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Intravitreal Tissue Plasminogen Activator, Ranibizumab, and Gas Injection for Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy

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Purpose: To investigate the efficacy of intravitreal injection of recombinant tissue plasminogen activator (rt-PA), ranibizumab, and gas without vitrectomy for submacular hemorrhage.

Design: Prospective, interventional, consecutive case series.

Participants: Twenty consecutive patients (20 eyes) with submacular hemorrhage secondary to exudative age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV).

Methods: Ranibizumab, rt-PA (25 μg/0.05 ml), and 100% perfluoropropane (0.3 ml) were injected intravitreally, followed by 2-day prone positioning.

Main Outcome Measures: The primary outcome measure was best-corrected visual acuity (BCVA) 6 months after treatment. Secondary outcome measures included central retinal thickness (CRT), central pigment epithelial detachment (PED) thickness, central ellipsoid zone, recurrence rate, and complications.

Results: Underlying disease was exudative AMD in 1 eye and PCV in 19 eyes. Submacular hemorrhage ranged in size from 2 to 31 disc diameters. Complete displacement of submacular hemorrhage was achieved in 17 eyes (85%), and partial displacement was achieved in 3 eyes (15%). Snellen BCVA improved from 20/139 before treatment to 20/65 at 6 months ($P = 0.0061$). Mean change in Early Treatment Diabetic Retinopathy Study score from baseline was +13 letters ($P = 0.0040$). Mean CRT decreased from 599 μm before treatment to 208 μm at 6 months ($P < 0.0001$), and central PED thickness decreased from 188 to 88 μm ($P = 0.0140$). Three eyes developed vitreous hemorrhage, and 1 eye developed retinal detachment; all were treated surgically, and Snellen BCVA improved at 6 months ($P = 0.0012$). Recurrence was observed in 10 eyes (50%) within 6 months, but visual acuity was preserved with intravitreal injection of anti–vascular endothelial growth factor (VEGF) pro re nata (PRN). The factors that affect BCVA at 6 months after treatment were pre- and posttreatment central ellipsoid zone ($P = 0.0366$ and $P = 0.0424$), pretreatment BCVA ($P = 0.0015$), and pre- and posttreatment central PED thickness ($P = 0.0046$, $P = 0.0021$).

Conclusions: Subretinal hemorrhage treatment by intravitreal injection of rt-PA, ranibizumab, and gas is useful to achieve hemorrhage displacement and lesion improvement. To preserve visual acuity, early detection of posttreatment recurrence and intravitreal anti-VEGF injection PRN are necessary. *Ophthalmology 2016;■:1–9 © 2016 by the American Academy of Ophthalmology.*

Submacular hemorrhage is a serious complication of exudative age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) that leads to severe and irreversible damage to the photoreceptors and outer nuclear layer.[1,2]

Experimental studies using animal models showed that subretinal blood causes significant retinal damage within 24 hours.[1] As for the natural history in humans, 90% of the patients would eventually have a final visual acuity of 20/200.[3] Thus, early treatment for submacular hemorrhage is necessary. Previous studies have shown that displacement of submacular hemorrhage can be achieved by both "vitrectomizing techniques"[4–6] and "nonvitrectomizing techniques,"[7–9] and results in improvement of visual acuity. A study reviewing 38 articles reported no differences between the 2 techniques with respect to complete displacement rate and rates of recurrent submacular hemorrhage and vitreous hemorrhage.[10] In regard to nonvitrectomizing techniques for submacular hemorrhage, recombinant tissue plasminogen activator (rt-PA) and gas treatment have been reported to have better visual outcome than bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) and gas, indicating the importance of displacing the submacular hemorrhage.[11] On the other hand, posttreatment visual outcome was found to be better after intravitreal injection of rt-PA, bevacizumab, and gas, compared with rt-PA and gas.[12] Therefore, treatment of the underlying lesion and

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simultaneous displacement of submacular hemorrhage may be a useful approach.

Observation of the natural history of submacular hemorrhage for a mean period of 24 months showed hemorrhage accompanying vascularized retinal pigment detachment in 28.3% of cases and recurrent submacular hemorrhage in 38.3% of cases, indicating the importance of treatment for recurrence.[3] However, although vitrectomizing techniques using subretinal co-application of rt-PA and bevacizumab and intravitreal gas tamponade achieved displacement of submacular hemorrhage, recurrence was observed in 41% during postoperative follow-up of 8.1 months.[13,14] Early detection of recurrence using appropriate markers and intravitreal injection of anti−vascular endothelial growth factor (VEGF) at the appropriate timing is necessary.[14]

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland; Genentech Inc., South San Francisco, CA) is not cleaved or functionally compromised by rt-PA or plasmin, whereas aflibercept (Eylea; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is cleaved and its VEGF-binding ability is reduced when co-applied with plasmin.[15] The half-life of intravitreally injected ranibizumab has been reported to be shortened in vitrectomized eyes compared with nonvitrectomized eyes.[16,17] Considering this evidence, a nonvitrectomizing technique by concurrent administration of rt-PA, ranibizumab, and gas seems to be a rational approach for treating submacular hemorrhage. We performed a prospective study to examine the efficacy of intravitreal injection of rt-PA, ranibizumab, and gas in 1 session for the treatment of submacular hemorrhage and to identify the factors affecting visual acuity 6 months after treatment. We measured central retinal thickness (CRT) and central pigment epithelial detachment (PED) thickness using optical coherence tomography (OCT) as parameters indicating recurrence and performed intravitreal injection of anti-VEGF pro re nata (PRN). In this study, we also analyzed the usefulness of this approach.

Methods

Patient Recruitment

This prospective study was performed at the Department of Ophthalmology of Nihon University Hospital between March 2014 and July 2015. The study adhered to the tenets of the Declaration of Helsinki. This study was approved by the Ethical Committee of the Nihon University School of Medicine (no. 110903). All subjects provided written informed consent after receiving full explanations of the study and the potential merits and risks. The inclusion criteria were thick submacular hemorrhage, including subretinal pigment epithelial hemorrhage, secondary to AMD or PCV involving the foveal center with sizes (measured from the radius centered on the fovea) greater than 2 disc diameters, and duration of symptoms not more than 30 days. The exclusion criteria were underlying causes other than exudative AMD or PCV, and the presence of a macular scar. Patients who had cerebrovascular infarction or myocardial infarction within 3 months before the study also were excluded. Exudative AMD and PCV were diagnosed by OCT (Heidelberg Spectralis; Heidelberg Engineering Inc., Heidelberg, Germany), fluorescein angiography, and indocyanine angiography as reported previously.[18–21] Polypoidal choroidal vasculopathy is characterized by a complex choroidal vascular network with multiple, terminal, reddish-orange polypoidal lesions.

Protocol

All patients were given 3 intravitreal injections in 1 session in an outpatient room: 0.05 ml of ranibizumab, 0.05 ml of rt-PA (Alteplase; Kyowa Hakko Kirin, Tokyo, Japan), and 0.3 ml perfluoropropane (C_3F_8; Alcon Laboratories Inc., Fort Worth, TX) after removing 0.3 ml of anterior chamber fluid. After the intravitreal injections, ocular pressure was tested by palpating with a finger, and vision was checked by hand motion. Perfusion of the optic disc was assessed using a binocular indirect ophthalmoscope. Then the patients were admitted for 3 days. They were placed in a sitting position for 2 hours and then maintained in a prone position for 2 days. The patients were examined before treatment, daily from 1 to 7 days after treatment as inpatients, and at 2 weeks and then monthly from 1 to 6 months as outpatients. All patients underwent visual acuity measurement, intraocular pressure measurement, slit-lamp biomicroscopy, indirect ophthalmoscopy, and OCT examination before and 1, 2, 3, 4, 5, and 6 months after treatment. Fluorescein angiography and indocyanine angiography were performed before and 1, 3, and 6 months after treatment.

Recurrence of submacular hemorrhage was evaluated by observation for rebleeding on color fundus photograph and by measuring CRT and central PED thickness on OCT as markers for early detection of recurrence. Intravitreal injection of ranibizumab was performed PRN when exudative or hemorrhagic changes were observed, such as accumulation of subretinal fluid and increase in macular edema or recurrence of submacular hemorrhage.

Outcome Measures

The primary outcome measure was best-corrected visual acuity (BCVA) 6 months after treatment, measured using the Snellen chart and Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Snellen BCVA was converted to logarithm of minimal angle of resolution scale for analysis.

The secondary outcome measures were displacement of submacular hemorrhage; changes in CRT, central PED thickness, and central ellipsoid zone after treatment; recurrence; and complications.

Tissue Plasminogen Activator, Ranibizumab, and Gas Injection

All intravitreal injections were conducted by 1 ophthalmologist (Y.K.). The procedures were performed in an outpatient injection room, which is separated from the outpatient clinic and equipped with a microscope and bed. After retrobulbar block using 4 ml of 2% Xylocaine, the eyelid skin was disinfected with 10% povidone-iodine (Meiji Seika Pharma Co., Ltd., Chuo-ku, Tokyo, Japan) and the conjunctiva was disinfected with 0.25% povidone-iodine diluted in physiologic saline.[22] Then the eye was draped, and a lid speculum was placed. After performing paracentesis of 0.3 ml, ranibizumab (0.5 mg/0.05 ml), rt-PA (25 μg/0.05 ml, 40,000 IU), and 100% perfluoropropane (C_3F_8; 0.3 ml) were injected intravitreally through the pars plana, successively in the same session. All 3 injections were performed using 30-G needles, and the ocular surface was disinfected with 0.25% povidone-iodine before and after each injection. After the injections, the patient was admitted.

Measurements of Clinical Parameters

The greatest diameter of subretinal hemorrhage was measured. Displacement of submacular hemorrhage was evaluated on a