Intravitreal Tissue Plasminogen Activator, Ranibizumab, and Gas Injection for Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy

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Purpose: To investigate the efficacy of intravitreal injection of recombinant tissue plasminogen activator (rt-PA), ranibizumab, and gas without vitrectomy for submacular hemorrhage.

Design: Prospective, interventional, consecutive case series.

Participants: Twenty consecutive patients (20 eyes) with submacular hemorrhage secondary to exudative age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV).

Methods: Ranibizumab, rt-PA (25 μg/0.05 ml), and 100% perfluoropropane (0.3 ml) were injected intravitreally, followed by 2-day prone positioning.

Main Outcome Measures: The primary outcome measure was best-corrected visual acuity (BCVA) 6 months after treatment. Secondary outcome measures included central retinal thickness (CRT), central pigment epithelial detachment (PED) thickness, central ellipsoid zone, recurrence rate, and complications.

Results: Underlying disease was exudative AMD in 1 eye and PCV in 19 eyes. Submacular hemorrhage ranged in size from 2 to 31 disc diameters. Complete displacement of submacular hemorrhage was achieved in 17 eyes (85%), and partial displacement was achieved in 3 eyes (15%). Snellen BCVA improved from 20/139 before treatment to 20/65 at 6 months (P = 0.0061). Mean change in Early Treatment Diabetic Retinopathy Study score from baseline was +13 letters (P = 0.0040). Mean CRT decreased from 599 μm before treatment to 208 μm at 6 months (P < 0.0001), and central PED thickness decreased from 188 to 88 μm (P = 0.0140). Three eyes developed vitreous hemorrhage, and 1 eye developed retinal detachment; all were treated surgically, and Snellen BCVA improved at 6 months (P = 0.0012). Recurrence was observed in 10 eyes (50%) within 6 months, but visual acuity was preserved with intravitreal injection of anti–vascular endothelial growth factor (VEGF) pro re nata (PRN). The factors that affect BCVA at 6 months after treatment were pre- and posttreatment central ellipsoid zone (P = 0.0366 and P = 0.0424), pretreatment BCVA (P = 0.0015), and pre- and posttreatment central PED thickness (P = 0.0046, P = 0.0021).

Conclusions: Subretinal hemorrhage treatment by intravitreal injection of rt-PA, ranibizumab, and gas is useful to achieve hemorrhage displacement and lesion improvement. To preserve visual acuity, early detection of posttreatment recurrence and intravitreal anti-VEGF injection PRN are necessary.

Submacular hemorrhage is a serious complication of exudative age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) that leads to severe and irreversible damage to the photoreceptors and outer nuclear layer.1,2

Experimental studies using animal models showed that subretinal blood causes significant retinal damage within 24 hours.1 As for the natural history in humans, 90% of the patients would eventually have a final visual acuity of 20/200.3 Thus, early treatment for submacular hemorrhage is necessary. Previous studies have shown that displacement of submacular hemorrhage can be achieved by both "vitrectomizing techniques"4–6 and "nonvitrectomizing techniques,"7–9 and results in improvement of visual acuity. A study reviewing 38 articles reported no differences between the 2 techniques with respect to complete displacement rate and rates of recurrent submacular hemorrhage and vitreous hemorrhage.10 In regard to nonvitrectomizing techniques for submacular hemorrhage, recombinant tissue plasminogen activator (rt-PA) and gas treatment have been reported to have better visual outcome than bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) and gas, indicating the importance of displacing the submacular hemorrhage.11 On the other hand, posttreatment visual outcome was found to be better after intravitreal injection of rt-PA, bevacizumab, and gas, compared with rt-PA and gas.12 Therefore, treatment of the underlying lesion and...
simultaneous displacement of submacular hemorrhage may be a useful approach.

Observation of the natural history of submacular hemorrhage for a mean period of 24 months showed hemorrhage accompanying vascularized retinal pigment detachment in 28.3% of cases and recurrent submacular hemorrhage in 38.3% of cases, indicating the importance of treatment for recurrence. However, although vitrectomizing techniques using subretinal co-application of rt-PA and bevacizumab and intravitreal gas tamponade achieved displacement of submacular hemorrhage, recurrence was observed in 41% during postoperative follow-up of 8.1 months. Early detection of recurrence using appropriate markers and intravitreal injection of anti–vascular endothelial growth factor (VEGF) at the appropriate timing is necessary.

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland; Genentech Inc., South San Francisco, CA) is not cleaved or functionally compromised by rt-PA or plasmin, whereas afibbercept (Eylea; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is cleaved and its VEGF-binding ability is reduced when co-applied with plasmin. The half-life of intravitreally injected ranibizumab has been reported to be shortened in vitrectomized eyes compared with nonvitrectomized eyes. Considering this evidence, a nonvitrectomizing technique by concurrent administration of rt-PA, ranibizumab, and gas seems to be a rational approach for treating submacular hemorrhage. We performed a prospective study to examine the efficacy of intravitreal injection of rt-PA, ranibizumab, and gas in 1 session for the treatment of submacular hemorrhage and to identify the factors affecting visual acuity 6 months after treatment. We measured central retinal thickness (CRT) and central pigment epithelial detachment (PED) thickness using optical coherence tomography (OCT) as parameters indicating recurrence and performed intravitreal injection of anti-VEGF pro re nata (PRN). In this study, we also analyzed the usefulness of this approach.

Methods

Patient Recruitment

This prospective study was performed at the Department of Ophthalmology of Nihon University Hospital between March 2014 and July 2015. The study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Ethical Committee of the Nihon University School of Medicine (no. 110903). All subjects provided written informed consent after receiving full explanations of the study and the potential merits and risks. The inclusion criteria were thick submacular hemorrhage, including subretinal pigment epithelial hemorrhage, secondary to AMD or PCV involving the foveal center with sizes (measured from the radius centered on the fovea) greater than 2 disc diameters, and duration of symptoms not more than 30 days. The exclusion criteria were underlying causes other than exudative AMD or PCV, and the presence of a macular scar. Patients who had cerebrovascular infarction or myocardial infarction within 3 months before the study also were excluded. Exudative AMD and PCV were diagnosed by OCT (Heidelberg Spectralis; Heidelberg Engineering Inc., Heidelberg, Germany), fluorescein angiography, and indocyanine angiography as reported previously. Polypoidal choroidal vasculopathy is characterized by a complex choroidal vascular network with multiple, terminal, reddish-orange polypoidal lesions.

Protocol

All patients were given 3 intravitreal injections in 1 session in an outpatient room: 0.05 ml of ranibizumab, 0.05 ml of rt-PA (Alteplase; Kyowa Hakko Kirin, Tokyo, Japan), and 0.3 ml perfluoropropane (C3F8; Alcon Laboratories Inc., Fort Worth, TX) after removing 0.3 ml of anterior chamber fluid. After the intravitreal injections, ocular pressure was tested by palpating with a finger, and vision was checked by hand motion. Perfusion of the optic disc was assessed using a binocular indirect ophthalmoscope. Then the patients were admitted for 3 days. They were placed in a sitting position for 2 hours and then maintained in a prone position for 2 days. The patients were examined before treatment, daily from 1 to 7 days after treatment as inpatients, and at 2 weeks and then monthly from 1 to 6 months as outpatients. All patients underwent visual acuity measurement, intraocular pressure measurement, slit-lamp biomicroscopy, indirect ophthalmoscopy, and OCT examination before and 1, 2, 3, 4, 5, and 6 months after treatment. Fluorescein angiography and indocyanine angiography were performed before and 1, 3, and 6 months after treatment.

Recurrence of submacular hemorrhage was evaluated by observation for rebleeding on color fundus photograph and by measuring CRT and central PED thickness on OCT as markers for early detection of recurrence. Intravitreal injection of ranibizumab was performed PRN when exudative or hemorrhagic changes were observed, such as accumulation of subretinal fluid and increase in macular edema or recurrence of submacular hemorrhage.

Outcome Measures

The primary outcome measure was best-corrected visual acuity (BCVA) 6 months after treatment, measured using the Snellen chart and Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Snellen BCVA was converted to logarithm of minimal angle of resolution scale for analysis.

The secondary outcome measures were displacement of submacular hemorrhage; changes in CRT, central PED thickness, and central ellipsoid zone after treatment; recurrence; and complications.

Tissue Plasminogen Activator, Ranibizumab, and Gas Injection

All intravitreal injections were conducted by 1 ophthalmologist (Y.K.). The procedures were performed in an outpatient injection room, which is separated from the outpatient clinic and equipped with a microscope and bed. After retrobulbar block using 4 ml of 2% Xylocaine, the eyelid skin was disinfected with 10% povidone-iodine (Meiji Seika Pharma Co., Ltd., Chuo-ku, Tokyo, Japan) and the conjunctiva was disinfected with 0.25% povidone-iodine diluted in physiologic saline. Then the eye was draped, and a lid speculum was placed. After performing paracentesis of 0.3 ml, ranibizumab (0.5 mg/0.05 ml), rt-PA (25 μg/0.05 ml, 40,000 IU), and 100% perfluoropropane (C3F8; 0.3 ml) were injected intravitreally through the pars plana, successively in the same session. All 3 injections were performed using 30-G needles, and the ocular surface was disinfected with 0.25% povidone-iodine before and after each injection. After the injections, the patient was admitted.

Measurements of Clinical Parameters

The greatest diameter of subretinal hemorrhage was measured. Displacement of submacular hemorrhage was evaluated on a
fundus photograph taken 1 week after treatment. Complete displacement was defined as no blood or only a scanty amount of blood within 1 disc diameter of the foveal center after completion of prone positioning. Partial displacement was defined as blood under the fovea that obscured the retinal pigment epithelium but that did not cause clinically visible elevation of the retina.3

Recurrence of the hemorrhagic lesion was detected by the presence of rebleeding on color fundus photograph. As parameters for early detection of recurrence, CRT and central PED thickness also were measured on OCT as shown in Figure 1. Central ellipsoid zone was detectable when the zone was present at the foveal center on OCT and as undetectable when such zone was absent. Complications were observed during the follow-up period.

Statistics

Statistical analyses were performed using SPSS software version 21 (SPSS, Inc., Chicago, IL). Values are expressed as mean ± standard deviation or percentage. Paired t test was used to compare factors affecting visual acuity 6 months after treatment. P values less than 0.05 were considered to be statistically significant.

Results

Baseline Data

Baseline patient data are shown in Table 1. Twenty eyes of 20 subjects (4 women and 16 men; mean age, 70±11 years; range, 48–88 years) were studied. Five eyes (25%) had previously been treated with photocoagulation, photodynamic therapy, or intravitreal injection of anti-VEGF drugs. In the 5 eyes with PCV that had prior treatment with anti-VEGF injection, the last injection was conducted 2 to 44 months before receiving the present treatment for subretinal hemorrhage. Three patients (15%) were receiving treatment with an oral anticoagulant (warfarin in 2 patients and rivaroxaban in 1 patient) for arrhythmia.

The mean ± standard deviation interval from the onset of subretinal hemorrhage symptoms to treatment was 9.9±9.8 days (range, 2–30 days). The underlying cause of submacular hemorrhage was exudative AMD in 1 eye and PCV in 19 eyes. The mean greatest diameter of submacular hemorrhage was 11.1±8.7 disc diameters (range, 2–31 disc diameters) (Fig 2). The mean pretreatment Snellen BCVA in the affected eye was 20/139 (range, 20/400–20/25), and the mean ETDRS score was 52±20 letters (range, 19–80 letters). The mean CRT was 599±319 μm (range, 172–1225 μm), and the mean central PED thickness was 188±251 μm (range, 0–837 μm).

Primary Outcome Measure

The results of posttreatment visual acuity are shown in Table 2. The mean Snellen BCVA at 6 months was 20/65 and improved significantly compared with pretreatment visual acuity (P = 0.0061). The mean ETDRS score was 65±22 letters at 6 months and significantly better than pretreatment visual acuity (P = 0.0040).

Secondary Outcome Measures

At 1 week after treatment, complete displacement of subretinal hemorrhage was observed in 17 eyes (85%) and partial displacement was observed in 3 eyes (15%). At 6 months after treatment, mean CRT was 208±71 μm and mean central PED thickness was 88±138 μm, showing significant improvements compared with the pretreatment thicknesses (P < 0.0001 and P = 0.0140, respectively). Central ellipsoid zone was detectable in 5 eyes (25%) before treatment and in 9 eyes (45%) after treatment. Figure 3 illustrates 1 case in which the central ellipsoid zone became visible after treatment.

In regard to posttreatment complications, retinal detachment was found in 1 eye after 1 week, and vitreous hemorrhage was observed in 1 eye after 3 days and in 2 eyes after 13 days. Retinal detachment was treated by buckling, and vitreous hemorrhage was treated by 25-gauge vitrectomy using the Constellation system (Alcon Laboratories Inc.). By comparing pretreatment with 6-month posttreatment data in these 4 eyes, Snellen BCVA improved significantly from 20/110 to 20/56 (P = 0.0204) and ETDRS score improved from 51±13 to 67±15 (P = 0.0058), whereas CRT (from 602±443 to 191±94 μm; P = 0.1042) and central PED thickness (from 211±328 to 40±58 μm; P = 0.3607) did not change significantly.

Subretinal hemorrhage recurred within 6 months after rt-PA, ranibizumab, and gas injections in 10 eyes (50%). In these 10 eyes, serous retinal detachment in 2 eyes was detected after 1 month, serous retinal detachment in 4 eyes and vitreous hemorrhage in 1 eye were detected after 4 months, serous retinal detachment in 1 eye was detected after 5 months, and serous retinal detachment in 2 eyes was detected after 6 months. Figure 4 illustrates the clinical course in 1 patient with recurrence. In these cases, intravitreal injection of ranibizumab or aflibercept was conducted an average of 1.2 times (range, 1–2 times). By comparing pretreatment with 6-month posttreatment data in these
Table 1. Patient Characteristics at Baseline

| No. | Age (yrs), Sex | Diagnosis | Duration of SRH (Days) | Size of SRH (DD) | Previous Anti-VEGF Treatment (Time from Last Injection, Type) | Anticoagulant Treatment | Before Treatment |
|-----|----------------|-----------|------------------------|------------------|-------------------------------------------------------------|-------------------------|----------------|-----------------|
| 1   | 75, M          | PCV       | 11                     | 15               | 44 mos, IVR                                                 | -                       | 20/40          |
| 2   | 67, M          | PCV       | 4                      | 3                | —                                                           | —                       | 20/50          |
| 3   | 79, M          | PCV       | 30                     | 2                | —                                                           | +                       | 20/63          |
| 4   | 58, F          | PCV       | 12                     | 17               | —                                                           | —                       | 20/63          |
| 5   | 69, M          | PCV       | 3                      | 16               | —                                                           | —                       | 20/125         |
| 6   | 75, M          | PCV       | 16                     | 27               | 20 mos, IVR                                                 | —                       | 20/200         |
| 7   | 76, M          | PCV       | 14                     | 3                | —                                                           | —                       | 20/25          |
| 8   | 73, M          | PCV       | 3                      | 3                | —                                                           | —                       | 20/40          |
| 9   | 59, F          | AMD       | 8                      | 31               | —                                                           | +                       | 20/280         |
| 10  | 56, M          | PCV       | 2                      | 20               | —                                                           | —                       | 20/320         |
| 11  | 48, F          | PCV       | 5                      | 17               | —                                                           | —                       | 20/320         |
| 12  | 79, M          | PCV       | 3                      | 4                | —                                                           | —                       | 20/125         |
| 13  | 48, M          | PCV       | 11                     | 13               | —                                                           | —                       | 20/40          |
| 14  | 68, F          | PCV       | 6                      | 3                | —                                                           | —                       | 20/32          |
| 15  | 76, M          | PCV       | 5                      | 14               | —                                                           | —                       | 20/400         |
| 16  | 79, M          | PCV       | 30                     | 9                | —                                                           | —                       | 20/400         |
| 17  | 67, M          | PCV       | 3                      | 7                | 2 mos, IVA                                                  | —                       | 20/40          |
| 18  | 88, M          | PCV       | 10                     | 2                | 2 mos, IVA                                                  | —                       | 20/50          |
| 19  | 87, M          | PCV       | 2                      | 2                | 4 mos, IVA                                                  | —                       | 20/63          |
| 20  | 69, M          | PCV       | 2                      | 13               | —                                                           | —                       | 20/100         |

AMD = age-related macular degeneration; DD = disc diameter; ETDRS = Early Treatment Diabetic Retinopathy Study; F = female; IVA = intravitreal aflibercept; IVR = intravitreal ranibizumab; M = male; PCV = polypoidal choroidal vasculopathy; PED = pigment epithelial detachment; SRH = subretinal hemorrhage; VEGF = vascular endothelial growth factor.

*Case 6 also received intravitreal bevacizumab and photodynamic therapy.

†Case 19 also received photocoagulation.

Figure 2. Pretreatment (A–C) and posttreatment (D–F) findings of polypoidal choroidal vasculopathy (PCV) in case 13. A, Before treatment, subretinal hemorrhage of 13 disc diameters involving the fovea center was observed. B, Indocyanine angiography showed hyperfluorescence at the superotemporal macula. C, On optical coherence tomography (OCT), subretinal hemorrhage and pigment epithelial detachment (PED) were observed. D, At 3 months after treatment, subretinal hemorrhage was no longer visible. E, Indocyanine angiography showed disappearance of hyperfluorescence at the superotemporal macula. F, On OCT, no subretinal hemorrhage or PED were observed. Green arrows indicate the locations of the OCT scans.
Table 2. Visual Acuity and Foveal Thickness after Intravitreal Injection of Recombinant Tissue Plasminogen Activator, Ranibizumab, and Gas

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<th>No.</th>
<th>SRH Displacement at 1 Week</th>
<th>Complications</th>
<th>Recurrence during 6 Months (IVR/IVA Times)</th>
<th>6 Months after Treatment</th>
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<td>Snellen BCVA (IVA/C2)</td>
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<td>1</td>
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<td>323</td>
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<td>Complete</td>
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BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IVA = intravitreal aflibercept; IVR = intravitreal ranibizumab; PED = pigment epithelial detachment; RD = retinal detachment; SRD = serous retinal detachment; SRH = subretinal hemorrhage; VH = vitreous hemorrhage.

Discussion

In this study, pretreatment and posttreatment OCT and angiographic examinations showed that PCV was the underlying cause of submacular hemorrhage in 95% of patients and that AMD was the underlying cause in 5% of patients. Polypoidal choroidal vasculopathy is an exudative maculopathy that affects vision, with a prevalence of 10% to 54% in Asian patients and 8% to 12% in white patients with presumed exudative AMD.23,24 The natural course of PCV is more stable than AMD, and PCV has been shown to cause occasional massive submacular hemorrhage, which eventually results in chorioretinal atrophy and permanent vision loss.18,25,26 In this study, some of the submacular hemorrhages were massive, ranging in size from 2 to 31 disc diameters, which would cause severe visual impairment if displacement was not achieved. Submacular hemorrhage secondary to PCV has been treated using “vitrectomizing techniques,”6,27 and

10 eyes, Snellen BCVA (20/123 vs. 20/119; P = 0.4151), ETDRS letters (54±18 vs. 60±25; P = 0.3415), CRT (688±340 vs. 237±74 µm; P = 0.0023), and central PED thickness (195±291 vs. 130±181 µm; P = 0.1233) were all preserved.

Factors Affecting Posttreatment Visual Acuity

Multiple regression analysis was conducted to identify the factors affecting BCVA 6 months after treatment. Pretreatment BCVA (P = 0.0015), pretreatment central ellipsoid zone (P = 0.0366), pretreatment central PED thickness (P = 0.0046), posttreatment central ellipsoid zone (P = 0.0424), and posttreatment central PED thickness (P = 0.0021) were identified as independent factors affecting posttreatment BCVA. Other variables such as previous treatment (P = 0.8162), anticoagulant therapy (P = 0.8162), size of subretinal hemorrhage (P = 0.2390), duration from onset to treatment (P = 0.4471), age (P = 0.3919), pretreatment CRT (P = 0.9489), posttreatment complications (P = 0.7530), recurrence (P = 0.2927), status of displacement of subretinal hemorrhage (P = 0.4893), and posttreatment CRT (P = 0.5278) were not significantly associated with posttreatment BCVA.

Injection-Related Adverse Events

No ocular and systemic adverse events associated with intravitreal rt-PA, ranibizumab, and gas injection, such as systemic thromboembolic event and endophthalmitis, were observed in this study. Ocular pressure was checked by palpation with fingers immediately after injection and measured by a tonometer every day during admission. Ocular hypertension ≥25 mmHg was not observed.
“nonvitrectomizing techniques.” However, even after achieving displacement of the submacular hemorrhage, intravitreal injection of ranibizumab or aflibercept for the treatment of PCV is important. In this study, we used ranibizumab because this agent is not cleaved or functionally compromised by rt-PA or plasmin. However, because aflibercept has been shown to be effective for PCV, we used aflibercept for the management of recurrence.

In this study, nonvitrectomizing treatment with rt-PA, bevacizumab, and gas achieved displacement of submacular hemorrhage and improvement of visual acuity. Table 3 summarizes previous studies using “vitrectomizing techniques” with co-application of anti-VEGF, rt-PA, and gas, as well as studies using “nonvitrectomizing techniques” by posterior anti-VEGF injection. The doses of rt-PA varied widely from 10 μg/0.05 ml to 6.25 mg/0.05 ml. However, intravitreal injection of a high concentration of rt-PA has a risk of retinal damage. A study of rabbit eyes observed retinal damage in eyes injected intravitreally with 50 μg/0.1 ml of rt-PA, but no toxicity when injected with 25 μg/0.1 ml. In another study using cat eyes, intravitreal injection of rt-PA at concentrations greater than 25 μg/0.1 ml caused retinal damage. The findings of these 2 studies suggest that when injecting rt-PA intravitreally, a concentration of 25 μg/0.1 ml does not cause retinal damage. By using an rt-PA dose of 20 μg/0.05 ml in the present study, we found no ocular or systemic adverse events such as systemic thromboembolic event and endophthalmitis associated with intravitreal injections of rt-PA, ranibizumab, and gas.

Despite the achievement of submacular hemorrhage displacement and visual acuity improvement by the initial treatment, a recurrence rate of 41% was reported, leading to deteriorated visual acuity, which indicates the necessity of early detection and treatment of recurrence. Also in this study, 50% of the cases recurred during the 6 months after injection, with 1 eye developing vitreous hemorrhage. In the case that developed vitreous hemorrhage (case 10), recurrence leading to vitreous hemorrhage was detected 4 months after the initial treatment and successfully treated by vitrectomy. Visual acuity at 6 months was 20/400. This patient did not receive prior treatment with an anti-VEGF agent. Detection of recurrence before the development of submacular or vitreous hemorrhage is important. In this study, we used CRT and central PED thickness measured on OCT as parameters for early detection of recurrence. With the use of this method, we were able to detect increased CRT due to serous retinal detachment as an early finding of recurrence in 9 of 10 eyes. This method is less invasive than angiographic examinations and has the additional merit that it can be conducted during the monthly follow-up. In this study, our treatment strategy was not to give anti-VEGF injections in all patients after the initial injection of 3 agents, but to monitor the patients for early recurrence and inject an anti-VEGF agent only when early recurrence was detected. If we had continued anti-VEGF treatment in all patients regardless of recurrence, a strategy used by Sacu.
et al.\textsuperscript{12} and Guthoff et al.\textsuperscript{12} all 20 patients would have been given anti-VEGF injections regularly. By the PRN approach, only 10 eyes (one half of all eyes) needed anti-VEGF injection. Reducing anti-VEGF injections has an economic advantage and reduces patient burden. However, in view of the 50% recurrence rate within 6 months, the optimal treatment regimen after the initial injection has to be studied further.

Postoperative vitreous hemorrhage and retinal detachment have been regarded to be problems of “non-vitrectomizing techniques.” However, the visual outcome of the patients who developed complications has not been studied in detail. In this study, complications occurred in 4 eyes: retinal detachment in 1 eye and vitreous hemorrhage in 3 eyes. When comparing the pretreatment with 6-month posttreatment visual acuity, Snellen BCVA improved significantly from 20/110 to 20/56 and ETDRS score also improved significantly from 51 to 67 letters. Although the number of cases (n = 4) was small, these results suggest that submacular hemorrhage treatment by intravitreal injection of rt-PA, ranibizumab, and gas achieves displacement of hemorrhage together with improvement of the underlying lesion and is a treatment method that can be expected to improve visual acuity even when complications arise.

Various factors have been reported to affect posttreatment visual acuity. Small subretinal hemorrhages had a better visual outcome than large subretinal hemorrhages.\textsuperscript{7,35} A short duration (≤14 days) from the onset of hemorrhage to treatment was associated with a better gain of lines of vision.\textsuperscript{7} A recent report suggests that preoperative detectable ellipsoid layers and submacular hemorrhage height <400 µm may predict good postoperative visual outcome.\textsuperscript{36} In this study, multiple regression analysis of factors affecting

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\includegraphics[width=\textwidth]{figure4.png}
\caption{Recurrence after displacement of subretinal hemorrhage in a case of polypoidal choroidal vasculopathy (PCV) (case 14). Infrared images (left) and optical coherence tomography (OCT) images after treatment (right). Green arrows indicate the locations of the OCT scans. \textbf{A}, Pretreatment OCT showed subretinal hemorrhage and a polypoidal lesion. \textbf{B}, Optical coherence tomography conducted 3 months after treatment showed a diminished polypoidal lesion and the disappearance of subretinal hemorrhage. \textbf{C}, Optical coherence tomography conducted 6 months after treatment showed that the polypoidal lesion remained small but detected a finding of serous retinal detachment recurrence.}
\end{figure}
BCVA 6 months after treatment detected a significant correlation with pre- and posttreatment central ellipsoid zone, pretreatment BCVA, and pre- and posttreatment central PED thickness. However, the size of the subretinal hemorrhage, treatment history, anticoagulant therapy, duration from onset to treatment, age, and CRT showed no association. A possible explanation is that concurrent injection of rt-PA, bevacizumab, and gas displaces the subretinal hemorrhage irrespective of its size and markedly decreases CRT. Therefore, in eyes with good pretreatment BCVA or thin central PED thickness, the central ellipsoid zone often is detected after treatment and posttreatment visual acuity also improves.

**Study Limitations**

This study had several limitations. It was not randomized, the sample size of 20 eyes was small, and the observation period of 6 months was short. Another limitation was that not all cases were treatment-naive. Furthermore, this prospective study was designed to investigate submacular hemorrhage in both exudative AMD and PCV, but only 1 of 20 eyes enrolled had AMD. Consequently, the results were those for PCV and may be different for AMD. A further randomized controlled clinical study with a large number of cases and long-term follow-up is required.

In conclusion, this study showed that subretinal hemorrhage treatment by intravitreal injections of rt-PA, ranibizumab, and gas achieved hemorrhage displacement and lesion improvement. After the initial treatment, early detection of posttreatment recurrence and intravitreal anti-VEGF injection PRN were necessary to preserve visual acuity.

**References**


Footnotes and Financial Disclosures

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