49:885–894; discussion 895.
29. Steigerwalt RD Jr, Belcaro GV, Christopoulos V, Incandela L, Cesarone MR, De Sanctis MT. Ocular and orbital blood flow velocity in patients with peripheral vascular disease and diabetes treated with intravenous prostaglandin E1. *J Ocul Pharmacol Ther*. 2001;17:529–535.
30. Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg*. 1997;13:388–391.
31. Arruga J, Sanders MD. Ophthalmologic findings in 70 patients with evidence of retinal embolism. *Ophthalmology*. 1982;89: 1336–1347.
32. Sharma S. The systemic evaluation of acute retinal artery occlusion. *Curr Opin Ophthalmol*. 1998;9:1–5.
33. Angelini A, Reimers B, Della Barbera M, et al. Cerebral protection during carotid artery stenting: collection and histopathologic analysis of embolized debris. *Stroke*. 2002; 33:456–461.
34. Block AJ, Feinberg H, Herbaczynska-Cedro K, Vane JR. Anoxia-induced release of prostaglandins in rabbit isolated hearts. *Circ Res*. 1975;36:34–35.
35. Zusman RM, Spector D, Caldwell BV, Speroff L, Schneider G, Mulbow PJ. The effect of chronic sodium loading and sodium restriction on plasma prostaglandin A, E, and F concentrations in normal humans. *J Clin Invest*. 1973;52:1093–1098.
36. Ferreira SH, Vane JR. Prostaglandins: their disappearance from and release into the circulation. *Nature*. 1967;216:868–873.
37. Steigerwalt RD Jr, Pescosolido N, Corsi M, Cesarone MR, Belcaro GV. Acute branch retinal arterial embolism successfully treated with intravenous prostaglandin E1—case reports. *Angiology*. 2003;54:491–493.
38. Steigerwalt RD Jr, Cesarone MR, Belcaro G, et al. Arteritic anterior ischemic optic neuropathy treated with intravenous prostaglandin E(1) and steroids. *Int J Angiol*. 2010;19:e113–e115.
39. Yamamoto M, Ohira A, Honda O, et al. Analysis of localization of adult T-cell leukemia-derived factor in the transient ischemic rat retina after treatment with OP-1206 alpha-CD, a prostaglandin E1 analogue. *J Histochem Cytochem*. 1997;45:63–70.
40. Yamamoto M, Sato N, Tajima H, et al. Induction of human thioredoxin in cultured human retinal pigment epithelial cells through cyclic AMP-dependent pathway; involvement in the cytoprotective activity of prostaglandin E1. *Exp Eye Res*. 1997; 65:645–652.

Investigative Ophthalmology & Visual Science