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RETINAL DISORDERS

Management of submacular hemorrhage with intravitreal versus subretinal injection of recombinant tissue plasminogen activator

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Abstract
Aim To compare the efficacy of pars plana vitrectomy (ppV) with intravitreal injection of recombinant tissue plasminogen activator (rtPA) and gas versus ppV with subretinal injection of rtPA and intravitreal injection of gas.
Methods Nonrandomized, retrospective, interventional, comparative consecutive series including 47 patients with submacular hemorrhage. Eighteen patients were treated with ppV, intravitreal injection of rtPA and 20% SF6 gas [group A: mean age 78 years, mean duration of symptoms 6.6 days, 15 age-related macular degeneration (AMD), three retinal arterial macroaneurysm (RAMA)]. Twenty-nine patients were treated with ppV, subretinal injection of rtPA and intravitreal injection of SF6 gas (group B: mean age 75 years, mean duration of symptoms 5.9 days, 26 AMD, two RAMA, one blunt ocular trauma). The main outcome measure was complete displacement of submacular hemorrhage from the fovea.
Results Complete displacement of submacular hemorrhage was achieved in less patients in group A (22%) than in group B (55%) (p=0.025). In group A, mean best-corrected visual acuity (BCVA) change was logMAR -0.14, standard deviation (SD)=0.64, and in group B logMAR -0.32, SD=0.68 without statistically significant difference between the two groups (p=0.2, Mann–Whitney test). Complications (retinal detachment, vitreous hemorrhage, and recurrence of submacular hemorrhage) were more frequent in group B than in group A.
Conclusion ppV with subretinal injection of rtPA and intravitreal injection of gas was more effective than ppV with intravitreal injection of rtPA and gas in terms of complete displacement of submacular hemorrhage; however, it may be associated with a higher rate of postoperative complications. Functional improvement in the majority of patients suggests the absence of direct retinal toxicity of subretinally applied rtPA.

Keywords Age-related macular degeneration · Retinal arterial macroaneurysma · Recombinant tissue plasminogen activator · Submacular hemorrhage

Introduction

Submacular hemorrhage is not an unusual cause of acute central visual loss, particularly in the elderly. It may be caused by a number of conditions, the most common of which are neovascular age-related macular degeneration (AMD) and retinal arterial macroaneurysm (RAMA). The prognosis is usually poor [1, 2]. Damaging consequences of subretinal blood to sensory retinal tissue are attributed to a limitation of passage of nutrients to the retina [3], shrinkage of the outer retinal layers due to clot formation [3, 4] and release of toxic substances, such as fibrin [4], iron [5, 6], and hemosiderin [7]. Toxic effects of subretinal blood can be demonstrated 24 hours after hemorrhage [3]. Resolution

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of submacular hemorrhage is often associated with subsequent subretinal scar formation, particularly in neovascular AMD [1, 2]. Surgical removal of a submacular blood clot through a retinotomy was proposed in the late 1980s but was abandoned soon afterwards because of poor functional outcome. The procedure usually resulted in a large atrophy of the retinal pigment epithelium (RPE), since RPE cells were extracted together with the clot [8, 9]. Furthermore, the operation was frequently complicated by retinal detachment (30–37%) given that a large retinotomy was produced in the posterior pole [9, 10]. In the early 1990s, recombinant tissue plasminogen activator (rtPA) was introduced to facilitate clot liquefaction and to alleviate the surgical trauma of the procedure, the latter mainly due to a reduction of the size of the retinotomy [11, 12]. According to Lewis et al., it was possible to achieve clot liquefaction in 70–80% of cases. Functional improvement was reported in up to 60–80% of patients, but postoperative visual acuity was still less than 20/200 in most cases [11]. The results of the Submacular Surgery Trial (SST) showed no clear benefit of surgical removal of AMD-associated hemorrhagic choroidal neovascularisation (CNV) lesions [13]. In an attempt to avoid surgical manipulation of the macular retina, the displacement of submacular hemorrhage by intravitreal injection of rtPA and gas was proposed. According to several case series, gas injection with intravitreal injection of rtPA successfully displaces the hemorrhage in 60–100% of patients [14–18]. Because of the size of the molecule, it is unclear whether or not intravitreally injected rtPA penetrates the retina to reach a subretinal clot [19–22]. Delivery of rtPA to the subretinal space may be ensured by subretinal injection [23, 24]. In a case series of 11 patients reported by Haupert et al., subretinal injection of rtPA was shown to effectively clear submacular hemorrhage, but the procedure was associated with a 27% risk of hemorrhage recurrence [23]. Olivier et al. reported complete blood displacement in 25 of 28 patients with this procedure, significant vision improvement in 17 patients, and minimal complications (four patients with vitreous hemorrhage) [24].

The use of rtPA in the management of acute submacular hemorrhage has become widely accepted. However, the question as to whether rtPA should be applied intravitreally or subretinally is the subject of an ongoing debate.

The primary aim of the present retrospective study was to compare the rate of successful hemorrhage displacement from the fovea after pars-plana vitrectomy (ppV) with *intravitreal* injection of rtPA and gas versus ppV with *subretinal* injection of rtPA and intravitreal injection of gas. Secondary aims were to compare improvement of best-corrected visual acuity (BCVA) and complications.

Methods

In this retrospective case series, we reviewed the medical records of all patients with submacular hemorrhage treated at the Dept. of Ophthalmology of the University of Regensburg, Germany between 2001 and 2005. A total number of 47 patients were included (Table 1). Inclusion criteria were different etiologies of submacular hemorrhage (AMD, RAMA, ocular trauma) because the main goal of the study was to assess the effectiveness of the procedures in regard to blood displacement, a minimum age of 18 years, and a maximum history of symptoms of 14 days. Exclusion criteria were massive submacular hemorrhage extending beyond the equator, macular scar, and pregnancy. Between 2001 and 2003, 18 consecutive patients were treated with standard three-port 20-gauge ppV with intravitreal injection of rtPA and 20% SF6 gas (group A). In 2003 we changed our general therapeutic approach from the procedure described for group A to the procedure described for group B: Twenty-nine consecutive patients were treated with standard three-port 20-gauge ppV with subretinal injection of rtPA and intravitreal injection of 20% SF6 gas (group B).

The main outcome measure was complete displacement of submacular hemorrhage from the fovea. The fovea was defined as the circular area with a diameter of 1.5 mm or approximately one disc diameter in the center of the macula. Secondary outcome measures were Snellen best-corrected visual acuity (BCVA) and complications. Preoperative evaluation included standard ophthalmologic examination with BCVA and fundus color photography. Surgery was performed the same day. When prior to the operation phenprocoumon had to be replaced by intravenous heparin, surgery was performed the following day.

Approval was obtained from the Ethics Committee of the University of Regensburg. Informed consent was obtained from all patients.

Surgical technique

Group A: After a standard three-port ppV, 0.2 ml (40 µg) of rtPA (Actilyse®, Boehringer Ingelheim, Ingelheim, Germany) was injected intravitreally followed by injection of 20% SF6 gas to a complete intravitreal fill.

Group B: Subretinal injection of rtPA included standard three-port ppV, subretinal injection of 10–20 µg (0.05–0.1 ml) of rtPA dissolved in BSS through a 41 Gauge subretinal flexible canula (D.O.R.C., Zuidland, The Netherlands) followed by intravitreal injection of 20%-SF6 gas to a complete intravitreal fill. In both treatment groups, patients were instructed to keep a prone position for at least 1 day postoperatively.

Table 1 Baseline patient characteristics in groups A and B

	Group A (n=18)	Group B (n=29)
Mean age (years ±SD)	78+/-6	74,5+/-13
Gender (female:male)	13:5	19:10
Anticoagulant therapy	1 (aspirin)	6 (5 phenprocoumon, 1 aspirin)
Etiology of hemorrhage	15 AMD, 3 RAMA	26 AMD, 2 RAMA, 1 trauma
Mean duration of symptoms before surgery (days ±SD)	6.6 ± 5.8	5.9 ± 5.2
Maximal diameter of submacular hemorrhage (disc diameter ±SD)	3.2 ± 2.1	4.4 ± 2.2
Mean preop BCVA (logMAR) ±SD	1.07 ± 0.47	1.24 ± 0.43
Range of preop BCVA (logMAR)	2.0–0.4	2.0–0.5

AMD = age-related macular degeneration, RAMA = retinal arterial macroaneurysm, SD = standard deviation, logMAR 2.0 eqivalent to counting fingers.

Follow-up

Postoperative follow-up 1–3 months after surgery included BCVA, fundus color photography, and fluorescein angiography.

Statistical methods

In the statistical analysis of the outcome measures the type I error (alpha) was set at 0.05. Statistical significance of differences between groups were calculated using chi-square test and Mann–Whitney test. The results were statistically analysed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA) and Statistica 7 software (StatSoft Inc., Tulsa, OK, USA).

Results

Baseline BCVA and size of the hemorrhage, as well as mean duration of symptoms, did not differ significantly between the groups (p>0.05, Mann–Whitney test) (Table 1).

Displacement of hemorrhage

In group A, partial blood displacement from the macular area was seen in most patients; complete displacement from the foveal area was found in four of 18 patients (22%). The rate of complete blood displacement from the foveal area was significantly higher in group B: 16 of 29 patients (55%), (p=0.025, chi-square test) (Fig. 1).

BCVA change

In group A, mean BCVA was preop logMAR 1.07 [standard deviation (SD)=0.47] and postop 0.93 (SD=0.49). BCVA improved in eight (44%), remained unchanged in five (28%), and worsened in five (28%) patients. Mean BCVA change was logMAR -0.14 (SD=0.64).

In group B, mean BCVA was preop logMAR 1.24 (SD=0.43) and postop 0.92 (SD=0.59). BCVA improved in 19 (65%), remained unchanged in six (21%), and worsened in four (14%) patients. Mean BCVA change was logMAR -0.32, SD=0.68.

The difference in BCVA change between group A and group B was not statistically significant (p=0.2, Mann–Whitney test) (Fig. 2).

Subgroup analysis of group A

Mean BCVA of 15 patients with AMD was preop logMAR 1.03 (SD=0.49) and postop 0.83 (SD=0.44). Mean BCVA of three patients with RAMA was preop logMAR 1.26 (SD=0.31) and postop 1.45 (SD=0.47).

Subgroup analysis of group B

Mean BCVA of 26 patients with AMD was preop logMAR 1.23 (SD=0.43) and postop 0.97 (SD=0.6). Mean BCVA of two patients with RAMA was preop logMAR 1.6 (SD=0) and postop 0.75 (SD=0.35). BCVA of one patient with blunt ocular trauma was preop logMAR 0.8 and postop 0.1.

Complications

Intraoperative In both groups, serious intraoperative complications including vitreous or subretinal hemorrhage were not observed.

Postoperative Group A: short-term postoperative complications included vitreous hemorrhage in one patient and a recurrence of submacular hemorrhage in another patient.

Group B: complications included three cases of retinal detachment. One of these cases was rhegmatogenous; in the other two cases, no retinal break was found during

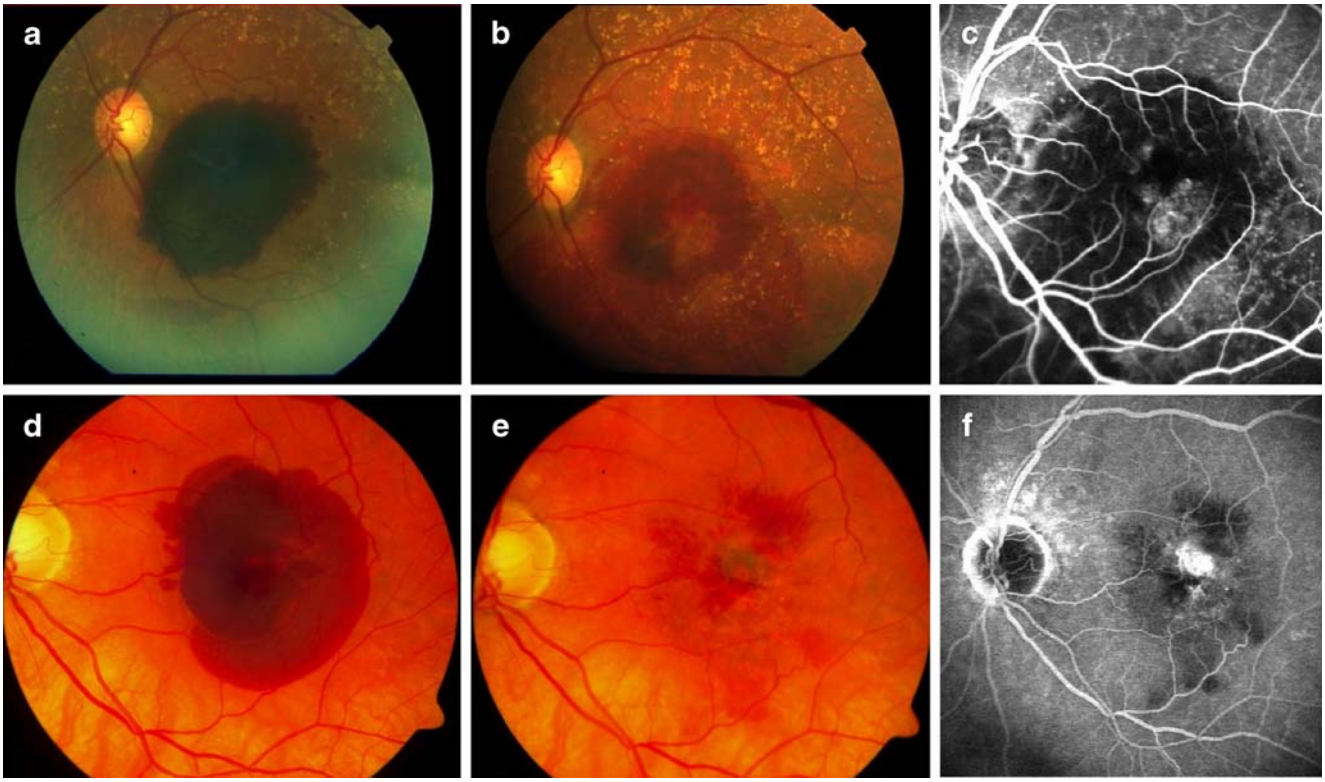

Fig. 1 **a**,**b**,**c** Submacular hemorrhage secondary to neovascular AMD treated with ppV with intravitreal injection of rtPA and 20% SF6 gas. **a** Preoperative fundus photo. **b** Postoperative incomplete displacement of hemorrhage. **c** Corresponding postoperative fluorescein angiogram showing occult choroidal neovascularization (CNV). **d**,**e**,**f** Submacular hemorrhage secondary to neovascular AMD treated with ppV, subretinal injection of rtPA and intravitreal injection of 20% SF6 gas. **d** Preoperative fundus photo. **e** Postoperative complete displacement of hemorrhage. **f** Corresponding postoperative fluorescein angiogram showing small CNV

vitrectomy. In one of these latter cases, retinal detachment was associated with a recurrence of submacular hemorrhage and vitreous hemorrhage. Additionally, there were two cases of vitreous hemorrhage without retinal detachment. There were two cases of recurrent submacular hemorrhage, and one case of RPE rip. The RPE rip was not associated with a decrease in visual acuity (BCVA increased from logMAR 1.3 to 0.7). One patient with RAMA-associated hemorrhage developed CNV 3 months postoperatively, notably away from the injection site. (Table 2).

Discussion

The primary aim of this retrospective study was to compare the efficacy of two procedures for displacement of

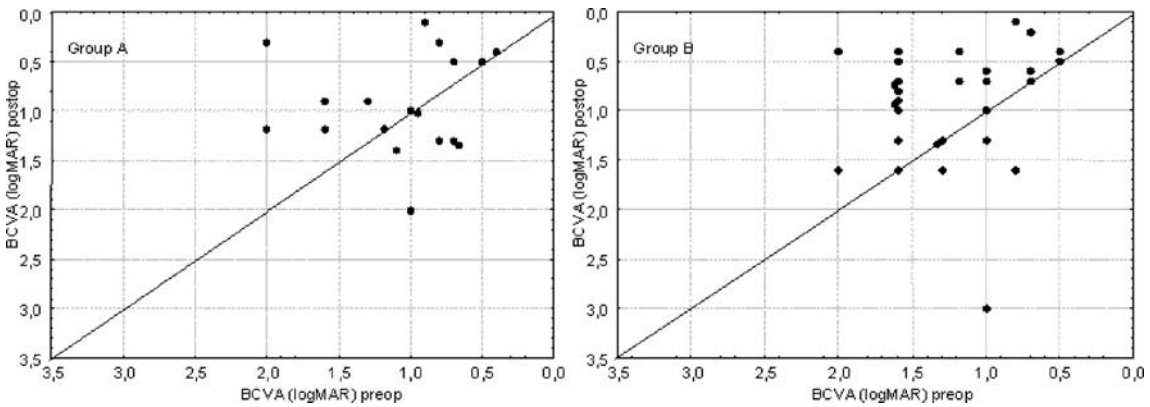

Fig. 2 Change of BCVA (logMAR) in group A and group B. Mean BCVA change was logMAR -0.14, SD=0.64 in group A, and logMAR -0.32, SD=0.68 in group B. The difference in BCVA change between group A and group B was not statistically significant (p=0.2, Mann–Whitney test)

Table 2 Complications

Complication	Group A (n=18)	Group B (n=29)
Retinal detachment	0	3
Vitreous hemorrhage	1	3 (once associated with retinal detachment)
Recurrence of submacular hemorrhage	1	2
RPE rip	0	1
postoperative development of CNV	0	1

submacular hemorrhage: ppV with intravitreal injection of rtPA combined with the intravitreal injection of 20% SF6-gas (group A) and ppV combined with subretinal injection of rtPA and intravitreal injection of 20% SF6 gas (group B).

The main finding of this study is a significantly higher rate of complete displacement of the hemorrhage from the fovea in group B (55% versus 22%).

Principally, two parameters can be used to assess the efficacy of a treatment of submacular hemorrhage: the rate of complete blood displacement from the foveal area, and short-term visual acuity change. In the present study, most cases of submacular hemorrhage were associated with neovascular AMD. In neovascular AMD, the functional outcome largely depends on the extent of the underlying disease, which is the main reason for the considerable scatter of postoperative BCVA data in both treatment groups (Fig. 2). The scatter of BCVA data also explains the absence of a statistically significant difference of BCVA change between the two groups, although BCVA improved in more patients (65% versus 44%) and mean improvement of BCVA (logMAR -0.32 versus -0.14) was greater in group B than in group A. The functional outcome may also be influenced by the duration and the size of submacular hemorrhage. We included only patients with a duration of the hemorrhage of ≤14 days because significantly better functional outcomes have been described when the duration of the hemorrhage was ≤14 days [25]. However, the discrepancy in results described in non-comparative case series [25] and retrospective studies [26] underlines the need for prospective randomized studies: Hattenbach et al. found that the functional outcome was not directly related to the size of hemorrhage [25], whereas Schulze et al. found a direct relationship [26]. To reliably compare the functional outcome of the two procedures described in the present study, a much greater number of patients would be required. The subgroup analysis of the functional outcome in both treatment groups shows that the outcome of patients with etiologies other than AMD (RAMA or blunt ocular trauma) was better in group B than in group A. The number of patients is too low to draw reliable conclusions; however, the difference in outcome suggests that the procedure of group B is more effective than the procedure of group A. The therapeutic strategy of an effective treatment of acute submacular hemorrhage in neovascular AMD must be to displace the blood as quickly as possible to save the foveal retina, because submacular hemorrhage progressively damages the neurosensory retina [1–6]. Others have reported hemorrhage displacement after intravitreal injection of rtPA, and a gas bubble in up to 60–100% of patients [14–18]. However, no information was given about the completeness of displacement. A higher rate of complete hemorrhage displacement following vitrectomy, subretinal injection of rtPA and gas tamponade could be explained either by a higher concentration of rtPA directly at the site of the hemorrhage and better fibrinolysis, and/or by dilution of hemorrhage by the rtPA solution. Lewis et al. have reported expedited hemorrhage absorption following subretinal injection of BSS alone [11]. Therefore, whether or not or to which extent rtPA in the solution assists in blood displacement remains uncertain. Furthermore, according to other reports, intravitreal injection of rtPA and gas was equally as effective as gas injection alone [27, 28]. Penetration of rtPA through the retina remains the subject of an ongoing debate. The rtPA molecule exceeds the experimentally determined molecular exclusion limit of human retina [21]. Indeed, in the experiments of Kamei et al., rtPA injected into the vitreous of rabbits failed to pass through the intact retina [19]. On the other hand, molecules with similar molecular weight (e.g. albumin) have been shown to penetrate the diseased retina [20]. Recently, Heiduschka et al. demonstrated that Bevacizumab, another large molecule exceeding the molecular exclusion limit of the retina, passed through the intact retina of cynomolgus monkeys [22].

The functional improvement in the majority of patients (65%) after subretinal injection in this study provides indirect evidence for the absence of significant retinal toxicity of rtPA in the dose used in this study. Experimental investigations have shown that a dose >50 µg injected intravitreally is toxic to rabbit and cat retina, leading to severe photoreceptor loss and RPE necrosis [29]. Clinical evidence of toxicity of a higher dosage of rtPA was observed by Chen et al., who describe diffuse granular RPE disturbance after two intravitreal injections of 50 µg with a 3-day interval [14]. Toxicity of a subretinally applied rtPA solution has not yet been studied thoroughly, although dosages up to 50 µg seem to be tolerated well in the subretinal space of rabbit eyes [29].

In accordance with our findings, Olivier et al. reported that 17 of 28 patients gained more than 2 Snellen lines of visual acuity after 3 months, and three of 28 patients lost more than 2 lines [24]. The rate of complications is also of interest. In the present study, complications occurred more frequently after subretinal injection of rtPA, including three cases of retinal detachment. This is comparable with the rate of retinal detachment of the SST Trial (Hemorrhagic CNV Group), where retinal detachment was observed in 16% of patients [13]. While once retinal detachment was clearly rhegmatogenous, we cannot exclude exudative retinal detachment in two other patients. Exudative retinal detachment has been reported by Hesse et al. following intravitreal injection of a higher (>50 μg) dose of rtPA [15]. Possibly, a greater amount of the drug may be sufficient to cause exudative retinal detachment when applied subretinally. Vitreous hemorrhage occurred in three patients (once associated with retinal detachment). Nearly the same rate of vitreous hemorrhage after subretinal rtPA and gas displacement is reported by Olivier et al. (4 of 28 patients) [24]. Vitreous hemorrhage after vitrectomy with rtPA could be caused by extended bleeding from sclerostomy sites. Notably, all patients with vitreous hemorrhage in our study were on anticoagulation treatment. We discontinued anticoagulation upon admission but performed surgery the following day, because we weighed the potential benefit of an early displacement of the hemorrhage from the fovea against the risk of recurrence of submacular hemorrhage or postoperative vitreous hemorrhage. This approach may have contributed to the increased risk of vitreous hemorrhage among patients on anticoagulation treatment in this study. In one of our patients, subretinal injection of rtPA led to an RPE rip which may have been caused by puncture of a pre-existing RPE detachment. The rip was not associated with significant functional decrease, presumably due to a relatively poor baseline visual acuity (logMAR 1.3). However, we would advise against injecting rtPA subretinally in patients with pre-existing RPE detachment. The rate of recurrence of hemorrhage after subretinal application of rtPA was relatively high (27%) in the study of Haupert et al. [23], but was not a significant problem in our study, perhaps because of the lower dose of rtPA used (10–20 μg vs 25–50 μg).

In conclusion, successful displacement of submacular hemorrhage allows postoperative fluorescein angiography testing and, potentially, subsequent further treatment. PpV with subretinal injection of rtPA and intravitreal injection of 20% SF6 gas seems to be more effective in blood displacement than ppV with intravitreal injection of rtPA and 20% SF6 gas. However, some complications are more frequent after subretinal injection, but this problem can be controlled in part by careful patient selection (e.g. excluding patients with pre-existing RPE detachment). Short-term functional improvement in the majority of patients suggests the absence of direct retinal toxicity of subretinally applied rtPA. Surgery should be performed soon after presentation. For clinical practice, it seems reasonable to recommend surgery to be performed within 24 to 48 hours.

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