Original Article

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.

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The prognosis of untreated submacular hemorrhage (SMH) due to neovascular age-related macular degeneration (nAMD) and other causes is poor.[1,2] Iron released from the hemorrhage as a result of the fibrinolytic process has a toxic effect on the photoreceptor cells and constitutes a mechanical barrier that prevents normal metabolism of the retina.[3]

The use of recombinant tissue plasminogen activator (r-tPA) with various treatment approaches has been used for the treatment of SMH. In part of the submacular surgery trials (SSTs), direct subretinal surgery was performed for the evacuation of SMH with the use of r-tPA that involved a 45-min intraoperative waiting period for clot liquefaction. Retinal pigment epithelium (RPE) and photoreceptor injury as well as postoperative high retinal detachment rates were the disadvantages of this technique.[4] In addition, there was no significant difference in visual improvement when comparing surgery and the long-term observation in the SST Group B.[5]

Heriot described a less invasive technique "expansile gas technique" of intravitreal r-tPA injection for clot liquefaction following perfluoropropane gas for displacement of the SMH (Heriot WJ. Intravitreal gas and t-PA: An outpatient procedure for SMH. AAO Annual Vitreoretinal Update, 1996; Chicago, IL, USA). Subsequently, several studies have evaluated the anatomical and functional results of this approach.[6-13]

We treated our patients with a vitrectomy technique previously described by Haupert *et al*.[14] Our surgical intervention involved vitrectomy, direct subretinal injection of r-tPA with a 41-gauge cannula through an inferior self-sealing retinotomy for clot liquefaction, and sulfur hexafluoride (SF_6) gas for tamponade. In the following study, we evaluated the effects of both the surgical method and other prognostic parameters on the anatomical and functional results in the treatment of SMH caused by nAMD.

Materials and Methods

This study was approved by the local Ethics Committee and adhered to the tenets of the Declaration of Helsinki. In this retrospective, nonrandomized, consecutive case series, medical

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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. SF_6 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 $P \leq 0.05$ 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

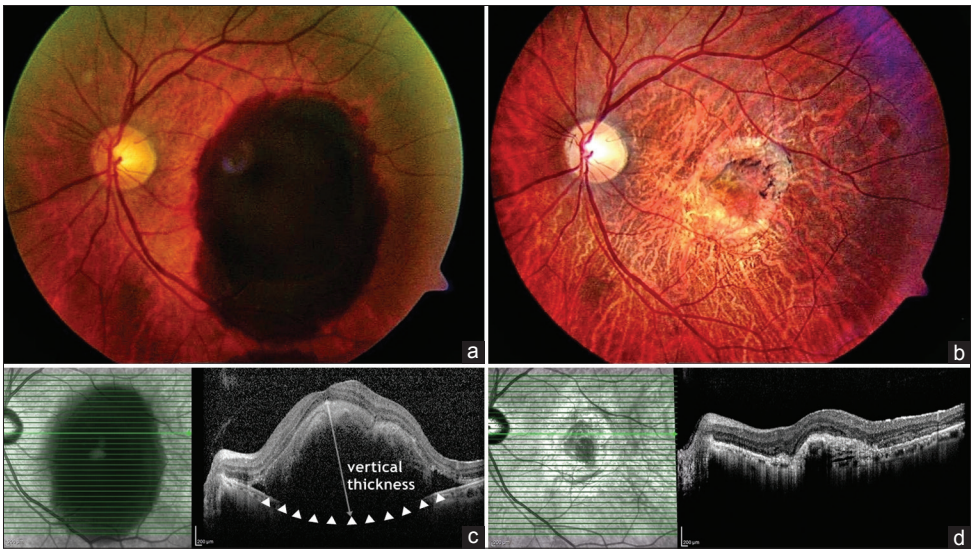

Figure 1: (a) Preoperative color fundus photograph of a 67-year-old female patient presented with a thick submacular hemorrhage. (c) Preoperative optical coherence tomography image of the same patient. The subfoveal central height of submacular hemorrhage measured through manually considering most detectable 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	5	8	20/200	1235	20/125	20/160	478	27	SMH recurrence
8	Female/73	7	7	CF ≤1 m	960	20/640	20/640	353	11	
9	Female/75	15	8	20/640	653	20/200	20/160	253	15	PDT × 2
10	Female/83	2	9	CF ≤1 m	577	CF ≤1 m	CF ≤1 m	253	17	
11	Female/82	120	25	CF ≤1 m	978	20/640	20/640	351	11	
12	Female/75	7	5	20/250	1150	20/63	20/50	280	18	IVR × 2
13	Male/49	1	15	CF ≤1 m	576	20/100	20/100	362	19	
14	Male/72	7	1	CF ≤1 m	681	20/400	20/320	472	14	
15	Female/66	5	9	CF ≤1 m	954	20/80	20/40	358	22	IVR × 3
16	Female/67	3	10	CF ≤1 m	847	20/125	20/125	369	10	
17	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

the final BCVA (mean logMAR, 0.97 ± 0.52) (Wilcoxon rank test, $P \leq 0.01$). 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 three 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, $P \leq 0.01$). 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, $r = -0.153$, $P = 0.559$). 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, $r = 0.274$, $P = 0.287$).

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.[15] Goverdhan and Lochhead[16] 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,[17,18] so there is currently inadequate data with which to establish a standard treatment protocol for SMH.

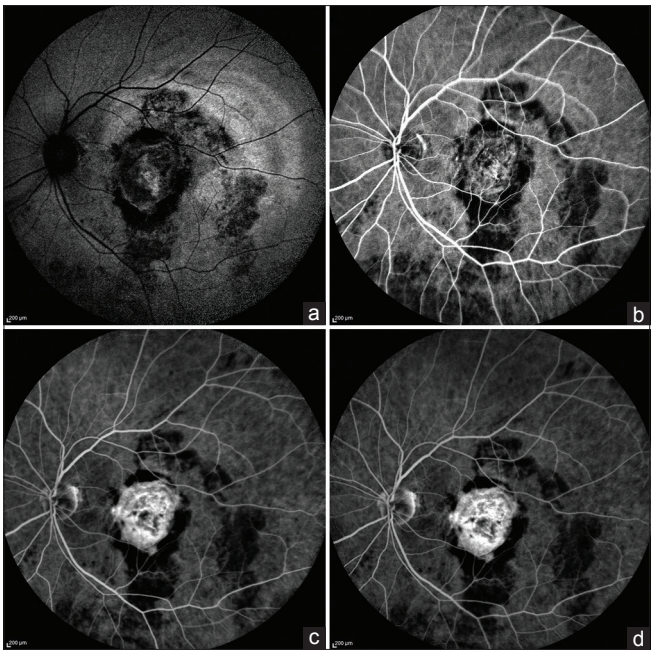

Figure 2: Postoperative fundus fluorescein angiography images of the same patient; there was no leakage from the underlying choroidal neovascular membrane. (a) Autofluorescence image of the lesion, (b) Early phase of the FFA, (c) Mid phase of the FFA (d) Late phase of the FFA

A number of parameters such as initial VA, the duration and size of hemorrhages, the status of nAMD causing SMH, and patient tolerability to the treatment must be taken into consideration when deciding on a treatment for SMH. Thus, numerous treatment modalities have been used to treat this disorder.

Direct surgical subretinal removal of the SMH caused photoreceptor and RPE damage, and a high incidence of postoperative RRD has been observed in SST reports. Furthermore, any significant superiority considering visual improvements has been determined in comparison to observation and surgery in SST Group-B.[4,5]

Shienbaum *et al*.[19] achieved significant visual improvement with anti-VEGF monotherapy for small SMHs in a 12-month follow-up. Kim *et al*.[20] also reported significant visual improvement with the use of anti-VEGF agents, but only in patients who had a better initial VA and a small SMH size, while more invasive surgical interventions were proposed for larger, older, and thicker lesions in this study.

The "expansile gas technique" first described by Heriot is better for the treatment of relatively new, elevated, and large lesions. Although several subsequent studies reported different results using this technique,[6-13] this less invasive procedure has advantages because it avoids vitrectomy and its complications.

Anti-VEGF agents were added to this treatment modality to improve treatment efficacy. Meyer *et al*.[21] reported that 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 the initial size of the subfoveal hemorrhages were 1–3 disc diameters. Guthoff *et al*.[22] reported statistically significant visual improvement in a group treated with intravitreal gas + r-tPA + BZB compared with a group treated with intravitreal gas + r-tPA alone.

However, some studies have suggested that intravitreally injected r-tPA cannot diffuse the subretinal space sufficiently.[23,24] Vitrectomy combined with subretinal r-tPA with old and large SMHs should therefore be performed in selected cases to preserve peripheral vision.[25]

We performed vitrectomy with the assistance of subretinal r-tPA as previously described by Haupert *et al*.[14] The average size of the SMH was 8.6 ± 5.3 disc areas, and the mean duration of symptoms was 12.8 ± 18.2 days in our study. We found 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*.[8] observed 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*.[26] reported that the minimum time for improved VA was 4 days for the treatment of SMH. Moisseiev *et al*.[27] found a significant correlation between the size and duration of SMH and the final VA. Dewilde *et al*.[28] 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*.[29] 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.[30]

In a large-scale study by Chang *et al*.[31] 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*.[32] 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.[14,27-32]

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.[25] 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.[25]

Hassan *et al*.[6] and Hesse *et al*.[7] reported that preoperative VA was a predictive parameter for postoperative visual improvement. In our study, we observed a weak positive correlation between the initial and postoperative VAs, but this correlation was not statistically significant. The results may depend on the nature of the previous underlying lesion and/or the degree of photoreceptor loss. OCT may therefore assist in determining the location (subretinal versus sub-RPE) of the SMH as well as predicting the postoperative visual recovery.

There was a significant difference between the pre- and post-operative central subfoveal thicknesses of the SMHs. Although it was not statistically significant, we observed a reverse correlation between the preoperative central subfoveal thickness of the SMH and the postoperative final BCVA. Hirashima *et al*.[33] recently reported that there was a significant relationship between a better postoperative BCVA and SMH height <400 milimicron. This report is the only one to evaluate vertical height and OCT findings of SMHs.

There are advantages of vitrectomy technique over the expansile gas technique. The r-tPA administered to the subretinal space in different doses provides a more effective hemorrhage dissolution and less shearing stress on the photoreceptors than does intravitreal administration.[10,23]

The disadvantages of vitrectomy include a reduced duration and more rapid clearance of intravitreal anti-VEGF agents after surgery.[34] Although several studies have reported the relationship between vitreomacular traction and nAMD, an another advantage of the vitrectomy technique is the elimination of this relationship.[35] In addition, increased macular oxygenation after vitrectomy has a positive effect on retinal functions.[36]

Various complications such as recurrent SMH, retinal detachment, vitreous hemorrhage, and cataract may occur after vitreoretinal surgery.[14,27-32] Postoperative recurrence of SMH may not be associated with vitrectomy combined with r-tPA because 40% of patients with AMD treated and followed after anti-VEGF therapy developed SMH in the natural course of the disease.[16] We observed recurrence of SMH in 1 patient after surgery. Besides, 10 of our patients were previously treated and followed under anti-VEGF therapy presented with SMH for the first time. During the follow-up, we diagnosed cataracts in 5 of the 11 phakic (45%) patients. These patients were scheduled for phaco surgery. r-tPA toxicity has been reported in several studies after surgery.[37] We did not observe any r-tPA toxicity in our study.

There were limitations of our study. The number of patients who were treated with additional anti-VEGF agents and photodynamic therapy after surgery because of nAMD activation was not enough to compare statistically with others for the visual improvement. Moreover, this work was noncontrolled and nonrandomized study and could not reveal a comparative result of different surgical techniques.

Conclusions

Vitrectomy combined with r-tPA + gas tamponade is an effective treatment to preserve and maintain vision in selected patients with thick and wide SMHs due to nAMD. Compared with expansile gas and other treatment modalities, vitrectomy 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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