The effect of subretinal recombinant tissue plasminogen activator application for submacular hemorrhage

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ABSTRACT

Purpose: The aim of the present study was to evaluate the outcomes of subretinal tissue plasminogen activator (r-tPA) injection with pars plana vitrectomy (PPV) in patients with submacular hemorrhage (SMH) extending towards the fovea.

Materials and Methods: The study included 10 eyes of 10 patients who underwent subretinal r-tPA injection with 23 G PPV due to SMH extending towards the fovea. Following standard 23 G PPV, r-tPA (Actilyse, 10 mg/mL, Boehringer-Ingelheim, Germany) at a concentration of 25 µg/0.1 ml was injected into the subretinal space with a 41 G needle at a concentration of 0.2-0.3 ml. Subsequently, fluid-air-12% C3F8 exchange was performed and intravitreal 1.25 mg bevacizumab was administered. After surgery, the patient was given appropriate head position according to the bleeding site.

Results: The mean age of the patients was 73.9 ± 4.7 years, 4 (40%) were male and 6 (60%) were female. Two patients (20%) developed SMH due to retinal macroaneurysm rupture, while choroidal neovascular membrane was the cause of hemorrhage in 8 patients (80%). Best corrected visual acuity was 2.53 ± 0.49 logMAR preoperatively, 1.28 ± 0.66 at one month, 1.08 ± 0.64 at three months and 1.04 ± 0.62 at six months postoperatively and the difference was significant ($p<0.001$ for each parameter).

Conclusions: In patients with submacular hemorrhage, r-tPA administered subretinally provides significant visual acuity improvement without serious complications.

Keywords: Pars plana, recombinant tissue plasminogen activator r-tPA, submacular hemorrhage, subretinal injection.

INTRODUCTION

Submacular hemorrhage (SMH) is a rare complication of choroidal or retinal vascular abnormalities such as choroidal neovascularization (CNV), polypoidal choroidal vasculopathy (PCV) and retinal macroaneurysms. The prognosis of SMH varies depending on the underlying etiologic cause and timing of treatment, with final visual acuity being lower in cases due to CNV.[1]

The main causes of visual loss following hemorrhage are blocked metabolic transmission between the retinal pigment epithelium (RPE) and the outer retina, mechanical stress on photoreceptors due to fibrin retraction, and most importantly, neurotoxicity due to iron released from lysed erythrocytes.[2] In untreated cases, irreversible severe visual loss may occur as a result of these mechanisms. The main strategy in treatment is to displace or remove the hemorrhage from this area. Air or gas tamponade application with pars plana vitrectomy (PPV) and appropriate head positioning in the postoperative period is recommended to ensure the displacement of hemorrhage. In recent years, the use of intravitreal or subretinal recombinant tissue plasminogen activator (r-tPA) in addition to this surgery has been introduced and successful results have been obtained.[1] Removal of hemorrhage from the submacular region is considered as an alternative treatment method that can be preferred especially in cases with very extensive hemorrhage. However, this subretinal surgery may cause many complications, especially proliferative complications.

The present study aims to evaluate the outcomes and complications of subretinal r-tPA injection with PPV in

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patients with SMH extending towards the fovea in the light of the literature.

MATERIAL AND METHOD

The necessary ethical permissions were obtained from the Mersin University Clinical Research Ethics Committee before the study. All patients participating in the study were informed about the study and informed consent forms were obtained. The study was conducted by the Declaration of Helsinki. Between March 01, 2021, and September 01, 2022, 10 eyes of 10 patients who applied to our clinic due to visual loss and underwent subretinal r-tPA injection with 23 G PPV for SMH extending towards the fovea were included in the study. Patients between 18-80 years of age, admitted due to new hemorrhage (first two-week period) and not treated after hemorrhage, with at least 6-month follow-up, with proper imaging and file records were included in the study. Patients outside the age range of 18-80 years, patients who were diagnosed late after hemorrhage, patients who received previous treatment, and patients with inadequate follow-up periods and inadequate file records were excluded from the study. Demographic data, comorbidities, time of presentation to the clinic, and visual acuity before and after surgery were recorded.

All surgeries were performed by a single specialist (ED) under general anesthesia. In cases with senile cataracts, cataract surgery with phacoemulsification was performed in the same session, and a one-piece acrylic hydrophobic monofocal posterior chamber intraocular lens was implanted. Following standard 23 G PPV, r-tPA (Actilyse, 10 mg/mL, Boehringer-Ingelheim, Germany) at a concentration of 25 µg/0.1 ml was injected into the subretinal space with a 41 G needle at a concentration of 0.2-0.3 ml. Subsequently, a fluid-air-12% C3F8 exchange was performed and intravitreal bevacizumab 1.25 mg was administered before the access sites were closed. After surgery, topical antibiotics and steroids were prescribed and the patient was given an appropriate head position according to the bleeding site. Anti-VEGF treatment was continued after surgery in cases deemed necessary. In addition, retinal laser was added to the treatment after the hemorrhage was removed in patients who underwent surgery for aneurysm.

SPSS (version 29.0.1, IBM Co., NY, US) package program was used for statistical analysis. The conformity of the numerical data to normal distribution was checked by the Shapiro-Wilk test. Numerical data were calculated as mean ± standard deviation. Paired t test and repeated ANOVA were used to compare dependent groups. Categorical data were presented as numbers and percentage. Pearson correlation coefficient was calculated for correlation analysis of numerical variables. For all analyses, $p<0.05$ was considered significant.

RESULTS

The mean age of the patients included in the study was 73.9 ± 4.7 years, 4 (40%) were male, and 6 (60%) were female. Five patients had a history of hypertension and 4 patients had a history of diabetes mellitus. Two patients (20%) developed SMH due to retinal macroaneurysm rupture, while choroidal neovascular membrane was the

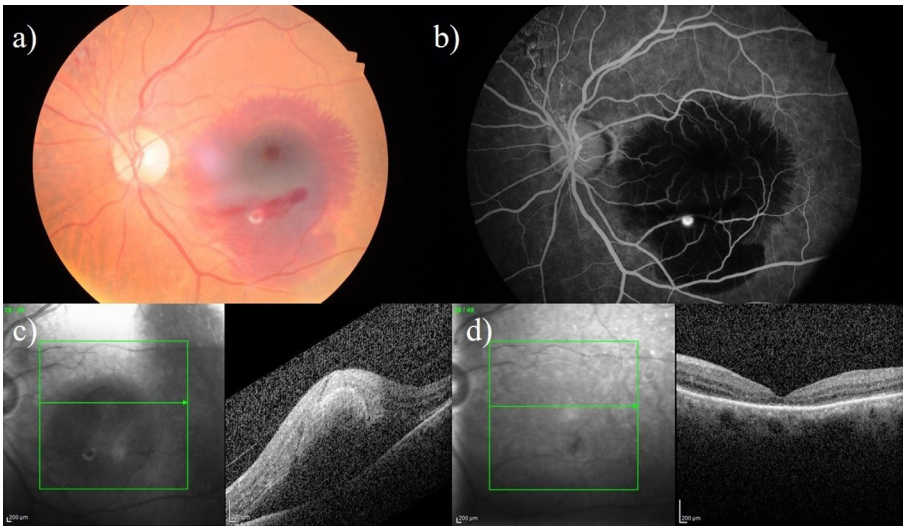

Figure 1: *Preoperative and postoperative appearance of a patient with subretinal hemorrhage due to retinal macroaneurysm, a) color fundus photograph, b) fundus fluorescein angiography image, c) preoperative optical coherence tomography image, d) postoperative optical coherence tomography image.*

cause of hemorrhage in 8 patients (80%) (Figure 1, Video 1). The interval between visual symptoms and presentation was 3.2 ± 1.47 days. Best corrected visual acuity was 2.53 ± 0.49 logMAR preoperatively, 1.28 ± 0.66 at one month, 1.08 ± 0.64 at three months, and 1.04 ± 0.62 at six months postoperatively and the difference was significant ($p<0.001$ for each parameter) (Table-1). Only 1 patient had recurrent intravitreal hemorrhage and hyphema following subretinal injection. No complications were encountered in the other patients. There was no correlation between postoperative visual acuity and age (r=-0.548, p=0.101), time of presentation (r=0.473, p=0.167), and preoperative visual acuity (r=0.414, p=0.234) (Table 2).

DISCUSSION

Submacular hemorrhage is an important complication of retinal vascular pathologies and can lead to irreversible severe visual loss. The underlying etiologic causes of such hemorrhages are categorized under two main headings: first, CNV-related pathologies (age-related macular degeneration, polypoidal choroidal vasculopathy, pathologic myopia, etc.) and second, non-CNV vascular causes (retinal aneurysm, Terson syndrome, trauma, etc.).[3] Among all these causes, CNV-related hemorrhages are the most common group. In the present study, most of the patients were found to have CNV-related hemorrhages and this result is consistent with the data in the literature. While hemorrhages caused by non-CNV causes have different degrees of visual improvement after hemorrhage withdrawal, visual results are poor in CNV-related cases.[1,4] The main reason for this is that CNV is a pathology that both causes hemorrhage and needs primary treatment.

Despite many studies, there is no consensus gold standard in the classification and treatment of SMH.[5] However,

Tablo 1: *Demographic and visual acuity data of patients included in the study.*

Patient	Age (years)	Gender	Co-morbidity	Diagnosis	Time to (day)	Treatment	Preoperative VA	Postoperative 1st month VA	Postoperative 3rd month VA	Postoperative 6th month VA	Postoperative Anti-VEGF
1	74	Female	None	Retinal Macroaneurysm	2	23 G PPV + 41 G Subretinal tPA + IV bevacizumab + 12% C3F8 tamponade	2.40	1.51	1.10	1.10	None
2	66	Male	None	Choroidal neovascular membrane	1		2.10	1.90	1.70	1.40	2 X IV Bevacizumab and 8 X IV Ranibizumab
3	80	Female	HT	Choroidal neovascular membrane	3		3.10	0.52	0.30	0.30	2 X IV Bevasizumab and 5 X IV Aflibercept
4	77	Female	Uterus Ca	Choroidal neovascular membrane	4		3.10	1.80	1.40	1.40	9 X IV Aflibercept
5	79	Female	DM, HT	Retinal Macroaneurysm	2		2.10	0.52	0.40	0.40	None
6	70	Male	HT, Prostate Ca	Choroidal neovascular membrane	4		2.40	0.30	0.15	0.15	1 X IV Bevacizumab
7	75	Female	DM, Arrhythmia	Choroidal neovascular membrane	3		1.80	1.00	0.90	0.90	2 X IV Bevacizumab
8	71	Male	DM, COPD	Choroidal neovascular membrane	5		3.10	2.10	1.80	1.80	2 X IV Bevacizumab and 1 X IV Ranibizumab
9	79	Male	DM, HT	Choroidal neovascular membrane	2	PHACO + 23 G PPV + 41 G Subretinal tPA + IV bevacizumab + 12% C3F8 tamponade	2.10	1.00	0.90	0.80	1 X IV Bevacizumab
10	68	Female	HT, Asthma	Choroidal neovascular membrane	6		3.10	2.10	2.10	2.10	1 X IV Bevacizumab

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, G: Gauge, PPV: pars plana vitrectomy, IV:intravitreal, PHACO: Phacoemulsification, VA: Visual acuity, VEGF: vascular endothelial growth factor

Tablo 2: *Relationship between study parameters and final visual acuity.*

		Postoperative 6th month VA
Age (years)	r	-0.548
	p	0.101
Time to (day)	r	0.473
	p	0.167
Preoperative VA	r	0.414
	p	0.234

VA: Visual acuity

the basic principle of treatment in newly developing hemorrhages is based on changing the location of the hemorrhage or removing the hemorrhage from this area. The main reason for this is the cellular destruction caused by hemorrhage. Studies have shown that photoreceptor destruction begins early after hemorrhage and this destruction is related to the duration of exposure to hemorrhage.[6,7] Therefore, it is of great importance that the patient is admitted early and the surgical intervention is not delayed. However, in the present study, there was no significant correlation between the onset of symptoms and final visual acuity. Possible reasons for this may be the late recognition of the onset of symptoms and the time elapsed for surgery.

In 1991, Peyman et al. first reported hemorrhage clearance with r-tPA in patients with SMH.[8] Later, it was reported that intravitreal anti-VEGF injections, pneumatic displacement, and intravitreal r-tPA injections alone can be performed in small hemorrhages.[9] In larger hemorrhages, successful results can be obtained with intravitreal or subretinal r-tPA application together with the use of gas as tamponade and the addition of anti-VEGF in necessary cases.[10] In addition to all these treatment alternatives, also reported that hemorrhage can be cleared with the use of r-tPA by performing small or large retinotomies depending on the case.[9]

In a study by Bell et al., the results of intravitreal r-tPA with pneumatic displacement and subretinal r-TPA with PPV were compared and no significant difference was found between the two groups in terms of visual acuity.[11] Similar results were reported by Tranos et al. and it was suggested that intravitreal r-tPA with pneumatic displacement may be preferred because it is a minimally invasive and more economical method.[12] Another study by Fassbender et al. compared the efficacy of pneumatic displacement(PD) alone, intravitreal r-tPA in combination with pneumatic displacement, and subretinal r-tPA in combination with PPV and found no significant visual improvement in the pneumatic displacement alone group.[13] In addition, vitrectomy with subretinal r-tPA injection reduced the final disciform scar in comparison to PD with or without intravitreal r-tPA.[13] These results show the efficacy of r-tPA application in treatment.

There have been studies in which pneumatic displacement of subretinal hemorrhages with intravitreal gas injection alone without tPA has been successful.[14-17]

In recent years, the use of air or intravitreal/subretinal anti-VEGF drugs with subretinal r-tPA application has been brought to the agenda and successful results have been obtained.[18] It has been reported that bleeding is displaced more easily with air given to the subretinal area. In the Submarine study, the efficacy and safety profiles of aflibercept, ranibizumab, and bevacizumab administered subretinally with subretinal r-tPA were evaluated. In this study, there was no significant difference in visual acuity between the groups, and a significant increase in visual acuity was achieved in all three groups.[10,19] Apart from all these studies, successful results have also been obtained with intravitreal anti-VEGF drug applications in combination with subretinal r-tPA application.[20] The most important point to remember here is the strict postoperative follow-up, especially in CNV-related hemorrhages and adherence to the intravitreal anti-VEGF treatment protocol in necessary cases. In the present study, intravitreal anti-VEGF treatment was applied with subretinal r-tPA injection, and significant increases in visual acuity were obtained in accordance with the literature. Again, a strict anti-VEGF treatment regimen was continued in necessary cases as stated in the literature and no recurrent hemorrhage was encountered in any patient. The possible underlying reason for this is the continuation of the anti-VEGF treatment regimen.

In the study by Hillenkamp et al, the complete resolution of submacular hemorrhages was 22% in the intravitreal r-tPA group and 55% in the subretinal r-tPA group. Complications such as retinal detachment, vitreous hemorrhage and recurrence of submacular hemorrhages were more frequent in the subretinal r-tPA group.[21]

Following the results of a study comparing SMH displacement by pneumatic displacement with intravitreal expansion gas to PPV with subretinal injection of tPA, anti-VEGF, and air, it was concluded that surgeons may

consider PPV with subretinal injection in cases of thick and wide SMH or as a secondary rescue procedure in selected cases that have not benefited from PD.[22]

In a study by Cakir et al. 21 eyes of 21 patients with severe submacular hemorrhage within the last 10 days were treated with intravitreal injection of pure C3F8 gas (0.4-0.5 mL) followed by face down position for pneumatic displacement. An additional intravitreal injection of 25-50 µg tPA was given to seven of these patients. In 20 out of 21 patients, an effective displacement of the hemorrhages was achieved within 7 days. Using additional tPA did not affect the final results.[23]

The need for anti-VEGF injections over 24 months was statistically significantly lower with subretinal aflibercept compared to intravitreal aflibercept in cases of SMH due to nAMD treated with PPV with r-tPA combined with subretinal or intravitreal aflibercept injections, resulting in better CNV management.[24]

In an experimental study investigating the effects of bevacizumab at a concentration of 0.25 mg/ml administered with 20 µg/ml subretinal r-tPA on ERG parameters, no significant retinal toxicity was observed. However, r-tPA concentrations higher than 20 µg/ml should not be used, as 60 µg/ml r-tPA caused a reversible but significant decrease in a-wave amplitudes. There was an irreversible decrease in ERG amplitudes at the highest concentration tested, 200 µg/ml r-tPA.[25] In a series of 17 patients using a dose of 48 µg/0,4 ml tPA, there was no evidence of retinal toxicity secondary to subretinal r-tPA.[1] The therapeutic range for subretinal r-tPA should be assumed to be narrow and to prevent the clot from separating from the photoreceptors, care must be taken to ensure that the cannula is injected into the clot and not between the clot and the retina.[1]

To minimize damage to the retina from the needle tip, the syringe is squeezed just before the needle touches the part of the retina to be punctured before subretinal tPA injection. Big clots may require more than one puncture to reduce the risk of complications from removing the clots.[26]

Another controversial factor in the treatment of patients with submacular hemorrhage is the use of air or gas as a tamponade after surgery. A study by Erdogan et al. showed that hemorrhage can be displaced by using only gravitational force without using tamponade after PPV and subretinal r-tPA application.[6] In the present study, gas tamponade was preferred and the patient was given a head position according to the bleeding site in the postoperative period.

There seems to be an increasing preference for vitrectomy and subretinal r-tPA administration, although there are reports of intravitreal r-tPA and gas administration.[27] This is probably due to the presumed higher concentration of r-tPA in the subretinal blood clot compared to intravitreal administration[28] and the availability of smaller gauge vitrectomy equipment. Subretinal r-tPA may cause more complications than intravitreal r-tPA because it is a more invasive procedure.[4] The small number of patients in the study is an important limitation. Nevertheless, the use of the same treatment protocol by one vitreoretinal surgeon for all patients allowed examination of the effects of other variables on outcome.

Submacular hemorrhage is an emergency that causes sudden visual loss and visual field defects due to CNVM or macroaneurysm. Displacement and removal of subretinal hemorrhages, especially those affecting the foveal region, will improve vision. tPA administration, air and/or gas administration and surgical removal are among the treatment options. Treatment of the underlying pathology should not be ignored during follow-up.

In conclusion, subretinal r-tPA can improve visual acuity in patients with SMH without causing any serious complications. Further studies are necessary for the determination of the best treatment algorithm for SMH.

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Declaration of interest

The authors report no conflicts of interest

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