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Original Article

Efficacy of Simultaneous Application of Subretinal Tissue Plasminogen Activator and Bevacizumab for Submacular Hemorrhages

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Abstract

Objectives: The aim of the study was to evaluate the patients who received simultaneous subretinal tissue plasminogen activator (tPA) and bevacizumab for submacular hemorrhages secondary to neovascular age-related macular degeneration.

Methods: This retrospective study included patients who underwent pars plana vitrectomy (PPV) with simultaneous subretinal tPA and subretinal bevacizumab with 18% SF6 tamponade. Anatomical and functional results of the patients before surgery and at the 1st, 6th, and 12th months after surgery, additional treatments, and complications after PPV were evaluated.

Results: Eight eyes of eight patients were included in the study. The mean age of the patients was 72.38±92.3. The mean time from the onset of symptoms to treatment was 5.13±1.88 days. The patients' mean best-corrected visual acuity (BCVA) was 2.23±0.14 logMAR at baseline. Mean BCVA increased significantly at 1st, 6th, and 12th months to 1.68±0.47 logMAR, 1.58±0.49 logMAR, and 1.51±0.58 logMAR, respectively (p=0.001 at all). The mean central foveal thickness (CFT) in measurable patients was 836.8±627.02 µm at baseline. Mean CFT decreased significantly to 370.13±66.13 µm in the 1st month, 373.38±78.33 µm in the 6th month, and 367.75±116.43 µm in the 12th month (p<0.05). The maximum measurable subretinal hemorrhage height at baseline was 814.2±556.45 µm. The mean number of anti-VEGFs performed for 12 months after surgery was 4.13±2.1. At month 12, the ellipsoid zone could not be detected in 6 (75%) patients.

Conclusion: Administration of subretinal bevacizumab and subretinal tPA effectively removes subretinal hemorrhage under the fovea. Intravitreal anti-VEGF treatment must be continued, as choroidal neovascular membrane activity continues after surgery.

Keywords: Age-related macular degeneration, bevacizumab, pars plana vitrectomy, subretinal hemorrhage, subretinal tPA

Introduction

Submacular hemorrhages (SMH) is the accumulation of blood between the neurosensory retina and the retinal pigment epithelium (RPE) and is an important cause of sudden visual loss (1). SMH can arise from the choroidal neovascular membrane (CNVM) secondary to neovascular age-related macular degeneration (AMD), arterial macroaneurysm, severe trauma, polypoidal choroidal vasculopathy, myopic CNVM, angioid streaks, and intraocular tumors (2). The natural history of untreated SMH is poor. SMH secondary to neovascular AMD is the cause with the worst prognosis (3). Especially if there is a large size and very thick SMH related to CNVM in neovascular AMD has a poor prognosis if untreated or delayed in the treatment (4).

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Well-known causes of visual impairment after SMH are the barrier effect of the blood accumulating between the RPE and the photoreceptors that disrupt the nutrition of the photoreceptors from the choroidal blood flow, the toxic effect of the released iron to photoreceptors and RPE cells, the mechanical photoreceptor damage caused by the contraction of the released fibrin, and fibrotic scar tissue occurring secondary to long-term SMH (5). Hattenbach et al. (6) found a higher proportion of patients who improved two or more Snellen lines among those with a duration of SMH ≤14 days than among those with a duration of SMH >14 days. For these reasons, early treatment of these patients is very important to prevent irreversible vision loss.

Generally, because of the poor natural history of SMH secondary to neovascular AMD, many researchers have explored various treatments. The methods used in the treatment of SMH at an early stage are intravitreal or subretinal tissue plasminogen activator (tPA) injection, pneumatic displacement, intravitreal or subretinal anti-VEGF injection, and a combination of these techniques with or without pars plana vitrectomy (PPV). Surgical removal of the SMH through small or large retinal incisions, macular translocation, and RPE choroid grafts are the treatment methods used in the long-standing SMH (7-9).

In this study, we evaluated the patients who received simultaneous subretinal tPA and bevacizumab for SMH secondary to neovascular AMD with functional and anatomical results in 12-month follow-up.

Methods

The protocol of the present study conformed to the Declaration of Helsinki. The study protocol ethics approval number was B.10.1.TKH.4.34.H.GP.0.01/173 (May 27, 2022).

Data Collection

In this retrospective study, we reviewed the medical records of all cases of SMH secondary to neovascular AMD occurring from 2016 to 2022. A detailed medical and ocular history, age, gender, documentation of medications, days to the presentation of symptoms to treatment, best-corrected visual acuity (BCVA) on Snellen charts, anterior and posterior segment examinations, intraocular pressure with Goldman applanation tonometry, optical coherence tomography (OCT) (Optovue, RTVue 100, CA, USA) findings, and length of follow-up were collected from the patient's charts. Furthermore, color fundus photography, fundus fluorescein angiography, and indocyanine green angiography were performed and collected preoperatively and postoperatively if needed. The data obtained before surgery and at the 1st, 6th, and 12th months after surgery were evaluated.

Inclusion Criteria

The following criteria were included in the study:

1. Patients with SMH secondary to neovascular AMD,
2. Patients with SMH that involved the center of the fovea with at least one disk diameter,
3. Patients treated with PPV, subretinal tPA, and subretinal bevacizumab,
4. Patients treated within 10 days of onset of symptoms,
5. Patients with at least 1 year of the follow-up period.

Exclusion Criteria

The following criteria were excluded from the study:

1. Other causes of SMH such as trauma, high myopia, and retinal arterial microaneurysm,
2. 2-Patients with inadequate data.

Measurements of OCT and Fundus Parameters

The caliper function of the OCT was used to measure the maximal SMH height and central foveal thickness (CFT). The maximum height of SMH was defined as the maximum distance between the upper surface of the SMH and the inner surface of the RPE. CFT was defined as the distance between the internal limiting membrane and Bruch's membrane. The maximum lateral width of the SMH was measured based on fundus photography and defined as the maximal distance between the terminations of the SMH. The Ellipsoid zone (EZ) was demarcated as the hyperreflective band above the RPE and EZ integrity was evaluated in the central 1 mm area. The maximum height and lateral width of SMH, CFT, and EZ integrity were estimated by a single examiner (U.L.).

Ocular Ultrasonography

In patients to whom the maximum SMH height could not be measured with OCT, the mean SMH height was measured with ocular ultrasonography.

Surgical Technique for SMH Treatment

All surgeries were performed by the same surgeon (U.L.) under retrobulbar or general anesthesia in the operating room. Information was given about the surgery's risks and benefits and then written informed consent was obtained from each patient. All cases were treated with PPV and subretinal bevacizumab (Altuzan, Roche, Basel, Switzerland), and subretinal tPA (Actilyse, 10 mg/mL, Boehringer-Ingelheim, Germany) with 18% SF6 tamponade. Combined phacoemulsification was done in patients with cataracts for best visualization. One-piece acrylic hydrophobic monofocal intraocular lens implantation was done in these patients' posterior chambers.

A standard transconjunctival three-port 23-gauge PPV was done with a constellation vision system (Alcon Laboratories, Inc. Fort Worth, Texas, USA). After a core vitrectomy was performed, intravitreal triamcinolone (40 mg/mL, Kenacort-A, DEVA) was used to visualize and remove the adherent posterior hyaloid if not already present a posterior vitreous detachment. We injected 25 μg/0.1 or 0.2 mL tPA and bevacizumab 1.25 mg/0.05 mL into subretinal space with a 41G flexible cannula at two or three separate sites to detach the retina from the underlying hemorrhage. The inferior retina was pene-

trated approximately 3 disc diameters from the fovea to make an inferior retinal detachment extending outside the inferior arcade for the accumulation of the liquefied hemorrhage with tPA. After checking the peripheral retina, intravitreal 18% SF6 gas tamponade was then administered. The cannulas were removed, and sclerotomy sites were sutured with vicryl 7.0. The patients were asked to keep in a supine position for 2 h after surgery to allow the tPA to spread sufficiently in the subretinal area. Then patients were instructed to head at a 45° angle to the ground for 24 h postoperatively. Afterward, the patients were asked to keep in a prone position for 5 days.

Complete displacement of SMH was defined as no hemorrhage or only a minimal amount of hemorrhage <1 disc diameter of the foveal center.

Re-treatment Criteria

Patients were re-treated with pro-re-nata anti-VEGF protocol with monthly visits. Re-treatment criteria were new or persistent intraretinal or subretinal fluid on OCT and visual acuity loss of 1 or more lines at monthly visits.

Primary Outcome Measures

Primary outcomes were changes in BCVA and anatomical improvement from baseline over the follow-up period.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 24.0 program was used for statistical analysis. While evaluating the study data, Independent Sample T was used for two-group comparisons of normally distributed parameters as well as descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, and Maximum). The repeated measures test was used to compare the changes seen over time according to positions. Pearson Correlation analysis was used to determine the relationship between the measurements. Significance was evaluated at $p<0.05$ levels (Mod statistic, Istanbul-Türkiye).

Results

The medical records of 11 cases of SMH secondary to neovascular AMD were reviewed. Eight eyes of eight patients whose data were fully available and met the criteria for entrance into the study were included in the study.

Baseline Characteristics

The mean age of the patients was 72.38±92.3. The mean time from the onset of symptoms to treatment was 5.13±1.88 days. The mean follow-up period was 15.38±5.01 months. The mean number of previously given anti-VEGF injections was 3.63±2.39 in 3 (37.5%) patients. In these three patients, the mean time from the last injection to SMH was 3.67±0.58 months. Five patients did not take any anti-VEGF injections before SMH. Table 1 shows the baseline characteristics of the patients.

Table 1. Baseline and demographic characteristics of the patients

Gender, n (%)	
Female	5 (62.5)
Male	3 (37.5)
Age, year mean±SD	72.38±92.3
Right eye, n (%)	3 (37.5)
Left eye, n (%)	5 (62.5)
The onset of symptoms to treatment, day, mean±SD	5.13±1.88
Hypertension, n (%)	8 (100)
CAD, n (%)	4 (50)
Diabetes, n (%)	3 (37.5)
Anticoagulant usage (aspirin or other platelet inhibitor and/or warfarin), (n/%)	6 (75)
Lens	
Phakic, n (%)	3 (37.5)
Pseudophakic, n (%)	5 (62.5)
BCVA, (logMAR)	2.23±0.14
CFT, µm	836.8±627.02
IOP, mmHg	14.88±2.23
MLW, µm	8.400±615.55
MHH, µm	814.2±556.45

Visual Outcomes

The patients' mean BCVA was 2.23±0.14 logMAR (hand movement) at baseline. The mean BCVA increased significantly in the 1st, 6th, and 12th months to 1.68±0.47 logMAR, 1.58±0.49 logMAR, and 1.51±0.58 logMAR, respectively (p=0.001 at all 3 months from baseline). At month 12, all patients' visual acuity was better than at baseline. Table 2 shows the summary of the cases.

Anatomical Outcomes

The mean maximum measurable SMH height in five patients at baseline was 814.2±556.45 µm. The maximum SMH height could not be measured with OCT in two patients due to too high SMH and in one patient due to vitreous hemorrhage. In these patients, the mean SMH height was 2.5 mm in ocular ultrasonography. The mean maximum lateral width of the SMH at baseline was 8.400±615.55 µm. The maximum lateral width of the SMH could not be measured in one patient due to vitreous hemorrhage. Complete inferior displacement of SMH from the fovea was achieved in all eyes at month 1.

CFT could not be measured by OCT in three patients at baseline. The mean CFT in measurable patients was 836.8±627.02 µm at baseline. Mean CFT decreased significantly to 370.13±66.13 µm in the 1st month, 373.38±78.33 µm in the 6th month, and 367.75±116.43 µm in the 12th month (p<0.05). EZ was not detectable in any of the patients at baseline. At month 12, while the EZ could be partially selected in 2 (25%) patients, it could not be detected in 6 (75%) patients.

Correlation Analysis

There was no correlation between BCVA and CFT at month 12 with age, the onset of symptoms to treatment, the maximal SMH height, and the maximum lateral width of SMH (Table 3).

Intravitreal Re-injections

Seven (87.5 %) patients required additional intravitreal bevacizumab treatment during the follow-up period. In these patients, the mean number of intravitreal bevacizumab injections performed for 12 months after surgery was 4.13±2.1. One (12.5%) patient did not require further treatment with an additional intravitreal bevacizumab injection. At month 12, only 1 (12.5%) patient had subretinal fluid on OCT, and the other patients did not need additional injections.

Complications

There were no intraoperative complications in any of the patients. RPE rupture developed in one patient in the 4th month after intravitreal bevacizumab injection. In 1 of the eyes, re-hemorrhage without foveal involvement has occurred in post-operative month 2. It was managed with additional anti-VEGF injections.

Color fundus photographs of the four representative patients are shown in Figures 1-4.

Discussion

The current study investigated the effect of simultaneous subretinal tPA and bevacizumab in patients with SMH secondary to neovascular AMD with functional and anatomical results in 12-month follow-up. Our favorable results indicate

Table 2. Summary of the cases

Case	Age(year)/ Gender (F/M)	Days to presentation	BCVA at presentation (logMAR)	CFT at presentation (µm)	MHH at presentation (µm)	MLW at presentation (µm)	BCVA at month 12 (logMAR)	CFT at month 12 (µm)	Postop number of bevacizumab injections
1	73/M	4	2.3	-	-	1410	1.3	557	6
2	69/F	4	2	504	356	640	1	248	6
3	62/F	4	2	512	564	430	0.5	251	3
4	77/M	7	2.3	-	-	-	2	232	0
5	58/F	3	2.3	-	-	810	2	354	3
6	84/F	4	2.3	556	521	920	1.3	454	6
7	83/M	8	2.3	659	880	720	2	390	4
8	73/F	7	2.3	1953	1750	980	2	476	5

F: Female; M: Male; logMAR: Logarithm of the minimum angle of resolution; CFT: Central foveal thickness; MHH: Maximal submacular hemorrhage height; MLW: The maximum lateral width of submacular hemorrhage.

Table 3. Correlation analysis

	BCVA at month 12	CFT at month 12
Age		
r	0.257	0.252
p	0.539	0.548
Onset of symptoms to treatment (day)		
r	0.438	0.013
p	0.277	0.976
Maximal SMH height (μm)		
r	0.667	0.700
p	0.219	0.188
Maximum lateral width of SMH (μm)		
r	0.472	0.357
p	0.237	0.385

r=Spermans' correlation; BCVA: Best-corrected visual acuity; CFT: Central foveal thickness; SMH: Submacular hemorrhage.

that mean BCVA improvement and CFT decrease were statistically significant at all follow-up visits. At the same time, we have shown that repeated injections are required to maintain the increase in visual acuity. Moreover, our findings demonstrate that there was no correlation between BCVA and CFT at month 12 with the maximal SMH height, and the maximum lateral width of SMH.

Ibanez et al. (10) created a retinotomy for surgical management of SMH in 47 consecutive cases and reported SMH secondary to AMD had a poor visual prognosis, with or without surgical drainage. Because of the unsuccessful results with surgical removal of SMH, researchers investigated

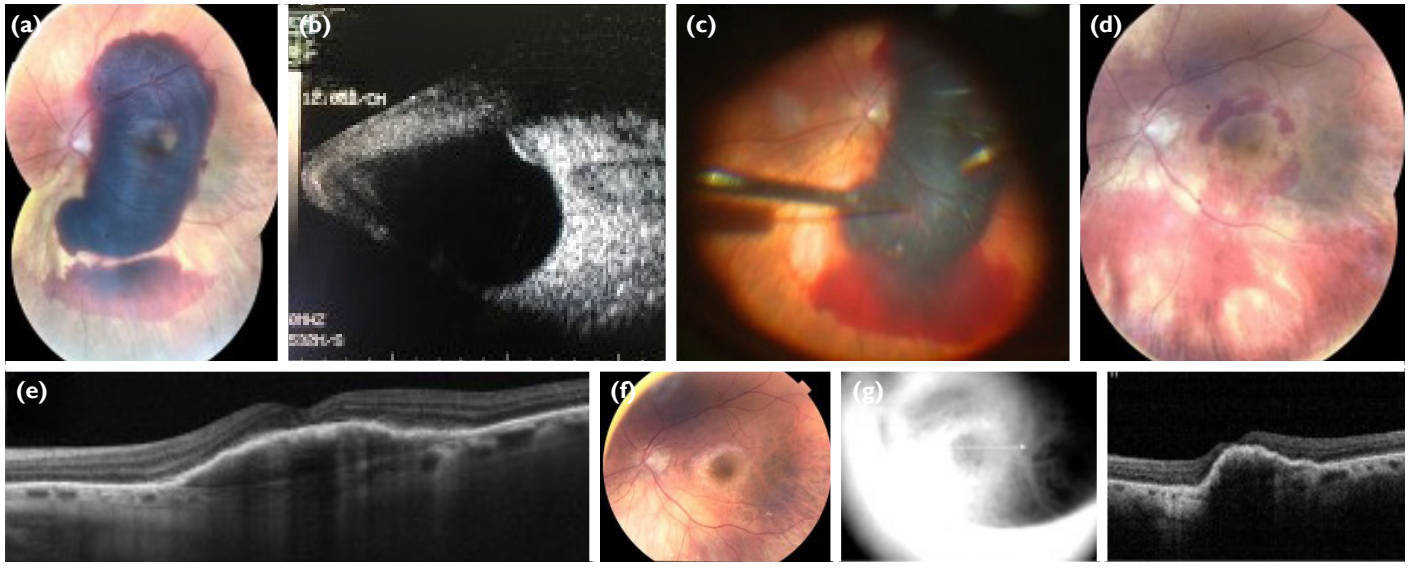

Figure 1. (Case-1) A 73-year-old male patient had a visual loss in his left eye for the past 4 days. His left vision is hand movements. **(a)** The appearance of large subretinal hemorrhage starting above the upper vascular arch and extending below the lower vascular arch in the left fundus image of the patient. **(b)** The appearance of the hemorrhage area in the macula in the horizontal section in the eye ultrasonography of the patient whose OCT image could not be obtained. **(c)** The subretinal tPA and bevacizumab injection appear in the intraoperative picture. **(d and e)** Fundus and OCT images were taken at postoperative 2nd week. The patient's visual acuity is 0.05 decimal in the left eye. **(f and g)** Post-operative 6th-month fundus and OCT images of the patient. Subretinal hemorrhage completely regressed, but retinal pigment epithelial (RPE) rupture due to recurrent bevacizumab injections is seen. Pigment epithelial detachment (PED) continues.

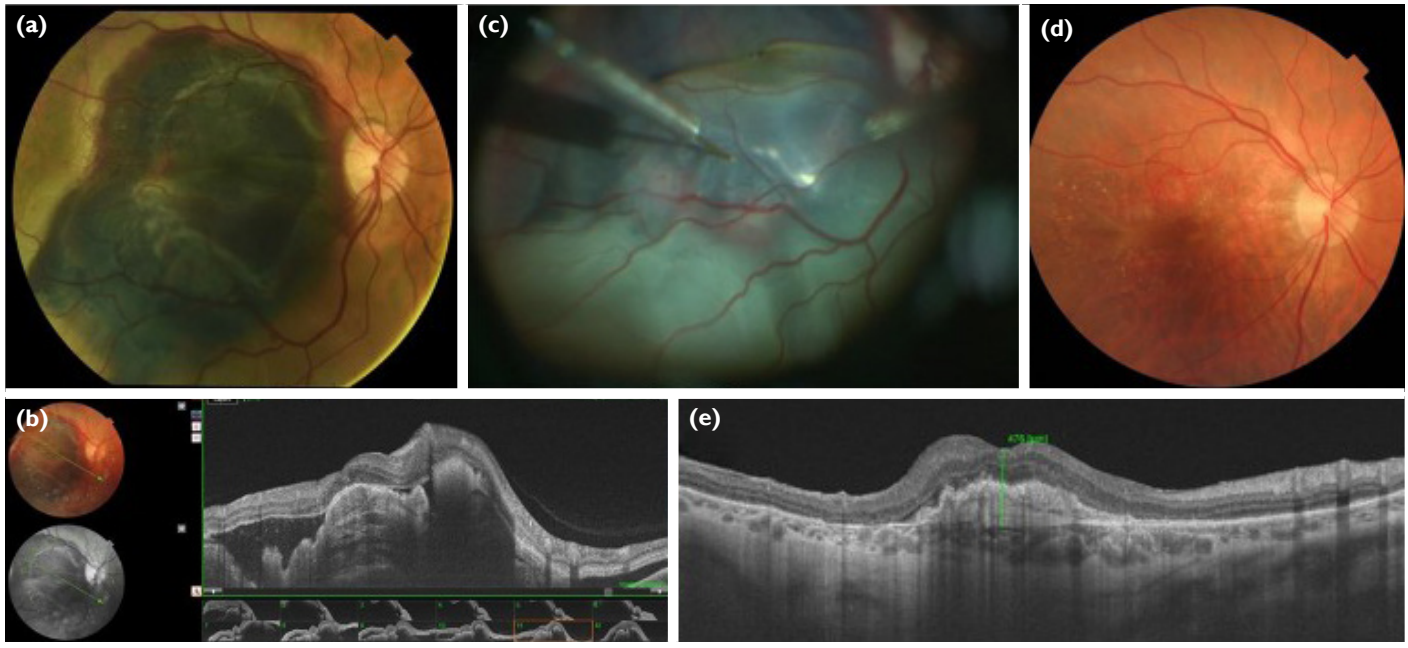

Figure 2. (Case-8) A 73-year-old female patient had vision loss in her right eye for the past 7 days. Her right eye visual acuity was hand movements. **(a)** The appearance of large and raised subretinal hemorrhage extending to the superior and inferior vascular arches in the patient's right fundus image. **(b)** The appearance of subretinal hemorrhage on the OCT image. **(c)** Creation of retinal detachment in the inferior retina with subretinal tPA and bevacizumab injection in the intraoperative image. **(d and e)** Fundus and OCT images taken at months 12 postoperatively. Subretinal fibrous tissue seen on OCT is an indicator of poor prognosis. The patient's right visual acuity was 2 mps. The number of anti-VEGFs performed for 12 months after surgery is 5.

possible ways to remove SMH. The tPA is a fibrinolytic agent. It has been used in the treatment of systemic and ocular conditions such as acute myocardial infarction, post-cataract, or vitrectomy fibrin reaction (11,12). In animal experimental models, it was shown that up to 50 µg/mL tPA administered to subretinal space is not toxic (13). With the application of subretinal tPA, the SMH liquefies and can be displaced to an area other than the fovea. However, in patients with subretinal tPA applications over 50 ug/ml dose, mild retinal pigment epithelial degenerative changes, exudative retinal detachment, and electroretinogram changes including a prolonged implicit time and reduced amplitude of the A-wave were reported (14). Therefore, we used a maximum dose of 50 µg/mL of subretinal tPA in our study. In one patient with a maximum lateral width of SMH lower than 600 µm we used 25µg/mL of subretinal tPA and in the other seven patients with a maximum lateral width of SMH >600 µm we used 50 µg/mL of subretinal tPA.

Kamei et al. (15) investigated the ability of tPA to diffuse into the subretinal space after intravitreal injection into the rabbit eyes. They reported intravitreal tPA did not diffuse through the intact retina to the subretinal space. Intravitreal injection of tPA is a less-invasive method however, Hassan et al. (16) reported that SMH was partially displaced and intravitreal hemorrhage developed after intravitreal tPA application. Therefore, we preferred to use subretinal tPA in our study.

Similar to our study results with adding subretinal bevacizumab to subretinal tPA successful results have been reported in the treatment of SMH secondary to neovascular AMD. Avcı et al. (17) co-applicated subretinal tPA and bevacizumab with C3F8 tamponade for SMH secondary to neovascular AMD. They reported that PPV with C3F8 tamponade with submacular tPA and bevacizumab injection appears to provide adequate displacement of the SMH, resulting in significant visual acuity improvement in patients with hemorrhagic neovascular AMD. Kumar et al. (18) investigated a modified approach in the management of SMH secondary to neovascular AMD. They applicated the mixture of tPA, bevacizumab, and air to create a localized bullous detachment encompassing and extending a little beyond the hemorrhage with 20% SF6 gas tamponade. They reported achievement of displacement of the submacular hemorrhage in all cases. They also reported improvement of BCVA in eight of ten patients and re-hemorrhage in 2 eyes.

This current study has revealed that BCVA gradually increased in the 1st, 6th, and 12th months after surgery. Regular intravitreal bevacizumab injections during the 12-month follow-up period are important in achieving this. Because recurrent bleeding and subretinal and intraretinal fluid accumulation occur due to ongoing CNVM activity. During the 12-month follow-up, our patients received an average of 4.13 intravitreal bevacizumab injections, and only 1 pa-

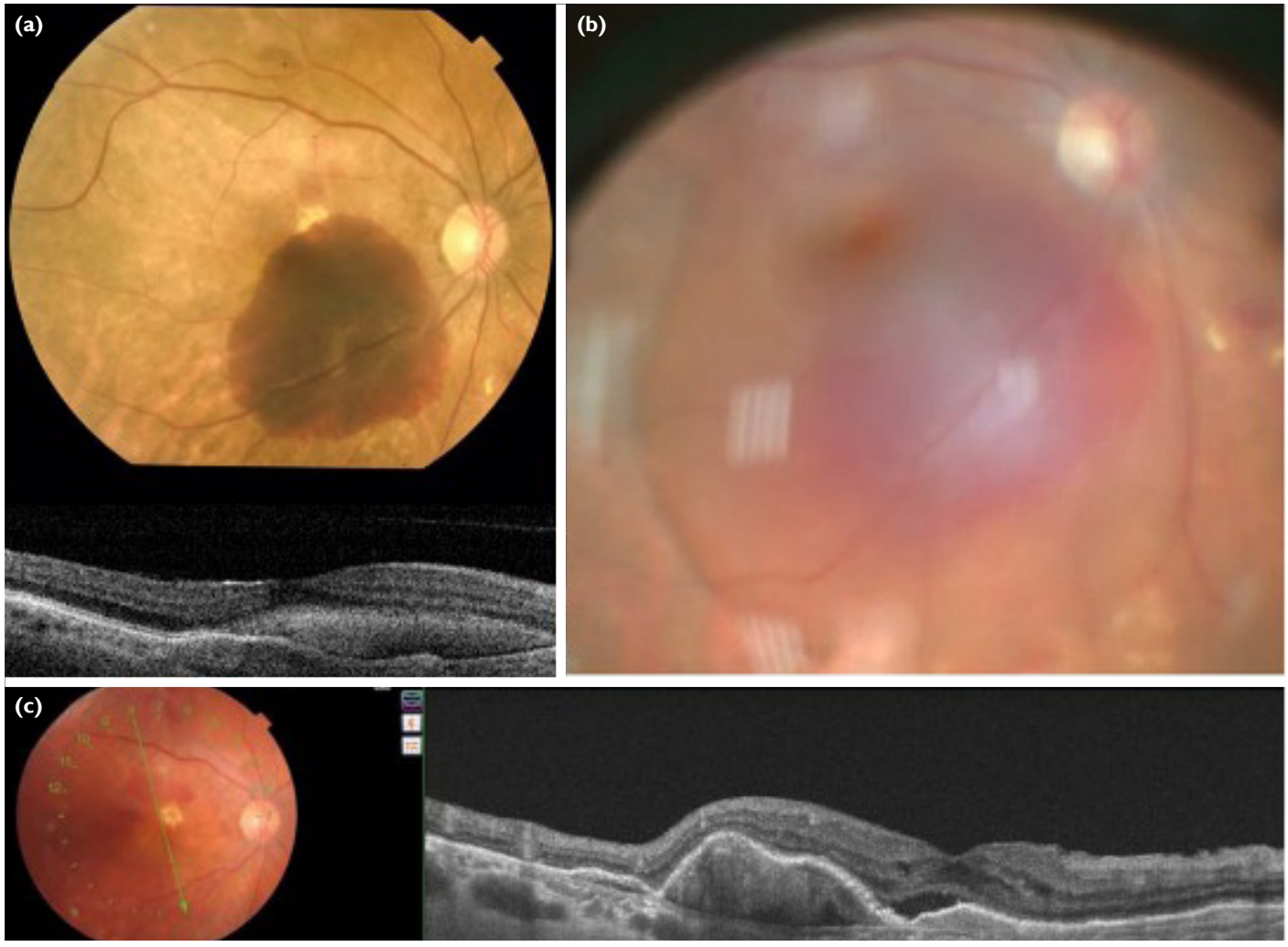

Figure 3. (Case-2) A 69-year-old female patient is being followed in our clinic for AMD. The patient, who could not receive anti-VEGF treatment due to the pandemic, applied to our clinic due to loss of right vision for the past 4 days. The patient was last treated with anti-VEGF 3 months ago. Right visual acuity was 1mps. **(a)** Subretinal hemorrhage extending to the lower half of the macula is seen in the right fundus and OCT image of the patient. **(b)** In the intraoperative picture of the patient, retinal detachment formed after subretinal tPA and bevacizumab injection is seen. **(c)** Despite 6 intravitreal anti-VEGF injections after surgery, PED and subretinal fluid persist in the month 12 on OCT. Left visual acuity was 0.1 decimal.

tient still needed additional injections per month 12. Chang et al. (19) investigated the management of thick SMH with subretinal tPA and pneumatic displacement for AMD. They reported that patients who continued anti-VEGF treatment after surgery were able to maintain their increased visual acuity at 6 months. Furthermore, they reported that, although the efficacy of anti-VEGFs decreases in vitrectomized eyes, CNVM continues to progress even after the development of thick SMH, and that ongoing anti-VEGF therapy in these eyes may help maintain post-displacement visual acuity.

Glatt and Machemer (20) showed that photoreceptor damage occurred in 24 h in their experimental subretinal hemorrhage study in rabbits. Bennett et al. (21) investigated the prognostic factors of visual outcome in patients with subretinal hemorrhage. They reported patients with SMH secondary to neovascular AMD had poorer final visual acuity than trauma and macroaneurysm. They also reported patients with very height SMH had worse final visual acuity than patients with thin SMH. The lateral width of the SMH was not a significant predictor of the outcome.

Schulze and Hesse (22) investigated tPA plus gas injection in patients with SMH caused by AMD to find the predictive variables for visual outcomes. They reported most of their patients who had a better prognosis were treated within 2 weeks after the bleeding. In addition, SMH with a longer duration is less likely to liquefy with subretinal tPA and it will be more difficult to displace it to the periphery. Therefore, early removal of SMH secondary to neovascular AMD could prevent visual loss. In our study, the mean onset of symptoms to treatment day was 5.13 days and we achieved complete SMH displacement at month 1 in all patients.

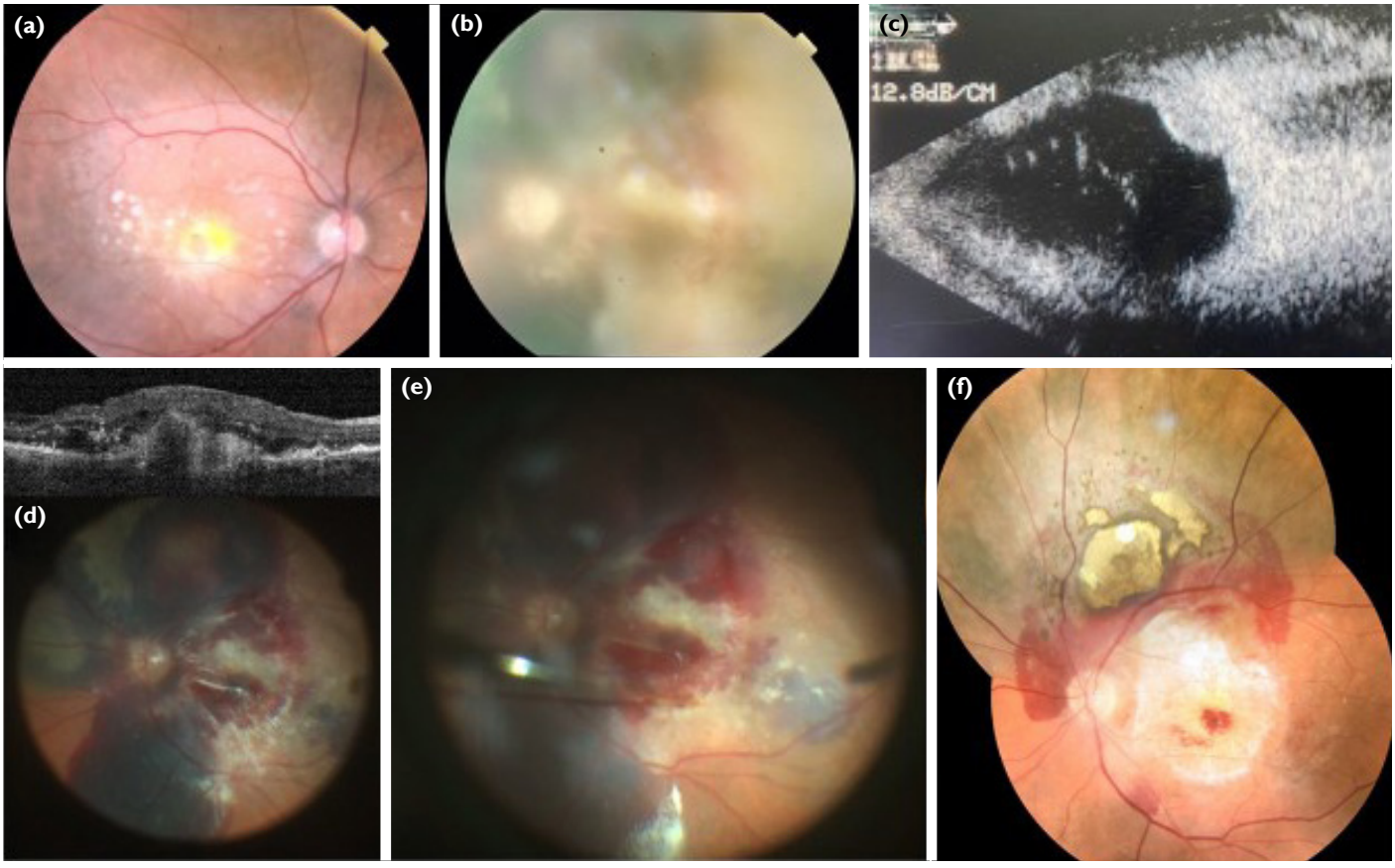

Figure 4. (Case-4) A 77-year-old male patient was admitted to our clinic with the decreased left vision for the past 7 days. **(a)** The patient's right fundus and OCT images show a fibrotic scar in his right eye. **(b)** There is a vitreous hemorrhage in the left fundus picture of the patient. A careful examination of the left fundus reveals subretinal hemorrhage under the retinal vessels. **(c)** A hemorrhage area is seen in the horizontal section of left eye ultrasonography. **(d)** Diffuse subretinal hemorrhage is seen after clearing the vitreous hemorrhage in the intraoperative image **(e)** subretinal tPA and bevacizumab injection. **(f)** Subretinal hemorrhages regressed in the fundus image in the 1st month postoperatively, but there is extensive atrophy in the fovea. The patient's left eye visual acuity was 2 mps.

In Hirashima et al. (23) study, OCT findings and surgical outcomes of tPA-assisted vitrectomy for SMH secondary to AMD were investigated. They reported that the mean height of the SMH was 557.6 μm and the mean lateral width of the SMH was 8,420.8 μm. The pre-operative status of the EZ was detectable in 4 eyes and absent in the remaining 5 eyes. Furthermore, they reported eyes with preoperative SMH heights <400 mm exhibited better BCVA and after a mean follow-up of 16.8 months, the BCVA was 0.97 logMAR.

Our results demonstrated that there was no correlation between BCVA and CFT at month 12 with the maximal SMH height and the maximum lateral width of SMH. In our study, the mean maximum measurable SMH height in five patients was 814.2 μm (greater than Hirashima et al. study and three patients in our study had a mean 2.5 mm SMH height with ocular ultrasonography) and the mean maximum lateral width of the SMH at baseline was 8400 μm. Furthermore, in our study, EZ was not detectable in any of the patients at baseline, and at month 12, EZ could be partially selected in 2 (25%) patients. At month 12 our patients' mean BCVA was 1.51 logMAR which is less than Hirashima et al. study.

Treumer et al. (24) investigated the long-term outcome of subretinal coapplication of tPA and bevacizumab followed by repeated intravitreal anti-VEGF injections for neovascular AMD with SMH. They reported this technique was effectively displacing the small and large SMHs. They also reported some complications such as inadvertent injection of the tPA and bevacizumab solution into the sub-RPE space in one patient, a macular hole in 1 patient during subretinal injection, and rhegmatogenous retinal detachment in one patient. Hillenkamp et al. (25) co-applicated the tPA and bevacizumab into the subretinal space for exudative AMD with SMH. They reported that co-application of tPA and bevacizumab simultaneously displaced the SMH from the fovea and effectively reduced CNVM activity.

Since CNVM is the main cause of SMH in AMD patients, CNVM activity can be suppressed more effectively by the injection of bevacizumab into the subretinal space than by

intravitreal bevacizumab. Thus, re-hemorrhages can be prevented by early suppressing the activity of the CNVM by applying subretinal bevacizumab injection. Iglicki et al. (26) investigated the application of pneumatic displacement, subretinal air, and tPA: subretinal versus intravitreal aflibercept in naïve SMH due to neovascular AMD. They reported better management of the CNVM, with a statistically significant lower need for anti-VEGF injections when treated with subretinal aflibercept compared to intravitreal application.

Although we did not encounter any intraoperative complications in our study, PRE rupture occurred in one patient, and re-hemorrhage occurred in one patient in the post-operative period. In our study, we slowly injected tPA and bevacizumab into the subretinal space with a 41G needle when the needle tip not facing the macula, and away from the significant sub-RPE hemorrhage confirmed on preoperative OCT after lowering and closing the infusion to prevent macular hole formation and inadvertent injection to sub-RPE space.

The limitations of our study are that it is single-centered, has a retrospective design, lack of a control group, and has a small number of patients. Future prospective studies with a greater number of patients are needed to help clarify the efficacy of subretinal anti-VEGF therapies and tPA for the treatment of CNVM-associated SMH.

Conclusion

SMH is a potentially devastating complication of neovascular AMD and different treatment options have been suggested to manage it. Early administration of subretinal bevacizumab and subretinal tPA effectively removes subretinal hemorrhage from under the fovea. However, intravitreal anti-VEGF treatment must be continued, as CNVM activity continues after surgery to extend the period of post-operative BCVA improvement.

Disclosures

Ethics Committee Approval: The protocol of the present study conformed to the Declaration of Helsinki. The study protocol ethics approval number was B.10.1.TKH.4.34.H.GP.0.01/173 (May 27, 2022).

Peer-review: Externally peer-reviewed.

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Authorship Contributions: Concept – U.L.; Design – U.L., T.A., G.A.; Supervision – U.L.; Resource – U.L., I.O.S.; Materials – U.L.; Data collection and/or processing – U.L., E.B.; Analysis and/or interpretation – U.L.; Literature search – U.L., E.K.; Writing – U.L.; Critical review – U.L., B.I.S.A.

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