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# Intravitreal Aflibercept With vs Without Pneumatic Displacement for Submacular Hemorrhage Associated With Polypoidal Choroidal Vasculopathy

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## Abstract

**Purpose:** To compare the visual outcomes of intravitreal (IVT) aflibercept with pneumatic displacement vs without pneumatic displacement for submacular hemorrhage (SMH) associated with polypoidal choroidal vasculopathy (PCV). **Methods:** This retrospective study assessed patients with SMH associated with PCV who were treated with aflibercept and pneumatic displacement with gas (aflibercept+gas group) or with aflibercept alone (monotherapy group). Patients were followed for at least 12 months, with the best-corrected visual acuity (BCVA) at 12 months the primary outcome measure. **Results:** Forty-seven eyes of 47 patients were retrospectively analyzed from August 2013 to March 2023. The aflibercept+gas group comprised 25 eyes and the monotherapy group, 22 eyes. The 2 groups had comparable baseline characteristics. The mean logMAR best-corrected visual acuity (BCVA) before treatment was 0.78 ± 0.46 in the aflibercept+gas group and 0.83 ± 0.66 in the monotherapy group ($P = .76$). The mean BCVA (0.26 ± 0.42 vs 0.85 ± 0.57) and the mean change in (−0.52 ± 0.55 vs 0.02 ± 0.75) 12 months postoperatively was significantly better in the aflibercept+gas group than in the monotherapy group ($P < .001$ and $P < .008$, respectively). The BCVA improved by 3 or more lines in 60.0% of eyes in the aflibercept+gas group but in only 18.2% of eyes in the monotherapy group. Vitreous hemorrhage developed in 16.0% of eyes in the aflibercept+gas group and in 13.6% of eyes in the monotherapy group and retinal detachment in 4.0% and 0%, respectively (both $P = 1.000$). **Conclusions:** Better visual outcomes were achieved with IVT aflibercept and pneumatic displacement than with aflibercept alone for SMH associated with PCV.

## Keywords

aflibercept, perfluoropropane, pneumatic displacement, polypoidal choroidal vasculopathy, submacular hemorrhage

## Introduction

Polypoidal choroidal vasculopathy (PCV), a variant of age-related macular degeneration (AMD), is characterized by polypoidal lesions and branching vascular networks.[1] Its prevalence varies, with a higher incidence reported among Asian populations, although it may occur in any race or ethnicity, including White, Black, and Hispanic populations.[2] PCV can result in subretinal and intraretinal fluid, pigment epithelium detachment (PED), and occasionally a large submacular hemorrhage (SMH), leading to acute and potentially irreversible vision loss.[1,3–6]

Treatment for SMH associated with PCV includes surgical approaches (eg, vitrectomy and administration of tissue plasminogen activator [tPA] into the subretinal space) and medical approaches (eg, intravitreal [IVT] injections of antivascular endothelial growth factor [anti-VEGF], pneumatic displacement with gas, and tPA, alone or in combination).[7–15] Although vitrectomy is effective for severe SMHs, it carries the risk for iatrogenic retinal breaks and consequent proliferative vitreoretinopathy (PVR), which may necessitate multiple surgeries.[16,17] In contrast, medical treatments are less invasive, carry a reduced (but not absent) risk for PVR, and are becoming

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more common because of the efficacy and easy administration of anti-VEGF drugs such as bevacizumab, ranibizumab, and aflibercept.[11–14,18] Whether aflibercept combined with gas injection or used alone as a monotherapy is more effective for improving visual outcomes is unclear.[18]

The purpose of this study was to analyze and compare the visual and anatomic outcomes of patients with SMH associated with PCV and determine whether the optimal treatment is with IVT aflibercept combined with pneumatic displacement using gas or IVT aflibercept alone.

## Methods

### *Patients*

This retrospective comparative clinical cohort study included a consecutive series of patients with SMH associated with PCV who were treated between August 2013 and March 2023 with IVT aflibercept in combination with pneumatic displacement using gas (aflibercept+gas group) or with aflibercept alone (monotherapy group) at the Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan. Institutional review board approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki. The patients provided written informed consent before beginning treatment.

Inclusion criteria were a large SMH (2 or more disc diameters) associated with PCV. Exclusion criteria were eyes with diagnoses other than PCV, including typical AMD or retinal arterial macroaneurysms, and those with a follow-up of less than 12 months. In line with previous studies, the diagnosis of PCV was made using indirect ophthalmoscopy, color fundus photography (TRC-50DX, Topcon Corp), swept-source optical coherence tomography (SS-OCT) (DRI OCT-1 Atlantis, Topcon Corp), spectral-domain OCT (Cirrus, Carl Zeiss Meditec Inc), fluorescein angiography, and indocyanine green angiography.[5]

### *Treatments*

Patients received IVT injections of 2 mg (0.05 mL) aflibercept in combination with gas injections or alone. The choice of treatment was at each surgeon's discretion.

In the aflibercept+gas group, most eyes had both IVT aflibercept and pneumatic displacement using gas on the same day. The aflibercept was administered intravitreally through the pars plana under sterile conditions, followed immediately by an anterior chamber paracentesis of 0.2 to 0.3 mL. Subsequently, 0.3 to 0.5 mL of 100% perfluoropropane ($C_3F_8$) (Alcon Laboratories, Inc) was injected using a 34-gauge or 30-gauge needle. In some eyes, aflibercept was injected within 1 week before or after the injection of gas.

In the monotherapy group, aflibercept was administered intravitreally through the pars plana under sterile conditions without paracentesis. Patients in the monotherapy group were advised to receive gas injection but were treated with aflibercept alone for various reasons, including an unwillingness to maintain the advised prone position for 2 to 4 days.

In both groups, vision was assessed with hand motions after the injection and optic disc perfusion was evaluated with a binocular indirect ophthalmoscope. The primary outcome measure was the best-corrected visual acuity (BCVA) 12 months after treatment, while secondary outcome measures included the anatomic outcome at 12 months and complications after treatment. The central retinal thickness (CRT) and central PED thickness were measured manually with SS-OCT. Displacement of the SMH, assessed 1 week after treatment, was defined as clearance that left no or a minimal hemorrhage within 1 disc diameter, as seen on fundus photographs. An evaluation of an intact ellipsoid zone (EZ) and macular fibrosis was done with SS-OCT at 12 months by 2 retina specialists (T.W., C.H.).

### *Statistical Analysis*

The BCVA was measured using the Landolt C acuity chart and converted to logMAR notation for statistical analyses. The *t* test or Mann-Whitney *U* test was used to compare parameters between the treatments. Univariate regression analysis was used to assess the association of the logMAR BCVA 12 months after treatment with the other variables. Statistical analyses were performed with SigmaStat software (version 4.0, SPSS Inc). Statistical significance was set at $P < .05$. Mean values are ± SD.

## Results

The study included 47 eyes of 47 patients, 25 in the aflibercept+gas group (Figure 1) and 22 in the monotherapy group (Figure 2). Table 1 shows the patients' baseline characteristics. The age, sex, duration and size of the SMH, and previous anti-VEGF treatment and anticoagulant treatment were comparable between the 2 groups (Table 1).

The mean baseline logMAR BCVA before treatment was 0.78 ± 0.46 (Snellen equivalent, 20/121) in the aflibercept+gas group and 0.83 ± 0.66 (Snellen equivalent, 20/135) in the monotherapy group ($P = .76$). The mean CRT and PED thickness did not differ significantly between the groups ($P = .39$ and $P = .44$, respectively); however, there was a trend toward a greater retinal detachment (RD) height in the aflibercept+gas group than in the monotherapy group ($P = .052$). Three eyes (12.0%) in the aflibercept+gas group and 2 eyes (9.1%) in the monotherapy group had an extrafoveal organized hemorrhage; however, no eye had an organized hemorrhage at the fovea ($P = 1.000$).

All patients were followed for at least 12 months. The mean total follow-up was 31.6 ± 21.2 months (range, 12-111). The length of the follow-up did not differ significantly between the groups ($P = .263$).

### *Visual Outcomes*

Table 2 and Figure 3 show the logMAR BCVA after treatment. After treatment, patients in the aflibercept+gas group achieved significant improvement in the BCVA at 12 months ($P < .001$).


**Figure 1.** (A) Color fundus photograph of a submacular hemorrhage associated with polypoidal choroidal vasculopathy treated with intravitreal aflibercept and gas (pneumatic displacement). The hemorrhage is confirmed with indocyanine green angiography, and swept-source optical coherence tomography (SS-OCT) shows retinal elevation associated with exudation and hemorrhage. (B) One month after treatment, the hemorrhage is displaced. (C) Three months after treatment. (D) Twelve months after treatment. (E) Two years after treatment. SS-OCT confirms resolution of the fluid and hemorrhage without macular scarring.

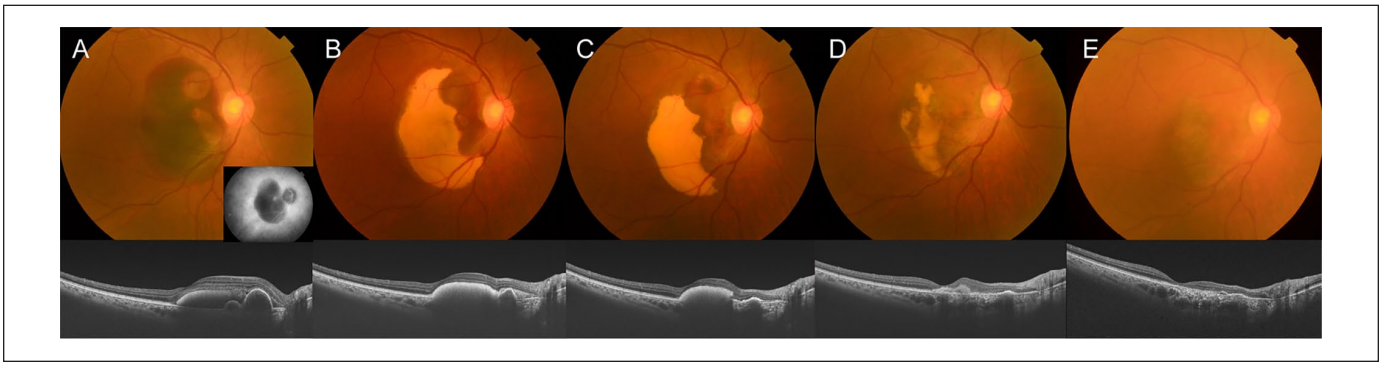


**Figure 2.** (A) Color fundus photograph of a submacular hemorrhage associated with polypoidal choroidal vasculopathy treated with intravitreal aflibercept alone. The hemorrhage is confirmed with indocyanine green angiography, and swept-source optical coherence tomography (SS-OCT) shows retinal elevation associated with exudation and hemorrhage. (B) One month after treatment, the hemorrhage has become organized. (C) Three months after treatment. (D) Twelve months after treatment, SS-OCT confirms macular scarring (fibrosis). (E) Six years after treatment, SS-OCT shows macular atrophy.

In contrast, there was no change in the BCVA from baseline to after treatment in the monotherapy group ($P = .931$). The BCVA was significantly better in the aflibercept+gas group (0.26 ± 0.42; Snellen equivalent, 20/36) than in the monotherapy group (0.85 ± 0.57; Snellen equivalent, 20/142) 12 months after treatment ($P < .001$). Likewise, the change in BCVA at 12 months was significantly better in the aflibercept+gas group (−0.52 ± 0.55) than in the monotherapy group (0.02 ± 0.75) ($P = .008$).

In the aflibercept+gas group, the BCVA at 12 months improved by 3 or more lines in 60.0% of eyes, did not change in 36.0% of eyes, and deteriorated by 3 or more lines in 4.0% of eyes. In the monotherapy group, the BCVA at 12 months improved by 3 or more lines in 18.2% of eyes, did not change in 50.0% of eyes, and deteriorated by 3 or more lines in 31.8% of eyes. The aflibercept+gas group had a significantly higher incidence of BCVA improvement and a lower incidence of deterioration in BCVA than the monotherapy group ($P = .004$).

At the final visit, the aflibercept+gas group had a significant improvement in BCVA ($P < .001$), although the monotherapy group did not ($P = .409$) (Table 2). The logMAR BCVA after treatment was significantly better in the aflibercept+gas group than in the monotherapy group (0.89 ± 0.58) at the final visit ($P < .001$). The change in BCVA was also significantly better in the aflibercept+gas group than in the monotherapy group at the final visit ($P < .001$).

In the aflibercept+gas group, the BCVA at the final visit improved by 3 or more lines in 56.0% of eyes, did not change in 40.0% of eyes, and deteriorated by 3 or more lines in 4.0% of eyes. In the monotherapy group, the BCVA at the final visit improved by 3 or more lines in 13.6% of eyes, did not change in 50.0% of eyes, and decreased by 3 or more lines in 36.4% of eyes. The aflibercept+gas group had a significantly higher incidence of BCVA improvement and a lower incidence of BCVA deterioration than the monotherapy

**Table 1.** Baseline Characteristics.

| Parameter | Aflibercept+Gas | Aflibercept Alone | *P* Value |
|---|---|---|---|
| Eyes (n) | 25 | 22 | |
| Patients (n) | 25 | 22 | — |
| Mean age (y) ± SD | 71.9 ± 8.8 | 74.8 ± 10.0 | .298 |
| Sex, n (%) | | | |
| Male | 19 (76) | 16 (73) | .797 |
| Female | 6 (24) | 6 (27) | |
| Duration of SMH (mo) | | | .761 |
| Mean ± SD | 8.2 ± 4.3 | 8.8 ± 7.2 | |
| Range | 2, 18 | 3, 30 | |
| Disc diameter of SMH | | | .621 |
| Mean ± SD | 13.7 ± 10.0 | 15.8 ± 17.9 | |
| Range | 4.5, 37.8 | 1.8, 77.5 | |
| Previous anti-VEGF treatment, n (%) | 8 (32) | 7 (32) | .989 |
| Baseline BCVA | | | .762 |
| Landolt C acuity chart | | | |
| Mean | 0.16 | 0.15 | |
| Range | 0.02, 0.7 | 0.001, 0.7 | |
| Mean logMAR ± SD | 0.78 ± 0.46 | 0.83 ± 0.66 | |
| Anticoagulant treatment, n (%) | 6 (24) | 5 (23) | .918 |
| CRT (μm) | | | .387 |
| Mean ± SD | 769 ± 329 | 664 ± 488 | |
| Range | 425, 1750 | 289, 2481 | |
| Central PED thickness (μm) | | | .437 |
| Mean ± SD | 95 ± 149 | 147 ± 285 | |
| Range | 0, 480 | 0, 1286 | |
| Height of RD (μm) | | | .052 |
| Mean ± SD | 551 ± 328 | 386 ± 220 | |
| Range | 206, 1503 | 86, 890 | |
| Organized SMH, n (%) | 3 (12) | 2 (9) | 1.000 |
| Fibrin formation at the fovea, n (%) | 1 (4) | 1 (5) | 1.000 |
| Follow-up duration (mo) | | | .263 |
| Mean ± SD | 26.7 ± 13.5 | 37.1 ± 26.7 | |
| Range | 12, 58 | 12, 111 | |

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retina thickness; PED, pigment epithelial detachment; RD, retinal detachment; SMH, submacular hemorrhage; VEGF, vascular endothelial growth factor.

group, although the latter difference was not statistically significant ($P = .002$).

## *Anatomic Outcomes*

Table 2 also shows the anatomic outcomes after treatment. Displacement of SMH was achieved in 21 eyes (84%) in the aflibercept+gas group and no eye in the monotherapy group ($P < .001$).

The mean CRT significantly decreased from 769 ± 329 μm before treatment to 219 ± 67 μm at 12 months in the aflibercept +gas group and from 664 ± 488 μm to 344 ± 429 μm in the monotherapy group (both $P < .001$). The CRT 12 months after treatment did not differ significantly between the groups ($P = .114$). However, the decrease in CRT was significantly greater in the aflibercept+gas group (−551 ± 326 μm) than in the monotherapy group (−321 ± 314 μm) ($P = .012$).

The EZ was intact on SS-OCT at 12 months in 9 eyes (36.0%) in the aflibercept+gas group and 6 eyes (27.3%) in the monotherapy group ($P = .744$). Macular scarring (fibrosis) developed in no eye in the aflibercept+gas group and in 7 eyes (31.8%) in the monotherapy group ($P = .003$).

In the aflibercept+gas group, the mean central PED decreased significantly from 96 ± 149 μm before treatment to 13 ± 31 μm at 12 months ($P = .005$). In the monotherapy group, the mean central PED decreased from 147 ± 285 μm before treatment to 60 ± 166 μm at 12 months; the change was not statistically significant ($P = .110$). The PED thickness after treatment and changes in PED thickness at 12 months did not differ significantly between the groups ($P = .886$ and $P = .785$, respectively).

## *Additional Treatments*

During the follow-up period, 24 eyes (96.0%) in the aflibercept+gas group and 19 eyes (86.4%) in the monotherapy group received

**Table 2.** Visual and Anatomic Outcomes After Treatment for SMH Associated With PCV.

| Parameter | Aflibercept+Gas | Aflibercept Alone | *P* Value |
|---|---|---|---|
| Mean logMAR BCVA ± SD | | | |
| At 12 months | 0.26 ± 0.42 | 0.85 ± 0.57 | <.001 |
| At final follow-up visit | 0.22 ± 0.35 | 0.88 ± 0.59 | <.001 |
| Mean change in BCVA (post-pre) ± SD | | | |
| At 12 months | −0.52 ± 0.55 | +0.02 ± 0.75 | .003 |
| At final follow-up visit | −0.50 ± 0.49 | +0.04 ± 0.80 | <.001 |
| CRT at 12 months (μm) | | | .156 |
| Mean ± SD | 219 ± 67 | 369 ± 429 | |
| Range | 90, 398 | 47, 1722 | |
| Central PED thickness at 12 months (μm) | | | .175 |
| Mean ± SD | 13 ± 31 | 66 ± 166 | |
| Range | 0, 141 | 0, 332 | |
| Macular fibrosis at 12 months, n (%) | 0 | 7 (32) | .003 |
| IVT aflibercept injections over 12 months (n) | | | .293 |
| Mean ± SD | 5.2 ± 2.8 | 4.4 ± 2.3 | |
| Range | 1, 12 | 1, 8 | |
| Change in BCVA at 12 months, n (%) | | | .004 |
| Improved | 15 (60) | 4 (18) | |
| No change | 9 (36) | 11 (50) | |
| Deteriorated | 1 (4) | 7 (32) | |
| Change in BCVA at final follow-up visit, n (%) | | | .002 |
| Improved | 14 (56) | 3 (14) | |
| No change | 10 (40) | 11 (50) | |
| Deteriorated | 1 (4) | 8 (36) | |
| Complications after treatment, n (%) | | | |
| Visually significant VH | 4 (16) | 3 (14) | 1.000 |
| RRD | 1 (4) | 0 | 1.000 |

Abbreviations: BCVA, best-corrected visual acuity; IVT, intravitreal; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RRD, rhegmatogenous retinal detachment; SMH, submacular hemorrhage; VA, visual acuity; VH, vitreous hemorrhage.

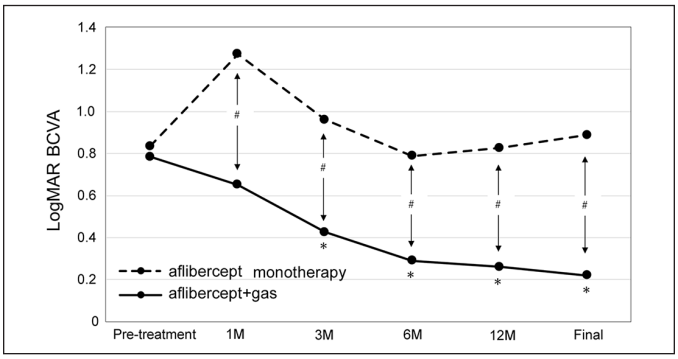


**Figure 3.** BCVA outcomes (*$P < .05$ compared with baseline visual acuity; #$P < .05$ between the groups).
Abbreviation: BCVA, best-corrected visual acuity.

additional IVT injections of aflibercept to reduce the neovascular activity associated with the PCV. Over 12 months, the mean number of additional injections of aflibercept (excluding the initial injection) was 4.2 ± 2.7 (range, 0-11) in the aflibercept+gas group and 3.4 ± 2.3 (range, 0-7) in the monotherapy group ($P = .274$). No additional injections were required after the initial injection in 4 eyes (8.5%) because there was no recurrent exudation. Two of these 4 eyes had macular fibrosis, and the other 2 eyes had macular atrophy.

## *Factors Associated With Visual Outcomes*

Table 3 shows the factors associated with logMAR BCVA at 12 months based on univariate regression analysis. The analysis showed that the better BCVA at 12 months was significantly associated with the use of gas ($P < .001$), a younger age ($P = .005$), a smaller baseline SMH ( $P < .001$), a lower CRT ($P = .017$), a lower PED thickness ($P = .022$), the absence of an organized hemorrhage ($P = .004$), the disappearance of SMH at 1 week ($P < .001$), a lower RD height at 1 month ($P < .001$), and an intact EZ at 12 months ($P < .001$). A trend toward better BCVA at 12 months was seen in eyes with a better baseline BCVA and fewer anticoagulant medications; however, this trend was not statistically significant ($P = .052$ and $P = .064$, respectively). The duration of SMH was not associated with the BCVA at 12 months ($P = .709$).

Table 4 shows the factors associated with changes in BCVA at 12 months based on univariate regression analysis. The visual improvement at 12 months was significantly associated with the use of gas ($P = .008$), a smaller baseline SMH ($P = .017$),

**Table 3.** Factors Associated With LogMAR BCVA at 12 Months Based on Univariate Regression Analysis.

| | Univariate Linear Regression | | |
|---|---|---|---|
| Variable | Regression Coefficient | $R^2$ | *P* Value |
| Gas injection (yes: 1, no: 0) | −0.565 | 0.252 | <.001 |
| Age (y) | 0.024 | 0.163 | .005 |
| Sex (male: 0, female: 1) | −0.134 | 0.012 | .488 |
| Disc diameter of SMH | 0.021 | 0.261 | <.001 |
| Symptom duration | −0.0056 | 0.0032 | .709 |
| Anticoagulant medication (yes: 1) | 0.378 | 0.081 | .052 |
| Baseline logMAR BCVA | 0.276 | 0.074 | .064 |
| Baseline CRT | 0.0005 | 0.120 | .017 |
| Baseline PED thickness | 0.0009 | 0.111 | .022 |
| Baseline height of the RD | 0.0036 | 0.034 | .218 |
| Baseline organized hemorrhage (yes: 1) | 0.224 | 0.167 | .004 |
| Displacement of SMH at 1 week (yes: 1) | −0.643 | 0.320 | <.001 |
| Height of the RD at 1 month | 0.0019 | 0.344 | <.001 |
| Intact EZ at 12 months (intact: 1, disrupted: 0) | −0.622 | 0.267 | <.001 |

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; EZ, ellipsoid zone; PED, pigment epithelial detachment; RD, retinal detachment; SMH, submacular hemorrhage.

**Table 4.** Factors Associated With Changes in BCVA at 12 Months Based on Univariate Regression Analysis.

| | Univariate Linear Regression | | |
|---|---|---|---|
| Variable | Regression Coefficient | $R^2$ | *P* Value |
| Gas injection (yes: 1, no: 0) | 0.515 | 0.146 | .008 |
| Age (y) | −0.013 | 0.030 | .246 |
| Sex (male: 0, female: 1) | −0.021 | 0.0002 | .930 |
| Disc diameter of SMH | −0.017 | 0.012 | .017 |
| Symptom duration | −0.013 | 0.011 | .481 |
| Anticoagulant medication (yes: 1) | −0.214 | 0.018 | .366 |
| Baseline logMAR BCVA | 0.724 | 0.355 | <.001 |
| Baseline CRT | −0.0002 | 0.016 | .395 |
| Baseline PED thickness | −0.0009 | 0.092 | .038 |
| Baseline height of the RD | 0.0002 | 0.010 | .506 |
| Baseline organized hemorrhage (yes: 1) | −0.130 | 0.080 | .053 |
| Displacement of SMH at 1 week (yes: 1) | 0.621 | 0.208 | .001 |
| Height of the RD at 1 month | −0.001 | 0.071 | .085 |
| Intact EZ at 12 months (intact: 1, disrupted: 0) | 0.236 | 0.027 | .272 |

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; EZ, ellipsoid zone; PED, pigment epithelial detachment; RD, retinal detachment; SMH, submacular hemorrhage.

worse baseline BCVA ($P < .001$), a lower PED thickness ($P = .038$), and displacement of the SMH at 1 week ($P < .001$).

## *Complications After Treatment*

A vitreous hemorrhage (VH) developed in 16.0% of eyes 4 days, 7 days, 14 days, and 28 days after the initial treatment in the aflibercept+gas group and in 13.6% of eyes in the monotherapy group 7 days, 14 days, and 28 days after the initial treatment ($P = 1.000$). A rhegmatogenous RD (RRD) developed 4 days after the initial treatment in 4.0% of eyes in the aflibercept+gas group and in no eye in the monotherapy group ($P = 1.000$). In the aflibercept+gas group, 3 eyes with a VH and 1 eye with RD were successfully treated with pars plana vitrectomy (PPV). In the monotherapy group, 1 eye with a VH had a PPV.

At the time of initial treatment, 20 eyes (80%) in the combination group and 16 eyes (73%) in the monotherapy group were phakic. However, a cataract resulting from the use of gas was not observed in any eye. There were no cases of endophthalmitis.

## Conclusions

Our study showed that combining IVT aflibercept with gas injection (pneumatic displacement) resulted in significantly greater BCVA improvement at 12 months and at the final follow-up in patients with SMH associated with PCV than in patients who had treatment with aflibercept alone. Specifically, eyes treated with both aflibercept and gas injection had significantly better BCVA, with 60.0% achieving a visual improvement of 3 lines or more at 12 months; only 18.2% of eyes treated with aflibercept alone achieved a similar improvement. The rationale behind using both aflibercept and gas injection is that gas displaces the SMH (which is toxic to photoreceptor cells) away from the fovea while concurrently reducing PCV activity, the primary cause of the hemorrhage. The better visual outcomes in the combination therapy group support the efficacy of this strategy for the treatment of this condition.

In the combination treatment group, 84% of the cases showed clearance of the SMH from the fovea after 1 week compared with 0% the monotherapy group. This suggests that aflibercept alone may not effectively or rapidly resolve the hemorrhage, potentially leading to macular scar (fibrosis) formation due to the prolonged existence of the hemorrhage. As a consequence, no eye in the combination group had macular fibrosis at 12 months, whereas 31.8% of the eyes in the monotherapy group had macular fibrosis, which was significantly associated with a poor BCVA. Given that the hemorrhages and macular fibrosis are detrimental to photoreceptors, the persistence of a hemorrhage and consequent macular fibrosis under the fovea may have caused significant retinal damage, while pneumatic displacement likely minimized this adverse effect. The better visual outcomes and no fibrosis in the combination group suggest that this treatment modality is effective in reducing the retinal damage associated with SMH, thereby preserving vision.

Several studies have reported the outcomes of anti-VEGF monotherapy for SMH associated with PCV. In a series of 27 eyes treated with bevacizumab or ranibizumab, Cho et al[13] reported a mean VA improvement of 0.26 logMAR at 12 months. Similarly, Kang et al[10] reported a VA improvement of 0.41 logMAR 12 months after treatment with IVT bevacizumab in 22 eyes with SMH associated with PCV. In contrast, and aligning with our findings, Inoue et al[9] reported no improvement in VA, with a slight deterioration of 0.02 logMAR over a mean follow-up of 18.1 months after anti-VEGF therapy for AMD, which predominantly included PCV. Compared with these studies, in the current study the improvement in BCVA of 0.52 logMAR at 12 months and 0.50 logMAR at the final visit in patients treated with the aflibercept combined with gas are favorable and better than the values reported previously after anti-VEGF injection was used alone to treat SMH associated with PCV.

In a study by Shin et al,[18] there was no significant difference in the overall visual outcomes at 6 months between combination therapy (anti-VEGF and pneumatic displacement) and anti-VEGF monotherapy for AMD-related SMH. However, in eyes with a hemorrhage thicker than 450 μm, combination therapy led to significantly better BCVA than monotherapy at 6 months. In our study, combination therapy was performed for SMHs of 551 ± 328 μm (mean thickness greater than 450 μm), resulting in significantly better VA outcomes. These results suggest that patients with a thicker hemorrhage may benefit more from combination therapy.

In the current study, univariate regression analysis showed that improved BCVA at 12 months was significantly associated with gas injection, younger age, a smaller baseline SMH, a thinner CRT and PED, the absence of an organized hemorrhage, and the absence of macular fibrosis, indicating that combination therapy leads to better outcomes in cases with a less severe hemorrhage. Younger patients may have recovered better or possibly adhered more rigorously to postoperative positioning, although we could not evaluate the adherence to facedown positioning. However, the symptom duration did not correlate with the visual outcomes.

Theoretically, recent hemorrhages are more amenable to pneumatic displacement; however, individual clotting times can vary, and patients with a recent SMH that is likely to be displaced with gas, regardless of duration, may benefit from pneumatic displacement. Although we did not include cases of highly chronic, organized SMH, because we do not consider pneumatic displacement effective for such patients, our study suggests that some organization within the hemorrhage may negatively affect vision despite treatment. Therefore, initiating treatment before the onset of coagulation is preferred. The relationship between the duration of the SMH and visual outcomes remains inconsistent in other studies of SMH associated with AMD.[19–21] Thus, further studies are needed to clarify these associations.

Although combination therapy with aflibercept and gas showed greater efficacy than aflibercept alone, our treatments were not without complications. Similar to previous studies on the treatments for an SMH,[12,22] a VH occurred in 16.0% of eyes treated with aflibercept and gas, compared with 13.6% with aflibercept monotherapy. In addition, 1 eye developed an RRD after the aflibercept and gas injection. Given that the incidence of RD after anti-VEGF injection in eyes with AMD is 1 in 7 532 to 11 941,[23,24] the use of gas may increase the risk for RD. We could not elucidate the exact cause of RD; however, we speculate that the gas may have promoted the progression of posterior vitreous detachment and subsequent development of the retinal break.

Despite these concerns, based on the current results, the visual outcomes of combination therapy are promising. However, patients should be informed before treatment regarding the potential need for additional surgery. All patients who required PPV for their VH and RD experienced successful surgeries, with each patient requiring only a single surgery. This suggests that although the risks are non-negligible, they can be managed with subsequent surgery.

Limitations of our study include its retrospective design and the relatively small number of patients, which was the result of the rarity of large SMHs in eyes with PCV. In addition, we did not evaluate the potential efficacy of adding IVT tPA. We used $C_3F_8$ gas for pneumatic displacement under the rationale that it can expand up to 4 times its original volume within 72 to 96 hours, resulting in a longer retention time and potentially greater

effectiveness for pneumatic displacement. However, based on our experience, sulfur hexafluoride gas is also effective, and the advantages and disadvantages of each should be examined in future studies. In addition, of the 25 eyes receiving combination therapy, 20 had IVT aflibercept and gas injection on the same day, whereas aflibercept was injected in 5 eyes within 1 week before or after the gas injection.

In conclusion, this comparative study showed a significant benefit of IVT aflibercept and pneumatic displacement with gas compared with aflibercept monotherapy as a treatment for SMH associated with PCV. The vision outcomes were better, and the risk for complications was acceptable. A larger prospective study is needed to validate our results and to determine the optimal treatment protocol.

## Ethical Approval

Ethical approval for this study was obtained from the Institutional Review Board, Osaka University Hospital (10039), and adhered to the tenets of the Declaration of Helsinki.

## Statement of Informed Consent

Verbal informed consent was obtained from legally authorized representatives before the study.

## Declaration of Conflicting Interests

None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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