

Subretinal recombinant human tissue plasminogen activator injection using a 41G needle for the management of submacular hemorrhages: a 3-case report

Dan Jiang¹, Zhi-Xiang Hu¹, Xiao-Ling Yang¹, Qi-Fei Shang², Rong-Han Wu¹

¹National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China

²Department of Ophthalmology, Fuyang People's Hospital, Hangzhou 311400, Zhejiang Province, China

Correspondence to: Rong-Han Wu. 270 West Xueyuan Road, Wenzhou 325027, Zhejiang Province, China. wuronghan@126.com

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Dear Editor,

Submacular hemorrhage (SMH) is the accumulation of blood in the macular region caused by changes in retinal or choroidal circulation^[1]. SMH may be caused by age-related macular degeneration (AMD), pathological myopia, polypoid choroidal angiopathy (PCV) or retinal macroaneurysm^[2]. The prognosis of untreated SMH will depend on how long it takes for the bleeding to be absorbed, as the extravascular blood is toxic to photoreceptors and the retina^[3]. Treatment options are broad and include intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs, subretinal or intravitreal injections of tissue plasminogen activator (tPA), and gas-pneumatic replacement or vitrectomy (with or without tPA), as monotherapies or combined with surgery^[4]. Among them, subretinal or intravitreal tPA has been reported to have good therapeutic effects in some cases involving the macula^[5]. The clinical efficacy of new injectable drug products and the safety of the injection method are the driving forces for the development of subretinal injection.

Microneedles offer a less invasive and more reliable way to enter the retina, and it is expected that the smaller the diameter of the needle is, the less retinal tissue damage associated with the injection^[6]. Liu *et al*^[7] reported good results using

a 30-gauge (30G) needle for external drainage of subretinal hemorrhages through a scleral tunnel during vitrectomy. Saito-Uchida *et al*^[8] reported subretinal injection of tPA with a 38G needle in 11 cases of subretinal hemorrhage, and retinal reattachment was achieved in all eyes. Venkatesh *et al*^[9] reported that 25G pars plana vitrectomy (PPV) was performed along with injection of vancomycin directly into the subretinal abscess in endogenous endophthalmitis using a 41G needle, which improved the visual acuity to 6/24. Here, we report that submacular recombinant human tissue plasminogen activator (rt-PA) injection with a 41G needle was successfully performed in three SMH with different causes, and all cases had good outcomes.

Ethical Approval This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Wenzhou Medical University (Approval number: 2019-165-k-157). The informed consent was obtained from the subjects.

Case Presentation A series of three patients with SMH is described. A 23G PPV with hyaloid removal was performed in all three patients, with or without phacoemulsification and intraocular lens implantation as appropriate. For submacular injection, a 41G microneedle (INCYTO Co., Ltd., Germany) was used in connection with a pneumatic injector (14 mm Hg, Constellation, Alcon Co., USA), and an appropriate amount of drug was slowly injected into the submacular space. Actilyse[®] (rt-PA, 10-25 µg in 10-25 µL 0.9% saline, Boehringer Ingelheim International GMBH, Germany) was injected at 1-4 points, depending on the size of the clot. Specifically, if the lesion was relatively large with some clotted blood, multiple injections were needed. If the lesion was small, limited to 1-2 papillae diameters (PDs) in the center of the macula or near the macula, usually one injection point was enough to infiltrate the entire lesion. In conclusion, regardless of how many injection points were used, the net effect was that the drug could penetrate the entire subretinal hemorrhage. After intraocular total fluid-air exchange, Case 3 received intravitreal injection of anti-VEGF. All patients were advised to face down for one week.

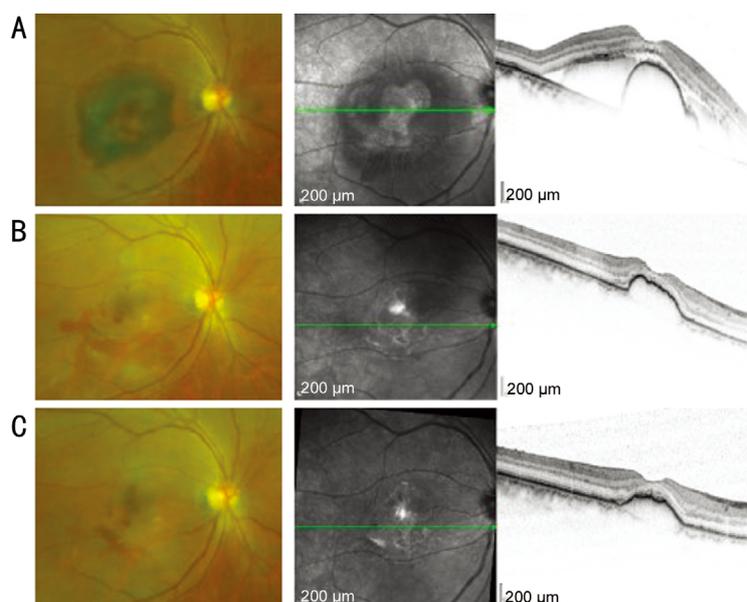


Figure 1 Optical coherence tomography (OCT) appearance and fundoscopic examination of Case 1 A: OCT and fundus at presentation showing massive subretinal hemorrhage with a significant increase in retinal thickness. The central retinal thickness (CRT) was 796 μm . B, C: One week and one month after surgery, persistence of subretinal blood in the center of the macula was observed on the fundus, with a significant decrease in retinal thickness (CRT was 338 and 344 μm , respectively). The hemorrhage disappeared almost completely, but retinal pigment epithelial detachment was observed on OCT.

Case 1 A 55-year-old woman with PCV presented with acute vision loss for 7d in the right eye. The best-corrected visual acuity (BCVA) at presentation was 0.2 (logMAR) in the right eye and 0.6 in the left eye, with no obvious abnormalities in the anterior segment. Fundoscopic examination revealed 9 PD-sized areas of subretinal hemorrhage in the macular area (Figure 1A), and retinal thickness was significantly increased on optical coherence tomography (OCT). OCT showed macular elevation with visible subretinal exudates and hemorrhages (Figure 1A). Pigment epithelium detachment was identified as localized, relatively dome-shaped elevations of the retinal pigment epithelium (RPE) band with low internal reflectivity within the detachment (optically empty). Clinical and laboratory tests were performed to rule out systemic diseases, including diabetes, arterial hypertension, dyslipidemia and blood cachexia. With a clinical diagnosis of PCV, a 23G PPV with hyaloid removal was performed. Subsequently, rt-PA was slowly injected into the submacular space by a 41G microneedle. The BCVA in the right eye was 0.4 at 1wk after surgery and remained unchanged after one month. A significant improvement in the fundoscopic and OCT examinations was observed at 1wk and 1mo after surgery (Figure 1B and 1C).

Case 2 A 67-year-old woman with PCV in the right eye who had received anti-VEGF therapy presented with a 3-day history of sudden vision loss and central scotoma. The BCVA at presentation was 0.2 (logMAR). At fundoscopic examination, SMH affecting the entire macula was observed (Figure 2A).

OCT showed marked retinal thickening (Figure 2A). The patient underwent PPV, submacular rt-PA injection, and fluid-air exchange. A significant improvement was observed in retinal structure (Figure 2B and 2C) at 2wk and 3mo after surgery. The BCVA was 0.3 (logMAR) at 2wk post-operatively and 0.4 (logMAR) at 3mo post-operatively.

Case 3 A 55-year-old woman was referred with acute vision loss for 17d in the left eye. She presented with systemic arterial hypertension and no apparent history of ophthalmology. The BCVA at presentation was counting fingers (FC) in the left eye, and the anterior segment showed bilateral mild cataracts. At the fundoscopic examination, a central SMH involving the fovea with a diameter greater than 4 PD areas was observed. OCT showed subretinal dense, highly reflective material (blood; Figure 3A). Relevant examinations were completed, and contraindications for operation were excluded. First, PPV and phacoemulsification with microincision and intraocular lens implantation were performed in the left eye. Next, opacified vitreous was removed, and a 1/2 PD orange hemangioma was found near the inferior temporal vessels, which was consistent with the diagnosis of macroaneurysm. Then, 0.1 mL rt-PA (10 μg) was injected into the submacular space of the macula area, followed by gas-liquid exchange. The BCVA of the left eye improved to 0.5 (logMAR), and the SMH was absorbed at 2mo after surgery (Figure 3). Three months after the surgery, the BCVA of the left eye was 0.6, the hemorrhage was completely absorbed, and the hemangioma near the inferior temporal vessel had shrunk (Figure 3).

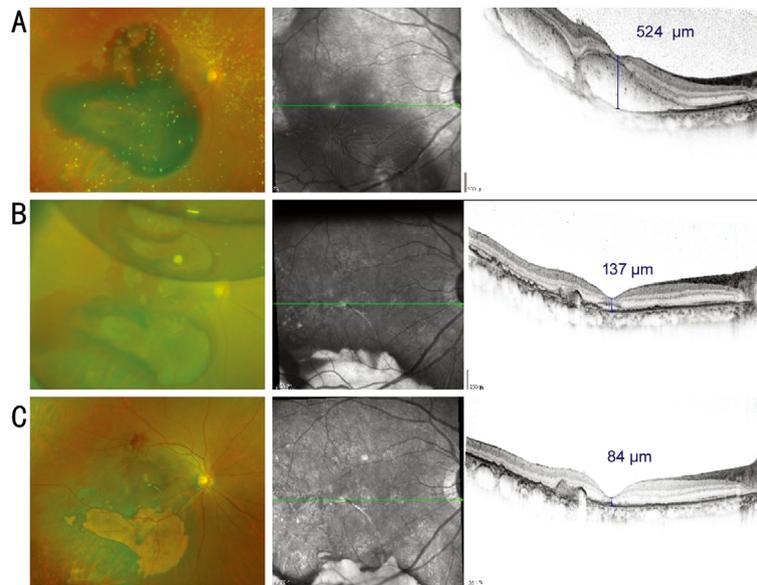


Figure 2 Fundus and optical coherence tomography (OCT) appearance of Case 2 A: Fundus and OCT at presentation, showing massive subretinal hemorrhage, significant retinal thickening, and neuroepithelium and retinal pigment epithelial detachment. The central retinal thickness (CRT) was 524 μm . B: Two weeks after surgery, the fundus of this case showed persistent subretinal hemorrhage with significant resorption. The CRT was 137 μm . C: The hemorrhage disappeared almost completely at 3mo after surgery, and the patient showed a significant decrease in retinal thickness with retinal pigment epithelial regeneration. The CRT was 84 μm .

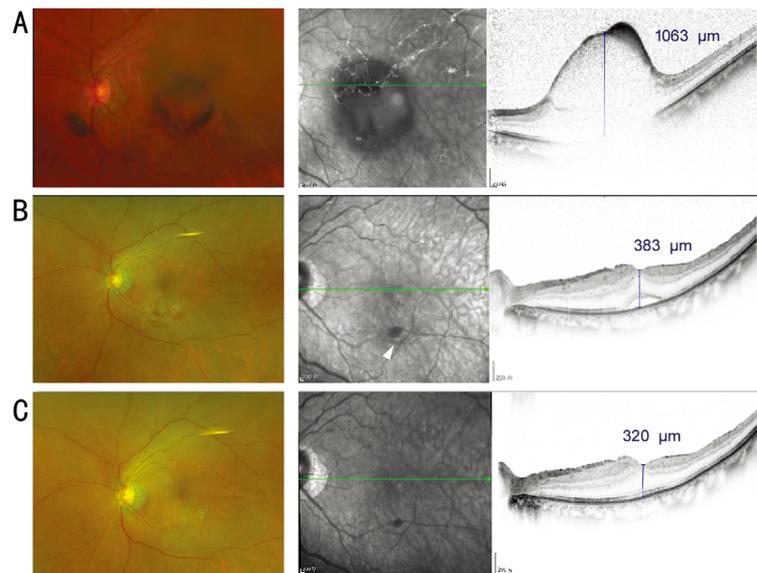


Figure 3 Fundus photographs and optical coherence tomography examination of Case 3 At presentation (A), 2 (B), and 3mo (C) after surgery, showing that the hemorrhage of the macular area was completely absorbed. White arrows show that the hemangioma near the inferior temporal vessel has shrunk. The central retinal thickness (CRT) before surgery and 2 and 3mo after surgery was 1063, 383, and 320 μm , respectively.

DISCUSSION

SMH is the rupture of aneurysmal dilated vessels or thickened venules/arteries caused by AMD, retinal angiomatous hyperplasia, PCV, high myopia, *etc.* Studies have shown that 7d after hemorrhage, the outer layer of the retina is damaged, the photoreceptors are damaged, and the microvilli at the top of the RPE are shortened^[10]. After 14d of hemorrhage, the outer layer of the retina is extensively and severely damaged, photoreceptors are severely damaged, and phagocytes on RPE increase rapidly, resulting in irreversible structural damage^[10].

Without prompt treatment, visual prognosis is poor, with only 11% of cases achieving 0.1 or better BCVA within 2y^[11]. Treatment options for SMH include intravitreal injections of anti-VEGF drugs, gas-liquid exchange with or without rt-PA, submacular injection of rt-PA, and photodynamic therapy^[12]. These strategies have been used individually or in combination, simultaneously or in phases.

This study reported 3 patients with SMH who underwent vitrectomy combined with submacular rt-PA injection. Cases 1 and 2 show SMH caused by PCV treated by vitrectomy

and submacular rt-PA injection. Although it was an SMH, good BCVA was achieved with prompt treatment. Case 3 demonstrates that submacular rt-PA treatment of SMH caused by retinal macroaneurysm improved vision. Following intravitreal injections of anti-VEGF, a decrease in the size of the retinal macroaneurysm was observed. The BCVA of 3 patients significantly improved from 0.2, 0.2, and FC to 0.4, 0.4 and 0.6 (logMAR), respectively. Of note, fundoscopic and OCT examinations showed that SMH was mostly absorbed one week after surgery. rt-PA has been reported to have two synergistic effects: enzyme-induced clot lysis and mechanical replacement of liquefied blood by air bubbles. The dose administered to the eye has not been determined, and 10 to 50 µg appears to be safe. Ren *et al*^[12] reported a case of SMH caused by a macroaneurysm that underwent subretinal injection of 40 µg rt-PA with a BCVA of 0.05 (logMAR). However, some studies have reported high toxicity of rt-PA^[13]. Reported complications include vitreous hemorrhage and retinal toxicity associated with atrophic changes, electroretinogram abnormalities, exudative retinal detachment, and neovascular membrane recurrence^[13]. A dose of less than 50 µg can reduce some of these adverse events^[13]. In our treatment, 10-25 µg rt-PA was injected according to the range of SMH, and no adverse reactions were found at this dose. The reported treatment effect of rt-PA varies widely, but most patients initially experience some improvement in visual acuity^[8].

In 2010, Hillenkamp *et al*^[14] reported that subretinal injection of rt-PA with vitrectomy and gas tamponade was more effective at replacing SMH than intravitreal injections of rt-PA and gas-tamponade vitrectomy. Complications of retinal detachment may be related to retinal holes caused by retinotomy or retinal injection. Damage to the retina layer can be reduced through tiny holes in the retina and the accurate placement of drug preparations under the retina^[6]. de Jong *et al*^[15] found that subretinal injection of rt-PA *via* a 41G needle and intravitreal rt-PA injection in SMH patients were both effective. In our 3 cases, the visual acuity of patients was restored quickly, and no significant complications were observed *via* 41G-mediated rt-PA injection. In the future, we expect that studies will focus on the improvement of active agents and drug delivery technology, especially ultraminimally invasive technology. Therefore, our successful and safe use of a 41G needle to inject rt-PA provided some practical experience for the treatment of SMH caused by PCV and retinal macroaneurysm.

In conclusion, our technique appears to be an effective surgical approach for the treatment of macular hemorrhage caused by PCV or retinal macroaneurysm. Larger studies are needed to confirm the safety of this approach.

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Authors' contributions: Jiang D participated in conceptualization, design and writing of the original draft. Hu ZX, Yang XL, and Shang QF were involved in the analysis and visualization of the results, the acquisition of the data and literature research. Wu RH did a critical interpretation of the data for the study and edited the manuscript. All authors revised the manuscript for important intellectual content, read and approved the final version of the manuscript to be published.

Conflicts of Interest: Jiang D, None; Hu ZX, None; Yang XL, None; Shang QF, None; Wu RH, None.

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