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Improving blood flow in occluded veins to reduce anti-vascular endothelial growth factor injections for branch retinal vein occlusion

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ABSTRACT

Purpose: To assess the relationship between improving blood flow via arteriovenous (AV) sheathotomy without vitrectomy and the total number of anti-vascular endothelial growth factor injections (VEGF) required to treat branch retinal vein occlusion (BRVO).

Methods: In this prospective, clinical case series, 16 eyes of 16 patients at the Toho University Sakura Medical Center with best-corrected visual acuity (BCVA) of 20/40 or worse due to macular edema associated with BRVO were analyzed for 12 months. AV sheathotomy was performed without vitrectomy for all cases. On the second day after surgery, anti-VEGF was injected into the operated eye. During the 12-month follow-up after surgery, *pro re nata* injections were administered when changes in foveal exudation and BCVA were evident. The blood flow of the occluded vein was assessed before and after AV sheathotomy during the operation using laser speckle flowgraphy. The total number of anti-VEGF injections, central retinal thickness (CRT), and BCVA 12 months after surgery were examined.

Results: The changes in CRT and BCVA from baseline to month 12 were statistically significant ($P < 0.01$). No additional anti-VEGF injections were required for nine of 16 eyes (56.3%) during the 12 months. The total number of anti-VEGF injections for 12 months correlated with the change rate of blood flow in an occluded vein before and after AV sheathotomy ($r = -2.816$, $P = 0.022$).

Conclusions and Importance: Improved blood flow in occluded vein may reduce the need for anti-VEGF injections in BRVO.

1. Introduction

Macular edema (ME) may naturally develop secondary to some cases of branch retinal vein occlusion (BRVO); however, a severe visual disorder may follow in chronic cases. Recent studies have shown that the administration of intravitreal triamcinolone acetonide (TA) and anti-vascular endothelial growth factor (VEGF) injections are moderately effective in treating ME secondary to chronic BRVO. However, the SCORE study showed that the difference between the TA injection and grid photocoagulation was not significant.[1] The BRAVO study reported that the mean improvement in BCVA at 12 months was 16.4 and 18.3 letters in the 0.3 and 0.5 mg ranibizumab groups, respectively; however, this was the result of monthly intravitreal injections for the initial 6 months.[2–4] The mean number of anti-VEGF injections was similar or smaller for the groups that received one initial injection followed by *pro re nata* (PRN) injections (1+PRN) than those that received three monthly injections initially and PRN injections over 12 months.[5,6] Reducing the number of anti-VEGF injections required for the treatment of BRVO is a current clinical goal.

BRVO essentially occurs at an arteriovenous (AV) crossing. Dissection of a common adventitial sheath at the AV obstruction site was first reported by Osterloh in 1988.[7] The rationale for this procedure, referred to as sheathotomy, was that it reduced or eliminated the pressure on the retinal vein at the AV crossing caused by the BRVO. In previous reports, the endpoint of sheathotomy was the elevation of the arteriole above the underlying vein.[8] However, in some cases, blood flow to the occluded vein could not be restored after sheathotomy. Thus, AV sheathotomy has not necessarily been proven to lead to reduction of ME and improvement in visual acuity, and its efficacy is considered low.[9,10]

In this prospective clinical study, we examined the total number of anti-VEGF injections required over 12 months after AV sheathotomy without vitrectomy and anti-VEGF injections in patients with ME secondary to BRVO.

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2. Materials and methods

2.1. Subjects

In this prospective, interventional case series, we enrolled consecutive patients with ME following BRVO at the Toho University Sakura Medical Center from March 2016 to January 2019. In all eligible patients, the BCVAs and central foveal thicknesses (CFTs) were 20/40 or worse and >300 μm, respectively; central foveal involvement was determined using optical coherence tomography (OCT; Spectralis OCT®, Heidelberg Engineering Inc., Heidelberg, Germany). The included patients with ME secondary to BRVO had their AV crossing and occluded vein beneath the adjacent artery at the AV crossing detected with an ophthalmoscope, fluorescein angiography and OCT angiography (OCTA; PLEX Elite 9000®, Carl Zeiss Meditec Inc., Dublin, CA, USA). Regarding the classification, all eyes had major BRVO. We did not enroll consecutive patients with AV crossing that could not be detected with an ophthalmoscope because it was covered by retinal bleeding or the occluded vein was detected over the adjacent artery. Patients who underwent laser photocoagulation and those with vitreous hemorrhage or formed collateral vessels, glaucoma, atrial fibrillation, hemodialysis, or uncontrolled hypertension were excluded from the study. All patients provided written informed consent to participate in the study. All procedures complied with the guidelines of the Declaration of Helsinki, and the study was approved by the Institutional Review Board of Toho University Sakura Medical Center (#S16111).

2.2. Treatment

All patients underwent AV sheathotomy at the responsible AV crossing site without vitrectomy using a 23-gauge BRVO knife (DORC Co. Ltd., Zuidland, The Netherlands) under topical anesthesia of 0.4% oxybuprocaine hydrochloride eye drop (Benoxil ophthalmic solution®, Santen, Osaka, Japan) and retrobulbar injection of 2% lidocaine hydrochloride (Xylocaine®, 2.5 ml; AstraZeneca, Osaka, Japan) and 0.75% ropivacaine hydrochloride (Anapeine®, 2.5 ml; AstraZeneca). Using a 23-gauge BRVO knife, the incision tearing off the retinal artery from the retinal vein was continued until complete separation of the arteriole from the vein was achieved at the responsible AV crossing site.

Patients were instructed to refrain from eating, smoking, or drinking coffee for 3 h before the surgery. Eye drops containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P®; Santen Pharmaceutical Co., Ltd., Osaka, Japan) were administered 7 times at 30-min intervals before the surgery. For patients older than 50 years, phacoemulsification and intraocular lens implantation were performed concurrently before the AV sheathotomy.

On the second postoperative day, ranibizumab, an anti-VEGF agent, was injected into the operated eyes under topical anesthesia, along with eye drops containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P®; Santen Pharmaceutical Co., Ltd.).

2.3. Re-injection criteria

All patients who underwent AV sheathotomy without vitrectomy in combination with anti-VEGF injections for the treatment of ME following BRVO were available for postoperative follow-up examinations for more than 12 months at Toho University Sakura Medical Center. All patients underwent postoperative complete eye examinations monthly from month 1 through month 12. All eyes received one initial intravitreal ranibizumab (IVR) injection followed by PRN injections. All eyes with a central retinal thickness (CRT) of >300 μm and a BCVA of 20/40 or worse received additional IVR injections at each visit. Notwithstanding intraretinal or subretinal fluid involving the fovea, if the CRT and BCVA conditions were not met, anti-VEGF treatment was withheld.

2.4. Measurement of blood flow

Laser speckle flowgraphy (LSFG), an optical technique recently developed in Japan, differs from fluorescein videoangiography in that it can measure blood flow non-invasively and quantitatively without fluorescence. The LSFG-NAVI™ device (Softcare Ltd., Iizuka, Japan) was approved as a medical apparatus by the Pharmaceuticals and Medical Device Agency in Japan in 2008. The mean blur rate (MBR) is an index of relative blood flow volume used in the LSFG-NAVI™ device. *In vivo*, MBR was significantly correlated with capillary blood flow determined with the hydrogen gas clearance method in rabbit optic nerve heads.[11] The principle and application of this method have been reported previously.[12,13] The commercially available LSFG-NAVI™ device was used to measure blood flow in outpatients while in a seated position; LSFG-NAVI-OPE was the adapted apparatus used to measure blood flow with patients in the supine position during surgery. The LSFG-NAVI-OPE device had a fixed arm to enable measurement in the supine position.[14,15] MBR was calculated automatically using the LSFG Analyzer software (Ver.7.0.26.0, Softcare Co. Ltd.).

The blood flow in the occluded vein was measured before and after AV sheathotomy during the operation using LSFG-NAVI-OPE under a stabilized infusion pressure of approximately 15 mmHg and the Constellation vented gas-forced infusion and intraocular pressure (IOP) control system (Alcon, Fort Worth, TX, USA). As retinal blood flow volume is sensitive to blood pressure and IOP, its measurement is essential when using LSFG.

2.5. Statistical analysis

All data are expressed as means ± standard deviations (SDs). The data were analyzed using SPSS ver. 23 (IBM Corp, Armonk, NY, USA). The differences between the changes in CRT or BCVA (logMAR) during the 12 months after the first injection were analyzed using single-factor analysis of variance (ANOVA), the Kruskal–Wallis test, Steel–Dwass test, or Tukey–Kramer test. The correlation between the total number of anti-VEGF injections during the 12-month follow-up and changes in MBR during surgery was analyzed using simple regression analysis. Statistical significance was considered at $P < 0.05$.

3. Results

The 16 patients included in the study were aged 42–86 years (65.8 ± 10.6 years). The best-estimated interval between the onset of BRVO and surgery was 2–32 weeks (8.3 ± 7.5 weeks). Before surgery, 1 of 16 patients had an intraocular lens implantation, and the other 15 had phakic eyes. The baseline demographic and clinical characteristics are summarized in Table 1.

The mean CRT changes during the follow-up period significantly decreased from 515.4 ± 126.0 μm at baseline to 257.1 ± 59.5 μm at month 12 ($P = 2.25 \times 10^{-7}$, Kruskal–Wallis test; Fig. 1).

The mean BCVA (logMAR) significantly improved from 0.49 ± 0.20 at baseline to 0.07 ± 0.13 at month 12 ($P = 1.37 \times 10^{-7}$, one-way ANOVA; Fig. 2). In 12 (75%) of 16 eyes, the BCVA improved by three lines or more in Snellen units.

Thirteen of 16 eyes (81%) showed improvement in the blood flow of the occluded veins measured before and after AV sheathotomy using LSFG-NAVI-OPE during surgery (Fig. 3). The blood flow in the occluded veins increased by an average 22.3% after AV sheathotomy in all eyes (Table 1). During the surgery, systolic and diastolic blood pressures and IOP were measured at the same time with the LSFG measurement, and there was no significant difference in ocular perfusion pressure before and after AV sheathotomy in any case.

The mean total number of anti-VEGF injections over the 12 months was 1.9 ± 1.3. In the present study, additional injections were required once for three cases, twice for two cases, thrice for one case, and four times for one case. All seven cases required an additional injection

Table 1
Clinical characteristics of the patients.

Case	Age (in years)	Sex	Eye	Interval (w)	Preoperative BCVA	Preoperative CRT (μm)	MBR before AVS (AU)*1	MBR after AVS (AU)*2	Ratio of MBR (%)	Total number of injections	Final BCVA	Final CRT (μm)
1	70–74	M	R	10	20/40	357	5.87	10.2	173.2	1	20/20	247
2	65–69	F	L	6	20/63	624	10.7	11.4	105.9	2	20/25	305
3	55–59	M	R	32	20/50	396	15.6	23.3	150.0	1	20/20	232
4	75–79	M	L	11	20/100	635	8.0	7.6	95.0	2	20/25	403
5	60–64	M	R	8	20/50	455	13.3	15.3	115.3	4	20/32	311
6	70–74	F	R	12	20/63	404	13.3	19.3	144.9	1	20/16	234
7	75–79	M	R	10	20/63	515	27.1	22.3	82.3	5	20/25	328
8	55–59	F	L	4	20/200	798	9.1	14.3	157.5	2	20/25	191
9	65–69	F	R	2	20/40	392	15.6	21.6	138.0	1	20/25	275
10	60–64	F	R	2	20/50	572	11.9	16.1	135.0	1	20/16	273
11	65–69	M	R	2	20/100	369	16.8	20.0	119.0	1	20/20	284
12	40–44	M	L	4	20/40	460	22.9	24.4	106.4	1	20/16	231
13	85–89	M	R	8	20/40	618	18.7	18.3	97.7	3	20/40	199
14	65–69	F	L	15	20/63	454	15.7	16.4	104.5	1	20/40	222
15	55–59	F	R	3	20/100	547	9.8	12.4	126.5	1	20/16	187
16	55–59	F	R	4	20/40	651	14.7	15.6	105.9	3	20/20	191

Age is shown as the age range for anonymization. Interval, estimated interval from the onset; BCVA, best-corrected visual acuity in Snellen units; CRT, central foveal thickness; MBR, mean blur rate; AVS, arteriovenous sheathotomy; ratio of MBR, *2/*1 ratio of MBR; AU, arbitrary units; M, male; F, female; R, right; L, left.

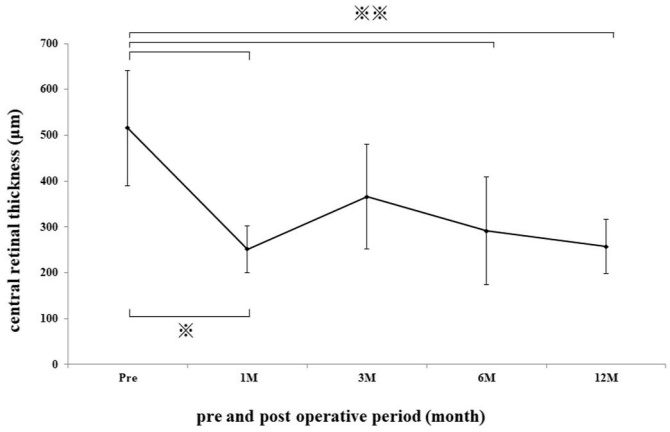

Fig. 1. Mean central retinal thickness (CRT) changes during the follow-up. Significant differences were detected between all pre- and post-treatment values ($P < 0.001$, Kruskal–Wallis test; ※: $P < 0.05$, ※※: $P < 0.01$, Steel–Dwass test).

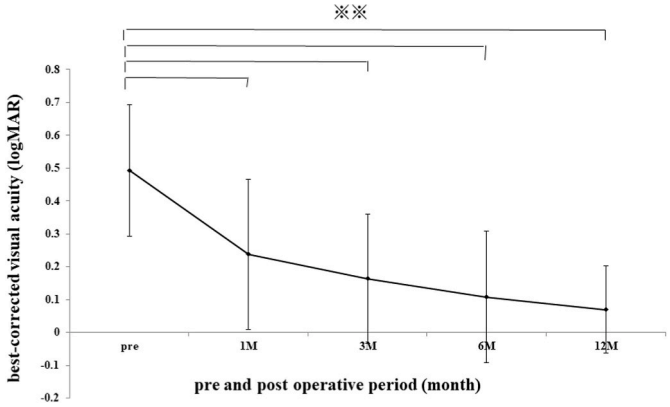

Fig. 2. Mean best-corrected visual acuity changes during the follow-up. Significant differences were detected between all pre- and post-treatment values ($P < 0.001$, one-way analysis of variance; ※※: $P < 0.01$, Tukey–Kramer test).

during the postoperative period: two cases at 2 months, one at 3 months, two at 4 months, three at 5 months, one at 6 months, two at 7 months, two at 10 months, and one at 11 months. The mean preoperative CRT of these seven cases was 614 μm, which was significantly thicker than the 439 μm of the other nine cases that did not require an additional injection ($P = 0.002$). The total number of anti-VEGF injections during the 12-month follow-up did not correlate with the preoperative CRT ($r = 0.003$). There was no statistically significant difference in the preoperative BCVA or best-estimated interval between the onset of BRVO and surgery. However, the total number of anti-VEGF injections during the 12-month follow-up negatively correlated with the change rate of blood flow in the occluded vein before and after AV sheathotomy ($r = -2.816$, $P = 0.022$; Fig. 4).

4. Discussion

Anti-VEGF injections have been the recommended treatment for BRVO globally. However, significantly reducing the total number of required injections remains challenging. The relationship between quantitative improvement of the blood flow in the occluded vein and BRVO-induced ME has not been reported. The current study improved the blood flow in the occluded vein via AV sheathotomy without vitrectomy, which is a novel approach to reducing the number of required anti-VEGF injections.

Miwa et al. reported that the mean total number of IVR injections during 12 months of treatment for ME after BRVO was 3.8 in the 1+PRN group and 4.6 in the 3+PRN group, although the difference between the groups was not statistically significant.[6] In the present study, the mean total number of IVR injections during the 12-month follow-up period was 1.9 ± 1.3, which was less than what has been previously reported for a single-injection group.[5,6] Moreover, 9 (56.3%) of 16 eyes did not require additional IVR in the current study. The focus of this study was AV sheathotomy without vitrectomy in addition to IVR injections for the treatment of ME after BRVO.

BRVO essentially occurs at AV crossings. Conventionally, almost 90% of morphological retinal vessels at the affected AV crossing are artery overcrossing[16]; however, OCT shows the proportion at 50%.[17] The pathogenesis of BRVO has been proposed for the AV crossing; it may be caused by turbulent blood flow and the impairment of vascular endothelium with platelet thrombus formation.[18] The occluded veins can narrow by 21% at the AV crossing as shown using OCT.[19] Furthermore, ME is caused by increased vascular pressure in the occluded vein that may lead to the leakage of fluid to the retinal tissue through the vascular wall, involving the macular area. Chronic or recurrent ME may

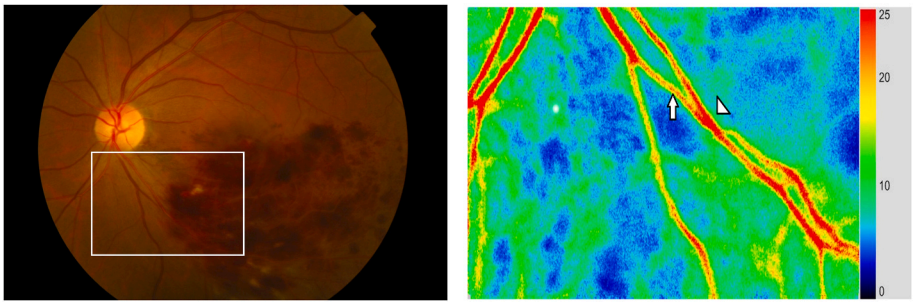

Fig. 3. Fundus image and blood flow map obtained via laser speckle flowgraphy for Case 8 in Table 1. The blood flow map obtained via laser speckle flowgraphy (right) corresponds to the area surrounded by the white square in the fundus image (left). The arrowhead represents the arteriovenous (AV) crossing, and the arrow represents the blood flow of the occluded vein measured before and immediately after AV sheathotomy during surgery (right).

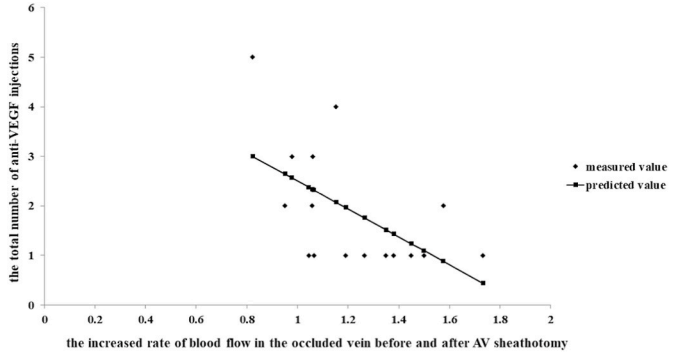

Fig. 4. Correlation between the total number of intravitreal ranibizumab injections over 12 months and the change rate of blood flow during surgery. The total number of injections and blood flow in the occluded vein are significantly negatively correlated.

be caused by VEGF produced by ischemia in the BRVO area after onset or by leakage from microaneurysms.[20,21]

AV sheathotomy for BRVO was devised to reduce the pressure of the vein by the artery at the AV crossing, thereby improving the blood flow of the occluded vein and reducing intravenous pressure. In the current study, we selected untreated patients with ME after BRVO who experienced early visual disturbance after BRVO occurrence at an average of 8.3 weeks after onset. We quantitatively measured changes in blood flow of the occluded vein before and after AV sheathotomy during surgery using LSFG-NAVI-OPE under stabilized infusion pressure. As a result, the blood flow of the occluded vein showed an average increase of 22.3% after sheathotomy. Furthermore, it may be suggested that sheathotomy for ME following BRVO in the early stage after onset can also reduce intravenous pressure, which suppresses chronic ME.

According to previous reports, vitrectomy and removal of the posterior hyaloid with peeling of the internal limiting membrane has appeared to be effective in treating ME following BRVO.[22,23] Regarding the relationship between vitrectomy and anti-VEGF, an experimental study reported that the half-lives of anti-VEGF in the aqueous humor were shorter in vitrectomized than in nonvitrectomized eyes.[24] In contrast, a clinical study provided little evidence that previous vitrectomy has long-term clinical benefits for patients with diabetic ME treated with anti-VEGF.[25] Therefore, in this study, we referred to a previous report on AV-crossing manipulation without vitrectomy for BRVO[26] and devised a method that evaluates the effect of blood flow change by AV sheathotomy on anti-VEGF treatment independent of vitrectomy.

This combination treatment did not reduce the initial effect of anti-VEGF, and ME did not recur for more than half of the cases. According to a previous report, anti-VEGF injection had little effect on retinal microcirculation[27]; therefore, the effects of anti-VEGF in suppressing vascular permeability and of AV sheathotomy in reducing the intravenous pressure of the occluded vein are considered mutually beneficial. Zhu et al. indicates that anti-VEGF treatment has a positive effect on macular ischemia and improves macular perfusion status.[28] Whether AV sheathotomy or anti-VEGF therapy should be administered first remains controversial, but a synergistic effect on retinal blood flow may be expected.

The preoperative CRTs in cases with the additional anti-VEGF treatment were thicker than in those without additional injections. However, the relationship between the total number of IVR injections during the 12-month follow-up and the preoperative CRT was not statistically significant; therefore, the preoperative CRT may not be an indication for this combination treatment.

In the current study, visual acuity improved by three lines or more in Snellen units in 75% of the patients and 50% achieved 20/20 or better. Since cataract surgery was performed in patients over 50 years of age, the improvement of visual acuity did not only depend on the combination treatment described. However, since ME can occur after cataract surgery, it cannot be concluded that cataract surgery was solely responsible for the improved visual acuity. Therefore, cataract surgery does not affect the total number of anti-VEGF injections in 12 months.

The possible complications of this surgical procedure include risk of retinal dialysis by vitreous traction using a 23-gauge BRVO knife without vitrectomy and postoperative endophthalmitis from incarceration of the vitreous at the surgical wound. However, in the current study, a trocar system prevented pulling the vitreous and oral dialysis by a 23-gauge BRVO knife. At an average age of 65.8 years in this study, the vitreous was quite liquefied; thus, there was little risk of its incarceration. Endophthalmitis also did not occur. As there was preoperative confirmation that the occluded vein was detected beneath the adjacent artery at the AV crossing, there was no uncontrollable intraoperative bleeding due to vascular damage associated with the AV sheathotomy.

This study has some limitations. This was a pilot study, and the sample size was relatively small. The treatment considers that intervention, especially in the form of anti-VEGF treatment, is recommended early after the onset of the condition. Since the optimal timing of surgical intervention has not been determined, further studies should be conducted to determine the period after onset for effective treatment. Muraoka and Miwa et al. reported that the veins of affected AV crossings in eyes with venous overcrossing are significantly narrower than those in eyes with arterial overcrossing and that the total nonperfusion areas in eyes with venous overcrossing are also larger than those in eyes with arterial overcrossing.[29,30] In the current study, the occluded vein was detected beneath the adjacent artery (i.e., arterial overcrossing) in all cases. The morphology at the AV crossing may be associated with the total number of injections required over 12 months. Therefore, it will be necessary to conduct a comparative study involving an IVR single-injection group including only cases with arterial overcrossing.

5. Conclusions

Improved blood flow in occluded veins may reduce the need for anti-VEGF injections in BRVO.

Patient consent

The patients consented to publication of the case in writing. Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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