Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy Treated by Vitrectomy and Subretinal Tissue Plasminogen Activator

SHUHEI KIMURA, YUKI MORIZANE, MIO HOSOKAWA, YUSUKE SHIODE, TETSUHIRO KAWATA, SHINICHIRO DOI, RYO MATOBA, MIKA HOSOGI, ATSUSHI FUJIWARA, YASUSHI INOUE, AND FUMIO SHIRAGA

- PURPOSE: To evaluate vitrectomy with subretinal tissue plasminogen activator (t-PA) injection, and air tamponade, followed by intravitreal anti–vascular endothelial growth factor (VEGF) therapy for submacular hemorrhage in polypoidal choroidal vasculopathy (PCV).
- DESIGN: Prospective, interventional case series.
- METHODS: SETTING: Two clinics. PATIENTS: Fifteen eyes of 15 consecutive patients (mean age 72 ± 7 years) with submacular hemorrhage attributable to PCV. INCLUSION CRITERIA: PCV diagnosis with unorganized submacular hemorrhage greater than 500 μm thick. EXCLUSION CRITERIA: Submacular hemorrhage attributable to maculopathies (eg, high myopia, typical age-related macular degeneration, retinal angiomatous proliferation, and angioid streaks). INTERVENTION: Vitrectomy with 4000 IU t-PA injected subretinally and fluid/air exchange. Patients remained facedown for 3 days after surgery. Anti-VEGF drugs were administered as exudative changes required. MAIN OUTCOME MEASURES: Submacular hemorrhage displacement from the macula and changes in best-corrected visual acuities (BCVAs).
- RESULTS: Mean time from onset to surgery was 9.5 ± 4.5 (range, 5–21) days. Mean follow-up period was 9.4 ± 3.1 (range, 6–17) months. Surgery successfully displaced submacular hemorrhages from the macula in all eyes. Mean BCVA at baseline (0.98 ± 0.44) had improved significantly both 1 month after surgery (0.41 ± 0.25, P < .01) and at final visits (0.23 ± 0.25, P < .001). In all eyes, exudative retinal changes relapsed after surgery but were completely resolved by anti-VEGF injections. No complications occurred in any patients.
- CONCLUSION: Treating submacular hemorrhage with vitrectomy and subretinal t-PA injection, followed by intravitreal anti-VEGF therapy, is a promising strategy for improving visual acuity in PCV patients warranting further investigation. (Am J Ophthalmol 2015;159:683–689. © 2015 by Elsevier Inc. All rights reserved.)

Submacular Hemorrhage CAN ARISE IN A VARIETY of diseases, including exudative age-related macular degeneration (AMD), retinal arterial macroaneurysm, pathologic myopia, choroidal neovascularization of various etiology, and trauma.1–4 Submacular hemorrhage causes sudden visual loss and results in a poor visual prognosis, especially when it is not appropriately treated. At present, the treatment options available for submacular hemorrhage are “nonvitrectomizing techniques,” with intravitreal injections of gas or tissue plasminogen activator (t-PA) or anti–vascular endothelial growth factor (VEGF) drugs or a combination of these, or “vitrectomizing techniques,” with injections of t-PA or anti-VEGF drugs or gas or a combination of these administered either as intravitreal or subretinal injections or by a combination of subretinal and intravitreal injections. Recently, Haupert and associates reported that the displacement of submacular hemorrhages by vitrectomy and subretinal injections of t-PA is effective in AMD patients. Furthermore, both intravitreal and subretinal injection of anti-VEGF drugs during vitrectomy and/or intravitreal injection of anti-VEGF drugs following vitrectomy have been reported to be effective in maintaining improved visual acuity.

Polypoidal choroidal vasculopathy (PCV) is an exudative maculopathy affecting vision, with a prevalence of 10%–54% in Asian patients and 8%–12% in white patients with presumed exudative AMD. Clinically, PCV is characterized by a complex choroidal vascular network with multiple, terminal, reddish-orange polypoidal lesions. Although, in general, the natural course of PCV is more stable than AMD, PCV has been shown to cause occasional, massive submacular hemorrhages, which eventually results in chorioretinal atrophy and permanent vision loss.

Previously, in PCV patients, we have reported the therapeutic effect of surgically removing submacular hemorrhages by retinotomy and the use of t-PA. Since the liquefaction of submacular hemorrhages by the subretinal injection of t-PA and the displacement of submacular hemorrhages by vitrectomy with air tamponade is a simpler
and safer surgical procedure than retinotomy with mechanical submacular hemorrhage removal, we have investigated the therapeutic effect and safety of this procedure for submacular hemorrhage displacement in PCV patients. In addition, we have investigated the mechanism of submacular hemorrhage removal, we have investigated the therapeutic effect and safety of this technique for submacular hemorrhage displacement in PCV patients. In addition, we have investigated the therapeutic effect and safety of this technique for submacular hemorrhage displacement in PCV patients. In addition, we have investigated the therapeutic effect and safety of this technique for submacular hemorrhage displacement in PCV patients.

**METHODS**

**STUDY DESIGN AND PATIENTS:** This study was a prospective, interventional case series and all investigations adhered to the tenets of the Declaration of Helsinki. Each patient was informed about the risks and benefits of the surgery and participation in this research study. Their written informed consent for both the surgery and participation in this research study was obtained. The study was approved by the Institutional Review Boards of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Inoue Eye Clinic.

Fifteen eyes of 15 consecutive patients who were diagnosed with submacular hemorrhage attributable to PCV between January 8, 2012 and February 15, 2014 were recruited to the study. Diagnosis of PCV was based on both the presence of elevated orange-red lesions observed at fundus examination and the presence of characteristic polypoidal vascular lesions by indocyanine green angiography (ICGA). The size of the submacular hemorrhage was recorded as the greatest linear dimension. The inclusion criteria used were: (1) submacular hemorrhage attributable to PCV, (2) the presence of submacular hemorrhage with a thickness greater than 500 μm, as measured by optical coherence tomography (OCT), and (3) unorganized submacular hemorrhage, as determined by fundus examination, in contrast to organized submacular hemorrhages, which we considered as white and/or fibrous in appearance. Patients with submacular hemorrhage attributable to other macular diseases, such as high myopia, typical AMD, retinal angiomatous proliferation, and angioid streaks, were excluded.

The patients’ demographic data are shown in the Table. The 1 female and 14 male patients had a mean age (±SD) of 72 ± 7 years, with a range of 61–84 years. The time from onset to surgery was 9.5 ± 4.5 days (range, 2–21 days), the mean diameter of submacular hemorrhages was 5.6 ± 4.7 disc diameters (range, 1.5–20 disc diameters), and the mean thickness of submacular hemorrhages was 793 ± 312 μm (range, 504–1422 μm). Six eyes were pseudophakic preoperatively and all 15 eyes were pseudophakic postoperatively. The mean follow-up period was 9.4 ± 3.1 months (range, 6–17 months). The mean number of anti-VEGF injections was 3.5 ± 1.9 (range, 1–7). No complications occurred during or after surgery in any patients.

All 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, and indirect and contact lens slit-lamp biomicroscopy. All eyes were examined by spectral-domain optical coherence tomography (SD OCT) before and after surgery and at follow-up, using commercially available instruments (Cirrus; Carl Zeiss Meditec, Inc, Dublin, California, USA; Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany; and DRI OCT-1 Atlantis; Topcon Medical Systems, Tokyo, Japan).

The main outcome measures were displacement of the submacular hemorrhage from the macula in OCT images and differences between preoperative and postoperative BCVAs.

**SURGICAL TECHNIQUE:** The submacular hemorrhage displacement was carried out using a surgical procedure inspired by the report by Haupert and associates. Briefly, after a 25 gauge microincision vitrectomy was performed, 4000 IU t-PA (Cliactor, Eizai, Japan) in 0.1 mL was injected subretinally using a 38 gauge subretinal infusion needle (MedOne, Sarasota, Florida, USA) to liquefy the submacular hemorrhage, which was 14%–28% of the doses previously used. Before finishing the operation, fluid-air exchange was performed to displace the submacular hemorrhage. The patients remained facedown for 3 days after surgery. In 9 phakic eyes, phacoemulsifications with implantation of an intraocular lens were carried out simultaneously. All surgeries were performed by the same surgeon (F.S.).

**POSTOPERATIVE ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY:** Intravitreal injections of anti-VEGF reagents were performed pro re nata (PRN) when exudative and/or hemorrhagic changes, such as the accumulation of subretinal fluid and recurrence of submacular hemorrhage, occurred after surgery. We used either 0.5 mg ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California, USA) or 0.5 mg aflibercept (Eylea; Bayer, Basel, Switzerland).

**DATA ANALYSIS:** BCVAs were recorded as decimal values and converted to the logarithm of the minimal angle of resolution (logMAR) units for statistical analysis. The preoperative, 1 month, and final postoperative BCVAs were compared using the Mann-Whitney U test. P values less than 0.05 were considered significant. All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS, Inc, Chicago, Illinois, USA). Data are presented as means ± standard deviation (SD).

**RESULTS**

**ANATOMICAL RESULTS:** Submacular hemorrhages had been successfully moved away from the macula to the inferior periphery in all eyes during surgery and were absorbed
thereafter. In all eyes, postoperative anti-VEGF therapy was administered as necessary and exudative and/or hemorrhagic manifestations attributable to polypoidal lesions had resolved completely by the patients’ final visits. In addition, inner segment ellipsoid zones were detectable in the macula in 11 of 15 eyes (73%) at these final visits.

**TABLE.** Characteristics of Patients Undergoing Submacular Hemorrhage Displacement Owing to Polypoidal Choroidal Vasculopathy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Duration (d)</th>
<th>Lesion Size (Disc Diameter)</th>
<th>Lens Status</th>
<th>BCVA (logMAR) Pre</th>
<th>1 Month</th>
<th>Final</th>
<th>Ellipsoid Line at the Final Visit</th>
<th>Follow-up (mo)</th>
<th>Postoperative Anti-VEGF Therapy</th>
<th>Reagents (No. of Treatments)</th>
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<td>75</td>
<td>6</td>
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<td>1.22</td>
<td>0.70</td>
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<td>+</td>
<td>17</td>
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<td>62</td>
<td>2</td>
<td>6</td>
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<td>0.52</td>
<td>0.15</td>
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<td>67</td>
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<td>1.05</td>
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<td>10</td>
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<td>+</td>
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<tr>
<td>7</td>
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<td>70</td>
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<td>0.22</td>
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<td>+</td>
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BCVA = best-corrected visual acuity; VEGF = vascular endothelial growth factor.

**FIGURE 1.** Graph showing the best-corrected visual acuity (BCVA) of patients with polypoidal choroidal vasculopathy at baseline, 1 month after surgery for submacular hemorrhage, and at their final clinic visits. Postoperative BCVAs were both significantly improved compared to baseline BCVA. Error bars represent standard deviations. logMAR, logarithm of the minimal angle of resolution; *P < .01; **P < .001.

**FIGURE 2.** Scatterplot comparing best-corrected visual acuities (BCVAs) before surgery and at the final clinic visits in patients with submacular hemorrhage attributable to polypoidal choroidal vasculopathy. logMAR = logarithm of the minimal angle of resolution.

- **POSTOPERATIVE VISUAL OUTCOME:** Mean BCVAs at baseline (0.98 ± 0.44) had improved significantly both 1 month after surgery (0.41 ± 0.25, P < .01) and at final visits (0.23 ± 0.25, P < .001; Figures 1 and 2). The final visual acuity had improved by more than 0.3 logMAR units in 13 of 15 eyes and was unchanged in the remaining 2
Twelve of 15 eyes (80%) achieved final visual acuities of 0.3 or better. Final visual acuity showed no significant correlation with either disease duration or hemorrhage size or preoperative visual acuity.

Figures 3 and 4 show the clinical results for 2 PCV patients with submacular hemorrhages who underwent vitrectomy, subretinal injection of 4000 IU t-PA, and intravitreal injection of air, followed by anti-VEGF therapy. In both patients, the submacular hemorrhages were moved to the inferior periphery. SD OCT images showed the complete regression of submacular hemorrhages at the patients’ final clinic visits.

DISCUSSION

At present, the treatment options available for submacular hemorrhage can be broadly divided into “nonvitrectomizing techniques” and “vitrectomizing techniques.” Both approaches have been combined with intravitreal injection of t-PA or anti-VEGF or gas or a combination of these. However, the intravitreal injection of gas into nonvitrectomized eyes can cause sudden retinal detachment and vitreous hemorrhage. Using a vitrectomizing technique it is possible to use subretinal injections of t-PA or anti-VEGF or air or a
combination of these and also to combine subretinal and intravitreal injections of different therapeutic agents. Interestingly, intravitreal injections of t-PA have been shown to be less effective than subretinal injections in completely liquefying submacular hemorrhages. In an animal model, intravitreal t-PA has been reported not to diffuse through the intact neural retina, so would not reach subretinal clots. By contrast, vitrectomy with subretinal t-PA injection and gas tamponade, which was initially conceived and adopted by Haupert and associates, has been shown to have fewer vitreoretinal complications and a high rate (50%–85%) of complete submacular hemorrhage displacement. In this study, we modified their surgical procedure, using a lower dose of 4000 IU t-PA, which was 14%–28% of the doses previously used, and using postoperative treatment with anti-VEGF drugs. We saw no vitreoretinal complications and achieved complete submacular hemorrhage displacement in all eyes. These results indicate that this surgical procedure is a promising strategy in the treatment of submacular hemorrhages attributable to PCV.

The results of our study suggest that the best time for surgery on submacular hemorrhages attributable to PCV may be 7–10 days after onset. Timing is a critical factor for the adequate displacement of submacular hemorrhages, so that a good improvement in visual acuity is achieved. If surgery is carried out too early, there is a risk of t-PA causing re-bleeding after surgery. If it is too late, it is impossible to liquefy organized submacular hemorrhages and to adequately displace them. In this study, we carried out submacular hemorrhage displacements at 9.5 ± 4.5 days from onset (range, 2–21 days; see Table). We did not see any re-bleeding or organizing submacular hemorrhages. However, to fully address the optimal time for displacing submacular hemorrhages, further studies with larger numbers of patients will be needed.

In this study, retinal exudative changes recurred in all eyes after submacular hemorrhage displacement. We therefore injected an anti-VEGF reagent PRN and this maintained the postoperative improvements seen in visual acuity. Our results are consistent with previous reports describing the efficacy of anti-VEGF therapy after submacular hemorrhage displacement in AMD patients. Recently, various treatment protocols for anti-VEGF reagents have been proposed in AMD, including monthly injections and treat-and-extend regimens, as well as PRN. Further studies to clarify the most appropriate injection protocol are needed, particularly considering reports concerning the effect of vitrectomy on the pharmacokinetics of anti-VEGF reagents.

Although this study was limited by a small sample size and relatively short follow-up periods, our results suggest that vitrectomy, subretinal injection of t-PA (4000 IU) to liquefy the submacular hemorrhage, and air tamponade to displace the submacular hemorrhage, followed by anti-VEGF therapy, might be effective and safe for the treatment of submacular hemorrhage associated with PCV. In our treatments, rapid displacement of submacular hemorrhage from the macula and subsequent inhibition of exudative and/or hemorrhagic changes owing to anti-VEGF therapy resulted in excellent visual outcomes. Further randomized controlled clinical studies involving a larger number of patients are needed to determine the impact that this treatment strategy could have in the management of submacular hemorrhage associated with PCV.
REFERENCES


Biosketch

Shuhei Kimura, MD, PhD, is an Assistant Professor, Department of Ophthalmology, Okayama University, Okayama, Japan. After graduation of Okayama University Graduate School of Medicine, he completed the residency in ophthalmology and retina fellowship at Okayama University Hospital. He specializes in vitreoretinal surgery.