Multifocal Electroretinography Assisted Comparison of Macular Photocoagulation versus Macular Photocoagulation and Intravitreal Bevacizumab Injection in Diabetic Macular Edema

Ali Abdollahi, MD[1] • Morteza Movassat, MD[1] • Mehdi Nili Ahmadabadi, MD[1]
Maryam Abdollahi[2] • Abasat Bashiri, MD[3]

Abstract

***Purpose*:** To evaluate the effect of intraviteral bevacizumab (IVB) in diabetic macular edema (DME), using multifocal electroretinography (mfERG)

***Methods*:** Sixty-four eyes of 32 patients with bilateral symmetric clinically significant macular edema (CSME) were included in the study. After taking a baseline mfERG, macular photocoagulation (MPC) was done in all eyes. After 7 days, 1.25 mg of bevacizumab was randomly injected in one eye of each patient and the other eye assigned for sham injection. mfERG was repeated 8 weeks after injection, and changes in visual acuity and mfERG compared in two groups.

***Results*:** The mean best corrected visual acuities (BCVAs) at baseline were 0.55 in IVB group and 0.51 in control group and at 8th week were 0.41 and 0.53 respectively, also the amplitude and implicit time showed significant improvement in mfERG. Significant improvement in visual acuity and amplitude of waves of mfERG were observed compared with sham group.

***Conclusion*:** IVB injection can augment the effect of MPC in DME and can be used as an adjunctive treatment in these cases.

***Keywords*:** Bevacizumab, Multifocal Electroretinography, Amplitude, Implicit Time, Diabetic Macular Edema, Photocoagulation

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1. Associate Professor of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences
2. Medical Student, Tehran University of Medical Sciences
3. Resident in Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences

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Correspondence to: *Morteza Movassat, MD*
Eye Research Center, Farabi Eye Hospital, Tehran, Iran, Tel:+98 21 55414941-6, Email: movassat456@yahoo.com

Introduction

Macular edema is an important cause of visual loss in diabetic patients.[1] Current treatment for the clinically significant macular edema (CSME) has been focal laser photocoagulation at the last decades.[2] This modality of treatment reduces the risk of moderate visual loss in diabetic macular edema (DME), but has limited value in diffuse macular edema.[3,4] Also, scotomas in visual field in repeated macular photocoagulation (MPC) can extend on surface and in time can cause extra limitations in central vision.[3,5]

Vascular endothelial growth factor (VEGF) is an important mediator of neovascularization and vascular hyperpermeability that is increased in eyes with DME.[1,6] Bevacizumab (Avastin, Genentech, Inc, California, USA) is a recombinant humanized monoclonal antibody that inhibits all active isoforms of VEGF-A.[6] Although it is an off-label drug for intraocular use, but has been used in vascular abnormalities in many centers all around the world and reported results are encouraging.[7-9]

The multifocal electroretinography (mfERG) is a noninvasive method that provides a topographical map of retinal function and records the electrical activity of the central 50° area of retina.[10] mfERG shows reduced response density in vascular retinal diseases compared with healthy subjects.[11] Many scientists have shown the changes of implicit time of mfERG in diabetic patients and its importance as a predictor of diabetic retinopathy, and according to the findings reported by Ng and colleagues, the P1 wave of mrERG is the most important and the easiest part to obtain and its amplitude and implicit time changes have a high sensitivity and specificity in diabetic retinopathy.[12] As these authors believe, in longer standing retinopathy the evaluation of mfERG is more important than in cases that retinopathy is transient.[12] In fact they showed that mfERG has high accuracy (88% sensitivity, 98% specificity) in discriminating between areas that remain retinopathy free and those with recurring retinopathy.[12]

Although conventional ERG can also show hypoxic condition of fundus, but, as Brad Fortune and colleagues say[13] its value is limited in macular edema, because it is a whole response of retina. In contrast, the mfERG developed by Sutter[14] and Tran and Bearse[12] can detect local changes in retina that can be used in vascular disease as diabetic retinopathy especially in macular edema. In previous studies, evaluation of macular function after intraviteral bevacizumab (IVB) injection were assessed by optical coherence tomography (OCT) & fluorescein angiography (FA) and it seems that there is no experience witch shows the result of IVB injection on macular function by mfER. Thus we decided to conduct this RCT study.

Methods

Sixty four eyes of 32 diabetic patients who were in nonproliferative diabetic retinopathy (NPDR) stage with bilateral nearly symmetrical CSME were included in this study. We included the patients with CSME in NPDR stage and those patients with previous history IVB injection or MPC were excluded from the study as well as proliferative diabetic retinopathy (PDR) patients. Best corrected visual acuity (BCVA) was measured according to the ETDRS chart by an optometrist who was masked to the groups. For mfERG test pupils were dilated with 1% tropicamide and 2.5% phenylephrine. After corneal anesthesia a mfERG test was done with International Standard Clinical Electrophysiology of Vision (ISCEV) protocol (By Metrovision unit, France) using Burien-Allen contact lens and monitor stimulus of 91 scaled hexagons stimulating 50° of posterior fundus. The test was done at distance of 40 cm from monitor with resolution of 1024×768 and frame frequency of 120 Hz of stimuli.

After recording the baseline mfERG, both eyes of patients were treated with green argon laser macular photocoagulation, by one surgeon who was masked to the groups. The guide for laser treatment was the FA. For focal leakage, direct laser therapy was applied to all leaking microaneurysms between 500 and 3000 µm from the center of the macula, and for diffuse leakage a grid pattern laser was applied to all areas of diffuse leakage more than 500 µm from the center of the macula. The spot size was 50-100 µ, and treatment was done in only one session.

One eye of each patient was randomly selected and included in IVB group and the other eye used for control group. Seven days

after laser photocoagulation, 1.25 mg (0.05 ml) of bevacizumab was injected intravitreally with a 27-gauge needle from 4 mm of limbus in superotemporal quadrant, and the other eye was just touched by a 27-gauge needle near the limbus. All eyes underwent an ophthalmic examination, checking for anterior chamber reaction and IOP rise, 1, 3 and 7 days after injection. Eight weeks after injection, BCVA was measured and mfERG was performed in both eyes.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (Version 11.5 SPSS Inc. Chicago, IL, USA). The demographic data were analyzed through descriptive statistics. The paired samples T-test was applied for comparing BCVA and mfERG with baseline values within each group. Independent samples T-test was used for comparing the changes in BCVA and mfERG between the two groups. $P<0.05$ was considered statistically significant.

This clinical trial was approved by the Review Board/Ethics Committee of Tehran University of Medical Sciences, Eye Research Center. The study protocol was explained to all of the patients, and informed consent was obtained in accordance to the Tenets of the Declaration of Helsinki.

Results

The mean age of patients was 60±7.19 years (Range, 45-71 years). 23 patients (71.9%) were females and 9 patients (28.1%) were males. The mean claimed duration of diabetes was 10.5±5.9 years (Range, 1-20 years). All patients had type II diabetes mellitus. Grid laser treatment was applied in 14 patients (28 eyes, 43.8%) and direct focal laser treatment in 18 patients (36 eyes, 56.2%).

As the table 1 shows, mean of the baseline mfERG variables in two groups are similar and there is not any statistically significant differences between them.

Table 2 shows BCVA in two groups before and 8 weeks after IVB injection. As this table shows visual improvement is more significant in IVB injection group.

Table 3 compares the amplitude and implicit time changes in both groups and shows statistically, significant improvement in mfERG variables among IVB receiving cases.

Table 1. Mean best corrected visual acuity at baseline and at 8 weeks in both groups

BCVA logMAR	Baseline	At 8th week	P-value
IVB group	0.55	0.41	<0.001
Control group	0.51	0.53	0.04

BCVA: Best corrected visual acuity

Table 2. Compares the change in best corrected visual acuity from baseline between two groups.

	IVB group	Control group	P-value
BCVA change from baseline (logMAR)	-0.143	0.02	<0.001

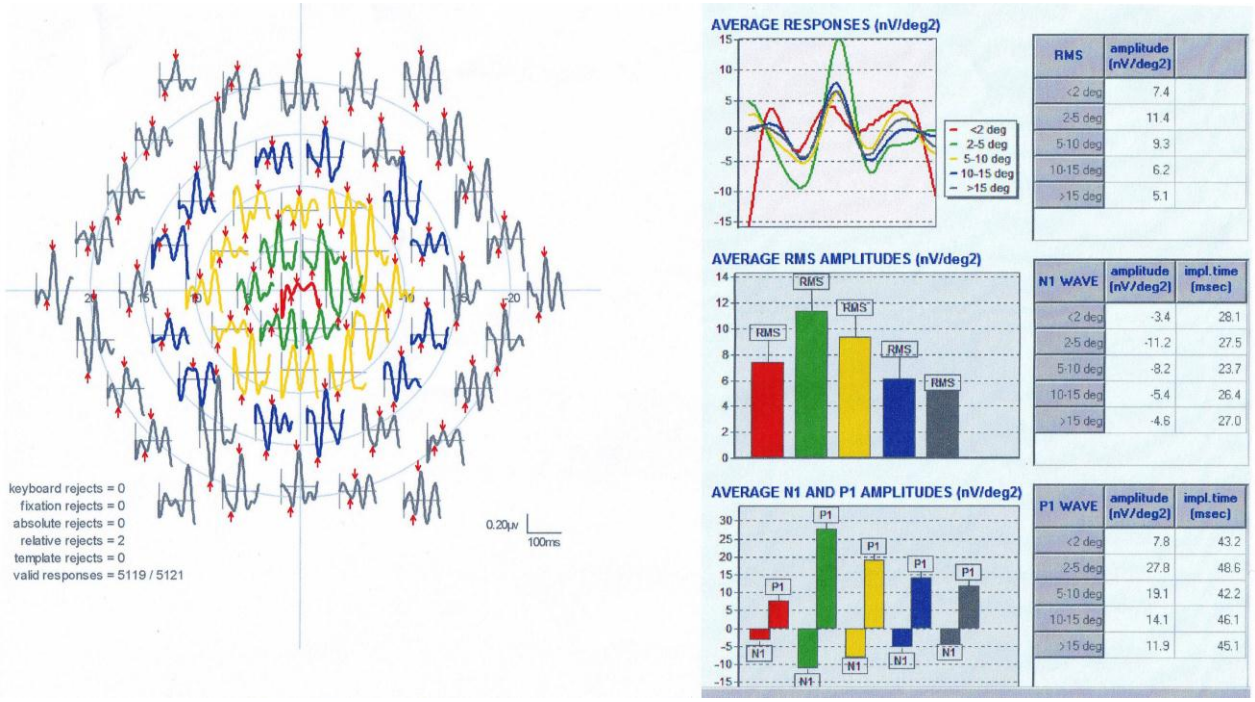
BCVA: Best corrected visual acuity
IVB: Intraviteral bevacizumab

Table 3. Changes in multifocal electroretinography parameters from baseline in both groups and the changes between the two groups are compared.

Changes from baseline	Zone I			Zone II			Zone III		
	IVB group	Control group	P-value	IVB group	Control group	P-value	IVB group	Control group	P-value
RMS amplitude (nv/deg^2)	6.44	-2.28	<0.001*	2.25	-1.02	0.009*	1.37	-1.12	0.002*
N-amplitude (nv/deg^2)	-6.81	5.51	<0.001*	-0.7	1.94	0.25	-0.6	3.27	0.014*
P-amplitude (nv/deg^2)	8.3	-10.11	0.003*	1.93	-4.35	0.14	1.54	-6.89	0.005*
N-implicit time (ms)	-2.3	0.24	0.08	-1.14	-0.02	0.53	-0.26	-1.3	0.3
P-implicit time (ms)	-2.11	0.22	0.27	-1.1	-1.2	0.96	-0.01	-2.43	0.2

*: Statistically significant values
IVB: Intraviteral bevacizumab
RMS: Root mean square

Date: 07.01.2007



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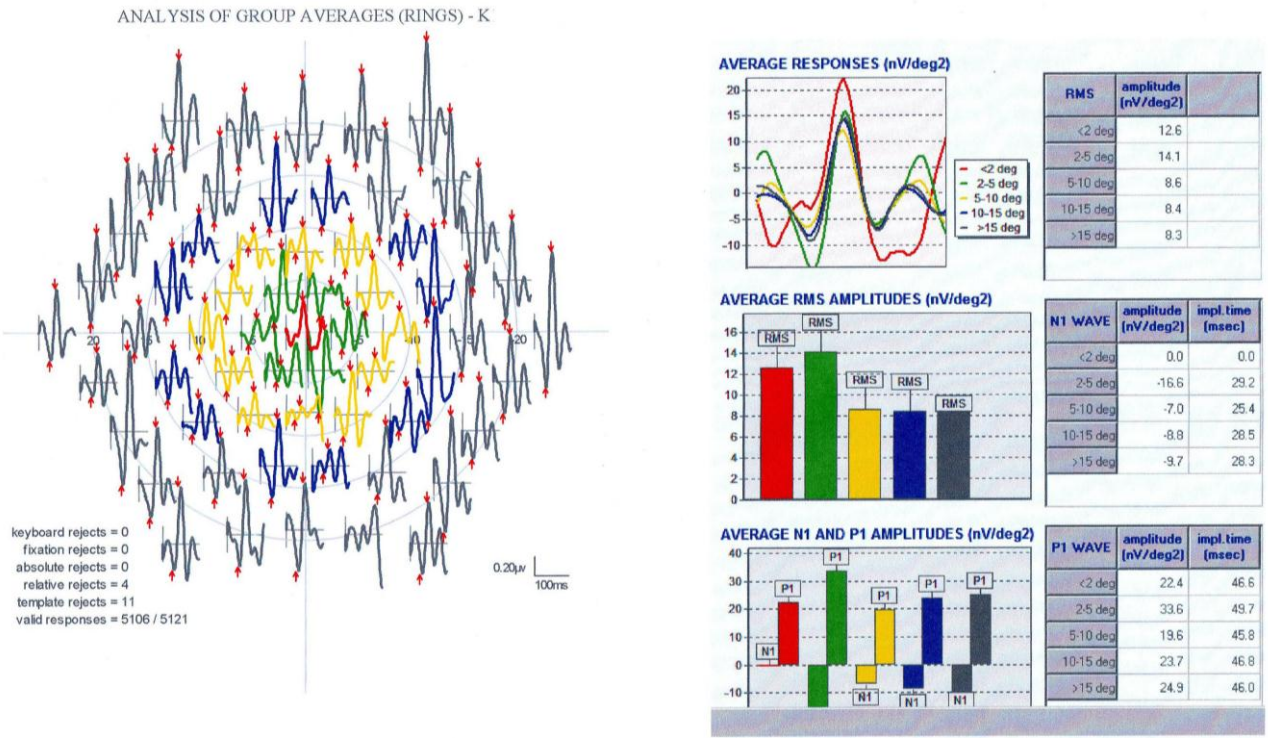

Figure 1. Multifocal electroretinography before (Top) and after (Bottom) macular photocoagulation and intravitreal bevacizumab injection which shows dramatic improvement in evoked potentials.

Discussion

One of the frequent causes of visual impairment in diabetic retinopathy is macular edema.[1] Focal laser photocoagulation is the current treatment for DME.[2] However, this modality of treatment has limited values in diffuse macular edema.[3,4] Also, it may result in macular scars.[3]

There are some studies that evaluate the efficacy of intravitreal triamcinolone acetonide in macular edema, and have shown improvement of vision, but this effect decreases with time.[14] Also, it is associated with some complications such as glaucoma and cataract,[15,16] thus new efforts are based on the application of anti-VEGF medications. Bevacizumab that inhibits all isoforms of VEGF-A, has been used for treatment of resistant diffuse macular edema.[17]

On the other hand, as Ng and colleagues[10] indicate the P_1 wave of mfERG which is the most prominent part of it, is generated by inner nuclear layer of retina, specially bipolar cells and this is the layer that is affected in diabetic retinopathy. In fact before the occurrence of clinical diabetic retinopathy, neural dysfunction of retina has occurred[10] which can be detected by mfERG, and electrophysiologist have shown the high sensitivity and specificity of this test for both prediction of diabetic retinopathy and follow-up of patients and detection of the effect of treatment.

In the study of Atul kumar et al, the intravitreal bevacizumab was used in patients with persistent diffuse macular edema unresponsive to laser photocoagulation, and they reported statistically significant improvement of visual acuity after 3 months of the injection, which remained significant at the end of 6 months.[1]

In another study, the intravitreal injection of bevacizumab for treatment of macular edema due to branch and central vein occlusion (BRVO, CRVO) and diabetic retinopathy, has significantely improved in the P-wave amplitude of mf ERG within central 20° of the retina at 2 months of treatment when compared with the baseline in all subjects, but there has been no significant change in the implicit time.[18]

In this study, the control group was the fellow eye of the IVB group, so the compounding factors such as age, sex, duration of disease, systemic conditions, hypertension, hyperlipidemia were distributed equally in the two groups. However, the great concern in this study was the possibility of systemic absorption of intravitreal bevacizumab, that may affect the mfERG responses in the fellow eye (Control group), although Bakri et al's[19] study showed only very low concentrations of bevacizumab in the fellow eye after the intravitreal injection.[19]

In our study there is significant improvement in P1 wave amplitude in patients receiving IVB plus MPC but changes in implicit time were not significant. Our study is in accordance with Hood DC, Holopigian, and Greenstein V[20,21] that claim P1 wave amplitude is more important to show tissue changes in diseases affecting bipolar cells, but implicit time of wave is related to outer retina and photoreceptors. But our results are in contrary to Jasons Ng and colleagues and Brad fortune and colleagues that say amplitude of P1 wave has a high variability and implicit time changes are more informative in retinal diseases.

We observed no adverse events including endophthalmitis, inflammation, IOP rise, thromboembolic events, cataract formation or progression, and retinal detachment.

Conclusion

In summery, our results show more improvement of visual acuity and mfERG responses in IVB group of DME and we suggest to use intravitreal bevacizumab as an adjunctive procedure for DME in whom MPC is applied.

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