Original Article

Retinal sensitivity improvement after intravitreal triamcinolone acetonide injection for macular edema secondary to branch retinal vein occlusion

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Purpose: To evaluate the effect of intravitreal triamcinolone acetonide (IVTA) on retinal sensitivity in cases of macular edema(ME) secondary to branch retinal vein occlusion (BRVO). **Materials and Methods:** Total of 14 eyes of 14 cases of BRVO were included in this prospective study. In each eye, at baseline and 1, 3, and 6 months after IVTA injection, logMAR visual acuity, central 4° retinal sensitivity by MP-1 microperimetry, and optical coherence tomography foveal thickness were assessed. **Results:** Cases ages ranged from 60 to 79 years (mean 68 ± 8 years). At 1, 3, and 6 months, the logMAR visual acuity had increased from 0.71 ± 0.21 to 0.42 ± 0.21, 0.46 ± 0.30, and 0.46 ± 0.27; the mean foveal thickness had decreased from 540 ± 88 μm to 254 ± 51 μm, 288 ± 84 μm, and 280 ± 91 μm; and the mean retinal sensitivity had increased from 4.7 ± 2.5 dB to 7.9 ± 2.7 dB, 8.2 ± 3.6 dB, and 8.3 ± 4.6 dB, respectively. **Conclusion:** In eyes with ME secondary to BRVO, IVTA injections result in a significant increase in not only the visual acuity but also the central 4° retinal sensitivity in 6 months follow-up.

Key words: Branch retinal vein occlusion, cystoid macular edema, intravitreal triamcinolone acetonide, microperimetry, visual acuity

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Macular edema (ME) is the most frequent complication of branch retinal vein occlusion (BRVO), occurring in about 60% of cases.[1] The Branch Vein Occlusion Study Group[2] demonstrated that grid laser photocoagulation is effective in reducing the visual acuity loss due to ME secondary to BRVO. Unfortunately, conventional grid laser treatment leads to a very limited improvement of visual acuity and may be associated with the occurrence of several complications, including enlargement of laser scar, choroid neovascularisation, subretinal fibrosis, and visual sensitivity deterioration.[3-5] Intravitreal triamcinolone acetonide (IVTA) has been the treatment of various intraocular neovascular, proliferative, and edematous diseases.[6,7] IVTA also has been shown to be effective for treating ME secondary to BRVO.[8-12] Visual recovery after IVTA treatment in patients with BRVO is usually evaluated by measurement of visual acuity that reflects spatial resolution of small area (fovea). Visual acuity is still considered the gold standard in clinical practice of vision testing, but it does not entirely reflect functional vision. We need different visual testings to understand more precisely retinal functional changes due to disorders. Microperimetry, a technique for accurately testing retinal sensitivity and retinal fixation, with strict correspondence of visual parameters and macular morphology, was used for the examination of macular function.[13,14]

The purpose of this study was to obtain a measure of retinal function before and after IVTA injection in cases of ME secondary to BRVO. To accomplish this, microperimetry was performed on 14 eyes of 14 cases of ME secondary to BRVO before and after IVTA injection, and the central 4° retinal sensitivity determined from the result of microperimetry.

Materials and Methods

In this clinical trial, the data were collected between June 2006 and February 2009. Fourteen eyes of 14 cases of ME secondary to BRVO (5 men and 9 women) were prospectively evaluated. Cases ages ranged from 60 to 79 years (mean ± SD, 68 ± 8 years). The eligibility criteria for this study included the following: presence of ME secondary to BRVO during fundus examination. In all of eyes with BRVO, there is occlusion of the major branch in the temporal quadrant; presence of angiographically confirmed ME documented by optical coherence tomography (OCT); no evidence of ocular disorders that might potentially result in ME, such as diabetic retinopathy, uveitis, macular pucker, or vitreomacular traction; and no evidence of glaucoma or ocular hypertension. Because several diseases may influence microperimetry and visual acuity, we excluded the cases of corneal opacities, a history of refractive surgery, a history of retinal detachment, a history of ocular trauma, and optic neuropathy. In this prospective series, no eyes had received previous laser photocoagulation. The procedures used in this study conformed to the tenets of the Decleration of Helsinki, and an informed consent was obtained from all cases after the nature and possible consequences of the study were explained.

All eyes underwent complete ophthalmic examination, including corrected visual acuity measurement (with ETDRS chart), slit lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, fluorescein angiography, and OCT. Best-corrected visual acuity, expressed as logMAR, was obtained from a distance of 4 m. Fluorescein angiograms were performed on a Heidelberg scanning laser ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany). OCT examinations were performed using the OCT 3000 scanner (Carl Zeiss Ophthalmic

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System Inc., Humphrey Division, Dublin, CA, USA). All OCT examinations were done by the same operator, and all scans were done with a scan length of 6 mm. The foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment epithelium in the center of the fovea.

Macular edema was evident by fluorescein angiography by the typical oval or petaloid hyperfluorescent cystoid spaces radiating from the fovea and by OCT by hyporeflective intraretinal cavities radiating from the center of the macula on cross-sectional scans.

For the injection of triamcinolone acetonide (Kenacort-A; 40 mg/mL; Bristol-Myers Squibb Co, Princeton, NJ, USA), topical 0.5% proparacaine hydrochloride was applied to the ocular surface followed by preparation with 5% povidone iodine. A cotton-tipped applicator soaked in proparacaine hydrochloride was then applied to the injection site 4 mm posterior to the limbus. The injection consisted of 0.1 mL (4 mg) of a commercially available suspension of triamcinolone acetonide. Indirect ophthalmoscopy was used to confirm proper intravitreal localization of the suspension. Cases were examined on days 1 and 7 to detect any infection.

The response to treatment was monitored functionally by visual acuity and microperimetry assessment and anatomically by OCT foveal thickness after injection. Potential corticosteroid-induced and injection-related complications were also observed.

Retinal sensitivity was evaluated by MP-1 microperimetry (Nidek, Vigonza, Italy). The MP-1 provides a 45° nonmydriatic view of the fundus with an automated correction for eye movements. Goldmann III stimuli and a 4-2-1 staircase strategy were used, and a circular test grid with 74 stimulus locations covering an area of 20° was applied. The stimuli were projected on a white background with background illumination set to 1.27 cd/m^2 and a stimulus presentation time of 200 ms. To assess central macular retinal sensitivity, differential light threshold values were compared by calculating the mean of the central 4° (12 test points), which was averaged automatically by the MP-1 microperimetry software program of mean sensitivity in a polygon.

All patients had to demonstrate good collaboration in performing microperimetry test, which means a prompt and correct understanding of the technique and a good concentration capacity. Each patient underwent preliminary practice test prior to the definitive microperimetry test to avoid learning effect.

Recurrent ME was defined as an increase of more than 100 μm (compared with the foveal thickness at 1 month after the initial injection) or as a decrease 1 or more line in visual acuity. Changes in visual acuity, retinal sensitivity, and foveal thickness in eyes with ME 1, 3, and 6 months after baseline IVTA injection were compared with baseline values by the repeated ANOVA test. Statistical analysis was performed using the Statistical Package for Social Sciences (Version 17.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

The right eye was involved in 8 cases (57%) and the left eye in 6 (43%). A history of hypertension was present in 12 cases (86%), and history of smoking was present in 11 (79%). No case had diabetes mellitus and coagulopathy. No case had an afferent pupillary defect, angiographic areas of capillary nonperfusion, iris neovascularization, or vessels in the angle. Before triamcinolone injection, no eyes had been treated with systemic or local medication and laser photocoagulation. All cases were pseudophakic in this study. The duration of cataract surgery and the diagnosis of BRVO was more than 9 months in all cases. The duration of symptoms ranged from 1 to 6 months (mean 3.5 ± 1.6 months). At 1 month examination, mean intraocular pressure ± SD increased from 15 ± 2 to 18 ± 5 mmHg. At the 3- and 6-month follow-up, mean intraocular pressure ± SD was 17 ± 3 and 16 ± 2 mmHg, respectively. Seven eyes (50%) with intraocular pressure of >21 mm Hg at a given examination were treated with a beta-blocker at the subsequent examination. No endophthalmitis or injection-related complications were encountered. There was no posterior capsule opacity requiring laser capsulotomy during follow-up. The clinical characteristics of eyes with ME observed at baseline and 1, 3, and 6 months after treatment are reported in Table 1. At 1, 3, and 6 months of follow-up, the mean foveal thickness had decreased from 540 ± 88 to 254 ± 51 μm, 288 ± 84 μm, 280 ± 91 μm, respectively. One, 3, and 6 months after IVTA injection, the mean retinal sensitivity within central 4° had increased from 4.7 ± 2.5 to 7.9 ± 2.7 dB; 8.2 ± 3.6 dB; 8.3 ± 4.6 dB, respectively. One, 3, and 6 months after IVTA injection, the mean visual acuity had increased from 0.71 0.21 to 0.42 ± 0.21 logMAR, 0.46 ± 0.30 logMAR, 0.46 ± 0.27 logMAR, respectively. The comparison of functional and morphological data at baseline and 1, 3, and 6 months after treatment are reported in Table 2. One, 3, and 6 months after IVTA injection, eyes with ME showed a significant reduction in foveal thickness ($P < 0.001$), and there was statistical significant increase in logMAR visual acuity ($P < 0.001$) and MP-1 retinal sensitivity ($P < 0.001$). In Fig. 1, fluorescein angiography, MP-1 microperimetry, and OCT images of case #1 are shown.

At the 3-month follow-up, cases 2, 3, 5, 10, and 13 showed recurrence of ME; at the 6-month follow-up, cases 6, 7, 13, and 14 showed recurrence of ME. Retreatment was performed for these cases, and successful results were obtained after treatment [Table 1].

Discussion

Without treatment, one third of patients who have BRVO end up with visual acuity better than 20/40; however, two thirds have decreased visual acuity secondary to ME, macular ischemia, macular hemorrhage, or vitreous hemorrhage in 3 years of period.[2] ME is the most frequent complication of BRVO, occurring in about 60% of cases.[1] Corticosteroids have long been used in the treatment of ME because of their ability to inhibit the arachidonic acid pathway. Corticosteroids may also downregulate the production of vascular endothelial growth factor, a known vascular permeability factor. It has been shown that triamcinolone acetonide significantly decreases major histocompatibility class II expression, which plays a role in microglial morphology.[15] Triamcinolone acetonide modulates the expression of intracellular adhesion molecule-1. The modulation of intracellular adhesion molecule-1 expression *in vitro* correlates with clinical observations, suggesting that reestablishment of the blood-retinal barrier and downregulation

Table 1: Clinical characteristics of patients with ME due to branch retinal vein occlusion

Case	Age (years)	Visual acuity (logMAR)				MP-1 Microperimetry sensitivity within central 4°				OCT foveal thickness (μm)			
		B	1 mo	3 mo	6 mo	B	1 mo	3 mo	6 mo	B	1 mo	3 mo	6 mo
1	60	0.4	0.1	0.1	0.1	7.5	9	12.8	15.5	550	230	234	220
2	79	0.9	0.7	0.7	0.7	2.5	5.2	3.7	5	530	255	387*	220
3	63	0.7	0.4	0.6	0.3	8.5	12.5	7.7	12.8	515	270	388*	230
4	60	0.4	0.2	0.2	0.2	9	10.2	13	12.7	550	250	230	220
5	76	1	0.7	1	0.7	1	2.3	1.1	3	610	380	400*	240
6	77	1	0.7	0.6	1	1.8	6.5	7.7	2	613	330	240	410*
7	60	0.7	0.3	0.2	0.4	2.3	5.1	10.2	5.5	650	210	210	456*
8	62	0.7	0.4	0.3	0.3	4.2	10	11.1	12.6	680	254	260	250
9	79	0.9	0.7	1	0.7	3.3	7.7	3.2	5	480	200	410*	207
10	74	0.4	0.1	0.1	0.1	5.3	8	9.6	9.8	487	240	220	234
11	63	0.7	0.4	0.3	0.3	4.4	11	12.5	12	380	194	190	210
12	68	0.6	0.4	0.6	0.3	7.5	10.8	8.4	12.5	400	210	388*	230
13	63	0.7	0.5	0.5	0.7	5.2	7.4	7.8	3.9	510	280	255	420*
14	65	0.9	0.4	0.3	0.7	4	6.2	7	4.2	610	260	222	380*

B: Baseline (pretreatment); 1 mo: 1 month after treatment; *: Retreatments

Table 2: The visual acuity, MP-1 microperimetry central 4° retinal sensitivity. and OCT foveal thickness in eyes with macular edema due to branch retinal vein occlusion at 1, 3. and 6 months after treatment were compared with baseline with repeated ANOVA test

Mean ± SD	Baseline	1 mo*	3 mo	6 mo
Visual acuity (logMAR)	0.71 ± 0.21	0.42 ± 0.21**	0.46 ± 0.30**	0.46 ± 0.27**
MP-1 microperimetry retinal sensitivity (dB)	4.7 ± 2.5	7.9 ± 2.7**	8.2 ± 3.6**	8.3 ± 4.6*
OCT foveal thickness (μm)	540 ± 88	254 ± 50**	288 ± 84**	280 ± 91*

*1 mo: 1 month after treatment, **$P < 0.001$

of inflammatory markers are the principal effects of IVTA *in vivo*. The results further indicate that triamcinolone acetonide has the potential to influence cellular permeability, including the barrier function of the retinal pigment epithelium.[16]

Several studies reveal that intravitreal triamcinolone had been successfully used for the treatment of BRVO.[8-12] Currently published randomized studies are very rare and limited by virtue of evaluating patients with ME of varied etiologies, making comparison difficult. In various studies, triamcinolone acetonide has been reported to be effective in doses ranging from 1 to 25 mg.[8-12] The recently published SCORE study compareed the effectiveness and safety of standard care versus triamcinolone acetonide injection in the treatment of ME in patients with central retinal vein occlusion and BRVO. In the SCORE report 6, no difference was identified in the visual acuity at 12 months for the standard care (grid laser photocoagulation) group compared with the triamcinolone groups (1 and 4 mg); however, rates of adverse events (particularly elevated intraocular pressure) were highest in the triamcinolone 4-mg group. Our study data collections were completed before SCORE study. That is why we have used 4 mg triamcinolone acetonide in this study. Our elevated intraocular pressure rate was 7 (50%) cases within 6-month follow-up. This rate was similar to the SCORE study.[12]

In these studies, visual acuity is a standard way to measure the visual performance, but it poorly describes the functional impact on visual performance in patients with compromised central visual field. Evaluation of retinal sensitivity and central retinal field function using microperimetry, that is a functional evaluation technique, is more informative than testing of visual acuity alone.[13] MP-1 microperimetry allows automated functional analysis of the macula associated with real-time correction of eye movements. The procedure provides exact localization of the tested region on the retina, even in patients with unstable fixation. Recently, Yamaike *et al*.[17] evaluated the change in microperimetric macular function after intravitreal injection of bevacizumab for the treatment of ME associated with retinal vein occlusion. They found that eyes with ME showed a mean improvement in visual acuity and microperimetric retinal sensitivity after bevacizumab injection during 6 months follow-up. Our results were also comparable with the same. In our knowledge, our study is the first study that used simultaneous OCT and microperimetry to examine the ultrastructural changes and retinal sensitivity deficits after IVTA injection therapy for treating ME in BRVO. The results of our study showed that after IVTA injection, besides significant increase in logMAR visual acuity and a significant decrease

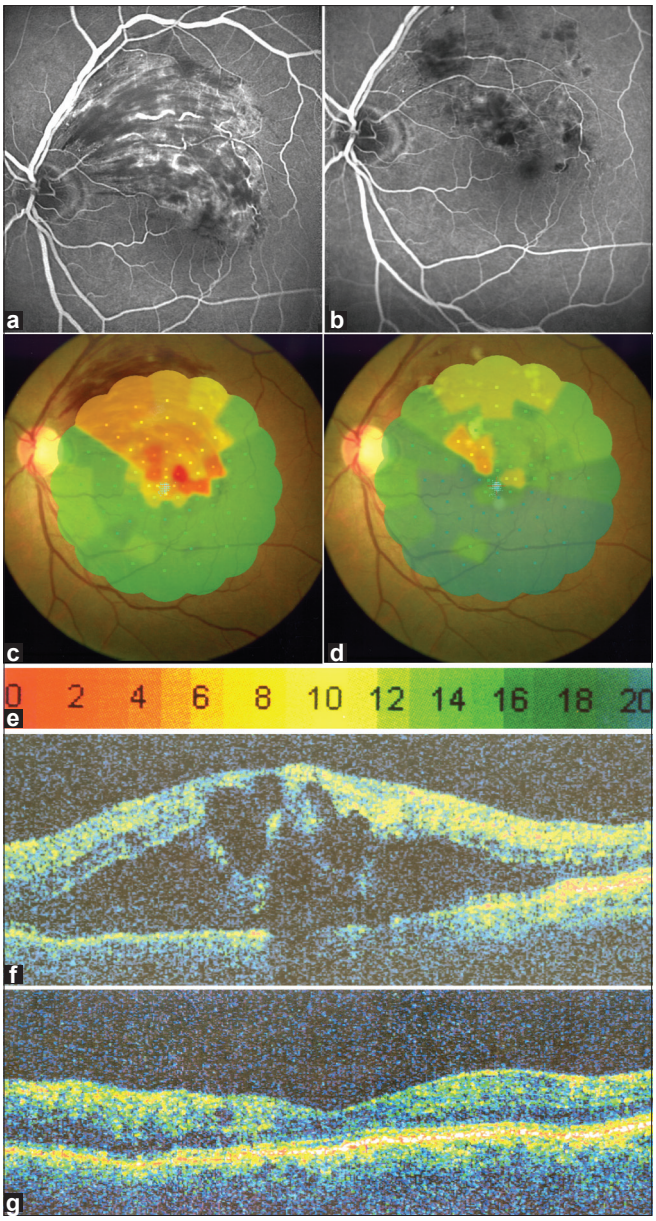

Figure 1: Fluorescein angiograms and MP-1 images of case 1. Late-phase fluorescein angiograms of the left eye show a retinal area of upper temporal branch retinal vein occlusion at the first examination (a) and 6 months later after IVTA injection (b). MP-1 image show that reduced retinal sensitivity points are concentrated in the retinal area of branch retinal vein occlusion at the first examination (c) and MP-1 image show that improved retinal sensitivity at the examination 6 months later after IVTA injection (d). Blue data points represent the locations used for fixation during microperimetric test in all the MP-1 images. The color-coded, numeric scale shows the threshold in 2 dB steps from 0 to 20 dB (e). OCT image shows ME at first examination (f) and ME resolved 6 months later after IVTA injection (g)

in the foveal thickness, a significant increase in mean retinal sensitivity was obtained.

The results obtained from our study for increase in mean retinal sensitivity by IVTA injection support many investigation outcomes obtained for distance visual acuity.[8-12] Decrease in retinal sensitivity may reflect photoreceptor dysfunction because of intraretinal and subretinal fluid and photoreceptor cell loss itself. When extensive leakage resolved which means decrease in intraretinal fluid, the area of scotoma was decreased. This beneficial effect was obtained even 1 month after IVTA injection. With multiple additional injections, an enlargement of functional defect was not noted. So these may at least show that multiple IVTA injection did not damage retina tissues and retinal pigment epithelium. Improvement of retinal sensitivity offers important safety information. At least in follow-up, significant toxic effects on the retina and retinal pigment epithelium were not detected.

In addition to an anatomical restoration and increase in visual acuity, IVTA injection also improved retinal function. Although 6 months results are insufficient to draw conclusions on any treatment, it is appreciable that the use of the MP-1 microperimetry enables us to evaluate accurately the retinal sensitivity in eyes with ME due to BRVO that had received IVTA injection. In addition to visual acuity, measurement of retinal sensitivity would be a great help for evaluation of the effectiveness of IVTA injection in eyes with BRVO. One limitation of this study was that microperimetry examination is a subjective psychophysic test and there might be intervisit variability for any of outcome measures. And because this study consisted of a small number of patients with short follow-up period, further prospective studies are necessary to determine the effectiveness of IVTA injection on retinal sensitivity.

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