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The efficacy of intravitreal triamcinolone acetonide on macular edema in branch retinal vein occlusion

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PURPOSE. *To evaluate the effectiveness of intravitreal triamcinolone acetonide as primary treatment of macular edema in branch retinal vein occlusion.*

METHODS. *Fifteen eyes of 15 patients with macular edema due to branch retinal vein occlusion (Group 1) who received 8 mg/0.2 ml of intravitreal triamcinolone injection as primary treatment were retrospectively evaluated. The control group (Group 2) consisted of 19 eyes of 19 patients who had received laser treatment for macular edema. The main outcome measures included best-corrected visual acuity, intraocular pressure, and macular edema map values of Heidelberg Retinal Tomograph II.*

RESULTS. *In Group 1, mean visual acuity improved significantly from a mean logMAR (logarithm of minimal angle of resolution) value of 0.98±0.19 at baseline to a maximum of 0.24±0.24 during a mean follow-up time of 6.3 months. In the control group, the mean baseline logMAR visual acuity before laser treatment was 1.02±0.22, and it was 0.50±0.28 at 6-month examinations. Mean improvement in visual acuity at 1-, 3-, and 6-month examinations was significantly higher in Group 1 when compared with the control group (for each, p<0.001). The mean edema map value of Group 1 significantly decreased by 40% at 6-month examinations when compared with preinjection value (p<0.001). In Group 1, mean increase in intraocular pressure elevation was 19.8% at the 1-month, 26.9% at 3-month, and 5.7% at 6-month visits, but intraocular pressures were under control with topical antiglaucomatous medications.*

CONCLUSIONS. *Intravitreal triamcinolone acetonide injection may be a new and promising approach as initial therapy for macular edema due to branch retinal vein occlusion. (Eur J Ophthalmol 2005; 15: 96-101)*

KEY WORDS. *Intravitreal triamcinolone injection, Laser treatment, Macular edema, Branch retinal vein occlusion*

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INTRODUCTION

Macular edema is a common cause of vision loss in patients with branch retinal vein occlusion (BRVO) (1, 2). Sixty to one hundred percent of such patients will eventually have macular edema at some point in their clinical course (3), and approximately one third of the patients followed for more than a year will exhibit persistent macular edema (4). It has been reported that eyes with ischemic macular edema that is not associated with significant hyperfluorescent leakage on fundus fluorescein angiography (FFA) show a relatively

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greater frequency of spontaneous improvement in visual acuity than eyes with good macular perfusion (5). Cystoid macular edema with normal perfusion is more often associated with a disruption of the blood–retinal barrier and a persistent decrease in visual acuity (6). This vasogenic macular edema is less likely to resolve spontaneously, and macular grid laser photocoagulation has been shown to be effective in the treatment of macular edema in a large prospective multicenter randomized clinical trial of BVOS (7). However, some treated eyes may be resistant to grid laser photocoagulation or efficient laser treatment could not be performed. Moreover, some complications such as exudative retinal detachment (8), submacular fibrosis (9), and choroidal neovascularization (10) may occur after laser photocoagulation for macular edema. Therefore, novel and simple approaches with promising results are needed in the treatment of macular edema in BRVO.

Triamcinolone acetonide is a corticosteroid with no known toxicity when injected intravitreally in vitrectomized (11) and nonvitrectomized eyes (12) and has been shown to reduce breakdown of the inner blood–retinal barrier and stabilize it (13). Therefore, we considered that intravitreal triamcinolone (IVT) injection might be effective in rapid clearance of macular edema in BRVO by reducing breakdown of the inner blood–retinal barrier. The purpose of this study was to investigate the effectiveness of IVT injection as primary treatment of macular edema in patients with BRVO, and to compare the outcomes with patients who had received laser treatment for macular edema.

PATIENTS AND METHODS

The study included 15 eyes of 15 patients with macular edema due to BRVO (Group 1) who received intravitreal injection of triamcinolone acetonide as primary treatment of macular edema. Mean ± SD age of the patients was 65.0±6.2 years, and there were 9 men and 6 women. Before IVT injection, all patients had a visual acuity worse than 20/63 for at least 3 months and had macular edema with hyperfluorescent leakage on FFA (Fig. 1A). The eyes had received laser photocoagulation treatment for peripheral retinal ischemia if required, but macular laser photocoagulation was not performed. Intravitreal injection of triamcinolone acetonide was offered as the initial treatment of macular edema. The patients were fully informed about the character of the treatment, and informed consent was obtained from each patient. The study followed the tenets of Declaration of Helsinki. Baseline parameters were documented including best-corrected visual acuity, macular edema map values by Heidelberg Retinal Tomograph II (HRT II, Heidelberg Engineering GmbH, Heidelberg, Germany), FFA findings, and intraocular pressure (IOP). All IVT injections were performed by the same surgeon (A.Ö.) under topical anesthesia. The standard, commercially available preparation of triamcinolone acetonide (Kenacort-A, Bristol-Myers Squibb, NY) in a concentration of 40 mg/ml was used. After the eye was anesthetized with topical instillation of proparacaine hydrochloride 0.5% and lidocaine 4%, the lid was prepped with povidone-iodine 5% applied directly to the eye, and triamcinolone acetonide (8 mg/0.2 ml, the solvent agent was not removed) was injected transconjunctivally after a paracentesis had been performed to decrease the volume of the globe. Indirect ophthalmoscopy was used to confirm proper intravitreal localization of the suspension and perfusion of the optic nerve head. Topical ciprofloxacin drops were applied, and the IOP was measured 5 minutes afterwards.

The eyes were examined at the first day after IVT injection, at the end of the first week, and every 4 weeks thereafter, unless IOP spikes required more frequent examinations. IOPs were measured using Goldmann applanation tonometer. Response to treatment was monitored by visual acuity assessment, HRT II, and FFA. Potential corticosteroid- and injection-related complications were also recorded, if present.

The analysis of macular edema was performed using the HRT II macula edema module. The 670 nm wavelength diode laser was used to image the macula using a 15° by 15° field of view. The HRT II is a confocal laser scanning system that requires a series of optical section images at different locations of the focal plane. This series of section images forms a layered three-dimensional image of the retina or the optic nerve head. For each location (x,y) in the image planes, the series of optical section images gives the distribution of reflected light intensity along the optical axis z. The distribution is called the confocal intensity profile. The measurement of the confocal intensity profile width at each location (x,y) in the image planes results in a matrix of 384x384=147,456 local width measurements. Normalization of the local

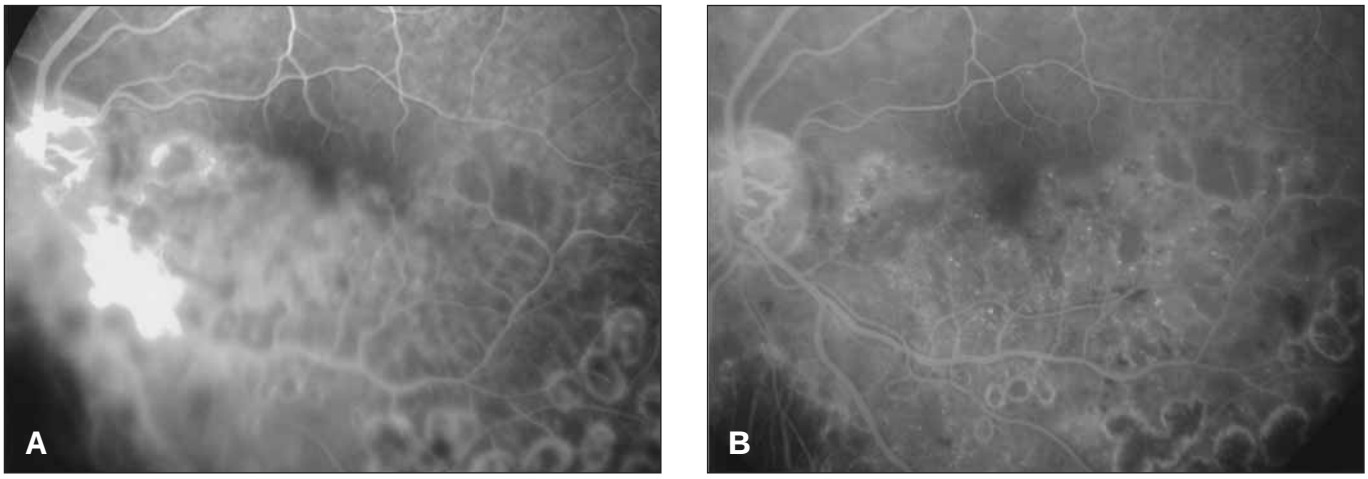

Fig. 1 - *Late phase of fundus fluorescein angiography.* **(A)** *Before injection;* **(B)** *3 months after intravitreal triamcinolone injection. Note the decrease in fluorescein leakage after treatment.*

sign width to the local reflectance therefore produces an index that emphasizes the presence of edema: e(x,y)=w(x,y)/r(x,y) ((e(x,y)=edema index at location (x,y); w(x,y)=signal width at location (x,y); r(x,y)=normalized reflectance at location (x,y)). Applied to all measurement points (x,y), computation of the edema index results in the so-called edema map (14).

The patients of the study group were compared with 19 control group patients. The control group (Group 2) was retrospectively formed by including the patients who had received argon laser photocoagulation for treatment of macular edema due to BRVO. There were no significant differences in age, sex, or pretreatment visual acuities between the two groups (for each, $p>0.05$).

Statistical analysis

Results are presented as means ± SD. Statistical evaluation of the data was performed with Mann-Whitney *U* test and two-way analysis of variance, as indicated. Findings with an error probability $p<0.05$ were considered statistically significant.

RESULTS

Pretreatment characteristics of the patients in each group are demonstrated in Table I. The mean duration of macular edema was 4.8±2.1 months (range, 3–9 months) in Group 1 and 5.2±4.5 months (range, 2–13 months). In Group 1, two eyes received a second intravitreal injection, and one eye received a third injection. Mean visual acuities of the patients in each group before and after treatment are shown in Table II. In Group 1, mean visual acuity improved significantly from a mean logMAR value of 0.98±0.19 at baseline to a maximum of 0.24±0.24 during a mean follow-up time of 6.3 months. Mean increase in visual acuity was 5.4, 5.9, and 5.8 Snellen lines at the 1-, 3-, and 6-month examinations, respectively. There were statistically significant differences between pre- and postinjection visual acuities (for each, $p<0.001$). In the control group, the mean baseline logMAR value for visual acuities of the patients before laser treatment was 1.02±0.22, and it was 0.71±0.30, 0.52±0.26, and 0.50±0.28 at the 1-, 3-, and 6-month follow-up examinations, respectively. Mean visual acuity improved by 1.5 Snellen lines at the 1-month, 3.3 lines at 3-month, and 3.4 lines at the 6-month follow-up examinations in control group (for each, $p<0.001$). Mean improvement in visual acuity at 1-, 3-, and 6-month visits was significantly higher in the study group when compared with the control group (for each, $p<0.001$).

In the study group, baseline mean edema map values averaged 2.0±0.9, and were 1.3±0.5, 1.1±0.3, and 1.2±0.4 at the 1-, 3-, and 6-month examinations. All eyes showed a reduction in macular edema value during study (Fig. 1B). Mean reduction of macula edema map value at the 1-, 3-, and 6-month visits was 35%, 45%, and 40%, respectively, and the differences were statistically significant (for each, $p<0.001$).

Mean IOPs of the patients before and after intravitreal injections are shown in Table II. In Group 1, mean IOPs at 1- and 3-month examinations were significantly higher when compared with pretreatment values (for each, p<0.001). The mean IOPs of control group at 1- and 3-month measurements were significantly lower when compared with the study group (for each, p<0.001). In Group 1, an elevation of IOP measurement exceeding 21 mmHg was observed in 3 eyes (20%) at 1 month and 4 eyes (26.6%) at 3 months, but IOPs were treated successfully with topical antiglaucomatous medications. Cataract progression was observed in 2 eyes (13.3%), and phacoemulsification with intraocular lens implantation was performed. No other injection- or corticosteroid-related complications were observed due to intravitreal injection during a mean follow-up period of 6.3 months.

DISCUSSION

Macular edema is a common cause of visual loss in patients with BRVO. A disruption of the inner blood-retinal barrier is due to the elevation of distal intravascular pressures and is often associated with significant hyperfluorescent leakage and a relatively poor prognosis. The macular edema usually persists, and laser photocoagulation may be effective in the treatment of edema (6). The Branch Retinal Vein Occlusion Study Group evaluated the effectiveness of grid laser photocoagulation in patients with fluorescein-proven perfused macular edema involving the foveal center (usually 3 to 18 months' duration) and a visual acuity worse than 20/40 after best refraction, and reported that treated eyes were twice as likely to improve two or more lines with achievement of visual acuity of 20/40 or better as untreated controls (7).

Another approach for the treatment of macular edema is to reroute the blood flow by a laser-induced chorioretinal venous anastomosis, but this technique may be associated with some complications, including fibrovascular proliferation, hemorrhage, and tractional retinal detachment (15, 16). Vitrectomy with mechanical separation of the arteriovenous sheath at the site of occlusion is another option in the treatment of macular edema in patients with BRVO (17-19). Intravitreal tissue plasminogen activator administration has also been tested with mixed results (20).

TABLE I - BASELINE CHARACTERISTICS OF THE PATIENTS

Characteristics	Group 1 (no.=15 eyes)	Group 2 (no.=19 eyes)
Mean age, yr, mean±SD	65.0±6.2	63.0±7.0
Sex, M/F, n (%)	9 (60)/6 (40)	11 (57.8)/8 (42.1)
Eye, R/L, n (%)	8 (53.3)/7 (46.6)	8 (42.1)/11 (57.8)
Lens status, P/PP, n (%)	11 (73.3)/4 (26.6)	13 (68.4)/6 (31.5)
Systemic disorders, HT/HC, n (%)	13 (86.6)/10 (66.6)	18 (94.7)/16 (84.2)

P = Phakic; PP = Pseudophakic; HT = Hypertension; HC = Hypercholesterolemia

TABLE II - PRE- AND POSTTREATMENT VISUAL ACUITIES (VA) AND INTRAOCULAR PRESSURES (IOP) OF THE PATIENTS

	Group 1(no.=15 eyes)	Group 2 (no.=19 eyes)
Mean VA (best-corrected) Preinjection	0.98 ± 0.19	1.02 ± 0.22
1-mo	0.30 ± 0.28	0.71 ± 0.30
3-mo	0.24 ± 0.24	0.52 ± 0.26
6-mo	0.28 ± 0.23	0.50 ± 0.28
Mean IOP (mmHg) Preinjection	15.6 ± 1.3	15.9 ± 2.0
1-mo	18.7 ± 1.7	16.2 ± 1.9
3-mo	19.8 ± 3.3	16.1 ± 2.1
6-mo	16.5 ± 1.8	16.3 ± 2.0

Values are mean±SD

Corticosteroids inhibit phospholipase A_2 and subsequent release of arachidonic acid, which is the precursor of prostaglandins and leukotrienes, the inflammatory mediators implicated in the pathogenesis of macular edema (21). Corticosteroids may also downregulate the production of vascular endothelial growth factor, a known permeability factor (22). Triamcinolone acetonide is a corticosteroid suspension with no known retinal toxicity when injected intravitreally and has been shown to reduce breakdown of the inner blood–retinal barrier and stabilize it (13).

Sub-Tenon, retrobulbar, or topical applications of corticosteroids are insufficient to deliver adequate drug levels to the vitreous and retina. Although oral prednisone delivers effective levels of intraocular steroids, systemic side effects are present that outweigh the benefit. In addition, animal studies have shown that triamcinolone crystals can be visualized in the vitreous humor for 23 to 41 days after the injection (23). Therefore, maximal bioavailability of triamcinolone without extraocular side effects is only possible if it is delivered intravitreally.

In the present study, all patients had macular edema supported by leakage on FFA. Results of our study showed that IVT application was effective in rapid improvement of visual acuity and treatment of macular edema in patients with BRVO. All eyes showed a significant reduction in edema map value. This effect may be explained by rehabilitation and stabilization of the breakdown of inner blood–retinal barrier and decrease in vascular permeability. Moreover, rapid decrease in macular edema may prevent compression to retinal cells and decrease cellular damage at the macula. So, IVT injection may play an important role in prevention of permanent visual loss in such patients. In addition, improvement in visual acuity was significantly higher in Group 1 when compared with the control group.

There are some favorable results in limited numbers of patients evaluating the efficacy of triamcinolone on macular edema in central retinal vein occlusion (CRVO) (24-27). As macular edema occurs with the same mechanism both in CRVO and BRVO, we can compare our results with those in CRVO. Jonas et al (24) reported an increase in visual acuity of a patient with cystoid macular edema due to CRVO after IVT injection. Bynoe and Weiss (25) treated two patients with unilateral CRVO and reported that one patient recovered 8 lines of visual acuity whereas the other recovered 11 lines. Greenberg et al (26) demonstrated that visual acuity of a patient with macular edema after CRVO improved from counting fingers to 20/80 6 weeks after intravitreal injection. In our study, mean visual acuity improved by 5.8 Snellen lines, and macular edema map values decreased by 40% at the 6-month visits after IVT injection. Maximal improvement in visual acuity was observed at 3-month examinations. There was a small decrease in visual acuity at 6-month examinations, but the difference was not statistically significant. However, the effect of triamcinolone acetonide may be temporary and reinjection may become necessary. In the present study, four reinjections of triamcinolone acetonide were performed in three eyes.

In conclusion, IVT application is a novel and effective approach with promising results for the treatment of macular edema as a result of BRVO. The effects occur immediately with a rapid resolution of macular edema and improvement in visual acuity. However, further studies are needed to examine the long-term results of such application.

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