Original Article

Multifocal electroretinogram changes after panretinal photocoagulation in early proliferative diabetic retinopathy

Fathy Mohamed Abo Elftouh Elsalhy [1], Mahmoud Mohammed Ahmed Ali [1], Mahmoud Fawzy Zaky Morsy [1], Abdelrahman Ahmed Ali Khattab [1], Ezzat Nabil Abbas Ibrahim [1], Hazem Elbadry Mohammed Mohammed [1], Ramadan Mohamed Abdelrahman Elgohary [1], Hossam El Din Hassan El Sayed El Baz [1] and Mohamed Sayed Taha Abouzeid [2]

[1] *Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt*
[2] *Department of Ophthalmology, Faculty of Medicine, Beni Suef University, Beni Suef, Egypt*

ABSTRACT

Background: Panretinal photocoagulation (PRP) impacts macular function in eyes with early proliferative diabetic retinopathy (PDR). Herein, we used the multifocal electroretinogram (mfERG) to objectively investigate this concept.

Methods: In this prospective interventional case series, we enrolled patients with treatment-naive early PDR, absence of clinically significant macular edema, and requirement for PRP. All participants underwent detailed ocular examinations. We measured the best-corrected distance visual acuity (BCDVA), conducted optical coherence tomography imaging to measure central macular thickness (CMT), and performed mfERG at baseline and 3 months post-PRP. Amplitude and latency of the mfERG response were evaluated within the innermost four of the five concentric rings.

Results: We enrolled 29 eyes of 23 patients with a mean (standard deviation) age of 54.3 (8.8) years and male-to-female ratio of 1:1.3. The mean BCDVA was unchanged post-treatment ($P > 0.05$), and the BCDVA in 26 eyes (89.7%) was either improved or unchanged, whereas in three eyes (10.3%) it decreased. The mean CMT was unchanged post-PRP ($P > 0.05$). Concerning the mfERG, the mean P1 amplitudes decreased significantly in all four concentric rings from the foveola at 3 months post-PRP compared with baseline values (all $P < 0.05$); however, the latencies were unchanged (all $P > 0.05$). At baseline, BCDVA correlated significantly with both the amplitude ($r = +0.55$; $P < 0.05$) and latency ($r = -0.38$; $P < 0.05$) of the mfERG in the central ring, whereas a significant correlation was detected with only the amplitude at 3 months post-PRP ($r = +0.52$; $P < 0.05$).

Conclusions: Macular function was decreased 3 months post-PRP in patients with early PDR, as indicated by decreased amplitude of the mfERG, whereas the functional and anatomical parameters were stable. The mfERG served as an objective tool for measuring retinal function and predicting visual outcomes post-PRP in eyes with early PDR. A higher amplitude in the mfERG correlated substantially with a better visual outcome post-PRP. Further multi-center longitudinal studies with robust designs including different PDR severity levels may reveal additional objective after-effects of PRP.

KEYWORDS

electroretinographies, multifocal electroretinogram, photocoagulation, panretinal photocoagulation, light coagulation, diabetic retinopathy, proliferative diabetic retinopathy, diabetic angiopathies, visual acuity, optical coherence tomography

Correspondence: Abdelrahman Ahmed Khattab, Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt. Email: abdulrahmankhattab88@gmail.com, abdelrahman_khattab@azhar.edu.eg. ORCID iD: https://orcid.org/0000-0003-4632-8506

How to cite this article: Elsalhy FMAE, Ali MMA, Morsy MFZ, Khattab AAA, Ibrahim ENA, Mohammed HEM, Elgohary RMA, Elbaz HEHE, Abouzeid MST. Multifocal electroretinogram changes after panretinal photocoagulation in early proliferative diabetic retinopathy. Med Hypothesis Discov Innov Ophthalmol. 2024 Fall; 13(3): 121-128. https://doi.org/10.51329/mehdiophthal1503

Received: 21 July 2024; Accepted: 12 October 2024

INTRODUCTION

The global prevalence of diabetes mellitus (DM) in 2010 was 6.4%, and it is expected to increase to 7.7% by the end of 2030. Diabetic retinopathy (DR) is the most frequent blinding microvascular complication of DM [1]. Non-proliferative DR (NPDR) becomes proliferative DR (PDR) due to retinal ischemia and progressive capillary non-perfusion, which is a major cause of vision impairment in patients with DM [2].

Panretinal photocoagulation (PRP) reduces the risk of vision loss in eyes with PDR. However, it may have adverse effects, such as impaired central visual acuity, due to macular edema, visual field constriction, and serous retinal detachment [3]. Extended visual recovery time, heightened sensitivity to glare, and reduced color vision have been documented post-PRP, indicating that the laser beam directly destroys targeted retinal areas and affects the surrounding untreated macular region [4]. However, most investigations on the negative effects of PRP have focused on subjective parameters such as visual acuity, photostress tests, contrast sensitivity tests, and perimetry measurements [5, 6].

Electrophysiological tests evaluate the electrical characteristics caused by ion flow in tissues and cells and retinal function. The electroretinogram (ERG) is commonly performed according to the standard International Society for Clinical Electrophysiology of Vision (ISCEV) protocol. The most frequently used ERG modalities are full-field flash ERG (ffERG), multifocal ERG (mfERG), and pattern ERG [7]. Studies have used ffERG to examine electrical alterations of the whole retina following PRP [8, 9]. However, ffERG is unable to specifically assess macular function [10]. In contrast, mfERG can quantitatively evaluate macular function [11]. This method involves stimulation of localized electrical retinal responses using a predetermined hexagonal pattern and distinct on-and-off sequences, enabling the concurrent assessment of responses from all retinal areas and identifying localized abnormalities [12].

In this study, mfERG was used to assess macular function post-PRP in patients with early PDR and without clinically significant macular edema (CSME).

METHODS

In this prospective interventional case series, Egyptian patients with type 2 DM, early PDR, lack of CSME, and who underwent PRP from January 2023 to December 2023 at Al-Azhar University Hospitals, Cairo, Egypt, were enrolled. The study followed the tenets of the Declaration of Helsinki and received ethical approval from Al-Azhar Medical Research Ethical Committee. Each patient provided written informed consent pre-enrollment. All procedures and follow-up visits were held in the ophthalmology departments at Al-Azhar University Hospitals.

DR grading and treatment decisions were rendered by a single experienced retina specialist (M.M.A.A.) based on the recommendation of the early treatment of diabetic retinopathy trial [13]. Early PDR was defined as the presence of new vessels ≤ 1/3 of the disc diameter, without any pre-retinal, sub-hyaloid, or vitreous hemorrhage or new vessels elsewhere in the retina. Additionally, eligible participants had a best-corrected distance visual acuity (BCDVA) of ≥ 6/60, spherical refractive error ≤ ± 6 D, astigmatism ≤ ± 3 D, and foveal fixation.

The exclusion criteria included: eyes with previous therapies for DR, such as intravitreal injection of any drugs, laser treatment, or vitreoretinal surgery; with media opacities such as corneal opacity, cataract, or vitreous opacity; with retinal diseases other than DR, such as age-related macular degeneration, pathological myopia, or vascular occlusion; those with glaucoma; those with a history of ocular trauma or inflammation; those with CSME or macular ischemia; and individuals with type 1 DM.

Demographic data were gathered, including age, sex, diabetes duration, glycated hemoglobin levels, coexistence of hypertension, and refractive errors. Clinical examinations included BCDVA assessment using a Snellen chart (Auto Chart Projector CP 670; Nidek Co., Ltd., Gamagori, Japan) with values converted to decimals for statistical analysis, detailed anterior segment examination using a slit-lamp biomicroscope (Photo-Slit Lamp BX 900; Haag-Streit, Koeniz, Switzerland), intraocular pressure measurement using a Goldmann applanation tonometer (AT900, Haag-Streit), and fundus examination using a slit lamp with + 78 D indirect lens (Volk Optical, OH, USA) and by indirect ophthalmoscopy (Heine Omega 200; Heine Instruments Canada, Kitchener, Canada) with a + 20 D indirect lens (Volk Optical).

Baseline fundus fluorescein angiography (FFA), spectral domain optical coherence tomography (SD-OCT), and mfERG were performed for all participants. FFA was performed using a Topcon TRC-50DX retinal fundus camera (Topcon Co., Tokyo, Japan) to rule out macular ischemia and confirm early PDR. The patients were informed about the considerable associated risks before dye injection.

SD-OCT images were acquired using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). A fast-volume scan was performed (20 × 20° [6 × 6 mm] raster scans comprising 25 horizontal slices) to measure central macular thickness (CMT).

mfERGs were recorded according to the ISCEV guidelines with a slight modification [12]. The stimulation and recording of mfERG responses were performed using the RETI-Port/Scan 21 (Roland Consult, Brandenburg, Germany) with H-K loops under topical anesthesia. The patient's pupils were dilated using tropicamide 0.5% (Mydrapid 0.5%®; Alexandria Co., Alexandria, Egypt), and a 61-scaled hexagon-based pattern stimulus, covering approximately 30° of the visual field, was utilized. The hexagon sizes were adjusted with eccentricity to achieve consistent amplitude responses at all locations. The hexagons flickered with a distinct on-and-off sequence (m-sequence) of white and black display at a 75-Hz frequency. Following correction of refractive error, the patient focused on a central spot on the monitor with a viewing distance of 30 cm. The recording sessions were split into eight trials, each lasting 30 s, resulting in a total recording duration of approximately 4 min. The amplitude and latency of the first positive wave (P1) of the first-order response within the innermost four rings (approximately 20°) of the five concentric rings were recorded by the mfERG. The P1 amplitude was measured from the trough of N1 to the peak of P1 and expressed as a response amplitude per unit area (nV/deg^2). P1 latency was estimated from the presentation of the stimuli in milliseconds (ms). A single expert ophthalmologist performed all examinations and was unaware of the examination time point. Additionally, a single technician performed all imaging procedures and was unaware of the time point of examinations.

A single retina specialist (F.M.A.E.E.) performed PRP for each participant, in two sessions with 2-week interval, using the VISULAS green laser (Carl Zeiss Meditec AG, Jena, Germany). PRP was applied outside the great vascular arcade. An argon laser (532 nm) with a spot size ranging from 200 to 300 μm, power ranging from 250 to 450 mW, and constant exposure duration of 150–200 ms was applied. Laser burns were spaced approximately one-half burn width apart. During the entire therapeutic procedure, 2000–2500 laser burns were applied. All laser sessions were conducted under topical anesthesia (0.4% benoxinate hydrochloride ophthalmic solution, BENOX®; Egyptian Int. pharmaceutical industries Co., Cairo, Egypt). A Volk Super Quad 160 wide-field contact lens (Image Mag 0.5 ×; Laser Spot 11 2.0 ×; Volk Optical) was used. PRP was applied in a sequence of inferior retina followed by nasal, superior, and temporal retina.

BCDVA, CMT using SD-OCT, and mfERG were evaluated at baseline and 3 months post-PRP for all included eyes. Data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (SPSS, IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was applied to determine the normality of data distribution. Quantitative parameters are reported as means (standard deviations [SDs]). Qualitative parameters are reported as numbers (%). The paired samples *t*-test was employed to determine the significance of changes between the two examination time points. Pearson's product-moment correlation test was used to measure the significance and strength of the relationship between two sets of parameters. The confidence interval was set at 95%, and the acceptable margin of error was 5%. *P*-values were considered significant if < 0.05 and highly significant if < 0.001.

RESULTS

Out of 33 eyes of 27 consecutive patients with type 2 DM, 29 eyes of 23 patients have met the inclusion criteria; 17 patients had unilateral and six had bilateral early PDR. Four eyes were excluded because three patients failed to attend the follow-ups. One patient developed macular edema with CMT > 350 μm and BCDVA < 6/12 at 3 months post-PRP and required intravitreal injection; this eye was also excluded. Table 1 summarizes the demographic and baseline clinical characteristics of the participants.

The mean BCDVA and CMT did not change significantly at 3 months post-PRP (both $P > 0.05$; Table 2). BCDVA improved or was stable in 26 eyes (89.7%) and deteriorated in three eyes (10.3%).

We observed a significant positive correlation between the baseline (r = + 0.55; $P = 0.001$) and post-PRP (r = + 0.52; P = 0.006) BCDVAs with the P1 amplitudes of the baseline and post-PRP mfERGs in the central ring corresponding to the foveola (Ring 1), respectively. However, despite a significant negative correlation between baseline (r = - 0.38; $P = 0.032$) BCDVA and latency of the baseline mfERG in the central ring corresponding to the foveola (Ring 1), the correlation did not reach statistical significance (r = - 0.17; $P = 0.262$) at the 3-month post-PRP visit. The first-order mfERG responses revealed that the mean P1 amplitudes of the four mfERG areas significantly decreased at 3 months post-PRP (all $P < 0.05$; Table 2). However, the mean P1 latencies of the four mfERG areas remained unchanged at 3 months post-PRP (all $P > 0.05$; Table 2). Therefore, PRP may correlate more closely with amplitude than with latency (Figure 1).

Detailed posterior segment examinations at 3 months post-PRP revealed that neovascularization had regressed in all included eyes, and none needed further treatment.

Table 1. Demographic and baseline clinical characteristics of study participants

Variable	Values
Age (y), Mean ± SD (Range)	54.3 ± 8.8 (34 to 69)
Sex (Male / Female), n (%)	10 (43.5) / 13 (56.5)
Duration of DM (y), Mean ± SD (Range)	12.2 ± 4.9 (7 to 21)
HbA1c (%), Mean ± SD (Range)	7.9 ± 0.9 (6.1 to 9.6)
Coexistence of hypertension, n (%)	14 (60.9)
IOP (mmHg), Mean ± SD (Range)	16.4 ± 3.2 (12 to 21)

Abbreviations: y, years; SD, standard deviation; n, number; DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; %, percentage; IOP, intraocular pressure; mmHg, millimeter of mercury.

Table 2. Comparison of BCDVA, CMT, and mfERG amplitudes and latencies between pre- and post-PRP

Variable	Pre-PRP	Post-PRP	*P*-value
BCDVA (decimal), Mean ± SD (Range)	0.4 ± 0.2 (0.2 to 0.8)	0.4 ± 0.2 (0.1 to 0.8)	0.279
CMT (µm), Mean ± SD (Range)	251.8 ± 21.3 (212 to 300)	260.2 ± 29.1 (219 to 320)	0.219
mfERG (Amplitudes [nV/deg²]), Mean ± SD			
Ring 1	56.4 ± 12.8	43.0 ± 8.3	**0.001**
Ring 2	36.4 ± 5.1	29.1 ± 5.3	**0.001**
Ring 3	22.8 ± 5.2	17.8 ± 4.6	**0.011**
Ring 4	15.0 ± 3.7	11.3 ± 3.4	**0.025**
mfERG (Latencies [ms]), Mean ± SD			
Ring 1	46.2 ± 2.9	47.7 ± 2.1	0.611
Ring 2	45.5 ± 2.4	46.7 ± 2.3	0.428
Ring 3	45.0 ± 2.8	44.4 ± 2.7	0.405
Ring 4	46.8 ± 2.5	46.9 ± 1.8	0.875

Abbreviations: BCDVA, best-corrected distance visual acuity; CMT, central macular thickness; mfERG, multifocal electroretinogram; PRP, pan retinal photocoagulation; SD, standard deviation; µm, micrometer; nV/deg²; nano volts per square degree of visual field, ms, milliseconds. Notes: *P*-values < 0.05 are shown in bold.

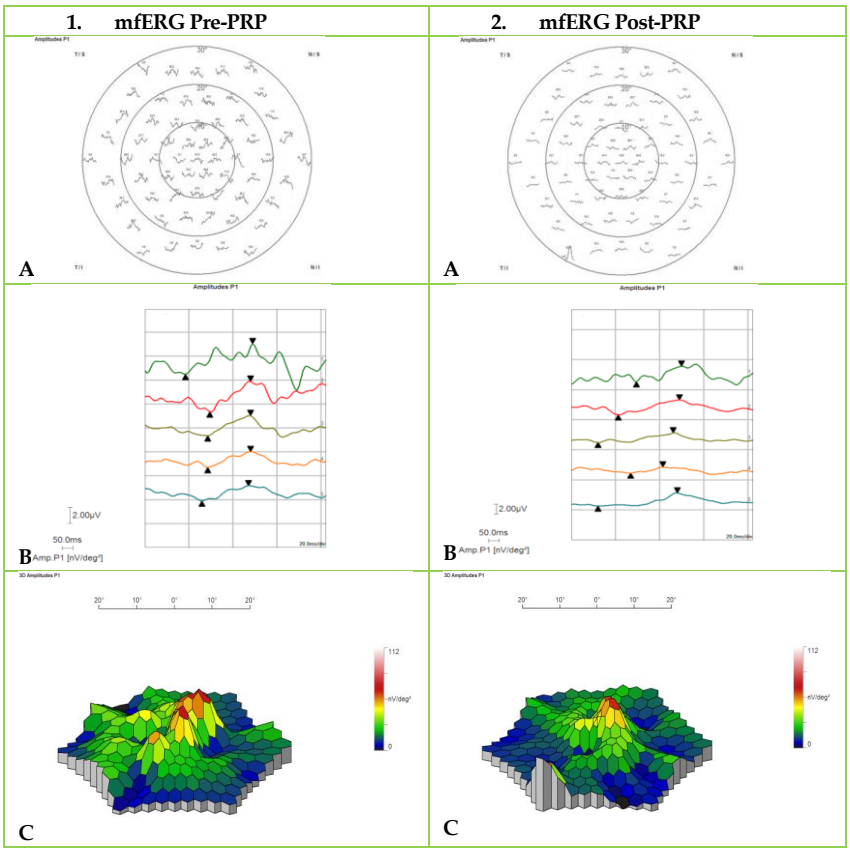

Figure 1. Multifocal electroretinogram (mfERG) changes (RETI-Port/Scan 21, Roland Consult, Brandenburg, Germany) (1) before and (2) after panretinal photocoagulation (PRP) for one eye of a patient with type 2 diabetes mellitus and early proliferative diabetic retinopathy, showing (A) decreased amplitudes and mfERG trace arrays displayed 61 elements. (B) mfERG responses were grouped into five concentric rings. (C) Topographic three-dimensional response density plots.

DISCUSSION

Herein, vision improved or remained stable in 89.7% of eyes, and the mean BCDVA and CMT remained unchanged 3 months post-PRP. However, using objective mfERG measures, foveal function was impacted. The amplitudes decreased significantly in four concentric rings from the fovea, while the latencies remained unchanged. Meanwhile, a significant positive moderate correlation was observed between BCDVA and the P1 amplitude at baseline and 3 months post-PRP. However, despite a significant negative weak correlation between baseline BCDVA and the P1 latency, this correlation was not significant 3 months post-PRP. Therefore, spotlighting the value of mfERG as an objective measure of retinal function in patients with PDR.

PRP can induce macular edema, resulting in short- or long-term visual impairment. However, eyes without macular edema may still experience a decrease in color vision and contrast sensitivity [14]. Consistent with our findings, in a study by Soman et al. [15] on eyes with early PDR and without CSME, most eyes experienced improvement or stability in vision (81.58%) at the post-PRP visit, whereas the vision worsened in 18.42% of eyes. The eyes experienced early and transient deterioration of vision post-PRP that was normalized at the 3-month visit [15]. However, in contrast with our findings, the central foveal thickness significantly increased 3 months post-PRP [15]. Likewise, in a prospective non-comparative interventional case series of 64 patients, Shimura et al. [16] recorded vision stability in 54 eyes (84%) 6 months post-PRP in those with DR; however, 11 and 5% of eyes had stable vision and a transient decrease in vision, respectively [16]. These results were due to a prominent increase in foveal thickness, and measured both foveal and parafoveal thickness, revealing that eyes with transient and sustained visual deterioration had parafoveal thicknesses of >275 and >300 μm, respectively. Thus, they concluded that parafoveal thickness is an important parameter for the prediction of post-PRP visual outcomes [16]. At follow-up examinations, in a study by Faghihi et al. [17], the 39 eyes of 21 patients with very severe non-proliferative DR or early PDR without substantial macular edema displayed a significant increase in central subfield thickness and unchanged mean visual acuity at the 6 months post-PRP follow-up [17]. However, none of these studies [15-17] conducted electrophysiological testing along with functional and anatomical macular assessments. Thus, the complete comparison between this study outcome and theirs is inequitable.

In a cross-sectional study of electroretinography characteristics, Ba-Ali et al. [18] recruited non-diabetic patients (control) and diabetic patients with no-DR or NPDR. They observed that the mfERG amplitudes in all five rings (R1–R5) were significantly reduced in those with NPDR compared to those of the controls, whereas a significant reduction in mfERG amplitude in eyes with no-DR was detected only in R2. Patients with NPDR and no-DR had significantly prolonged implicit times in only R4 and R5, whereas those of R1–R3 were comparable between the diabetic and control groups [18]. However, Ba-Ali et al. excluded eyes with early PDR and those that received treatment [18]. In contrast, in this study, a significant positive moderate correlation of baseline and post-PRP BCDVA with baseline and post-PRP P1 amplitude, respectively, were perceived. Thus, a reduction in P1 amplitude may indicate vision deterioration post-PRP in eyes with early PDR. The mean (SD) values of baseline and post-PRP P1 amplitude in our participants with early PDR were 56.4 (12.8) and 43.0 (8.3) nV/deg^2, respectively, with a significant deterioration at the 3 months post-PRP visit. In patients with DM, Ba-Ali et al. [18] observed mean (SD) P1 amplitudes for those with no-DR and with NPDR of 87.9 (31.8) and 68.5 (27.4) nV/deg^2, respectively, with significant differences between two groups with dissimilar DR severity levels [18]. Comparing the mean P1 amplitudes of our participants with those of their cases [18], this parameter deteriorates simultaneously with an increase in DR severity, and further declines post-PRP intervention. Thus, P1 amplitude may predict BCDVA in various DR severity levels and post-treatment interventions in this patient group. Because P1 amplitude in the central ring corresponding to the foveola displayed a significant correlation with BCDVA in our study, and its mean value decreasing with the increasing severity of DR [18]. However, further longitudinal studies including eyes with various DR severities treated with different available or novel therapies are required to verify the ability of this parameter to accurately predict visual outcomes in patients with DM.

Consistent with our findings, Du et al. [19] observed a significant impairment in para-macular function using mfERG in patients with severe NPDR, revealing increased deterioration of central macular function post-PRP in a short-term follow-up of 2 weeks [19]. In addition, a significant reduction in the P1 and N1 response densities at rings 2–3 and 3–4, respectively, were detected in eyes with NPDR versus controls, whereas their implicit times were comparable. The P1 and N1 response densities in ring 1 decreased significantly at the 2 d post-PRP follow-up, and remained lower than pre-PRP values at the 2 weeks post-PRP follow-up. However, the implicit times remained unchanged [19]. Similar to our findings, in Du et al.'s study [19] the macular thickness remained unchanged post-PRP

compared with baseline values. A negative correlation between the P1 response density in ring 1 and macular thickness at the 2 d post-PRP follow-up were noted [19]. In our study, patients with DR severity levels different from those of their participants [19], mfERG revealed a significant reduction in the mean amplitude values of rings 1–4, whereas the mean latency values were stable at the 3 months post-PRP follow-up. The outcomes of these two studies may indicate the unfavorable short- [19] and long-term effects of PRP on mfERG parameters among various DR severity levels, whereas anatomical changes, as indicated by stable macular thickness post-PRP in both studies [19], were not perceived. Further studies with larger sample sizes and wider DR severity ranges are required to confirm the precedence of electrophysiological changes over detectable anatomical or functional changes post-PRP.

Lovestam-Adrian et al. [4] recorded mfERG, anatomical, and visual outcomes at the 6 months post-PRP follow-up in 10 consecutive patients with treatment-naive PDR, a mean (SD) age of 57 (10) years, and DM duration of 21 (10) years. Focal laser was performed 3 weeks pre-mfERG recording in some of the patients, and significant reduction was detected in the mean amplitudes of rings 1 + 2 (summed response), 3, and 4 at the 6 months post-PRP follow-up. Meanwhile, the mean implicit times were unchanged [4]. Accordingly, similar to our findings, the visual acuity and retinal thickness remained unchanged 6 months post-PRP. There was no correlation between retinal thickness measured by the OCT and amplitudes of mfERG waveforms [4]. We observed similar outcomes in our participants with early PDR, a shorter post-PRP follow-up duration, and reduced DM duration. Therefore, the outcomes of our study and that of Lovestam-Adrian et al. [4] may indicate the persistence of mfERG amplitude deterioration despite stable anatomical and functional outcomes in eyes with PDR at short- or long-term post-PRP follow-up.

Greenstein et al. [20] observed that focal laser treatment for CSME affected latency more than amplitude in mfERG, and caused limited or no changes in visual function [20]. Meanwhile, Lovestam-Adrian et al. [21] observed that focal or grid laser of macular areas with retinal edema and exudates improved retinal function as demonstrated by the increased amplitudes on mfERG at the 3 months post-laser visit [21]. In the current study, eyes with CSME were excluded; however, 3 months post-PRP, a reduction in the mean amplitude of mfERG waveforms and stable mean implicit times were detected. The discrepancy between study outcomes [20, 21] could arise from differences in DM status, DR severity, location of applied laser burns, or specific laser parameters; future studies are required for further in-depth investigations of such topics.

Tyrberg et al. [22] studied patients with type 1 or 2 DM, no history of DR treatment, and eyes with preserved visual acuity and a foveal avascular zone >650 μm. Therefore, increasing foveal avascular zone diameter and prolonged implicit times in the mfERG were significantly correlated. Thus, indicating an alteration in neuronal macular function due to ischemia prior to visual acuity deterioration [22]. Likewise, in eyes with early PDR, despite vision preservation, a significant reduction in the amplitudes of mfERG waveforms were observed in the current study, 3 months post-PRP.

Khojasteh et al. [23] investigated the potential correlation between structural macular abnormalities on OCT, functional characteristic changes in mfERG parameters, and deterioration of BCDVA in patients with DM and macular edema. They observed a significant correlation of some mfERG parameters with structural macular changes and vision loss [23]. Zhu et al. [24] recorded mfERG, anatomical, and visual outcomes at the 6 months post-PRP visit in patients with treatment-naive severe NPDR or early PDR at baseline examination. They observed a significant correlation between final BCDVA and the amplitude or latency of mfERG in nine sectors, with the amplitude having stronger correlation than latency [24]. In this study, we observed a significant positive correlation between baseline and post-PRP BCDVA with baseline and 3-month post-PRP P1 amplitude of mfERG waveforms, respectively. Despite a significant negative correlation between baseline BCDVA and P1 latency, this correlation was not significant at the 3 months post-PRP follow-up. Thus, our findings and those of the previous studies [23, 24] may suggest the importance of mfERG as an objective predictor of BCDVA in patients with DM and DM-induced retinal changes.

Our results and those of previous studies support the substantial role of objective electrophysiological recordings in patients with DM and retinopathic changes. However, our investigation is limited by its exclusion of eyes with different DR severity levels and CSME, having no healthy controls, and a short follow-up duration. The application of artificial intelligence (AI) and machine learning in cardiac and visual electrophysiology has been widely investigated, revealing promising uses for AI algorithms in managing patients [25-27]. We hypothesize that similar AI patterns using mfERG waveforms may predict visual outcomes post-PRP for different severity levels of DR and its suitability should be investigated in future pilot and feasibility studies.

CONCLUSIONS

Most eyes with early PDR experienced stability or improvement in BCDVA with unchanged CMT 3 months post-PRP. However, our objective assessment by mfERG revealed the negative impact of laser treatment on foveal function. The amplitudes decreased significantly in four rings concentric from the fovea, while the latencies remained unchanged. The significant correlation between the BCDVA and P1 amplitude at baseline and 3 months post-PRP highlights the potential of mfERG as an objective measure of retinal function in individuals with PDR. Further multi-center longitudinal studies with robust designs including different PDR severity levels may reveal additional objective after -effects of PRP.

ETHICAL DECLARATIONS

Ethical approval: The study followed the tenets of the Declaration of Helsinki and received ethical approval from Al-Azhar Medical Research Ethical Committee. Each patient provided written informed consent pre-enrollment.

Conflict of interest: None.

FUNDING

None.

ACKNOWLEDGMENTS

We express our gratitude to our colleagues at Al-Azhar University Hospitals.

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