Original Paper

Long-Term Anatomical and Functional Outcome of Three Intravitreal Bevacizumab Injections for Persistent Macular Edema after Idiopathic Macular Epiretinal Membrane Peeling

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Key Words

Antivascular endothelial growth factor · Epiretinal membrane · Macular edema

Abstract

Purpose: The aim of this study was to investigate the effect of three consecutive intravitreal bevacizumab injections (IVB) on long-term outcome for patients with macular edema after epiretinal membrane (ERM) removal. **Methods:** All patients in both the treatment and control groups had persistent macular edema 3 months after ERM removal. The patients in the treatment group received three consecutive IVB in an interval of approximately 4 weeks. The main outcome measures included logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) and central foveal thickness (CFT) determined by optical coherence tomography. **Results:** Two weeks after the first IVB, CFT decreased significantly by $24.1 \pm 4.2 \mu\text{m}$ in the treatment group versus $4.2 \pm 2.1 \mu\text{m}$ in the control group ($p < 0.001$). However, the mean reduction in CFT after 12 months did not differ significantly between the two groups (35.2 ± 4.9 vs. $33.7 \pm 4.6 \mu\text{m}$, $p = 0.824$). No significant differences were found for logMAR BCVA between the two groups at each follow-up. **Conclusion:** IVB could significantly decrease macular edema 2 months after the initial injection but failed to make significant differences in final CFT and logMAR BCVA.

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Introduction

Idiopathic macular epiretinal membrane (ERM) is a cellular avascular membrane, which occurs during the process of posterior vitreous detachment (PVD) [1]. Pars plana vitrectomy (PPV) with membrane peeling, which was first described by Machemer [2] in 1978, has become a well-established surgical procedure for the removal of ERM with favorable results. Surgical removal of the membranes in patients with significant symptoms can improve visual acuity and reduce metamorphopsia in approximately 70–90% of the cases, whereas others do not benefit from this procedure [3–5]. Bevacizumab, a humanized full-length antibody against all isoforms of vascular endothelial growth factor (VEGF) A, has been successfully used off-label for the management of neovascular age-related macular degeneration and macular edema from various etiologies [6–9]. However, in the literature review, there is only one short-term follow-up study regarding single intravitreal bevacizumab injection (IVB) for persistent macular edema after ERM removal, with no beneficial effects on visual improvement [10]. Therefore, in our present study, we enrolled patients who underwent vitrectomy and removal of ERM, but macular edema showed no tendency to resolve 3 months after surgery. The purpose of this study is to determine the long-term efficacy of three consecutive IVB for treating persistent macular edema after complete removal of idiopathic ERM.

Patients and Methods

Study Population

This study is a retrospective, non-randomized study including patients who were diagnosed as idiopathic ERM between January 2008 and December 2010. The described research adhered to the tenets of the Declaration of Helsinki 1964. The treating physician (W.-C.W.) is a retinal specialist experienced in ERM and cataract surgeries as well as intravitreal injection. All patients previously underwent a standard three-port PPV assisted with triamcinolone and membrane peeling using high-magnification viewing and intraocular forceps. PVD was induced with active suction of ocutome over the optic disc if the PVD was not already present. Concomitant cataract surgery was performed on phakic patients. After surgery, tobradex eye drops (0.3% tobramycin and 0.1% dexamethasone) 4 times daily and mydriacyl (0.5% tropicamide) 3 times daily were administered to all patients for 2 weeks. There were no significant complications such as retinal detachment, iatrogenic macular hole, postoperative vitreous hemorrhage or endophthalmitis that affected visual outcome during or after the surgeries.

Three months after PPV, patients who met the following criteria were suggested for IVB treatment: (1) presence of a macular edema $\geq 250 \mu\text{m}$ as detected by optical coherence tomography (OCT) 3 months after complete idiopathic ERM removal by PPV, and (2) best-corrected visual acuity (BCVA) $< 20/50$ after surgery.

Patients with preexisting ocular diseases (i.e., glaucoma, high myopia, retinal vascular occlusion, chronic inflammatory or neoplastic disorders) were excluded, as were those with systemic diseases (diabetes or uncontrolled hypertension).

Methods of Intervention and Follow-Up

The decision to treat with IVB was made by the eligible patients after a complete discussion of the risks, benefits and alternatives to treatment. If the patients decided to proceed with IVB therapy, they signed a consent form before treatment. In the treatment group, each patient received their first intravitreal injection of bevacizumab (0.05 ml/1.25 mg) approximately 3

Table 1. Demographic data

	Treatment group	Control group	p value
Number of patients	25	23	
Male:female	12:13	12:11	0.990
Age, years	62.8±5.8	61.5±5.7	0.460
Right eye:left eye	11:14	11:12	0.790
Lens status pre-PPV			
Phakic	13	10	0.555
Pseudophakic	12	13	
Lens status 3 months after PPV			
Phakic	0	0	1.0
Pseudophakic	25	23	
BCVA (logMAR)			
Pre-PPV	0.88±0.33	0.87±0.35	0.919
Three months after PPV	0.55±0.33	0.54±0.36	
CFT, µm			
Pre-PPV	431.0±88.3	433.9±80.5	0.904
Three months after PPV	334.5±63.4	331.0±56.2	
Interval from PPV to IVB, weeks	13.5±1.7	N/A	

months after PPV. Postoperatively, gentamycin eye drops were administered 4 times daily for 1 week. Additional injections were given to each patient in the treatment group at an interval of approximately 1 month. A total of three consecutive injections were performed on each patient in the treatment group. In the meantime, no other interventions were performed on patients in the control group.

For better comparison of all parameters between the treatment and control groups, we defined ‘baseline’ as the time point that was 3 months after PPV. After the start of the follow-up period, the patients were seen at 0.5, 1, 2, and 3 months and then every 3 months until 12 months after baseline. To evaluate the effects and safety of treatment, all recruited patients underwent comprehensive ophthalmic examinations including OCT, visual acuity by Snellen charts, slit-lamp biomicroscopy, Goldmann applanation tonometry and ophthalmoscopy at each follow-up visit. Retinal thickness measurements were performed using the OCT Stratus III device (Carl Zeiss Meditech, Dublin, Calif., USA). In all measurements, the central foveal thickness (CFT) was assessed within a 1-mm diameter circle in the central macula. For better comparison of visual acuity between the groups, the visual acuity by Snellen chart was converted to the logarithm of the minimum angle of resolution (logMAR) at baseline and each follow-up visit.

Statistical Analysis

All data were statistically analyzed by Student’s t test, the χ^2 test or Pearson correlation test using SPSS statistical software (version 10.0; SPSS Inc., Chicago, Ill., USA). A p value of ≤ 0.05 was considered statistically significant.

Results

Baseline Demographic Data

During the period of 2 years, a total of 150 eyes of 140 patients with idiopathic ERM who underwent PPV and ERM peeling were reviewed. According to the inclusion criteria, there were 48 eyes of 48 patients included in this study. Table 1 shows the participants’ baseline

Fig. 1. Temporal change of CFT after IVB. The reduction in CFT differed significantly between the two groups during the first 0.5, 1 and 2 months after IVB. The mean CFT remained stable 6 months after IVB in the treatment group. In the control group, the mean reduction in CFT increased gradually during the 6 postoperative months and remained stable thereafter. The table below the graph shows the absolute values of the mean CFT for each follow-up visit. Base = Baseline; M = months; * $p \leq 0.05$ compared between the groups at each follow-up visit.

demographics. Twenty-five eyes of 25 patients and 23 eyes of 23 controls were enrolled and followed-up for at least 12 months after baseline (i.e., 15 months after PPV). The pre-PPV BCVA was 0.88 ± 0.33 and 0.87 ± 0.35 logMAR in the treatment and control groups, respectively (table 1). Thirteen eyes in the treatment group and 10 eyes in the control group underwent combined surgery of PPV, phacoemulsification and intraocular lens implantation. Others with pseudophakia (12 eyes in the treatment group and 13 eyes in the control group) had PPV only. The pre-PPV CFT by OCT was 431 ± 88 and 434 ± 80 μm in the treatment and control groups, respectively (table 1). In the treatment group, the mean interval from PPV to IVB was 13.5 ± 1.7 weeks (table 1).

Temporal Change of CFT

The mean CFT at baseline was 334.5 ± 63.4 μm for the treatment group and 336.5 ± 56.2 μm for the control group ($p = 0.911$). All patients in the treatment group received three consecutive IVB with a minimal interval of 4 weeks (range: 4–6). Compared to baseline, the mean CFT at 0.5 months after IVB decreased rapidly by 24.1 ± 4.2 to 309.3 ± 57 μm for the treatment group and by only 4.2 ± 2.1 to 335.1 ± 56.4 μm for the control group ($p < 0.01$). At 6 months, the mean CFT decreased by 35.5 ± 4.9 to 304 ± 49.3 μm for the treatment group and by 31.2 ± 4.1 to 303.3 ± 52.5 μm for the control group. Six months after baseline, the reduction in CFT became stable in both groups. At the last follow-up visit, the mean CFT was

Fig. 2. Temporal change of BCVA by line after IVB. In both groups, BCVA improved gradually during the first 6 months after baseline and remained stable thereafter. There were no significant differences in BCVA line improvement between the treatment and control groups at baseline and each follow-up visit. The table below the graph shows the absolute value of the mean logMAR BCVA for each follow-up visit. Base = Baseline; M = months; * $p \leq 0.05$ compared to baseline.

decreased by 35.2 ± 4.9 to $301.5 \pm 47.7 \mu\text{m}$ for the treatment group and by 33.7 ± 4.6 to $302.4 \pm 52.0 \mu\text{m}$ for the control group. The mean reduction in CFT differed significantly between the treatment and control groups at 0.5, 1 and 2 months after baseline ($p < 0.05$). Figure 1 shows the mean reduction in CFT over the course after IVB.

Temporal Change of Visual Acuity

At baseline, the mean BCVA was 0.55 ± 0.33 and 0.54 ± 0.36 logMAR in the treatment and control groups, respectively ($p = 0.964$). In both groups, the BCVA improved gradually after baseline. At 1 month, the mean BCVA was increased by 0.44 ± 0.34 and 0.30 ± 0.33 lines from baseline in the treatment and control groups, respectively ($p = 0.779$). At 6 months, the mean BCVA was increased by 1.92 ± 0.50 and 1.83 ± 0.57 lines from baseline in the treatment and control groups, respectively ($p = 0.902$). Six months after baseline, the line improvement of BCVA became stable in both groups. At 12 months, the mean BCVA was increased by 1.74 ± 0.51 and 1.78 ± 0.56 lines from baseline in the treatment and control groups, respectively ($p = 0.955$). At 12 months, the mean BCVA improved to 0.37 ± 0.15 and 0.36 ± 0.17 logMAR in the treatment and control groups, respectively ($p = 0.849$). The logMAR BCVAs and line improvement did not differ significantly at 0.5, 1, 2, 3, 6, 9 and 12 months after treatment between the two groups. Figure 2 illustrates the line improvement in BCVA over the course of the study.

Table 2. Correlations between BCVA and CFT in the treatment group (n = 25)

	BCVA _{Base}	BCVA _{0.5 M}	BCVA _{1 M}	BCVA _{2 M}	BCVA _{3 M}	BCVA _{6 M}	BCVA _{9 M}	BCVA _{12 M}
CFT _{Base}	r = 0.7951 p < 0.0001	r = 0.8126 p < 0.0001	r = 0.8371 p < 0.0001	r = 0.7846 p < 0.0001	r = 0.8234 p < 0.0001	r = 0.7086 p < 0.0001	r = 0.6393 p = 0.0006	r = 0.6761 p = 0.0002
CFT _{0.5 M}		r = 0.7784 p < 0.0001	r = 0.8128 p < 0.0001	r = 0.7688 p < 0.0001	r = 0.8151 p < 0.0001	r = 0.7089 p < 0.0001	r = 0.6396 p = 0.0006	r = 0.6761 p = 0.0002
CFT _{1 M}			r = 0.7940 p < 0.0001	r = 0.7634 p < 0.0001	r = 0.8085 p < 0.0001	r = 0.7029 p < 0.0001	r = 0.6370 p = 0.0006	r = 0.6699 p = 0.0002
CFT _{2 M}				r = 0.7407 p < 0.0001	r = 0.7887 p < 0.0001	r = 0.6835 p = 0.0002	r = 0.6267 p = 0.0008	r = 0.6529 p = 0.0004
CFT _{3 M}					r = 0.7748 p < 0.0001	r = 0.6759 p = 0.0002	r = 0.6140 p = 0.0011	r = 0.6428 p = 0.0005
CFT _{6 M}						r = 0.6775 p = 0.0002	r = 0.6014 p = 0.0015	r = 0.6398 p = 0.0006
CFT _{9 M}							r = 0.6112 p = 0.0012	r = 0.6449 p = 0.0005
CFT _{12 M}								r = 0.6509 p = 0.0004

Base = Baseline; M = months; r = Pearson correlation coefficient.

Table 3. Correlations between BCVA and CFT in the control group (n = 23)

	BCVA _{Base}	BCVA _{0.5 M}	BCVA _{1 M}	BCVA _{2 M}	BCVA _{3 M}	BCVA _{6 M}	BCVA _{9 M}	BCVA _{12 M}
CFT _{Base}	r = 0.5713 p = 0.0044	r = 0.5564 p = 0.0058	r = 0.6666 p = 0.0005	r = 0.5504 p = 0.0065	r = 0.5795 p = 0.0038	r = 0.6316 p = 0.0015	r = 0.6316 p = 0.0012	r = 0.6525 p = 0.0007
CFT _{0.5 M}		r = 0.5425 p = 0.0075	r = 0.6613 p = 0.0006	r = 0.5456 p = 0.0071	r = 0.5719 p = 0.0044	r = 0.6269 p = 0.0014	r = 0.6222 p = 0.0015	r = 0.6517 p = 0.0008
CFT _{1 M}			r = 0.6211 p = 0.0015	r = 0.5100 p = 0.0129	r = 0.5350 p = 0.0085	r = 0.6087 p = 0.0021	r = 0.5929 p = 0.0029	r = 0.6297 p = 0.0013
CFT _{2 M}				r = 0.5134 p = 0.0122	r = 0.5395 p = 0.0079	r = 0.6100 p = 0.0020	r = 0.5860 p = 0.0033	r = 0.6279 p = 0.0013
CFT _{3 M}					r = 0.5017 p = 0.0147	r = 0.5822 p = 0.0036	r = 0.5669 p = 0.0048	r = 0.5958 p = 0.0027
CFT _{6 M}						r = 0.5793 p = 0.0038	r = 0.5583 p = 0.0056	r = 0.5792 p = 0.0038
CFT _{9 M}							r = 0.5696 p = 0.0046	r = 0.5914 p = 0.0030
CFT _{12 M}								r = 0.5698 p = 0.0045

Base = Baseline; M = months; r = Pearson correlation coefficient.

Correlations between Visual Acuity and CFT

The changes in CFT and BCVA followed a similar course at each follow-up visit in both groups. The BCVA and CFT were well correlated at baseline and each follow-up visit in both groups ($p < 0.01$). The detailed data are summarized in tables 2 and 3.

During the follow-up of the patients in the treatment group, no thromboembolic events or deaths occurred. No intraocular complication occurred either.

Discussion

PPV and membrane peeling has been proven an effective surgical procedure for VA improvement in patients with ERM [4–6, 11, 12]. However, studies of long-term follow-up after surgery have indicated that visual improvement and resolution of macular edema may take up to 12 months or longer to reach maximum improvement. In addition, residual macular edema after the removal of ERM is quite common [13–16]. In order to reduce postoperative residual macular edema, some authors use intravitreal injection of triamcinolone acetonide (IVTA) after successful removal of ERM [12, 14]. A short-term non-comparative study indicated an increase in visual acuity and a marked decrease in CFT during the first postoperative week with further functional and anatomical improvement over a 6-month period [12]. However, a long-term comparative study demonstrated no significant differences between patients undergoing ERM removal with or without IVTA, but IVTA increased the risk of high intraocular pressure that required medication [14].

In our study, IVB significantly reduced CFT 0.5, 1 and 2 months after the first bevacizumab injection. However, there was no concomitant better visual improvement observed in the treatment group. The possible explanation for this inconsistency may be due to the multifactorial pathogenesis of ERM. It is widely believed that idiopathic ERM is produced by retinal glial cells that migrate through defects in the internal limiting membrane to proliferate and contract on the inner retinal surface [17–19]. The pathogenesis of macular edema in idiopathic ERM has not been well studied. Increases in the macular thickness in patients with ERM could be considered the result of deformation of the neurosensory retina by mechanical traction or macular edema caused by a breakdown of the blood-retinal barrier [20]. Mandelcorn et al. [21] demonstrated that VEGF and transforming growth factor- β have been found in idiopathic ERM, and that these growth factors correlated with the degree of the breakdown of the blood-retinal barrier in the fluorescein angiogram. Therefore, bevacizumab might work as an anti-VEGF agent to somewhat reduce macular edema caused by a biochemical pathway, which is believed to play a minor role in the pathogenesis of idiopathic ERM [12].

From the literature review, there were several reports regarding the correlation between foveal thickness and visual acuity [16, 22–25]. Some authors reported that there was no correlation between visual acuity and foveal thickness after surgery [22, 23], whereas others reported that visual acuity was well correlated with foveal thickness [16, 24, 25]. In our study, baseline and postoperative foveal thickness were found to be well correlated with visual outcome in both the treatment and control groups.

In summary, postoperative visual improvement of idiopathic ERM is favorable, as a stable vision is usually achieved approximately 9 months after PPV.

The final BCVA was correlated significantly with baseline CFT. Three consecutive IVB could reduce macular edema within the first 2 months after baseline but failed to significantly reduce CFT by the third injection. In our study, the long-term follow-up of final visual and anatomical outcome showed no significant difference between patients with or without IVB. Therefore, IVB may not be advocated as an effective treatment for this condition.

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Disclosure Statement

No conflicting relationships exist for any of the authors.

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