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CLINICAL INVESTIGATION

Outcomes of vitrectomy combined with subretinal tissue plasminogen activator injection for submacular hemorrhage associated with polypoidal choroidal vasculopathy

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Abstract

Purpose To examine the outcomes of vitrectomy with subretinal tissue plasminogen activator (tPA) injection and postoperative intravitreal antivascular endothelial growth factor (VEGF) injection for submacular hemorrhage (SMH) associated with polypoidal choroidal vasculopathy (PCV).

Study design Retrospective, consecutive case series.

Methods Patients who underwent vitrectomy for SMH associated with PCV and who were followed up for at least 12 months were included. Surgery consisted of vitrectomy with subretinal tPA and air tamponade. Postoperative intravitreal anti-VEGF was administered pro re nata. The following were examined: best-corrected visual acuity (BCVA) at baseline, at 1 month, and at the final visit; the percentage of patients requiring anti-VEGF postoperatively; and the number of injections administered.

Results This study included 23 eyes of 23 patients (21 men, 2 women) with a mean age of 72.5 ± 9.0 years. The mean duration from disease onset to surgery was 9.0 ± 6.6 days. The mean maximum SMH size was 5.8 ± 4.8 disc diameters. The mean follow-up period was 33 ± 14 months. The BCVA was significantly improved when compared with baseline 1 month after surgery and at the final visit. Postoperative anti-VEGF was required for 91% of the eyes. In eyes that underwent anti-VEGF therapy until the final visit, the mean injection number was 4.1/year.

Conclusions Vitrectomy with subretinal tPA and air tamponade improved visual acuity in patients with SMH associated with PCV. Postoperative intravitreal anti-VEGF injection maintained the improved BCVA throughout a mean period of 33 months.

Keywords Antivascular endothelial growth factor · Polypoidal choroidal vasculopathy · Submacular hemorrhage · Tissue plasminogen activator

Introduction

Submacular hemorrhage (SMH) is one of the major complications of polypoidal choroidal vasculopathy (PCV) and can cause sudden, severe, and permanent vision loss [1, 2]. Whereas a thin SMH can be absorbed naturally, a thick SMH is rarely absorbed and requires surgical displacement from the macular area [3–7]. The treatment options currently available for SMH fall into 2 broad categories: nonvitrectomizing techniques and vitrectomizing techniques. Nonvitrectomizing techniques include intravitreal injections of gas, tissue plasminogen activator (tPA), antivascular endothelial growth factor (VEGF), or a combination thereof [3, 4, 8–10], whilst vitrectomizing techniques include treatment with tPA or anti-VEGF, gas, or a combination of these administered as subretinal injections, intravitreal injections, or both [5–7, 11–16].

We previously investigated vitrectomizing techniques, that is, a combination of vitrectomy, subretinal injection of tPA, and air tamponade [7, 16], and we reported the effectiveness of these techniques in patients with SMH

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associated with PCV in terms of both the displacement of the SMH and improvement in visual acuity. However, the mean postoperative follow-up period in our previous study was only 9 months; consequently, the visual acuity outcomes, frequency of complications, and number and effect of postoperative anti-VEGF injections were not sufficiently examined. Therefore, in the present study we conducted a longer follow-up of patients who underwent vitrectomy with subretinal tPA injection and air tamponade as well as postoperative intravitreal anti-VEGF injections for SMH associated with PCV to assess whether postoperative intravitreal anti-VEGF injections facilitated the maintenance of improved visual acuity after the displacement of SMH.

Patients and methods

Study design and patients

This study was a retrospective case series. All the investigations adhered to the tenets of the Declaration of Helsinki. Each patient was informed of the risks and benefits of the surgery, and written consent was obtained. The study was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Twenty-three eyes of 23 consecutive patients with SMH associated with PCV who received a diagnosis of SMH associated with PCV between November 2012 and June 2016 were included.

Diagnosis

All the patients underwent comprehensive ophthalmologic examinations before and after surgery, including measurement of best-corrected visual acuity (BCVA) with refraction using the 5-m Landolt C acuity chart as well as indirect and contact lens slit-lamp biomicroscopy. To measure the SMH height, postoperative exudative changes, and continuity of the ellipsoid zone, all the eyes were examined before and after the surgery by either spectral-domain optical coherence tomography (SD-OCT) or swept-source OCT using commercially available instruments (Cirrus, Carl Zeiss Meditec; Spectralis, Heidelberg Engineering; or DRI OCT-1 Atlantis, Topcon Medical Systems). A single optical coherence tomography (OCT) machine was used for all the examinations of each individual patient.

The diagnosis of PCV was based on both the presence of elevated orange-red lesions observed on fundus examination and the presence of characteristic polypoidal vascular lesions detected via indocyanine green angiography, which was performed either preoperatively or postoperatively [17]. The greatest linear dimension was recorded as the size of each SMH [18]. The inclusion criteria were as follows: (1) SMH associated with PCV; (2) presence of SMH with a maximum height from the retinal pigment epithelium greater than 500 μm, as measured via OCT, or associated with a choroid that could not be seen through with color fundus photography; and (3) unorganized SMH, as determined via fundus examination. We considered organized SMHs to be those that were white and/or fibrous in appearance. Patients who exhibited vitreous hemorrhage and SMH associated with other macular diseases, such as retinal macroaneurysm, high myopia, typical age-related macular degeneration (AMD), retinal angiomatous proliferation, and angioid streaks, were excluded. All the patients were followed up every month for the first 6 months and less frequently (approximately once every 1 to 3 months) thereafter. Visual acuity was assessed and OCT was performed at every visit.

Surgical techniques

SMH displacement was conducted using a surgical procedure based on a report by Haupert et al. [5]. Briefly, after a 25-gauge microincision vitrectomy was performed using the Constellation Vision System (Alcon Laboratories), 4000 IU tPA (GRTPA, Mitsubishi Tanabe Pharma Corporation) in 0.1 mL was injected subretinally using a 38-gauge subretinal infusion needle (MedOne, Sarasota) to liquefy the SMH [7, 16]. From 2015, we injected the tPA at a very low pressure (6 psi) using a viscous fluid control system after the local removal of the internal limiting membrane (ILM) [19]. Before finishing the operation, fluid-air exchange was performed to displace the SMH. The patients remained face-down for 3 days after the surgery. In phakic eyes, phacoemulsification and implantation of an intraocular lens were conducted simultaneously.

Postoperative anti-VEGF therapy

Postoperative intravitreal anti-VEGF injections were given pro re nata (PRN) when exudative and/or hemorrhagic changes, such as the accumulation of subretinal fluid or the recurrence of retinal hemorrhage, occurred [7, 16]. We used either 0.5 mg ranibizumab (Lucentis, Genentech) or 2.0 mg aflibercept (Eylea, Bayer).

Outcome measures

The main outcome measures were the differences between the preoperative and postoperative BCVA values as well as the number of times anti-VEGF injections were required after surgery.

Data analysis

The BCVA values were recorded as decimal values and converted to logMAR units for the statistical analysis. All visual acuity results are presented as logMAR units. Preoperative and postoperative BCVA values were compared using the Wilcoxon signed rank test. Probability values <0.05 were considered significant. All statistical analyses were performed using SPSS for Mac, version 22.0 (SPSS). Data are presented as means ± standard deviations (SDs).

Results

This study included 23 eyes of 23 patients (21 men, 2 women) with a mean age of 72.5 ± 9.0 years who were followed up postoperatively for a mean period of 33 ± 14 months (range, 12–51 months). Intravitreal anti-VEGF injections and photodynamic therapy (PDT) were performed before SMH onset in 5 eyes: intravitreal anti-VEGF injections only in 3 eyes (13%) and intravitreal anti-VEGF injections + PDT in 2 eyes (9%). The remaining 18 eyes were treatment-naive. The mean duration from SMH onset to surgery was 9.0 ± 6.6 days. The mean SMH diameter was 5.8 ± 4.8 disc diameters. The mean SMH height was 829 ± 310 µm. Ten patients (43%) had a history of hypertension, 2 patients (9%) were using anti-platelet drugs, and no patients were using warfarin (Table 1). Before the surgery, 18 eyes (78%) were phakic, whilst 5 eyes (22%) were pseudophakic. After the surgery, all 23 eyes were pseudophakic.

In all the cases, the SMH was almost completely displaced beyond the arcades at 1 week postoperatively. SMH recurred in 4 eyes (17%). In 2 of these eyes (9%), displacement of the SMH was performed again, and the hemorrhages were subsequently observed to be displaced beyond the arcades. Recurrence of the SMH in these eyes occurred at 46 months and 38 months after the surgery, and the SMH was displaced 18 days and 3 days later, respectively. For the remaining 2 eyes (9%), further surgery was not performed because the patients declined it. An epiretinal membrane was observed as a postoperative complication in 1 eye (4%) 11 months after the surgery, and this was surgically removed soon after. Complications such as retinal detachment, vitreous hemorrhage, tPA-induced rebleeding (intraoperative or early postoperative), and tPA-induced retinal pigment epithelium atrophy were not observed.

The mean baseline BCVA (logMAR) was 0.98 ± 0.53. The BCVA was significantly improved from baseline both at 1 month postoperatively and at the final visit (0.39 ± 0.26, $P < 0.001$ and 0.59 ± 0.58, $P < 0.01$, respectively; Fig. 1). At the final visit, ellipsoid zone continuity was observed in 3 eyes (13%). These eyes demonstrated a tendency towards favorable visual acuity when compared with the 20 eyes (87%) with an ellipsoid zone defect (unpaired *t* test, $P = 0.08$; Table 1).

Following surgery, 21 eyes (91%) demonstrated PCV activity and thus required intravitreal anti-VEGF injections, whereas 2 eyes (9%) did not require anti-VEGF therapy. In 3 of the 21 eyes (13%) that required intravitreal anti-VEGF injections, injections were not administered because the patients did not desire further treatment. In the 18 eyes that underwent anti-VEGF therapy, the mean number of anti-VEGF injections was 4.1 ± 2.1 per year. Figure 2 shows the imaging data from a representative patient.

Discussion

In the present study, vitrectomy with subretinal tPA injection and air tamponade improved the visual acuity of SMH associated with PCV, and postoperative intravitreal anti-VEGF injections facilitated the maintenance of favorable visual acuity over a mean follow-up period of 33 months (Fig. 1). In the long-term postoperative course, the greatest problem was recurrence of postoperative exudative changes, including SMH. In the present study, 78% of cases (18 eyes) were treatment-naïve, and the initial symptom of PCV for these eyes was visual disturbance associated with SMH. In this type of PCV, baseline disease activity is considered to be higher than it is in typical cases of PCV [1, 2]. In addition, it has been reported that once bleeding occurs in PCV, rebleeding is more likely to occur within a short period [20]. Indeed, 21 of the eyes (91%) in the present study exhibited postoperative exudative changes, and 4 of these exhibited recurrence of SMH. In these 21 cases, anti-VEGF drugs were administered with a PRN regimen, and improved visual acuity after the displacement of the SMH was maintained for at least 1 year. To the best of our knowledge, no reports have been published on the current operative procedure for SMH associated with PCV other than a short-term study performed at our own institution [7]. Therefore, comparisons can be made only with reports on the current operative procedure for SMH associated with other conditions. For example, Treumer et al. [21] reported a protocol involving 2 postoperative intravitreal anti-VEGF (bevacizumab or ranibizumab) injections applied monthly followed by intravitreal anti-VEGF injections applied PRN thereafter. With a mean of 4.2 PRN injections per year, improved visual acuity was maintained for 20 months in the AMD patients of that study. Similarly, Gonzalez-Lopez et al. [22] reported a protocol involving 2 postoperative intravitreal injections of ranibizumab applied monthly followed by injections applied PRN thereafter. They reported a mean of 3.1 injections per year resulting in improved visual acuity maintained for 12.9 months in AMD patients. The results of the present study reflect therapeutic effects that are similar to

Table 1 Preoperative and postoperative patient characteristics

No.	Age	Gender	Eye	Follow up (month)	Preoperative lens status	Treatment before surgery (number)	Days before surgery	SMH		Recurrence of SMH	Number of anti-VEGF therapy after surgery	Pre BCVA (logMAR)	1M BCVA (logMAR)	Final visit	
								Diameter (DD)	Height (μm)					BCVA (logMAR)	Defect of ellipsoid zone
1	88	M	L	45	Pseudphakic	–	10	20	843	−	5	1.40	0.30	1.52	+
2	62	M	R	51	Phakic	–	2	6	1227	−	25	0.52	0.52	0.00	+
3	78	M	R	47	Pseudphakic	–	7	8	658	+	1	1.30	0.22	1.40	+
4	70	F	R	20	Phakic	–	12	3.5	795	−	2	0.70	1.00	0.40	+
5	71	M	L	43	Phakic	IVA 1	2	7	432	−	2	0.40	0.15	−0.08	+
6	77	M	L	51	Phakic	–	21	5	510	+	Dropped out	2.00	0.15	2.00	+
7	80	M	L	49	Pseudphakic	–	12	6	732	−	17	1.52	0.52	0.82	+
8	84	F	R	46	Phakic	–	10	1.5	1089	−	15	1.00	0.30	0.10	+
9	70	M	R	46	Phakic	–	8	20	1422	−	22	0.70	0.52	0.05	+
10	66	M	R	13	Phakic	IVR 1	10	3	1002	−	0	0.52	0.15	−0.08	−
11	72	M	R	41	Phakic	–	14	1.5	184	−	19	0.82	0.70	0.40	+
12	61	M	R	43	Phakic	–	5	3	1028	+	17	0.30	0.22	0.70	+
13	79	M	R	38	Phakic	–	7	3.5	563	+	18	1.52	0.70	0.52	+
14	74	M	L	18	Phakic	–	4	5.5	1219	−	Dropped out	1.15	0.15	0.82	+
15	82	M	R	32	Phakic	–	0	4	638	−	Dropped out	0.70	0.30	1.22	+
16	70	M	L	34	Phakic	PDT 2, IVA 3	7	3	556	−	10	0.52	0.05	0.00	+
17	91	M	L	27	Phakic	–	12	6	943	−	0	0.82	0.70	1.15	+
18	72	M	L	16	Phakic	–	6	7	1054	−	13	2.00	0.22	0.22	+
19	67	M	L	37	Phakic	–	9	2	361	−	10	0.52	0.00	−0.08	−
20	62	M	L	17	Phakic	–	30	4.5	1014	−	1	0.82	0.70	1.00	+
21	69	M	R	24	Phakic	PDT 1, IVR 6, IVA 1	6	4.5	1147	−	16	0.82	0.40	0.52	+
22	68	M	L	12	Pseudphakic	IVA 3	12	5.5	828	−	6	0.52	0.52	0.15	−
23	54	M	L	13	Phakic	–	1	3.5	813	−	4	2.00	0.52	0.70	+

SMH submacular hemorrhage, *DD* disc diameter, *IVA* intravitreal injection of aflibercept, *IVR* intravitreal injection of ranibizumab, *PDT* photodynamic therapy, *PCV* polypoidal choroidal vasculopathy, *VEGF* vascular endothelial growth factor, *BCVA* best-corrected visual acuity, *logMAR* logarithm of minimal angle of resolution

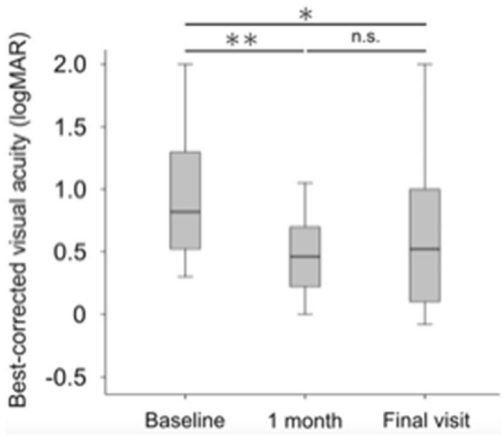

Fig. 1 Changes in best-corrected visual acuity (BCVA) after surgery for submacular hemorrhage associated with polypoidal choroidal vasculopathy. Postoperative BCVA values at both 1 month and the final visit were significantly improved from the baseline BCVA values. Error bars represent standard deviations. logMAR, logarithm of the minimum angle of resolution.*$P<0.01$; **$P<0.001$; n.s., not significant

those of these 2 previous reports. Currently used anti-VEGF drug regimens include PRN as well as fixed interval dosing and treat-and-extend protocols [23–25]. Because the postoperative treatment period is long, it is important to closely examine which regimen best reduces the treatment burden on patients. Anti-VEGF monotherapy has been shown to be effective for treating AMD, whilst PDT in combination with anti-VEGF therapy has been shown to be effective for treating PCV [23, 26–28]. The EVEREST II study reported that compared with ranibizumab monotherapy, combination of ranibizumab and PDT yielded similar improvements in visual acuity and fewer intravitreal injections of ranibizumab [29]. In contrast, the PLANET study reported that more than 85% of participants who were treated with intravitreal aflibercept injection monotherapy achieved improvement in visual and/or functional outcomes without PDT [24]. Further study is necessary on the effectiveness of anti-VEGF monotherapy, PDT monotherapy, and the combined application of these treatments to improve the postoperative course of the current operative procedure [23, 26–28].

With regard to performing vitrectomy in active PCV, the effect of vitrectomy on the therapeutic effect of postoperative anti-VEGF drug injection remains unknown. Previous studies have reported that vitrectomized eyes require more frequent injections of anti-VEGF drugs owing to increased clearance and a shorter half-life [30–32]. However, Ahn et al. [33, 34] reported no significant differences in anti-VEGF drug clearance in vitrectomized versus nonvitrectomized rabbit eyes. Furthermore, although their study involved diabetic macular edema rather than PCV, Bressler

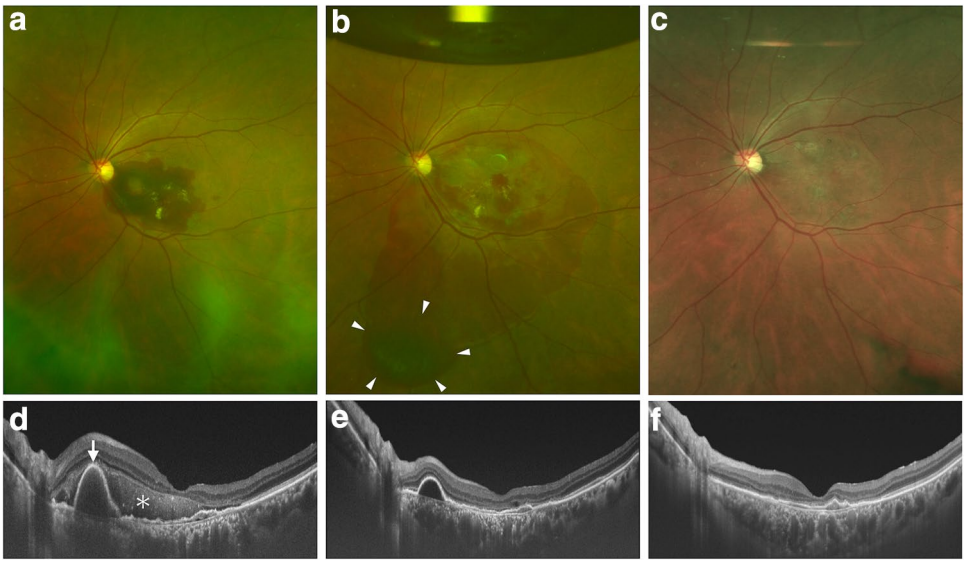

Fig. 2 Results of submacular hemorrhage displacement in a 70-year-old man with submacular hemorrhage associated with polypoidal choroidal vasculopathy. **a** Fundus photograph at the initial visit showing submacular hemorrhage 3 disc diameters in size. **b** Fundus photograph 5 days after the surgery showing that most of the submacular hemorrhage had moved to the inferior periphery (arrowheads). **c** Fundus photograph at 34 months after the surgery showing complete disappearance of the submacular hemorrhage. **d** Spectral-domain optical coherence tomography (SD OCT) at the initial visit showing dense submacular hemorrhage (556 μm in height, asterisk) and pigment epithelium detachment (PED, arrow). **e**. SD OCT image 5 days after the surgery showing disappearance of the submacular hemorrhage. **f** SD OCT image 34 months after the surgery showing complete disappearance of the submacular hemorrhage and PED. Best-corrected visual acuity (logMAR resolution) improved from 0.52 before the surgery to 0.05 at 1 month after the surgery and to 0.00 at the final visit 34 months after the surgery

et al. [35] compared the therapeutic effects of anti-VEGF drugs in vitrectomized and nonvitrectomized eyes and reported no differences in the degree of improvement in visual acuity or in the number of anti-VEGF intravitreal injections. In recent studies, Inoue et al. [25] reported that nonvitrectomized eyes with PCV required a mean of 5.0 PRN injections of anti-VEGF per year (mean follow-up period, 12 months), whilst Cho et al. [36] and Hikichi et al. [37] reported 4.9 PRN injections per year (mean follow-up period, 12 months) and 3.6 PRN injections per year (mean follow-up period, 6 years), respectively. The present study used a PRN regimen of anti-VEGF therapy for vitrectomized eyes and observed that a mean of 4.1 injections per year was administered over a mean follow-up period of 33 months. This result suggests that vitrectomy has little effect on postoperative anti-VEGF therapy. In addition to the effect of vitrectomy on the clearance of anti-VEGF drugs, vitrectomy is reported to exert other effects on postoperative anti-VEGF therapy, such as the vitrectomy itself increasing the supply of oxygen to the retina and inhibiting VEGF production in the retina, and the relief of vitreoretinal adhesion increasing clearance of VEGF and inflammatory cytokines in the retina, thereby inhibiting the pathology of PCV [20, 38–41]. Further study is necessary to clarify the effects of vitrectomy on the therapeutic effects of postoperative anti-VEGF drug injection.

In the present study, retinochoroidal damage conceivably associated with SMH displacement was not observed for at least 1 year. With regard to SMH displacement, concerns have been raised that subretinal injection of tPA can induce retinal toxicity due to hemolysis as well as mechanical damage to the retinal pigment epithelium and choroid due to the subretinal injection procedure [19, 42]. To avoid the induction of retinal toxicity by tPA, we used a concentration of tPA that was only 14% to 28% (4000 IU) of the conventional concentration. In a previous study, we used this low concentration of tPA to displace the SMH and by microperimetry confirmed favorable postoperative retinal sensitivity [16]. This result indicates that the retinal toxicity induced by the concentration of tPA used in the present study is negligible. With regard to mechanical damage to the retinal pigment epithelium and choroid due to the subretinal injection procedure, it is considered important to limit the tPA injection pressure to the minimum necessary level. The ILM is the greatest source of resistance to subretinal injection [43]; therefore, it is advantageous to remove the ILM at the injection site. We recently reported that removing the ILM makes it possible to keep the injection pressure extremely low [19]. In all of the cases of the present study, removal of the ILM enabled safe and reliable subretinal injection of tPA with an injection pressure of 6 psi using a viscous fluid control system.

The present study has several limitations: it was a retrospective study, the number of cases was small, and it was impossible to rule out a visual acuity improvement effect associated with cataract surgery. Furthermore, the angiography and retinal autofluorescence data were not examined to investigate the presence of retinochoroidal toxicity after subretinal tPA injection.

In conclusion, vitrectomy with subretinal tPA injection and air tamponade improved the visual acuity in cases of SMH associated with PCV, and postoperative intravitreal injections of anti-VEGF drugs facilitated the maintenance of favorable visual acuity over a mean follow-up period of 33 months.

Conflicts of interest S Kimura, None; Y. Morizane, None; M. Morizane Hosokawa, None; Y. Shiode, None; S. Doi, None; M. Hosogi, None; A. Fujiwara, None; T. Okanouchi, None; Y. Inoue, None; F. Shiraga, None.

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