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ORIGINAL RESEARCH ARTICLE

Electrophysiological and structural assessment of the central retina following intravitreal injection of bevacizumab for treatment of macular edema

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Abstract *Purpose* To evaluate with electrophysiological responses and Optical Coherence Tomography (OCT), the short term functional and structural effects at the macula following intravitreal injection of bevacizumab for macular edema. *Methods* Prospective, non-randomized, interventional case study. In total, 17 eyes of 17 patients with macular edema due to vein occlusions and diabetic retinopathy received intravitreal bevacizumab. All Patients underwent complete ophthalmic examination including Snellen visual acuity testing, Multifocal Electroretinography (mfERG) and Full Field Electroretinography (FERG), OCT scanning at baseline at 1 week and 2 months after intravitreal bevacizumab. *Results* FERG did not show any change in waveform parameters following intravitreal injection of bevacizumab. Average mfERG macular responses within central 20° showed increased P_1 amplitude ($P < 0.05$) at 2 months after treatment as compared to the baseline recordings in all subjects. No changes were seen in the implicit time. There was 22% improvement in central retinal thickness (CRT) at 2 months compared to the baseline ($P < 001$). *Conclusion* Intravitreal injection bevacizumab resulted in reduction in the central retinal thickness and mild to moderate improvement in the mfERG amplitudes in this short-term study. The visual acuity changes did not directly correlate with the reduced central retinal thickness or improvement in mfERG. The short-term results showed no serious ocular adverse effects. Therefore on short-term follow up the off label drug showed improvement of macular edema secondary to vein occlusion and diabetic retinopathy with no demonstrable toxic effects.

Keywords Bevacizumab · Macular edema · Electroretinography

Abbreviations

BRVO	Branch retinal vein occlusion
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular edema
FERG	Full field electroretinography
ISCEV	International Society for Clinical Electrophysiology of Vision
IOP	Intraocular pressure
MfERG	Multifocal Electroretinography
OCT	Optical coherence tomography
VEGF	Vascular endothelial growth factor

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Introduction

Retinal vascular disorders like diabetic retinopathy and vein occlusions are the common causes of macular edema. There is no proven gold standard therapy for macular edema associated with CRVO. Laser photocoagulation is recommended for perfused macular edema due to BRVO and CSME due to diabetic retinopathy. Intravitreal triamcinolone has been used for macular edema associated with various retinal vascular disorders, but is associated with side effects like glaucoma and cataract [1, 2].

VEGF is implicated as one of the major angiogenic stimuli responsible for many retinal vascular disorders [3, 4]. Bevacizumab (Avastin, Genentech, Inc, San Francisco, CA) is a full-length humanized monoclonal antibody against VEGF. Use of bevacizumab in various retinal disorders is increasingly being reported [5–7]. In a short-term study, Maturi et al. [8], found no significant measurable photoreceptor toxicity following intravitreal use of bevacizumab based on the FERG and mfERG recordings in age related macular degeneration. The efficacy and safety of single dose of intravitreal bevacizumab in the treatment of macular edema has been established [9–14].

The mfERG is a noninvasive, sensitive method of recording spatial resolution of focal ERG's within the posterior pole and it reflects retinal function under photopic conditions. It is an invaluable tool in assessing retinal toxicity [15, 16] as well. The relationship of mfERG to the activity of retinal cells [17–19] in various retinal pathological process is reasonably well understood [20]. Although diabetic retinopathy, CRVO and BRVO are inner retinal layer disorders, macular or retinal edema in these conditions occur secondary to damage of outer blood retinal barrier and hence ERG can be used to measure the disease process and drug toxicity if any. Thrombotic areas of the retina showed lower response amplitudes and prolonged mfERG implicit times in BRVO [21]. The mfERG in CRVO showed reduced P_1 amplitudes and delayed P_1 implicit times in the affected as well as fellow eyes [22]. A recently conducted study on bovine retina which used ERG recording to monitor toxicity concluded that intraocular application of 0.25 mg/ml bevacizumab for the treatment of CNV was reasonable [23].

In this study, 1.25 mg in 0.05 ml of intravitreal bevacizumab was given in macular edema due to vein occlusion and diabetic CSME. The study aims to record and analyze the changes in electrophysiological responses from the full field and central 20° of the retina before and after injection of intravitreal bevacizumab thereby trying to provide an insight into the safety profile of this off-label drug. The OCT which gives a quantative assessment of the CRT was measured to monitor the response of the treatment to the structural integrity of the macula.

Materials and methods

Prospective, non-randomized, interventional, cohort study of 17 eyes of 17 patients with macular edema due to BRVO, CRVO and diabetic, CSME were included. Informed consent was obtained from all subjects after explanation of the procedures. The study was conducted in accordance with the tenets of the declaration of Helsinki and the requirements of the hospital Human Research Ethics Committee of Narayana Nethralaya Eye Hospital. This study has been registered with clinicaltrials.gov and the registration information is available to the public through the website "http://www.clinicaltrials.gov/", registration number NCT00403026. Data from eight of the patient's eyes included in the present report have been included in a previous report [10].

All the patients underwent detailed clinical examination, visual acuity assessment by Snellen chart, IOP measurement, fundus photography, OCT, FERG and mfERG at base line and at follow up visits of 1 week and 2 months. None of the patients with retinal vein occlusions had undergone any modalities of treatment. All the patients with diabetic macular edema had undergone at least one sitting of focal/grid laser.

CRT was measured by fast macular scans using OCT (Stratus OCT, Carl Zeiss Meditec, Dublin California, USA). The map was created from six consecutive diagonal 6-mm scans that intersected at the fovea. CRT was measured as distance between the vitreo-retinal interface and the anterior surface of retinal pigment epithelium.

The FERG and mfERG recordings were done with Metrovision ERG system (Pérenchies, France). Maximal pupillary dilatation with tropicamide 0.5% and necessary optical correction for the testing distance was done. For signal acquisition ERG-jet electrode was used. FERG recording parameters were in

accordance with ISCEV standards and guidelines [24]. For analysis, amplitude and implicit time of 'b' wave of scotopic ERG, amplitudes and implicit times of 'a' and 'b' waves of single flash photopic ERG and implicit time of 30 Hz flicker response were considered. The mfERG responses were recorded using a pseudorandom m-sequence with a stimulus matrix of 61 scaled hexagonal elements displayed on a cathode ray tube color monitor driven at a frame of 75 Hz. A field size of 20° was assessed. The recording parameters were in accordance with ISCEV standards and guidelines [25]. The P_1 and N_1 components of the first order kernel of the mfERG from two concentric rings centered on the fovea (Ring 1: 0–5°, Ring 2: 5–10°) were averaged and the mean amplitude and mean implicit time of P_1 and N_1 from each ring summation was analyzed.

Intravitreal injection of 1.25 mg bevacizumab was given under all aseptic precautions and prophylactic antibiotics were given for 1 week. Snellen visual acuity was converted to LogMAR before analysis. Comparisons within groups were made using Paired '*t*' test. P value < 0.05 was considered statistically significant The data was analyzed using Statistical Software (SPSS < 10.5, SPSS Inc, Chicago, Illinois, USA).

Results

Of the 17 eyes, 6 had macular edema secondary to BRVO, 5 due to CRVO and 6 due to diabetic retinopathy. The age of the patients ranged from 36 to 73 years. The mean age of the patients was 56.24 (±11.15). Thirteen males and 4 females participated in the study. Mean baseline visual acuity was 0.89 (±0.40) which improved to 0.66 (±0.24) at 1 week, and 0.50 (±0.30) at 2 months ($P = 0.001$) (Table 1).

All 17 eyes showed decrease in CRT. The mean CRT reduced from 474.18 μ at baseline to 422.88 μ ($P < 0.001$) at 1 week and 366.53 μ ($P < 0.001$) at 2 months after intravitreal bevacizumab injection (Table 1). There was 22% improvement in CRT at 2 months compared to baseline.

FERG responses to all scotopic and photopic stimulus testing parameters showed no statistically significant improvement or worsening at 1 week and at 2 months of treatment when compared to baseline (Table 1).

The mean mfERG responses in the central two rings were analyzed. The mean P_1 amplitude in ring 1 showed significant improvement of 16% by 2 months of intravitreal bevacizumab ($P = 0.01$). The P_1 amplitudes in ring 2 showed 15% improvement at 2 months ($P = 0.002$) (Fig. 1). The P_1 implicit time did not show significant change at 1 week and 2 months post bevacizumab injection in both ring 1 and ring 2. The N_1 amplitudes in the ring 1 showed moderate improvement by 1 week and 2 months ($P = 0.002$ and 0.010 respectively). However the N_1 amplitude in ring 2 did not show significant improvement at 2 months. The N_1 implicit time did not show any significant changes from the baseline in both ring 1 and ring 2 at 1 week and 2 months. Figure 2 shows baseline and 2-month mfERG trace arrays of a patient.

Correlation between decrease in CRT at 2 months post bevacizumab compared to the baseline and changes in mfERG values in ring 1, 2 months following intravitreal injection of bevacizumab were evaluated (Fig. 3). No statistically significant correlation was observed between improvement of P1 amplitude in the central 0–5° and decrease in CRT at 2 months (Pearson correlation co-efficient = –0.308; $P = 0.229$). No statistically significant correlation was seen between the improvement of P1 amplitude of mfERG in ring 1 and improvement of Snellen's visual acuity (Pearson correlation co-efficient = 0.012; $P = 0.963$).

No serious ocular adverse effects were seen in any of the eyes. Intraocular pressure remained within normal limits. Mean visual acuity (logMAR), CRT, FERG and mean mfERG data are summarized in Table 1.

Discussion

One of the major causes of impairment of vision in diabetic retinopathy and retinal vein occlusion is macular edema. There are many studies which report the effectiveness of intravitreal injection of triamcinolone acetonide in macular edema and subsequent improvement of vision [26–29], but it is associated with increased complications of cataract and glaucoma [1, 2]. Moschos et al. [29] showed improvement in mfERG waveforms in ring 1 at 3–6 months after intravitreal injection of triamcinolone acetonide for macular edema resulting from vein occlusions.

Table 1 Mean visual acuity (logMAR), CRT, FERG and mean mfERG data of rings 1 and 2 at baseline, 1 week and 2 months

Parameters	Baseline	1 Week	2 Months
Visual acuity (LogMAR)	0.89 ± 0.40	0.66 ± 0.24	0.50 ± 0. 30
CRT (μm)	474.18 ± 144.88	422.88 ± 130.62	366.53 ± 125.59
Scotopic 'b' wave implicit time (ms)	110.05 ± 9.12	111.07 ± 9.80	112.46 ± 11.76
Scotopic 'b' wave amplitude (μV)	136.77 ± 68.61	138.11 ± 66.29	130.27 ± 66.07
Combined maximal 'a' wave implicit time (ms)	31.82 ± 2.67	32.08 ± 2.29	31.87 ± 2.63
Combined maximal 'a' wave amplitude (μV)	–93.42 ± 38.3	–89.63 ± 30.38	–86.11 ± 39.2
Combined maximal 'b' wave implicit time (ms)	64.17 ± 7.24	63.65 ± 7.33	64.69 ± 7.74
Combined maximal 'b' wave amplitude (μV)	315.35 ± 105.9	316.53 ± 94.72	309.71 ± 107.33
Photopic 'a' wave implicit time (ms)	23.35 ± 2.65	23.5 ± 2.56	23.38 ± 2.83
Photopic 'a' wave amplitude (μV)	–12.89 ± 6.06	–14.79 ± 4.36	–14.77 ± 4.69
Photopic 'b' wave implicit time (ms)	40.88 ± 4.37	40.56 ± 4.47	40.45 ± 4.18
Photopic 'b' wave amplitude (μV)	54.4 ± 23.4	59.26 ± 20.59	58.01 ± 26.24
30 Hz flicker 'b' wave implicit time (ms)	40.33 ± 4.49	40.25 ± 4.68	40.56 ± 4.58
MFERG P_1 amplitude (0–5°) (nv/deg^2)	34.95 ± 7.96	38.43 ± 9.41	40.84 ± 9.94
MFERG P_1 amplitude (5–10°) (nv/deg^2)	33.52 ± 7.49	36.04 ± 8.30	38.8 ± 9.04
MFERG N_1 amplitude (0–5°) (nv/deg^2)	–15.64 ± 5.74	–19.74 ± 6.96	–22.26 ± 8.56
MFERG N_1 amplitude (5–10°) (nv/deg^2)	–13.70 ± 5.26	–15.92 ± 4.44	–15.5 ± 6.97
MFERG P_1 implicit time (0–5°) (ms)	49.35 ± 6.42	50.64 ± 6.13	51.11 ± 6.83
MFERG P_1 implicit time (5–10°) (ms)	49.46 ± 4.24	49.15 ± 4.38	48.78 ± 4.34
MFERG N_1 implicit time (0–5°) (ms)	28.78 ± 5.23	28.98 ± 3.22	28.18 ± 4.27
MFERG N_1 implicit time (5–10°) (ms)	30.38 ± 6.95	30.54 ± 7.59	27.6 ± 3.1

Mean visual acuity improved significantly at 2 months, Mean CRT reduced significantly at 2 months. The FERG did not show significant change from baseline. The mfERG P_1 amplitude improved significantly at 2 months

Rosenfeld et al. [5] were the first to report the efficacy of intravitreal injection of bevacizumab and OCT changes following injection of the same for macular edema due to CRVO. In a recent study it was reported that there was clearing of vitreous hemorrhage and regression of neovascularization due to proliferative diabetic retinopathy following intravitreal injection of bevacizumab [6]. It is also been postulated that, if intravitreal bevacizumab could safely and reliably resolve macular edema, bevacizumab would be the first-line pharmacologic therapy for the treatment of macular edema due to vein occlusion [5].

A standard mfERG is largely a response of bipolar cells [17, 18]. A disease process that substantially decreases the mfERG amplitude must be acting at, or before, the bipolar cells. A large delay in the timing of mfERG is associated with damage to the photoreceptors or outer plexiform layer [20, 30, 31]. The mfERG has been used to study vascular retinal diseases [32], post macular surgery changes [33], and toxicity of drugs such as chloroquine [15] and Vigabatrin [16].

Although diabetic retinopathy, CRVO and BRVO are inner retinal layer disorders, macular or retinal edema in these conditions occur secondary to damage of outer blood retinal barrier and hence ERG can be used as a noninvasive and sensitive method to assess the functional integrity of the outer retinal layers and assist in monitoring any abnormalities due to drug toxicity [15, 16].

The scotopic and photopic FERG did not show any significant change in amplitude and implicit times at 2 months post intravitreal bevacizumab when compared to baseline. This is possibly due to the fact that 12 of our patients had only segmental retinal edema (6 of our patients did have only diabetic CSME and another 6 had macular edema with segmental retinal edema) not severe enough to produce reduction in global response of FERG at baseline. Two consistent

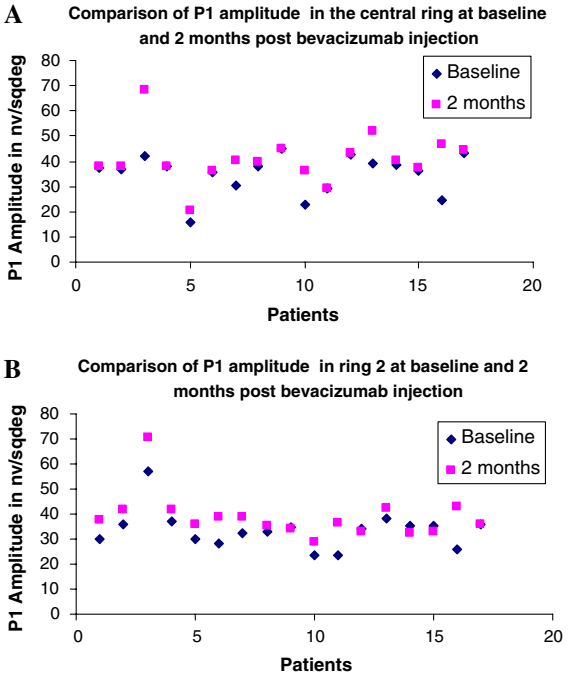

Fig. 1 Comparison of baseline P1 amplitude in the central two rings of mfERG with 2 months post bevacizumab injection amplitude. Increase in P1 amplitude post intravitreal bevacizumab noted. (**a**) Comparison of P1 amplitude at baseline and at 2 months post bevacizumab injection in ring 1 (0–5°) of the patients. (**b**) P1 amplitude at baseline and at 2 months post bevacizumab injection in ring 2

findings noted in all the eyes following intravitreal bevacizumab injection were the significant reduction in the CRT and mild to moderate improvement in the mfERG amplitudes. The P_1 amplitude improved significantly in the central 20° with no significant change in the implicit time. Thus effectiveness of bevacizumab in CSME due to retinal vein occlusion and diabetes is demonstrated structurally and electrophysiologically.

Change in visual acuity did not directly correlate with the reduced CRT or mfERG responses following intravitreal injection of bevacizumab. Although in all patients there was reduction in CRT and improved mfERG responses, there was no improvement in vision in some of the patients.

In our study, we have performed electrophysiological tests to provide an additional insight into the safety of intravitreal injection 1.25 mg of bevacizumab particularly to the retina in patients with macular edema due to vein occlusions and diabetic CSME. In all the seventeen eyes, the FERG showed no significant changes in the scotopic or photopic responses, at either 1 week or 2 months after treatment. The improvement in P_1 amplitude in the central 20°, improvement of N_1 amplitude in the central 5° ring and no worsening of other mfERG wave parameters suggests that the off-label use of bevacizumab therapy improves the macular function and probably is nontoxic to the retina. However improvement in mfERG parameters did not show any significant correlation to the reduction in CRT. The off label use of bevacizumab did not have serious ocular adverse effects or retinal toxicity in this short-term study. However, when repeat injections or dose

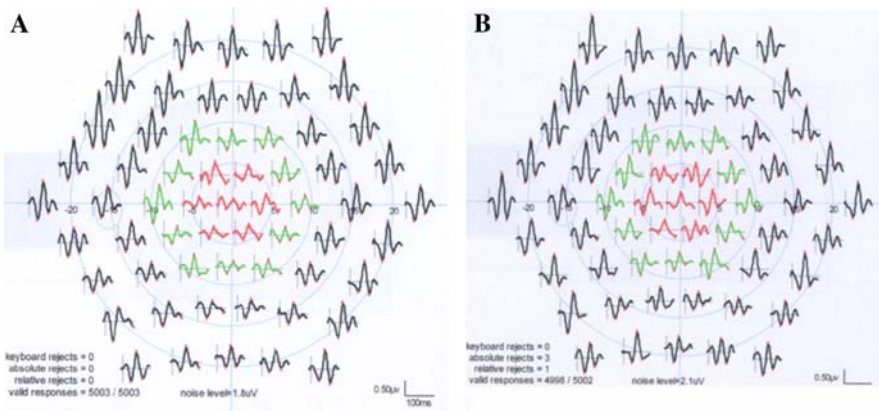

Fig. 2 The mfERG recordings of patient number 7 at baseline and 2 months following Intravitreal injection of bevacizumab. The P1 amplitude in the central ring (0–5°) improved from 30.1 nv/deg^2 at baseline to 40.3 nv/deg^2 at 2 months. The mean P1 amplitude in ring 2 improved from 32.2 nv/deg^2 at baseline to 39 nv/deg^2 at 2 months. (**a**, **b**) Baseline and 2 months post bevacizumab injection respectively

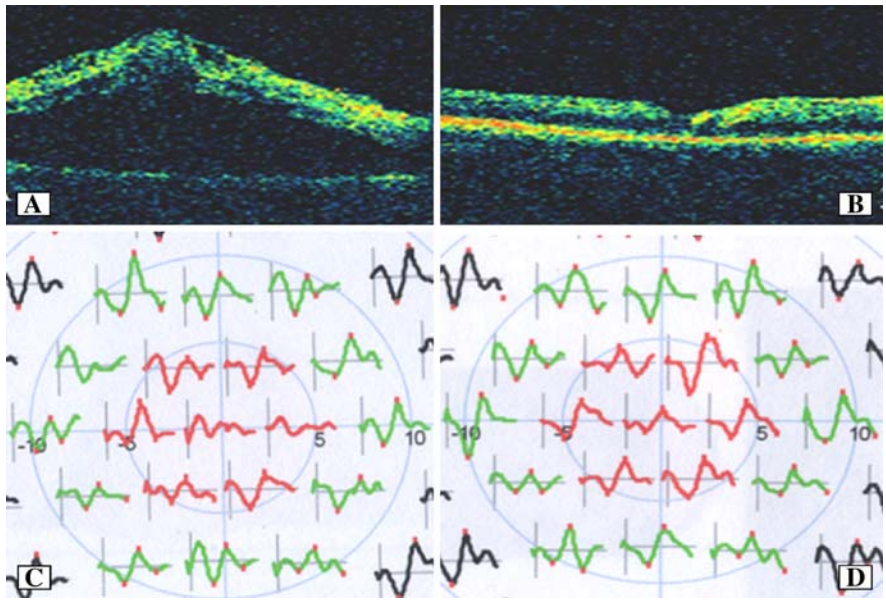

Fig. 3 OCT scan showing CRT of the patient number 10 with CRVO and macular edema and corresponding MFERG data of central 10° trace arrays. (**a**) OCT showing macular edema with increased CRT of 720 μm at baseline. (**b**) OCT showing decrease in CRT to 228 μm 2 months after bevacizumab injection. (**c**) The mfERG data of central two rings at baseline. The P1 amplitude in the central ring was 22.7 nv/deg^2 and the mean P1 amplitude in ring 2 was 23.7 nv/deg^2. (**d**) The mfERG data of central two rings at 2 months. The P1 amplitude in the central ring improved to 36.4 nv/deg^2 and the mean P1 amplitude in ring 2 improved to 29.7 nv/deg^2. Although the OCT scans shows, gross reduction in CRT, there is only moderate increase in the central MFERG waveform amplitudes

escalation is required a long term controlled, randomized studies on adequate number of patients are required to establish its safety.

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