Tissue plasminogen activator-assisted vitrectomy for submacular hemorrhage due to age-related macular degeneration

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Purpose: The purpose of this study was to evaluate the treatment efficacy of vitrectomy combined with subretinal recombinant tissue plasminogen activator (r-tPA) and factors affecting visual improvement in patients with submacular hemorrhage (SMH) due to neovascular age-related macular degeneration (nAMD).

Materials and Methods: Medical records of 17 consecutive patients diagnosed with SMH secondary to nAMD were retrospectively reviewed. The initial surgical procedure involved a 23-gauge transconjunctival vitrectomy, subretinal r-tPA application through a self-sealing inferior retinotomy, and sulfur hexafluoride gas for tamponade in all patients. The duration, size, and thickness of the hemorrhage and the pre- and post-operative visual acuity (VA) using a Snellen chart were recorded. VA was converted to logMAR for statistical analysis.

Results: The average duration and size of the SMH were 12.8 ± 18.2 days and 8.6 ± 5.3 disc areas, respectively. The mean follow-up time was 16.9 ± 4.7 months. A statistically significant visual improvement was found when comparing initial VA with postoperative best-corrected VA (BCVA) and final BCVA (Wilcoxon rank test, \( P \leq 0.01 \)). There was no significant correlation between the size of the hemorrhage and postoperative BCVA and final BCVA (Spearman’s rho test). There was no statistically significant correlation between the initial VA and postoperative BCVA and final BCVA (Spearman’s rho test). There was no significant correlation between the duration of hemorrhage and postoperative BCVA and final BCVA (Spearman’s rho test). The preoperative thickness of hemorrhage (747.5 ± 30 μm) was not correlated with postoperative BCVA or final BCVA (Pearson’s test).

Conclusions: Vitrectomy combined with subretinal r-tPA injection and gas tamponade is an effective surgical intervention to preserve VA in selected patients with apparent SMH.

Key words: Expanse gas, recombinant tissue plasminogen activator, subretinal hemorrhage, vitrectomy
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records of 17 patients presenting with SMH due to nAMD were reviewed. Informed consent forms were signed by all patients before the surgery. A complete ophthalmic examination was performed before the treatment, 1–7 days after surgery, and at 4–6-week intervals during follow-up. Biomicroscopy showed thick subretinal hemorrhage involving the foveal zone, causing an obvious elevation of the retina with obscuration of the RPE in all patients.

Baseline data such as age, sex, initial visual acuity (VA), and duration and dimension of the hemorrhage were recorded. Pre- and post-operative optical coherence tomography (OCT) images (including measurement of the central subfoveal thickness of the SMH) and color fundus photographs of the patients were taken. In addition, fundus fluorescein angiography (Heidelberg Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) was performed at the surgeon’s discretion for certain visits. The central subfoveal thickness of the SMH was obtained by measuring the distance between the upper surface of the SMH and the inner surface of the RPE [Fig. 1].

All patients were treated by the same experienced vitreoretinal surgeon (VLK). After a 23-gauge three-port transconjunctival pars plana vitrectomy (Alcon Accurus®; Alcon Laboratories, Fort Worth, TX, USA), a posterior vitreous detachment was created if not already present. Subretinal r-tPA (Actilyse; Boehringer, Ingelheim, Germany) was injected to the subretinal space through an inferior self-sealing retinotomy using a 41-gauge cannula at a concentration of 12.5 μg in 0.1 mL (injected volumes ranged from 0.05 to 0.15 mL) until sufficient retinal detachment was created in the posterior pole. After clot liquefaction, a complete fluid-air exchange was performed. SF6 gas (18% or 20%) was used for the tamponade. After surgery, patients remained in the prone position for a minimum of 3 days.

Eleven of the 17 eyes in the study were phakic, and 6 eyes were pseudophakic. During the follow-up, 5 (45%) patients were scheduled for phacoemulsification surgery because of cataract development. Patients with massive SMH extending to the equator, with vitreous hemorrhage, or with old khaki-colored hemorrhages were excluded from the study. Patients who could not tolerate the postoperative prone position were also excluded from the study.

VA was converted to logMAR for statistical analyses. At the discretion of the treating physician, postoperative photodynamic therapy and antivascular endothelial growth factor (anti-VEGF) agents were used to treat some patients because of reactivation of the lesions. Second surgeries were performed in two patients because of recurrence of SMH and rhegmatogenous retinal detachment (RRD) [Table 1].

The Shapiro–Wilk test was used to determine whether variables were distributed normally. The Wilcoxon signed-rank test was used to compare initial and final VA and OCT data. Pearson’s test was used for the correlation analyses of normally distributed variables, and Spearman’s rho test was used for the correlation analyses of nonnormally distributed variables. All values were expressed as means ± standard deviations, and values of P ≤ 0.05 were considered statistically significant.

**Results**

Of the 17 patients included in the study, 6 were male and 11 were female with a mean age of 70.8 ± 11.2 years (range, 49–90 years). The average duration of SMH was 12.8 ± 18.2 days. The size of the SMH ranged from 5 to 25 macular photocoagulation study disc areas, and the average size was 8.6 ± 5.3 disc areas. The mean follow-up time of patients was 16.9 ± 4.7 months. The demographic and pre- and post-operative baseline data of the patients are presented in Table 2.

There was a statistically significant difference between the initial VA (mean logMAR, 1.8 ± 0.3) and the postoperative best-corrected VA (BCVA) (mean logMAR, 1.0 ± 0.5) and

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**Figure 1:** (a) Preoperative color fundus photograph of a 67-year-old female patient presented with a thick submacular hemorrhage. (c) Preoperative optical coherence tomography image of the same patient. The subfoveal central height of submacular hemorrhage measured through manually considering most detectable foveal depression and a presumed retinal pigment epithelium line that connecting the evident retinal pigment epithelium at the both edge of the hemorrhage. (b) Postoperative color fundus photograph; total displacement of submacular hemorrhage have been achieved. (d) Postoperative optical coherence tomography image
Table 1: Summary of patient data

| Patient number | Sex, age | Duration (days) | Diameter (DD) | Preoperative VA | Preoperative OCT (SMH thickness) | Postoperative BCVA | Final VA | Postoperative OCT (SMH thickness) | Follow-up (months) | Complication/secondary procedures |
|----------------|---------|----------------|---------------|----------------|-------------------------------|-------------------|---------|-------------------------------|------------------|----------------------------------|
| 1              | Female/54 | 1              | 5             | CF ≤1 m        | 550                           | 20/25             | 20/25   | 213                           | 14               |                                  |
| 2              | Female/66 | 15             | 5             | CF ≤1 m        | 340                           | CF ≤1 m           | CF ≤1 m | 242                           | 13               | RRD                              |
| 3              | Male/59   | 20             | 12            | 20/400          | 440                           | 20/100            | 20/125  | 242                           | 16               |                                  |
| 4              | Male/87   | 1              | 8             | CF ≤1 m        | 1351                          | 20/250            | 20/200  | 354                           | 18               |                                  |
| 5              | Male/90   | 2              | 9             | CF ≤1 m        | 520                           | 20/250            | 20/200  | 232                           | 21               |                                  |
| 6              | Male/73   | 2              | 6             | CF ≤1 m        | 360                           | 20/200            | 20/200  | 258                           | 23               |                                  |
| 7              | Female/67 | 7              | 7             | CF ≤1 m        | 960                           | 20/640            | 20/640  | 353                           | 11               |                                  |
| 8              | Female/75 | 15             | 8             | 20/640          | 653                           | 20/200            | 20/160  | 253                           | 15               | PDT × 2                          |
| 9              | Female/83 | 2              | 9             | CF ≤1 m        | 577                           | CF ≤1 m           | CF ≤1 m | 253                           | 17               |                                  |
| 10             | Female/82 | 12             | 25            | CF ≤1 m        | 978                           | 20/640            | 20/640  | 351                           | 11               |                                  |
| 11             | Female/75 | 7              | 5             | 20/250          | 1150                          | 20/63             | 20/50   | 280                           | 18               | IVR × 2                          |
| 12             | Male/49   | 1              | 15            | CF ≤1 m        | 576                           | 20/100            | 20/100  | 362                           | 19               |                                  |
| 13             | Male/72   | 7              | 1             | CF ≤1 m        | 681                           | 20/400            | 20/320  | 472                           | 14               |                                  |
| 14             | Female/66 | 5              | 9             | CF ≤1 m        | 954                           | 20/80             | 20/40   | 358                           | 22               | IVR × 3                          |
| 15             | Female/67 | 3              | 10            | CF ≤1 m        | 847                           | 20/125            | 20/125  | 369                           | 10               |                                  |
| 16             | Female/66 | 4              | 5             | CF ≤1 m        | 535                           | 20/63             | 20/63   | 272                           | 19               | IVR × 2                          |

DD: Disc diameter, CF: Counting fingers, IVR: Intravitreal ranibizumab, PDT: Photodynamic therapy, OCT: Optical coherence tomography, VA: Visual acuity, SMH: Submacular hemorrhage, BCVA: Best-corrected visual acuity, RRD: Rhegmatogenous retinal detachment

Table 2: Demographics and baseline data of the patients

| Data                         | Values                      |
|------------------------------|-----------------------------|
| Mean age                     | 70.8±11.2                   |
| Sex (male/female), n (%)     | 6 (35.3)/11 (64.7)          |
| Initial VA (mean logMAR)     | 1.8±0.3                     |
| Postoperative BCVA (mean logMAR) | 1.0±0.5                   |
| Final BCVA (mean logMAR)     | 0.97±0.52                   |
| Duration of SMH/mean days    | 12.8±18.2                   |
| Size of SMH/mean disc areas  | 8.6±5.3                     |
| Follow-up time/mean months   | 16.9±4.7                    |
| Preoperative subfoveal height of SMH/mean millimicron | 747.5±309.6 |
| Postoperative subfoveal height of SMH/mean millimicron | 314.2±80.8 |

VA: Visual acuity, SMH: Submacular hemorrhage, BCVA: Best-corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution

Discussion

SMH is a serious condition that can develop during nAMD. An increase in the incidence of SMH has been reported for certain nAMD subtypes treated with anti-VEGF agents. Goverdhan and Lochhead reported that 40% of patients with nAMD treated with bevacizumab (BZB) developed SMH during the follow-up. SMH has been considered an exclusion criterion in large-scale studies evaluating anti-VEGF effectiveness in patients with nAMD, so there is currently inadequate data with which to establish a standard treatment protocol for SMH. The final BCVA (mean logMAR, 0.97 ± 0.52) (Wilcoxon rank test, P ≤ 0.01). However, there was no statistically significant correlation between the initial VA and the postoperative BCVA (Spearman’s rho test, r = 0.417, P = 0.096) or the final BCVA (Spearman’s rho test, r = 0.227, P = 0.381). The VA improved by ≥2 lines in 8 (47%) patients, improved by 1 line in 4 (23.5%) patients, improved from CF ≤1 M to level of 1–5 M range in 3 patients (17.6%), remained unchanged in 1 (5.8%) patients (underlying old large scar), and worsened in 1 (5.8%) patient due to postoperative RRD. There was a significant difference in the comparison of pre- (mean, 747.5 ± 309.6 μm) and post-operative (mean, 314.2 ± 80.8 μm) thicknesses of the hemorrhages obtained from OCT images (Wilcoxon rank test, P ≤ 0.01). There was no significant correlation between the size of the hemorrhages and postoperative BCVA (Spearman’s rho test, r = 0.078, P = 0.765) or the final BCVA (Spearman’s rho test, r = 0.015, P = 0.955).

Total subfoveal blood displacement was achieved in 14 eyes (82.0%) [Figs. 1 and 2] with subtotal displacement in 1 (5.8%) eye. During the follow-up, recurrence of SMH (1 month after the initial surgery) developed in one patient and RRD in another patient. These patients were scheduled for secondary surgeries. Besides these two patients, fundus fluorescein angiography images were obtained from the other 15 patients. Because of activated lesions and leakage, three patients underwent intravitreal ranibizumab and one patient underwent photodynamic therapy at scheduled recurring intervals. There was no significant correlation between the initial thickness of the SMH (747.5 ± 30 μm) and the postoperative BCVA (Pearson’s test, r = 0.259, P = 0.315) or the final BCVA (Pearson test, r = −0.153, P = 0.599). There was also no significant correlation between the duration of hemorrhage and the postoperative BCVA (Spearman’s rho test, r = −0.109, P = 0.678) or the final BCVA (Spearman’s rho test, r = 0.274, P = 0.287).
Postoperative fundus fluorescein angiography images of longer than 30-day duration also reported significant visual recovery was achieved in 19 consecutive patients treated with intravitreal BZB + r-tPA + gas. The mean duration of symptoms was 9.3 days (range, 4–12 days), and no significant correlation among the size, duration of hemorrhage, and postoperative and final BCVAs.

However, some previous studies have reported different results. Hattenbach et al. reported a significant correlation between the size of the hemorrhage and postoperative VA, and a better postoperative visual improvement was detected in a subgroup of 21 eyes with a hemorrhage duration ≤14 days. Sobolewska et al. reported that the minimum time for improved VA was 4 days for the treatment of SMH. Moisseiev et al. found a significant correlation between the size and duration of SMH and the final VA. Dewilde et al. reported a correlation between delayed surgery and poor visual outcomes in a series of 74 patients treated with vitrectomy + r-tPA + gas. Sandhu et al. reported that SMHs with ≤5.5 disc diameters and a mean duration ≤12.5 days had better visual outcomes, but their results were not statistically significant. Another study reported by Gopalakrishan et al. longer than 30-day duration of SMH has been used as exclusion criteria.

In a large-scale study by Chang et al. using vitrectomy, the average duration of SMHs was 16 days (range, 1–60 days). Statistically significant visual improvement was reported after surgery in this study. However, there was no significant correlation between postoperative BCVA and the duration of the hemorrhage in this study. In the postoperative follow-up, a group of patients treated with anti-VEGF because of the progression of nAMD showed better visual improvement than did other patients. Retinal detachment, vitreous hemorrhage, and recurrence of SMH were the major postoperative complications in that study. In another recent study using vitrectomy, Rishi et al. reported a significant correlation among the size of the hemorrhage, duration of the hemorrhage, and postoperative BCVA.

In our study, RRD developed in one patient and recurrence of SMH in another patient. These two patients were successfully treated with secondary surgeries. Overall, we achieved complete anatomical success (total hemodisplacement of the SMH) in 82% of the patients. This result compares favorably with those of previous studies.

The localization of the hemorrhage rather than its size may be the most important determinant of postoperative VA. A small hemorrhage located very close to the fovea may be associated with a worse VA compared to lesions away from the fovea. Histological localization of the hemorrhage can also be a predictor of functional success. Subretinal lesions had better visual prognosis than sub-RPE lesions for both the vitrectomy technique and the expansile gas technique.
Surgery for hemorrhagic choroidal neovascularization has many advantages in the treatment of thick, wide, and sub-RPE SMHs. Our results compare favorably with previously reported studies that used expansile gas displacement and vitrectomy technique with the assistance of r-tPA. Large-scale, randomized, controlled clinical studies are therefore needed to provide a standard treatment algorithm for the patients presenting with SMH due to nAMD.

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Conflicts of interest
There are no conflicts of interest.

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