Long-Term Visual Outcome and Its Predictive Factors Following Treatment of Acute Submacular Hemorrhage with Intravitreous Injection of Tissue Plasminogen Factor and Gas

Bianka Sobolewska,1 Eray Utebey,2 Karl Ulrich Bartz-Schmidt,1 and Olcay Tatar1

Abstract

Purpose: To investigate the long-term functional outcome and its predictive factors of treatment of acute submacular hemorrhage secondary to age-related macular degeneration with intravitreal application of recombinant tissue plasminogen activator (rt-PA) and gas.

Methods: Twenty-six patients were enrolled in the retrospective case series. A complete history and ocular examination, including fluorescein angiography, were performed. The best-corrected visual acuity was measured with a Snellen chart. Patients were followed up for 12 to 131 months (mean: 49 months). All patients underwent intravitreal injection of rt-PA (50 μg) and expansile gas. Primary outcome measures were best postoperative and final visual acuity and degree of blood displacement.

Results: The size of the subretinal hemorrhage ranged from 0.5 to 28 disc diameters, and the degree of blood displacement was defined as complete (≥1 disc area from the center of the fovea), partial, or no displacement. Twenty-one (81%) patients showed partial or complete displacement of hemorrhage. Due to lack of displacement of hemorrhage in 5 patients (19%), submacular surgery was performed. In 13 of 21 (62%; P = 0.0001) patients with displacement of hemorrhage, the best postoperative visual acuity improved ≥2 lines. The final visual acuity improved ≥2 lines in 42.9% (9 of 21), was stable in 23.8% (5 of 21), and worse ≥2 lines in 33.3% (7 of 21) of patients. The short duration of hemorrhage (≤4 days) and complete displacement of blood, independent of the hemorrhage size, were significantly associated with better postoperative visual acuity (P = 0.0001, P = 0.0001, respectively).

Conclusion: Intravitreal injection of rt-PA and gas seem to be more effective when applied within the first 4 days of acute submacular hemorrhage. Preoperative visual acuity as well as displacement of hemorrhage might be useful to predict final visual acuity.

Introduction

Spontaneous resolution of untreated submacular hemorrhage secondary to choroidal neovascularization (CNV) is associated with poor visual prognosis.1–4 Through a 3-year follow-up, Avery et al. observed a decrease of 6 or more lines of visual acuity in 44% of eyes. The median change was a loss of 4 lines.1 In the study of Scupola et al., the visual acuity worsened in 80% of the eyes during a 2-year follow-up.4 The reduced visual outcome is attributed to the sensory retinal toxicity of subretinal blood, which includes limited diffusion of nutrients and oxygen, shearing off photoreceptor outer segments due to clot contraction and release of toxic substances resulting from fibrinolysis, such as hemoglobin-derived iron.5–7 However, surgical removal of subfoveal hemorrhage and any associated fibrovascular tissue, if possible, did not increase the chance of stable or improved visual acuity, and was associated with a high risk of rhegmatogenous retinal detachment in the Submacular Surgery Trials.8 In an attempt to minimize the damaging effects of submacular hemorrhage and to avoid invasive treatment of macular retina, Heriot proposed a new treatment modality of submacular hemorrhage using intravitreal injection of recombinant tissue plasminogen activator (rt-PA)

1Centre for Ophthalmology, Eberhard-Karls University Tuebingen, Tuebingen, Germany.
2Medical Faculty, Ankara University, Ankara, Turkey.
followed by long-acting gas. However, the information regarding its predictive factors is limited due to the lack of statistical evaluation and the small numbers of patients. The aim of our retrospective study is to determine the functional outcome and its predictive factors following treatment of submacular hemorrhage due to neovascular age-related macular degeneration (AMD) with intravitreal injection of rt-PA and gas.

Materials and Methods

In this retrospective, nonrandomized, consecutive case series, we reviewed the medical records of 26 patients, with acute submacular hemorrhage due to neovascular AMD, treated at the Centre for Ophthalmology of the University of Tuebingen in Germany between July 2001 and May 2011. All patients had acute subretinal hemorrhage (≤ 28 days). This work adhered to the tenets of the Declaration of Helsinki and the Institutional Ethics Committee of the University of Tuebingen granted approval with a waiver of informed consent for this retrospective study.

A complete history and ocular examination were performed, including pre- and postoperative fundus photography. The size of subfoveal hemorrhage and CNV was measured in standardized Macular Photocoagulation Study disc areas. The best-corrected visual acuity (BCVA) was obtained using a Snellen chart. The visual acuity less than 20/2000 on the Snellen chart was categorized as hand motions. The duration of follow-up ranged from 12 to 131 months with a mean of 49 months. All patients were examined before the treatment, 1 to 7 days after surgery, and at 4- to 6-week intervals. The etiology of submacular hemorrhage was confirmed to be neovascular AMD by postoperative fluorescein angiography. Further follow-up was determined by the treating ophthalmologist depending on the clinical course.

The procedure was performed under local anesthesia. Fifty micrograms of rt-PA, equal to a volume of 50 µL (rt-PA; Actilyse), and 0.5 mL pure gas such as perfluoropropane (n = 20), hexafluoroethane (n = 5), or sulfur hexafluoride (n = 1) were injected through the pars plana. Subsequently, perfusion of the central retinal artery was controlled by indirect ophthalmoscopy. An anterior chamber paracentesis was performed, if deemed necessary. All patients were instructed to maintain prone positioning.

Additional therapy like intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors (ranibizumab and/or bevacizumab) was given in 10 patients, with a duration of hemorrhage ≤ 14 days (case 9, 11–13, 15–17, 20–21, and 24) and in 1 patient with a duration of hemorrhage > 14 days (case 18), after rt-PA and gas injection (case 20, 21, and 24: 3 days after rt-PA and gas injection; other cases: 6–195 days after rt-PA and gas injection). One patient (case 3) underwent photodynamic therapy 12 months after rt-PA and gas injection. Intravitreal triamcinolone acetonide injection (0.1 mL) and focal laser coagulation were performed in another patient (case 19).

Primary outcome measures were (1) best postoperative visual acuity, (2) final visual acuity, and (3) degree of blood displacement. The degree of blood displacement was measured ophthalmoscopically after completion of prone positioning and defined as complete (≥ 1 disc area from the center of the fovea), partial, or no displacement. Secondary outcome measures included complications.

Statistical analysis

Visual acuity is presented as median ± range and mean. For statistical analysis, Snellen fractions were converted into logMAR. The two-sample Student’s t-test was performed for statistical analysis using the commercial software (SPSS version 19.0; SPSS, Inc.). P < 0.05 was considered to be statistically significant. The correlation between potential predictive variables (preoperative visual acuity, postoperative visual acuity, final visual acuity, patient’s age, displacement of hemorrhage, medical and anticoagulant history) was measured by Spearman’s or Pearson’s correlation coefficient. All statistical analyses were performed with commercial software (SPSS version 19.0; SPSS, Inc.).

Results

Twenty-six patients with acute submacular hemorrhage secondary to AMD have been reviewed retrospectively. Seven (27%) were men and 19 (73%) were women. The mean age of the patients was 78 years (range 61–89 years). The duration of subretinal hemorrhage ranged between 1 and 28 days. The size of the subretinal hemorrhage ranged from 0.5 to 28 disc diameters and the average size of CNV was 2.4 disc diameters. Fifteen patients were pseudophakic. The clinical features are summarized in Table 1.

In the group of 21 patients, 13 of 21 (62%) patients showed partial or complete displacement of hemorrhage. Due to lack of displacement of submacular hemorrhage in 5 of 26 patients (19%), submacular surgery of CNV extraction with macular translocation was performed after 11 to 236 days.

In the group of 21 patients, 13 of 21 (62%) patients showed complete displacement of hemorrhage (Fig. 1) and in 8 of 21 (38%) patients, partial displacement of hemorrhage was achieved. Five patients were men (24%) and 16 patients were women (76%). They were followed up for an average of 42 months (range 12–98 months).

The initial BCVA varied from hand movement to 0.6 (median 1.1 logMAR, mean 1.15 logMAR). The best postoperative visual acuity ranged from hand movement to 0.22 logMAR (median 0.7 logMAR, mean 0.8 logMAR), and the final BCVA ranged from 1.8 to 0.22 logMAR (median 0.92 logMAR, mean 0.96 logMAR) (Table 1). Compared to the initial acuity, the postoperative BCVA improved by 2 lines or greater in 13 of 21 (62%) patients (P = 0.0001), remained stable in 7 of 21 (33%), and worsened by 2 lines or greater in 1 of 21 patients (5%) (Fig. 2). The final BCVA was improved by 2 lines or greater in 9 of 21 (42.9%), stable in 5 of 21 (23.8%), and worse 2 lines or greater in 7 of 21 (33.3%) patients (Fig. 3). The decreased final visual acuity was probably correlated with subretinal fibrotic scarring in the macula or postoperative cataract development.

A better outcome was associated with the duration of hemorrhage. Submacular hemorrhage lasted ≤ 14 days in 18 of 21 (86%) patients and > 14 days in 3 of 21 (14%) patients (Table 1). In addition, a subgroup of 10 patients with duration of hemorrhage ≤ 4 days was distinguished. In 18 patients with duration of hemorrhage ≤ 14 days and in 10 patients with duration of hemorrhage ≤ 4 days, the best postoperative visual acuity improved significantly ≥ 2 lines in 12 of 18 (67%) patients (P = 0.0001) and in 9 of 10 (90%) patients (P = 0.0001), respectively. Besides, the final visual acuity also improved ≥ 2 lines in 8 of 18 (44%) patients with...
duration of hemorrhage ≤14 days and in 6 of 10 (60%) patients with duration of hemorrhage ≤4 days, but not significant. No significant changes in the visual acuity were seen between 5 and 14 days and after 14 days.

Moreover, the size and the duration of hemorrhage were compared concerning visual acuity. A submacular hemorrhage size ≥3 disc areas was observed in 12 of 21 (57%) and ≤2 disc areas in 9 of 21 (43%) patients, respectively (Table 1). There was a significant relationship between the best postoperative visual acuity improvement, large hemorrhage (≥3 disc areas), and a shorter duration of hemorrhage. In 12 patients with a large hemorrhage and with

Table 1. Clinical Features of 26 Patients with Acute Submacular Hemorrhage

<table>
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<tr>
<th>No.</th>
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CF, counting fingers; F, female; HM, hand motion; M, male; MT, macular translocation; postop., postoperative; PPV, pars plana vitrectomy; preop., preoperative; rt-PA, recombinant tissue plasminogen activator; SMH, submacular hemorrhage; VA, visual acuity.

FIG. 1. Fundus photographs (A, B) and fluorescein angiography images (C, D) of case 12. Preoperative submacular hemorrhage (A) was displaced completely (B) 25 days after intravitreal recombinant tissue plasminogen activator (rt-PA) and gas injection. Early (C) and late (D) fluorescein angiography images 25 days after rt-PA and gas injection displayed a hyperfluorescence due to choroidal neovascularization secondary to age-related macular degeneration.
duration of hemorrhage \( \leq 14 \) days and in 7 patients with duration of hemorrhage \( \leq 4 \) days, the best postoperative visual acuity improved significantly \( \geq 2 \) lines in 8 (67%) patients \((P=0.003)\) and in 7 (100%) patients \((P=0.001)\), respectively. However, the best postoperative visual acuity in association with small hemorrhage \((\leq 2 \text{ disc areas})\) and the duration of hemorrhage could not be confirmed because of the small number of patients in all subgroups. Any significant changes in the visual acuity were not observed between 5 and 14 days.

In our correlation analysis, factors such as patient age, medical and anticoagulant history were not significant. The best postoperative visual acuity was positively correlated with the preoperative visual acuity \((r=0.75, P=0.0001)\). The final visual acuity was also positively correlated but with displacement of hemorrhage \((r=0.47, P=0.03)\). Based on these results, the best visual outcomes could be anticipated in patients with better preoperative visual acuity and with complete deposition of hemorrhage. Moreover, in patients with complete deposition of submacular hemorrhage, the best postoperative and the final visual acuity were significantly better than in patients with partial deposition of hemorrhage \((\text{postoperative } P=0.0001\) and final \(P=0.02\) vs. not significant). The postoperative and the final visual acuity improved \(\geq 2 \) lines in 10 of 13 (77%) and in 9 of 13 (69%) patients with complete deposition, and in 3 of 8 (38%) patients with partial deposition, respectively.

Five of 26 patients were subjected to macular translocation owing to lack of displacement of blood after rt-PA and gas injection after 16 to 236 days. The age ranged between 68 and 89 years (mean age 78). Two patients were men (40%) and 3 patients were women (60%). They were followed up for an average of 60 months (range 18–131 months). The initial BCVA varied from hand movement to 0.8 logMAR (median 1.6 logMAR, mean 1.52 logMAR), the best postoperative BCVA \((\text{after rt-PA and gas injection})\) ranged from hand movement to 0.5 logMAR (median 1.3 logMAR, mean 1.3 logMAR), and the final BCVA after macular translocation ranged from hand movement to 0.92 logMAR (median 1.79 logMAR, mean 1.92 logMAR). The first operation did not influence the visual acuity significantly. After macular translocation, the visual acuity also did not change significantly. The clinical features and operations are summarized in Table 1.

We observed no postoperative complications in terms of retinal detachment, lens damage, and central retinal occlusion due to increased intraocular pressure. Nevertheless, 3 patients had recurrent subretinal hemorrhage \((\text{case 19 in 1 year, cases 20–21 in 1 month after treatment})\). In case 21, intravitreal rt-PA and gas injection was repeated. Due to recurrent subretinal hemorrhage, 4 years after second intravitreal rt-PA and gas injection, pars plana vitrectomy had to be performed. In any patient, breakthrough vitreous hemorrhage was observed.

**Discussion**

Intravitreal injection of rt-PA and gas is a minimally invasive treatment option for subretinal hemorrhage secondary to AMD. In our study, the postoperative and the final visual acuity improved \(\geq 2 \) lines in 62% and 43% of 21 patients with partial or complete displacement of hemorrhage. After a mean follow-up time of 42 months, the final visual acuity worsened \(\geq 2 \) lines in 33.3% of the patients. Our results of visual acuity outcomes, parallel those reported by Buhl et al., Hassan et al., Hesse et al., and Kung et al.10–12,16 However, in both case series of Hattenbach et al., the final visual acuity worsened in only 8%–9% eyes after an average of 4–7 months, but it has to be pointed out that they investigated patients with small size hemorrhage.13,14 Likewise, prospective case series of Buhl et al. showed a significant improvement of postoperative visual acuity in 49% of patients with acute submacular hemorrhage after intravitreal injection of rt-PA and gas. In 50% of patients, the visual acuity remained stable or worsened after the follow-up time ranged from 6 weeks to 3 months.10
Comparable percentage distribution of visual acuity was observed in our study, namely, half of the patients showed an improvement of visual acuity and the second half either deterioration or stabilization of visual acuity even during the longer period of follow-up time of 42 months.

In our study, the duration of hemorrhage seemed to have an impact on the visual outcome. Patients with duration of hemorrhage ≤ 14 days showed significant improvement of postoperative visual acuity. These results are in accordance with studies of Hattenbach et al.13,14 Still, our results revealed no significant change in visual acuity in patients with duration of hemorrhage between 5 and 14 days. However, the best postoperative visual acuity of patients with duration of hemorrhage ≤ 4 days improved significantly (the best postoperative visual acuity in patients with duration of hemorrhage ≤ 4 days vs. ≤ 14 days: 90% vs. 67%). The final visual acuity of patients with the duration of hemorrhage ≤ 4 days also tended to improve more but without significance. None of the previous studies differentiate between the duration of hemorrhage ≤ 4 days and between 5 and 14 days.11–15 To the best of our knowledge, our results display for the first time clearly that, the critical time point of intervention seems to be ≤ 4 days rather than 14 days. These findings may be explained by outer retinal degeneration such as photoreceptor shearing due to clot retraction, which occurred within 3 to 7 days in the rabbit retina17 and within 7 to 14 days in the cat retina.7,18

Despite similar postoperative and final visual acuity improvement, in the study of Hattenbach et al. (the mean of follow-up was 4–7 months) and Hassan et al. (the mean of follow-up was 10.5 months), the percentage of complete blood displacement was higher than in our study.11,13,14 However, Hattenbach et al.13 evaluated treatment of small submacular hemorrhage in 25 patients, and Hassan et al.11 also investigated management of small submacular hemorrhage with size ≤ 4 disc areas (except 2 patients) in 15 patients. In the larger study of Hattenbach14 with 42 patients, most of the patients (32 of 42) had also a smaller size of submacular hemorrhage (≤ 5 disc areas) in comparison to our study. In the other studies, this distribution in complete and partial displacement was not specified.10,12 However, in our study, complete deposition of hemorrhage seemed to be the positive predictor factor for final visual acuity.

In our study, not only the duration of hemorrhage but also the preoperative visual acuity and its complete deposition seem to be associated with better functional outcome. Preoperative visual acuity was also found to be a predictive factor in the studies of Hassan et al., Hesse et al., and Schulze-Bonsel et al.11,12,15

Of considerable interest is the finding that rt-PA treatment seems to prevent the development of fibrocellular subretinal scar formation. Although the pathogenic mechanism is unclear, rt-PA may increase phagocyte migration, phagocytosis, and it may reduce retinal pigment epithelial metaplasia, thereby facilitating the clearance process.19 If this finding is true, we await better functional outcome with delayed progression of visual loss for an extended period of time after rt-PA treatment. Correspondingly, in our study, 33.3% of patients worsened 2 or more visual acuity lines, 42.9% improved 2 or more visual acuity lines, and 23.8% had stable visual acuity within an average follow-up period of 42 months. In contrast, Avery et al. observed twice less improvement (21%) and twice more impairment of visual acuity (64%) in the study of natural course of submacular hemorrhage.1

Intravitreal injection of 50 µg rt-PA seems to be effective and safe. Only 12% of patients had recurrent subretinal hemorrhage. In addition, no postoperative breakthrough vitreous hemorrhage was observed in any of our patients following rt-PA and gas injection. Submacular surgery did not improve the visual acuity in patients without displacement of hemorrhage after rt-PA and gas. In our previous series, which were treated with only macular translocation without previous application of rt-PA and gas, the increased visual acuity has been detected in 56% of cases.20,21 It must be taken into consideration that patients in this retrospective evaluation were resistant to previous therapy. Whether previous therapy with rt-PA or longer duration of subretinal hemorrhage preoperatively has influenced the postoperative visual acuity must be evaluated in further studies with bigger series. It might be recommended that patients should be followed up closely to plan further treatments such as intravitreal injections of angiogenesis inhibitors or subretinal rt-PA injection or submacular surgery.

The retrospective design of our study with lack of control group must be taken into consideration when the results are evaluated. However, to the best of our knowledge, this is the first study with a long duration of follow-up. Our study revealed that intravitreal injection of rt-PA and gas may be recommended as a first-line, minimally invasive, safe and effective treatment modality for patients with short-lasting submacular hemorrhage secondary to neovascular AMD. Based on these results, it seems to be advisable to perform the intravitreal rt-PA with gas injection as early as possible, especially within 4 days of acute submacular hemorrhage. Expectedly, complete displacement (≥ 1 disc area from the center of the fovea) and good preoperative visual acuity predict better functional outcomes. Still, these patients must be followed up closely since further therapies might be essential due to lack of displacement or recurrent hemorrhages. Whether a triple therapy of intravitreal injection of VEGF inhibitors, rt-PA and gas, or subretinal injection of rt-PA is the better option to improve the functional outcome must be evaluated in further controlled studies.

Author Disclosure Statement

None of the authors has a financial or property interest in any material or method mentioned in this article.

References


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Address correspondence to:
Dr. Bianka Sobolewska
Centre for Ophthalmology
Eberhard-Karls University
Schleichstr. 12
72076 Tuebingen
Germany

E-mail: bianka.sob@gmx.de