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ORIGINAL ARTICLE

Changes in Electroretinogram Parameters after Panretinal Photocoagulation in Diabetic Retinopathy

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Objective: This study was performed to evaluate the effect of panretinal photocoagulation (PRP) on parameters of electroretinograms (ERG).

Methods: Retrospective study was performed on 58 eyes of 29 patients with proliferative diabetic retinopathy (PDR) who underwent PRP. ERG was performed in each patient before and after PRP, and each ERG parameters were compared between the pre- and post-PRP state. Also, the results of ERG performed after PRP were compared between two groups: one group showing obvious new vessels regression and the other group showing poor regression after PRP.

Results: Marked reduction in amplitude and delay in implicit time were observed in all patients ($P < 0.05$). The results also showed larger reduction of amplitude and delay in implicit time in b-wave than a-wave ($P < 0.05$). There were no significant differences in ERG parameter changes after PRP between the group showing obvious new vessel regression and the group showing poor new vessel regression after PRP ($P > 0.05$).

Conclusion: PRP in diabetic retinopathy patients may affect not only the outer retina but also the cells within the inner nuclear layer, causing changes in ERG parameters. However, ERG was not a good indicator for representing the amount of new vessel regression in PDR.

Keywords: Diabetic retinopathy; Electroretinography; Photocoagulation

INTRODUCTION

Proliferative diabetic retinopathy (PDR) is one of the major causes of blindness and its prevalence has been increased in both developing and developed countries. Panretinal photocoagulation (PRP) has been shown to be effective in reducing the incidence of severe visual loss in patients with proliferative diabetic retinopathy. Since the time when Meyer-Schwickerath first developed xenon photocoagulator in 1959 [1], many clinicians have tried to use different kinds of laser for the treatment of diabetic retinopathy. In 1969, Beetham et al. [2] reported the regression of new vessels occurring after broad laser photocoagulation of retina without direct photocoagulation on new vessels, and assumed that angiogenic factors released from ischemic retina caused neovascularization in diabetic retinopathy. Furthermore, to evaluate the effectiveness of PRP, Diabetic Retinopathy Study (DRS) [3,4] performed randomized prospective study in 1970s and proved that PRP lowered the occurrence of severe visual loss. Several studies also revealed that the laser photocoagulation has effects on preventing and treating diabetic macular edema, and PDR with high-risk characteristics [5,6].

Electroretinogram (ERG) reflects retinal activity as a mass response and is generally used as an objective index of retinal function. The function of inner and outer retinal layer can be analyzed from the amplitude and implicit time of different parameters of ERG. In this study, we have used ERG to evaluate the changes in the function of retina before and after PRP, and its role as an indicator for new vessel regression after PRP.

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MATERIALS AND METHODS

1. Subjects

The retrospective study was performed in 58 eyes of 29 patients who underwent panretinal photocoagulation for proliferative diabetic retinopathy. Patients with the following conditions were excluded: any type of glaucoma, rubeosis iridis, significant media opacity, any history of intra-ocular surgery except cataract surgery, previous retinal laser therapy, and patients with combined retinal detachment, and history of any systemic conditions other than diabetic mellitus.

2. Photocoagulation

PRP was performed with Novus 2000 argon laser photocoagulator (Coherent, Palo Alto, CA, USA) by one of the authors (Y.H.O). Pre-laser pupillary dilation and anesthesia was achieved with combination of tropicamide 1% drop for 3 times with 5-minute interval, 30 minutes before beginning of laser, and proparacaine 0.5% drop (Alcaine; Alcon, Fort Worth, TX, USA) for 3 times with 5-minute interval 15 minutes before laser. Wide-field contact lens (Volk SuperQuad 160 Panfundus lens; Volk Co., Mentor, OH, USA) was applied to the cornea with 1% methylcellulose gel. Scattered PRP with equal burn distribution was performed with following parameters: power setting of 200 to 800 mW, spot size of 100 to 500 μm, duration of 0.1 to 0.15 seconds. Laser energy was adjusted to achieve moderate whitening on the retina. An average of 1,428 applications per eye was done, divided into three to five sessions.

3. Electroretinogram

The ERG was performed using UTAS-E2000 System (LKC technologies, Gaithersberg, MD, USA) before and after PRP. The recording of ERG was performed 2 weeks before treatment and 2 months after treatment. The recordings of rod response, maximal combined response, oscillatory potentials, single-flash cone response, and 30 Hz flicker response were obtained according to the standard of International Society for Clinical Electrophysiology of Vision (ISCEV) [7,8].

All exams were performed in a shielded room to avoid noise and vibration. Subjects were informed about the test procedures, and pupils were fully dilated with 1% tropicamide and 2.5% phenylephrine. After the pupil dilation, subjects were dark adapted for 20 minutes. Topical anesthesia, 0.5% proparacaine was instilled and Burian-Allen contact-lens electrode was placed on the cornea with 1% methylcellulose gel to prevent comeal damage. Reference and ground electrodes were placed on the middle of the forehead and on the ear lobe, respectively. ERG recordings were performed in all patients according to the ISCEV standard. Amplitude and implicit time were measured on a display monitor with manual cursor adjustment. All procedures were conducted by one examiner, and choosing the peak of wave was also performed by same examiner to minimize the measurement bias.

4. Statistical analysis

The results were compared between the group of 38 eyes with obvious new vessel regression (group 1: mean age, 58.3 years) and the other group of 20 eyes with poor regression of new vessels (group 2: mean age, 51.7 years). The results were statistically analyzed by independent Student t-test using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant. Additionally, the mean changes of a-wave and b-wave amplitude were compared using paired t-test, and the results were compared between the sexes and different age group using independent Student t-test and analysis of variance, respectively.

RESULTS

In this study, 58 eyes of 29 patients who underwent panretinal photocoagulation for proliferative diabetic retinopathy were enrolled retrospectively. Twenty-nine enrolled patients consisted of 17 male and 12 female patients, and the mean age was 59.9 ± 18.4 years (Table 1). The results of ERG parameters before and after PRP are summarized in Table 2. A marked reduction in amplitude and delay in implicit time were observed in all patients ($P < 0.05$), and the amplitude of b-waves were more significantly reduced than the amplitude of a-waves ($P < 0.05$) in maximal combined response and cone response.

There were no significant differences between the two groups in the amount of changes in ERG parameters after PRP ($P > 0.05$). The group 1, which showed obvious regression of new vessels, demon-

Table 1. Age and sex distribution of subjects in this study

	No. (%)	Mean age ± standard deviation (yr)
Male	17 (57.5)	58.8 ± 17.3
Female	12 (42.5)	61.4 ± 19.7
Total	29 (100.0)	59.9 ± 18.4

Table 2. Mean value and standard deviation of electroretinogram parameters measured before and after panretinal coagulation

Response	Parameters	Before PRP			After PRP		
		Group 1	Group 2	Total	Group 1	Group 2	Total
Rod response	B-wave amplitude (μV)	131.8±27.0	114.9±37.0	125.6±42.0	54.6±19.0	45.3±23.0	51.1±28.0
	Implicit time (ms)	116.1±6.0	122.6±12.0	118.7±13.0	119.3±5.0	125.4±15.0	121.2±19.0
Maximal combined response	A-wave amplitude	169.0±30.0	164.5±52.0	168.6±49.0	97.5±24.0	98.6±45.0	98.3±43.0
	B-wave amplitude	379.3±52.0	356.9±82.0	377.5±71.0	187.7±46.0	138.4±58.0	168.1±54.0
	B/A ratio	2.4±0.1	2.3±0.8	2.4±0.6	1.9±0.3	1.7±0.6	1.8±0.4
	Implicit time	32.4±4.3	34.3±6.1	32.3±4.0	33.6±3.9	35.2±4.6	34.2±5.1
Oscillatory	Amplitude	75.8±15.0	82±18.0	77.5±31.0	26.3±11.0	35.4±9.0	31.3±10.0
Cone response	A-wave amplitude	28.6±8.0	36.3±58.0	30.0±6.0	16.6±4.0	18.8±8.0	17.3±10.0
	B-wave amplitude	87.2±22.0	91.1±26.0	88.3±31.0	28.9±10.0	41.6±2.0	35.9±21.0
	Implicit time	17.1±1.4	17.3±2.0	17.2±2.0	18.6±1.8	19.7±3.2	19.4±3.2
30 Hz flicker response	Amplitude	68.7±19.0	65.3±24.0	67.3±26.0	34.5±16.0	28.3±17.0	31.9±20.0
	Implicit time	34.6±1.5	32.6±4.3	34.2±3.0	36.2±3.7	34.6±5.4	36.9±4.1

Group 1, obvious new vessel regression; group 2, poor new vessel regression.
PRP, panretinal photocoagulation.

Table 3. Mean changes of electroretinogram parameters after panretinal photocoagulation

Response	Parameters	Patients subgroups		P-value[a]
		Group 1	Group 2	
Rod response	Changes in b-wave Amp (μV)	-77.2±32.0	-69.6±27.0	0.187
	Changes in implicit time (ms)	3.2±1.3	2.8±0.9	0.159
Maximal combined response	Changes in a-wave amplitude	-71.5±26.0	-65.9±28.0	0.170
	Changes in b-wave amplitude	-191.6±52.0	-218.5±83.0	0.214
	Changes in b/a ratio	-0.5±0.2	-0.6±0.3	0.097
	Changes in implicit time	1.2±0.5	0.9±0.2	0.076
Oscillatory	Changes in amplitude	-49.5±12.0	-46.6±17.0	0.431
Cone response	Changes in a-wave amplitude	-12.0±3.6	-17.5±5.4	0.079
	Changes in b-wave amplitude	-58.3±17.0	-49.5±23.0	0.278
	Changes in implicit time	1.5±1.1	2.4±1.2	0.086
30 Hz flicker response	Changes in amplitude	-34.2±18.0	-37±21.0	0.384
	Changes in implicit time	1.6±0.7	2.0±1.1	0.269

Group 1, obvious new vessel regression; group 2, poor new vessel regression.
[a]Tested by paired t-test.

strated marked changes in b-wave amplitude and implicit time of rod response, a-wave amplitude and b-wave implicit time of maximal combined response, oscillatory potentials, and b-wave amplitude of cone response. On the other hand, group 2 revealed marked changes in b-wave amplitude of maximal combined response, a-wave amplitude and b-wave implicit time of cone response, b/a ratio, and amplitude and implicit time of 30 Hz flicker. The parameters of ERG did not show any corresponding changes regarding to the amount of regression of new vessels, and there were no statistically significant differences between the two groups ($P>0.05$) (Table 3). Also, the ERG parameters were not significantly different between the sexes ($P>0.05$) (Table 4), and the parameters from different age groups also did not show any statistical differences ($P>0.05$) (Table 5).

Table 4. The comparison of mean values and standard deviation of electroretinogram parameters between male and female

Response	Parameters	Sexes		P-value[a]
		Male	Female	
Rod response	B-wave amplitude (μV)	113.8±26.0	109.9±22.0	0.237
	Implicit time (ms)	120.1±9.0	122.6±13.0	0.331
Maximal combined response	A-wave amplitude	121.7±13.0	119.5±23.0	0.270
	B-wave amplitude	226.7±34.0	234.7±54.0	0.384
	B/A ratio	2.1±0.5	2.3±0.3	0.097
	Implicit time	30.4±3.7	31.1±5.1	0.086
Oscillatory	Amplitude	82.4±33.0	80.2±28.0	0.079
Cone response	A-wave amplitude	33.6±13.0	32.1±12.0	0.384
	B-wave amplitude	75.1±32.0	73.3±35.0	0.278
	Implicit time	16.3±4.5	17.3±3.5	0.269
30 Hz flicker response	Amplitude	60.6±12.0	61.3±19.0	0.384
	Implicit time	34.3±5.5	33.6±7.6	0.517

[a]Tested by Student t-test.

Table 5. Mean values and standard deviation of electroretinogram parameters measured according to age

Response	Parameters	Age (yr)					P-value[a]
		30-39	40-49	50-59	60-69	>70	
Rod response	B-wave amplitude (μV)	120.8±21.0	109.9±27.0	121.6±32.0	105.6±17.0	103.3±17.0	0.517
	Implicit time (ms)	107.1±7.0	118.6±15.0	119.7±16.0	121.3±17.0	127.4±18.0	0.615
Maximal combined response	A-wave amplitude	131.0±17.0	141.3±35.0	121.5±39.0	118.3±27.0	107.3±25.0	0.591
	B-wave amplitude	256.3±42.0	289.9±67.0	232.5±31.0	218.7±35.0	197.4±76.0	0.517
	B/A ratio	2.2±0.3	2.3±0.5	2.2±0.6	2.3±0.5	1.9±0.8	0.691
	Implicit time	28.4±3.3	31.3±6.1	32.7±6.0	34.3±4.9	35.8±3.2	0.415
Oscillatory	Amplitude	85.4±35.0	82.2±28.0	80.5±21.0	80.3±19.0	78.4±18.0	0.517
Cone response	A-wave amplitude	38.6±16.0	36.1±18.0	33.5±17.0	34.6±7.0	28.8±12.0	0.133
	B-wave amplitude	82.2±32.0	78.1±29.0	72.3±39.0	73.9±20.0	67.6±13.0	0.195
	Implicit time	15.1±3.2	16.3±3.5	18.2±2.3	19.6±3.5	19.9±3.7	0.317
30 Hz flicker response	Amplitude	65.3±15.0	67.3±22.0	63.3±16.0	59.5±13.0	55.2±13.0	0.391
	Implicit time	34.6±2.5	35.6±4.6	34.5±3.5	33.9±3.7	36.6±4.4	0.513

[a]Tested by analysis of variance test.

DISCUSSION

There have been several studies on the effect of laser photocoagulation on neovalscularization in PDR patients. Meyer-Schwickerath [1] reported the result of laser photocoaulation for diabetic retinopathy using xenon arc laser and noticed new vessels not directly photocoagulated also regressed spontaneously, and concluded that laser photocoagulation has a regression effect on neovascularization in PDR patients. However, there have been many controversies concerning the Meyer-Schwickerath's hypothesis. DRS, established in 1971 and supported by National Eye Institute, reported that laser photocoagulation was an effective treatment for diabetic retinopathy and reduced the occurrence of severe visual loss in any stage of diabetic retinopathy, but was not effective in early PDR and non-proliferative diabetic retinopathy (NPDR) group [3,4]. In Early Treatment Diabetic Retinopathy Study (ETDRS), patients who received early laser treatment in one eye and delayed laser photocoagulation in the other were observed for 3 to 8 years [9,10]. They concluded that scattered laser photocoagulation was not indicated for mild to moderate NPDR, but should be considered when diabetic retinopathy approaches to the high-risk stage and should not be delayed when signs of high-risk stage is present. The intention of PRP is to destroy a substantial portion of the peripheral retina in order to reduce the difference between oxygen demand and oxygen supply, thereby reducing the stimulus for neovascularization. Also, side effects of PRP should be well considered before starting the treatment, which include macular edema [11], decreased visual field [12,13], visual loss [14,15], and color vision changes [16].

Electroretinogram is the recording process of a diffuse electrical response generated by neural and non-neuronal cells within the retina. The response occurs as the result of light-induced changes in the transretinal movements of ion, principally sodium and potassium, into the extracellular space. In ERG recordings, a-wave represented activity of photoreceptor while b-wave represented that of Muller cell and bipolar cell, and there have been several different opinions about changes in amplitudes of these waves occurring after PRP. The most evident consequence of PRP on ERG recordings is a decrease in peak amplitudes, more marked for scotopic than for photopic responses. This result is predictable, since panretinal laser treatment destroys a large portion of the peripheral retina, in which the majority of rod system is located. A previous report showed an equal depression in scotopic and photopic components after PRP [17].

Several studies have reported that a-wave was reduced more than b-wave after PRP, indicating that laser photocoagulation primarily destroyed photoreceptors than inner retinal layer [18]. Perlman et al. [19] reported that both a- and b-wave were proportionally reduced after PRP, whereas Liang et al. [17] revealed markedly reduced b-wave amplitude after PRP and showed more reduced amplitude of b-waves than that of a-waves, which indicated PRP not only destroyed the outer retinal layer directly photocoagulated, but also affected the inner retinal layer. Consistent with Liang's finding, our study also revealed more greatly reduced amplitude in b-waves when compared to that of a-waves in maximal combined response and cone response.

Frank [12] presented that b-wave amplitudes in ERG were reduced by an average of 40% in a group of 24 eyes those received extensive argon laser PRP for the treatment of proliferative or preproliferative diabetic retinopathy. From these results, he suggested that the photoreceptors in approximately 40% of the retinal area were destroyed by PRP treatments. Ogden et al. [20] performed argon laser and xenon arc PRP on 14 eyes and recorded ERG. They discovered a decrease in ERG amplitude that varied from 10% to 95% among the patients, and also an increase in ERG latency and implicit time in several patients. They suggested that there was a wide variability in the area of retina affected by the treatment and it is possible that adjacent untreated retina may have been affected in some diabetic patients during PRP. When considering such results, greatly reduced amplitudes of ERG parameters after PRP shown in this study were somewhat predictable.

Several previous studies revealed the effect of PRP on the ERG regarding the type of laser. Liang et al. [17] performed ERG on both eyes of 11 diabetic patients before the PRP and one month after the PRP. Each patient had one eye treated with argon laser and the fellow eye treated with the xenon arc laser. The results of ERG, which was performed one month after laser photocoagulation, showed symmetrically reduced amplitude, regardless of the type of laser modality. In this study, we used argon green laser only, therefore could not compare the results regarding the laser types.

There are several antecedent studies comparing the ERG results of pre-treatment and post- treatment, and controversies exist concerning the recovery of retinal function after PRP. Schechner et al. [21] performed argon laser PRP on 10 pigmented rabbits and retinal function was assessed using ERG before and after the laser treatment. They observed gradual recovery, and within 2 months, the ERG responses recovered to the normal pretreatment level. Imai and Iijima [22,23] reported that markedly reduced amplitude and delayed implicit time were observed after one day of PRP, and amplitude showed subtotal recovery while implicit time was significantly delayed after four weeks of PRP. However, Capoferri et al. [24] revealed different results by conducting ERG in 16 PDR patients before PRP, during intervals between the laser sessions, within 36 hours of the final session, and 4 months after its conclusion. The analysis of the obtained result revealed a significant reduction in peak amplitudes of both a- and b-waves in photopic and dark-adapted conditions which appeared as early as during the interval between the multiple sessions and further ERG results did not show significant change during subsequent follow-ups. In this study, the results of the ERG parameter showed consistent finding with Capoferri's study. The result of this study presented no recovery of ERG parameters after 2 months of PRP (data not shown). Several possibilities may explain these different ERG results observed in similar studies. First, laser treatment performed in studies showing recovery of ERG parameters after several months of PRP may have not induced enough retinal pigment epithelial damage, leading to recovery of pigment epithelium after certain period of time. Such results may have been caused by the different settings of laser application used in each study, resulting in inconsistent retinal damages. Second, studies with results of ERG recovery after PRP have used pigmented rabbits as the study subject, while studies with no ERG recovery enrolled patients instead of animals. Such differences may have yielded inconsistent ERG results, since human retina and rabbit retina have different ability of recovering from retinal insults.

In this study, we tried to analyze the effect of the PRP on the retina and compare the function of retina between regressed and non-regressed cases. A significant reduction in amplitude and delay in implicit time were observed in all patients, and b-waves were more reduced than the a-waves in maximal combined response and cone response. There were no significant changes in ERG parameters associated with the amount of new vessel regression. These results suggest that ERG is not an appropriate indicator for detecting the amount of neovascularization, and PRP is an aggressive treatment modality that affects not only the laser sites, but also the entire retina. Considering the data of this study, PRP may restore the anatomical integrity and induce new vessel regression, but can cause irreversible functional impairment of ablated peripheral retina.

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