

Management of Thick Submacular Hemorrhage With Subretinal Tissue Plasminogen Activator and Pneumatic Displacement for Age-Related Macular Degeneration

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- **PURPOSE:** To evaluate the outcome of pars plana vitrectomy, subretinal tissue plasminogen activator (t-PA) infusion and intraocular gas tamponade with and without postsurgical antivascular endothelial growth factor (VEGF) injection for thick submacular hemorrhage due to exudative age-related macular degeneration (AMD).
- **DESIGN:** Retrospective, comparative, interventional case series.
- **METHODS:** **SETTING:** 2 retina referral centers. The patient population included 101 eyes of 101 patients with neovascular AMD and thick submacular hemorrhage who underwent surgical displacement of the hemorrhage with or without postoperative anti-VEGF injections. Main outcome measures included degree of blood displacement, best and final postoperative visual acuity (VA), and adverse events. Snellen acuity was converted to logMAR for statistical analysis.
- **RESULTS:** All patients were followed for a minimum of 3 months (mean, 15.3 months, range, 3-70 months). In 83 (82%) of 101 eyes, the procedure resulted in complete hemorrhage displacement from the fovea. Mean preoperative VA was 20/2255 (2.05 logMAR). The acuity significantly improved to 20/893 (1.65 logMAR) at month 1 ($P < 0.001$) at month 1; 20/678 (1.53 logMAR) at month 3 ($P < 0.001$), and 20/1150 (1.76 logMAR) at month 12 ($P = 0.002$). Best postoperative visual acuity improved by at least 1 line in 83 (82%) of 101 eyes, and 19.6% of eyes gained 3 lines or more at month 3. The visual acuity of the group of eyes that received postoperative anti-VEGF injection ($n = 39$) showed greater visual acuity improvement 6 months postoperatively compared to the group of eyes that did not receive postoperative anti-VEGF. Postoperative complications included vitreous hemorrhage in 2 eyes, rhegmatogenous retinal detachment in 4 eyes, and recurrent thick subretinal hemorrhage in 6 eyes.
- **CONCLUSIONS:** Vitrectomy with subretinal t-PA injection and gas tamponade was found to be relatively

effective for displacement of thick submacular hemorrhage with a significant improvement in visual acuity. There is a loss of acuity over time; the addition of postoperative anti-VEGF therapy may help maintain the visual acuity gains. (*Am J Ophthalmol* 2014;157:1250-1257. © 2014 by Elsevier Inc. All rights reserved.)

THICK SUBMACULAR HEMORRHAGE CAN CAUSE sudden and severe vision loss in patients with age-related macular degeneration (AMD) and often results in visual acuity of 20/200 or worse.¹⁻³ Thick submacular hemorrhage interferes with retinal function through several mechanisms, including shearing of photoreceptors by fibrin clots and physical separation of photoreceptors from the retinal pigment epithelium (RPE) and choroid, and through direct toxic effects of iron.^{4,5}

Because of the poor prognoses these patients commonly experience, there have been various attempts to remove the blood from the submacular space. There are several reports of pars plana vitrectomy (PPV) with active clot removal, either with or without tissue plasminogen activator (t-PA).⁶⁻¹⁰ Thus far, the results of these approaches have been disappointing. Others have used intravitreal gas with or without t-PA as a less invasive and less costly approach. (Heriot WJ. Intravitreal gas and t-PA: an outpatient procedure for submacular hemorrhage. Paper presented at AAO Annual Vitreoretinal Update, 1996; Chicago, IL).¹¹

Although t-PA may help to liquefy the clot and aid in hemorrhage displacement, there is experimental evidence to suggest that t-PA may not cross the neurosensory retina.¹² To enable t-PA to more effectively enter the subretinal space, Hauptert and associates described a technique of injecting t-PA into the subretinal space through a transretinal small-gauge cannula.¹³ A larger series¹⁴ was published a few years later; although encouraging, these results were limited by small size and relatively short follow-up. Also, these studies were performed in the era before intravitreal antivascular endothelial growth factor (VEGF) use was available to control the underlying exudative AMD. The purpose of this study was to evaluate the outcome of PPV, subretinal infusion of t-PA, and intraocular gas tamponade with and without postoperative

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intravitreal anti-VEGF injection for the treatment of thick submacular hemorrhage caused by AMD.

METHODS

AFTER WILLS EYE HOSPITAL INSTITUTIONAL REVIEW BOARD approval was obtained, the medical records of 101 consecutive patients from 2 centers (Wills Eye Hospital and Midwest Eye Institute) with AMD and thick submacular hemorrhage who underwent PPV with subretinal t-PA injection and pneumatic displacement between April 1, 2001, and September 31, 2009, were reviewed. A thick submacular hemorrhage was defined as blood under the fovea causing an obvious elevation of the retina, with obscuration of the RPE on biomicroscopic examination. Patients with thick submacular hemorrhages treated with anti-VEGF therapy alone were not offered the procedure and were excluded from the study. Patients who were thought clinically to have extensive hemorrhage under the RPE, as well as patients with massive subretinal hemorrhage (defined as hemorrhage extending to the equator) were excluded. Although the duration of the hemorrhage was not an exclusion criterion, patients with chronic, khaki-colored hemorrhage generally were not offered the procedure. Optical coherence tomography (OCT), fluorescein and/or indocyanine green angiography, B-scan ultrasonography, and color fundus photography were performed at the discretion of the examining surgeon. However, as the hemorrhage often limited image quality, preoperative imaging was inconsistently performed. All operations were performed at the Wills Eye Hospital (Philadelphia, PA) or at the Midwest Eye Institute (Indianapolis, IN). After August 2005, some patients received postoperative anti-VEGF injections at various intervals at the discretion of the treating physician. The patients who underwent PPV with subretinal t-PA are defined as Group A. Those patients who also received postoperative anti-VEGF injection are defined as Group B.

The surgical procedure was as follows. After informed consent was obtained, a standard 3-port PPV was performed and a posterior vitreous detachment was created if not already present. Using a 41-gauge flexible cannula, t-PA (25 µg/0.1 mL) (Wedgewood Pharmacy, Swedenboro, NJ) was slowly injected into the subretinal space, and the injection was stopped once the retina was completely separated from the underlying hemorrhage (approximately 0.25 mL to 0.5 mL of t-PA). Between 1 and 4 separate infusion sites were created in order to detach the retina from the underlying hemorrhage. A subtotal air/fluid exchange (approximately 75%) was performed. The eye was left with either air, 18%-20% SF₆ or 12%-14% C₃F₈ gas fill at the surgeon's discretion. All patients were instructed to tilt their face forward at 45 to 60 degrees for approximately 1-5 days postoperatively.^{15,16}

The medical records were reviewed for the following data: age, gender, best corrected Snellen visual acuity using either manifest refraction or spectacle correction with pinhole preoperatively as well as at 1, 3, 6, and 12 months postoperatively, duration of hemorrhage, gas used, results of fluorescein angiography before submacular hemorrhage, postoperative fluorescein angiography, use of photodynamic therapy (PDT) and postoperative use of intravitreal anti-VEGF medications. Because OCT image quality is limited in cases with extensive hemorrhage, OCT was obtained sporadically and was not included in the analysis. Visual acuities were analyzed on a logarithm of minimal angle of resolution (logMAR) scale. For this purpose, counting fingers at 6 feet was converted to 48/1600; 3 feet to 24/1600; 1 foot to 20/8000; hand motions to 20/16,000; and light perception to 20/32,000. The degree of blood displacement was determined ophthalmoscopically or with the aid of fundus photographs and was graded as complete, partial or no displacement. Complete displacement was defined as no blood or only a scant 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. The use of postoperative anti-VEGF medications was left to the discretion of the treating physician. The Wilcoxon signed-rank test was used for comparison of preoperative and postoperative visual acuities, and the chi-square test or the Fisher exact test was used for subgroup analysis. SPSS v 18.0 for Windows (IBM Corporation, Armonk, New York, USA) was used for statistical analysis. All tests were 2-tailed, and significance was defined as $P \leq 0.05$.

RESULTS

INCLUDED IN THE STUDY WERE 101 EYES OF 101 PATIENTS (61 women, 40 men). The mean age was 80 years (range, 60-98 years). All patients were followed for a minimum of 3 months (mean, 15.3 months; range, 3-70 months). Of 101 patients 95 (94%) had at least 3 months of follow-up; 73/101 (72%) had 6 months of follow-up; 63/101 (62%) had 12 months of follow-up, and 17/101 (16%) had 24 months of follow-up. At baseline, 47 eyes were phakic, 43 were pseudophakic, 2 were aphakic, and 9 did not have phakic status recorded. Of the 101 patients, 51 were taking some form of anticoagulant (aspirin or other platelet inhibitor and/or warfarin). The average duration of submacular hemorrhage before surgery was 16 days (range, 1-60 days). Mean preoperative visual acuity was 20/2255 (range, 20/100 to hand motion). The hemorrhage was completely displaced from the fovea in 83 eyes (82%) (Figure 1). There was partial displacement in 17 eyes (17%) (Figure 2). There was no displacement in 1 eye

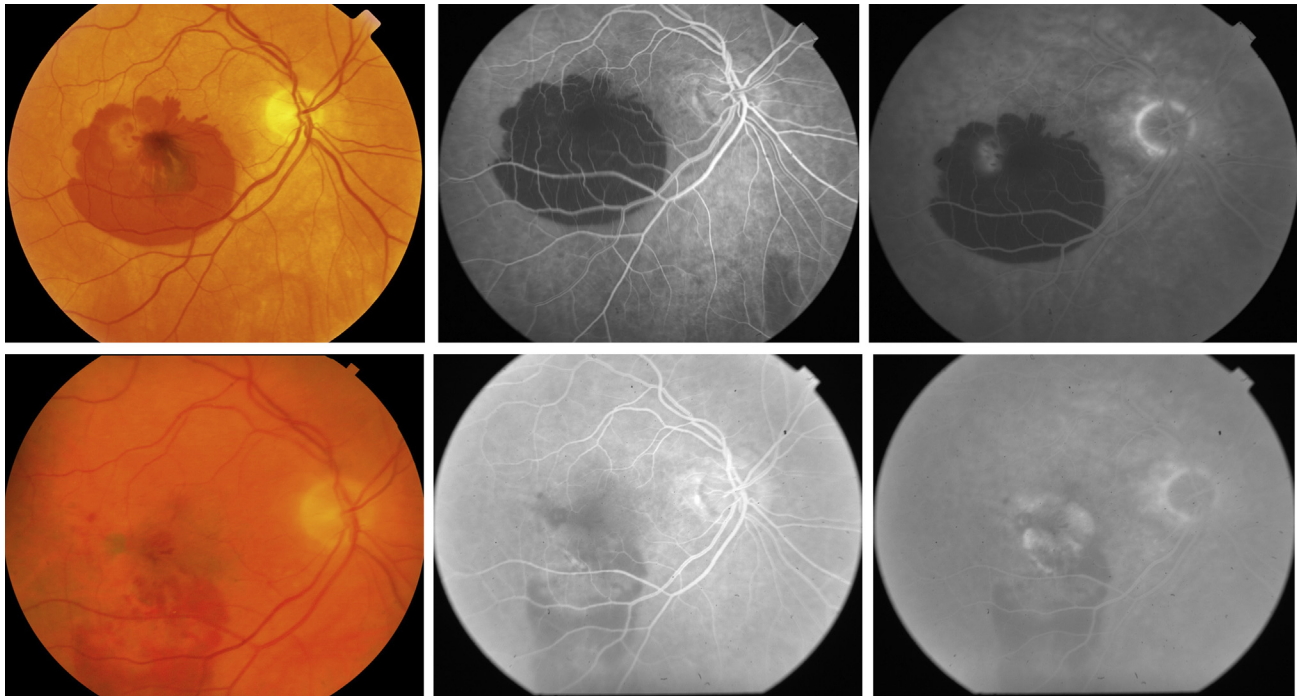


FIGURE 1. Submacular hemorrhage due to exudative age-related macular degeneration, before and after vitrectomy. (Top left) The patient had a thick submacular hemorrhage with 20/800 vision. (Top middle) The early frame of the angiogram shows blocking from the hemorrhage. (Top right) The late frame of the angiogram demonstrates hyperfluorescence from the choroidal neovascular membrane. One month after vitrectomy, the vision improved to 20/60. (Bottom left) The hemorrhage has been displaced. (Bottom middle) The early frame of the angiogram demonstrates mild blocking while the (Bottom right) late frame of the angiogram demonstrates hyperfluorescence from the choroidal neovascular membrane.

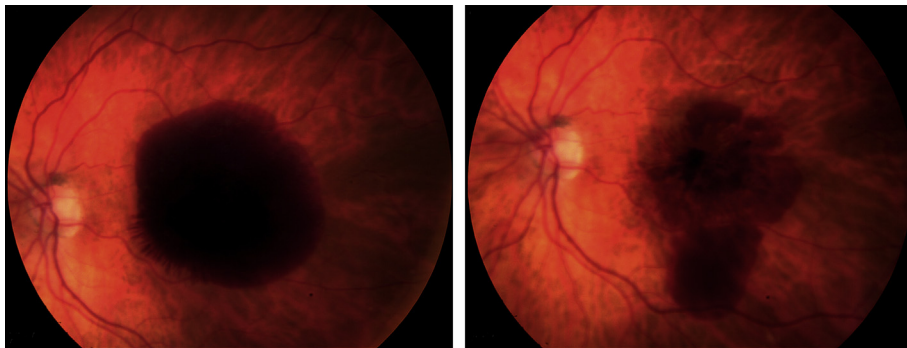


FIGURE 2. Submacular hemorrhage due to exudative AMD. (Left) The patient had a large submacular hemorrhage with 20/2000 preoperative vision (counting fingers at 2 feet/logMAR 2). (Right) One month after vitrectomy, the patient's vision was 3/200 (counting fingers at 3 feet/logMAR 1.82) with incomplete displacement. The vision remained stable through final follow-up.

(1%) that had hemorrhage onset 2 days before surgery. As OCT, B-scan ultrasonography, and indocyanine green angiography were performed in fewer than 20 eyes, imaging analysis was not included in further analysis.

Mean preoperative baseline visual acuity was 20/2255 (2.05 logMAR). The visual acuity was 20/893 (1.65 logMAR) ($P < 0.001$) at month 1; 20/678 (1.53 logMAR) at month 3 ($P < 0.001$); 20/914 (1.66 logMAR) at month 6

($P < 0.001$); and 20/1150 (1.76 logMAR) at month 12 ($P = 0.002$) (Figure 3). Best postoperative visual acuity improved by at least 1 line in 83 of the 101 (82%) eyes, and 19.6% of eyes gained 3 lines or more at month 3. Postoperatively, 12 eyes showed no improvement, and 6 eyes had at lost at least 1 line of vision. Visual acuity at last follow-up improved by at least 1 line in 62 eyes (61%); remained unchanged in 19 (19%) eyes; and worsened by

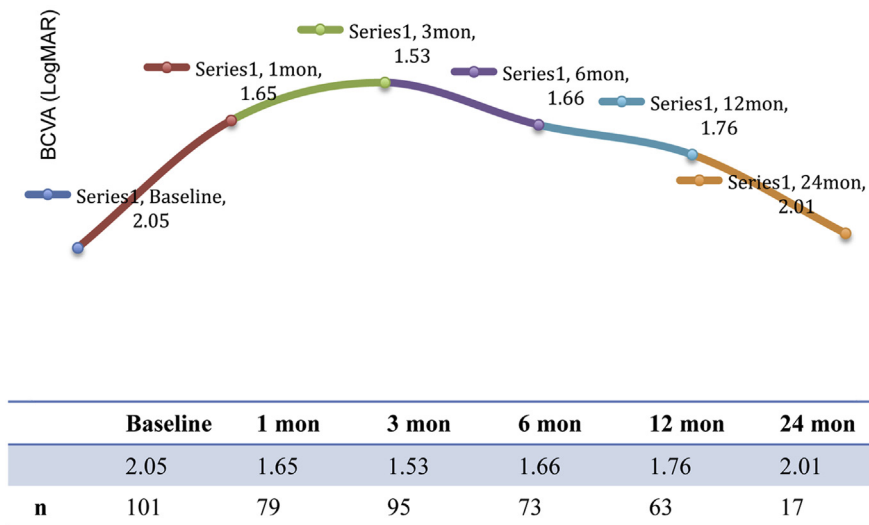


FIGURE 3. Change in vision (logMAR) over time of all 101 patients who underwent vitrectomy with subretinal t-PA and pneumatic displacement. Initial visual acuity was logMAR 2.05 (Snellen 20/2255), and at month 3 was logMAR 1.53 (Snellen 20/678). There was some loss of visual acuity over time.

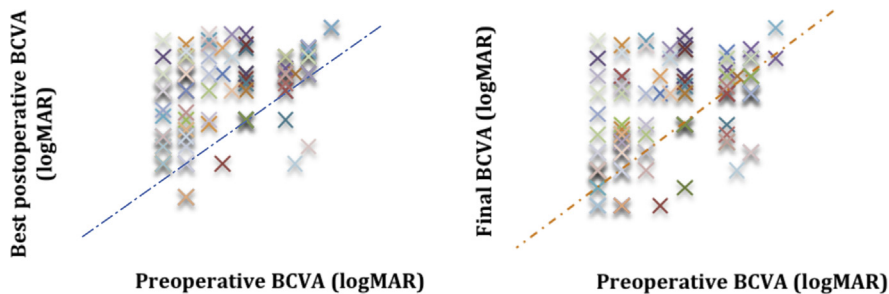


FIGURE 4. Illustration of the best and final visual acuity after vitrectomy with subretinal t-PA and pneumatic displacement. (Left) The graph illustrates the best postoperative visual acuity at any time point for each patient compared to preoperative baseline. (Right) The graph demonstrates the visual acuity at final follow-up compared to preoperative visual acuity for each patient.

1 line or more in 20 (20%) eyes ($P < 0.001$, Figure 4). The visual acuities of the 45 patients who were pseudophakic at baseline were 20/4477 (logMAR 2.35) preoperatively; 20/957 (logMAR 1.68, $n = 45$) at month 3; 20/1074 (logMAR 1.73, $n = 36$) at month 6; and 20/1663 (logMAR 1.92, $n = 28$) at month 12. Linear regression analyses identified no statistically significant correlation between hemorrhage duration and postoperative visual acuity at any time point (final visual acuity, best visual acuity; $P = 0.999$, $P = 0.375$, respectively). Duration of hemorrhage of <2 weeks, 2 to 4 weeks or longer than 4 weeks also did not appear to correlate with visual outcome (baseline vs final logMAR $P = 0.571$, baseline vs best logMAR $P = 0.981$, respectively.) The longest duration of hemorrhage associated with visual improvement was 41 days in this series.

Prior to 2005, 8 eyes had undergone postoperative PDT. Of the 8 eyes, 7 had had complete anatomic displacement of the hemorrhage prior to PDT. The

mean preoperative vision in this subgroup was 20/618 (logMAR 1.49). The best mean postoperative and post-PDT vision was 20/152 (logMAR .88), and the final visual acuity was 20/276 (logMAR 1.14).

In August 2005, intravitreal injection of the anti-VEGF agent bevacizumab (Avastin; Genentech, South San Francisco, California, USA) and shortly thereafter, ranibizumab (Lucentis, Genentech, South San Francisco, California, USA) became available. Prior to occurrence of submacular hemorrhage, 24 patients had been treated with either ranibizumab or bevacizumab using several different treatment regimens, and 21 of these patients continued to receive postoperative anti-VEGF injections. An additional 18 patients who had never received anti-VEGF therapy preoperatively began anti-VEGF therapy postoperatively. Of 101 patients, 59 never received anti-VEGF injections at any point, either because they were treatment-naïve or because they presented prior to the

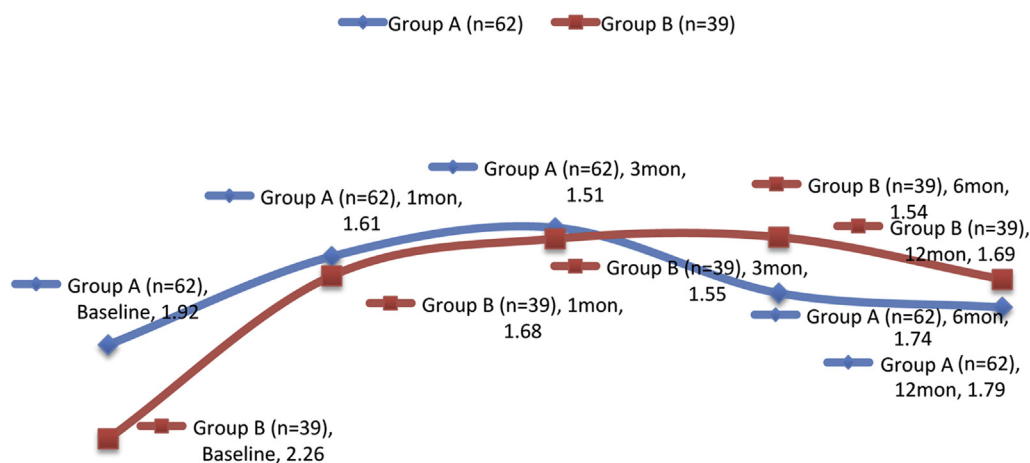


FIGURE 5. Change in visual acuity over time comparing patients who received postvitrectomy anti-VEGF injection to those that did not receive postvitrectomy anti-VEGF injection. Group A (Blue): The 62 patients did not receive any postvitrectomy anti-VEGF injection. Although there was statistically significant improvement in visual acuity at month 3, there was loss of treatment effect over time. Group B (Red) received some postvitrectomy anti-VEGF injection. This group reached peak visual acuity at month 6 and had better maintenance of visual acuity.

routine use of anti-VEGF agents. Peak visual acuity improvement was reached at month 3 in the no postoperative anti-VEGF group (group A, n = 62). The patients who received postoperative anti-VEGF (Group B, n = 39) reached their peak visual acuity at month 6. Baseline visual acuity was better in group A (20/1664 [logMAR 1.92]) than in group B (20/3639 [logMAR 2.26], $P = 0.018$). By month 3, group A patients had improved to 20/815 (logMAR 1.55, $P = 0.001$ vs baseline), but by month 6, they had regressed to 20/1100 (logMAR 1.74, $P = 0.206$ vs baseline) (Figure 5). Eyes in Group B received intravitreal anti-VEGF injection an average of 2.2 months (range, 0.5 to 12.6) after surgery and received a mean of 5.6 (range, 1-12) postoperative injections. By month 3, Group B's visual acuity had improved to 20/710 (1.55 logMAR) and at month 6 was 20/693 (1.54 logMAR = 0.001 vs baseline).

Intraoperative complications were few; 1 patient developed a retinal tear around a sclerotomy, and it was successfully lasered. Postoperative complications included vitreous hemorrhage in 2 eyes, both of which cleared spontaneously. In 4 eyes postoperative rhegmatogenous retinal detachment developed, and all were successfully repaired with vitrectomy, endolaser photocoagulation and intraocular gas tamponade. Recurrent thick subretinal hemorrhage developed in 6 patients. Of the 6 patients, 4 had recurrent hemorrhage at 2 months, 2 months, 3 months, and 4 months after surgery. The precise time of recurrent hemorrhage was not able to be reliably ascertained in the other 2 patients. Of these 6, 2 patients were receiving anticoagulants and 3 of these 6 patients were given postoperative anti-VEGF injection. One patient developed a retinal pigment epithelial tear. Of 47 (36%) phakic patients, 17 underwent cataract surgery during the follow-up period.

DISCUSSION

THICK SUBMACULAR HEMORRHAGE IS A POTENTIALLY devastating manifestation of exudative AMD. This study reviewed the efficacy of PPV with subretinal t-PA injection and pneumatic displacement in a large cohort of patients and showed a clinically meaningful degree of visual acuity improvement on average, compared to the natural history, in which visual improvement is rare.¹⁻³ There was loss of treatment benefit over time, presumably due to progression of the underlying exudative AMD. However, concurrent postoperative use of an anti-VEGF agent appeared to help prevent regression of the treatment's effect. Finally, the duration of hemorrhage did not appear to correlate with treatment effect. However, there exists a selection bias because patients with hemorrhage of longer duration (roughly 8 weeks or more posthemorrhage) were generally not offered the procedure.

Many treatments for submacular hemorrhage have been tried, including anti-VEGF treatment alone, as well as both office-based and operating-room-based procedures, with or without t-PA. There have been several reports of treating submacular hemorrhage with anti-VEGF treatment alone. Many of the eyes included in these series appeared to have smaller or thinner hemorrhages and better vision than those included in our study^{17,18} or did not necessarily have foveal involvement.¹⁹ A large, retrospective review of submacular hemorrhage treated with anti-VEGF medications alone found significant visual acuity improvement.²⁰ Baseline acuity was 20/479 and mean acuity improved to 20/182 at 6 months. Although that study had the advantage of color fundus photographs with more accurate preoperative assessment of size, the average hemorrhage size of approximately 8 disc areas (ranging from 3 to

20 disc areas) was generally smaller than that of the patients in our series, and that is supported by the worse initial visual acuity in our series. A recent study by Sacu and associates compared intraocular t-PA with gas and anti-VEGF injection to anti-VEGF injection alone.²¹ They found some benefit in both techniques but did not find one to be consistently superior to the other.

Heriot and colleagues described a technique in which both intravitreal t-PA and gas were injected into the vitreous cavity. In addition to providing moderate visual improvement, these techniques also have the advantage of being fairly straightforward, office-based procedures that avoid vitrectomy.^{11,22–28} However, some authors have questioned the utility of this approach, suggesting that intravitreal t-PA does not gain access to the subretinal space.¹² Others reported successful displacement in some cases with intravitreal gas injection alone (without t-PA), but the degrees of displacement and visual improvement are variable.^{29,30}

Various vitrectomy-based approaches to managing large submacular hemorrhages (with and without t-PA) have been utilized. In the Submacular Surgery Trial for Hemorrhagic Choroidal Neovascular lesion (Group B), vitrectomy with active removal of the clot and choroidal neovascular membrane was performed. There was no difference in mean visual acuity outcomes in the treated vs the observation group, and t-PA was used in only 38% of cases.⁶ Another vitrectomy technique in which subretinal t-PA was infused followed by active removal of the clot also showed modest visual benefit but was limited by a 45-minute waiting period between submacular t-PA injection and evacuation of the hemorrhage.⁷

Our technique was first described by Hauptert and colleagues.¹³ The goal of this approach was to displace the subretinal hemorrhage away from the macula, similar to the office-based injection procedures. This vitrectomy-based displacement technique offers some potential advantages over other displacement approaches: t-PA is placed into the subretinal space, facilitating greater liquefaction of the entire hemorrhage, and a larger volume of t-PA and fluid allows total separation of the retina from the underlying clot, which may also facilitate hemorrhage displacement. Other investigators also showed promising results with this approach.¹⁴ These studies were limited by small sample sizes and relatively short follow-up periods and were performed before the anti-VEGF era. More recent studies have used a combination of submacular t-PA and concurrent submacular anti-VEGF administration, with promising results in small series.³¹

Our series has the advantages of larger numbers and a much longer follow-up period, and a large number of eyes underwent surgery both before and after advent of anti-VEGF medications.

Because submacular hemorrhage causes both structural and functional changes to the macula, prompt evacuation (within 30 days) of the hemorrhage has been advocated,

and a longer than 30-day duration of hemorrhage has been used as exclusion criteria in other studies.^{25,32} In contrast, our data suggest that even hemorrhages that have been present for more than 1 month can be successfully displaced, often with some visual improvement.

In the current study, the large majority of patients (82%) achieved total hemodisplacement, which is comparable to the level seen in the earlier studies.^{13,14} Although the 1 case without any displacement had occurrence of hemorrhage 2 days before surgical displacement was attempted, the short hemorrhage duration likely is not related, as other eyes have had successful displacement even 1 day after hemorrhage onset.^{11,13}

We found that there was a significant improvement in mean visual acuity within the first 3 months after surgery, but this effect decreased with time. However, although the visual acuity 12 months after surgery was not as good as it was at postoperative month 6, it was still significantly higher than the preoperative visual acuity ($P = 0.002$).

Unlike older studies that were performed before the era of anti-VEGF therapy, our study included approximately 40% of patients who were receiving intravitreal anti-VEGF injections after vitrectomy. Compared to the patients who had vitrectomy without postsurgical anti-VEGF treatment, patients who received intravitreal anti-VEGF injections maintained the improved visual acuity for 6 months, despite having poorer preoperative vision. Although the therapeutic effect of drugs injected into a vitrectomized eye does not last as long as in nonvitrectomized eyes,³³ the results of our study suggest that the underlying exudative AMD continues to progress even after the development of thick submacular hemorrhage, and that ongoing anti-VEGF therapy in these eyes may help maintain postdisplacement visual acuity. A recent study found that the addition of an anti-VEGF injection to intravitreal gas and t-PA injection resulted in a more favorable visual outcome than intravitreal t-PA and gas alone.³⁴ Another study reported that subretinal anti-VEGF injection along with subretinal t-PA injection produced a favorable visual outcome.^{31,35,36} Based on the findings of our study, we suggest that anti-VEGF treatment should be continued following subretinal hemorrhage displacement using this technique.

There are several limitations to our study such as: its retrospective nature with some patients lost to follow-up; selection bias because surgeons did not randomize the study population to different treatments; the lack of a control group; the inclusion of multiple surgeons; and difficulty in controlling for the effects of cataract development and removal. There was variable anti-VEGF delivery postoperatively, and patients whose maculas had more normal postoperative appearances or better postoperative vision might have been offered anti-VEGF therapy more frequently than those who were thought to have less optimal surgical outcomes. A more regimented schedule

for injections may have produced a more robust postoperative visual outcome.^{37–39}

In summary, thick submacular hemorrhage is one of the most serious complications of exudative AMD, and various therapeutic options have been suggested to manage it.

Vitrectomy with subretinal t-PA injection and gas tamponade was found to be relatively effective for displacement of thick submacular hemorrhage. The addition of postoperative anti-VEGF therapy could extend the period of postoperative visual acuity improvement.

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