TRANSCORNEAL ELECTRICAL STIMULATION THERAPY MAY HAVE A STABILIZATION EFFECT ON MULTIFOCAL ELECTRORETINOGRAPHY FOR PATIENTS WITH RETINITIS PIGMENTOSA

DIDEM DIZDAR YIGIT, MD, MEHMET ORKUN SEVIK, MD, ÖZLEM ŞAHIN, MD

Purpose: To assess the effects of transcorneal electrical stimulation (TES) on several measures of visual function in retinitis pigmentosa.

Methods: This prospective, randomized, fellow-eye–controlled study includes 30 eyes of 15 patients with retinitis pigmentosa. Each patient's eyes were randomly selected as treatment (TE) and control eye (CE), and 30 minutes/week TES was applied for 6 months. Patient evaluations were performed before and after TES, including comprehensive ophthalmological examination, visual fields, full-field and multifocal electroretinography, microperimetry, and optical coherence tomography. All parameters were compared before and after TES and between TE and CE.

Results: After TES, the mean signal amplitudes in multifocal electroretinography were stabilized in TE. The mean signal amplitudes in CE decreased in every ring, reaching significance in the fifth ring (847.15 ± 393.94 and 678.77 ± 282.66 nV, $P = 0.039$, before and after TES, respectively). The changes in the mean signal amplitudes of TE and CE were −0.38 ± 295.53 and −185.15 ± 332,62 nV in second ($P = 0.046$), 36.69 ± 326.4 and −143.38 ± 317,41 nV in fourth ($P = 0.028$), and −17.46 ± 333.07 and −168.38 ± 297,14 nV in fifth rings ($P = 0.046$), respectively. The decrease in the mean signal amplitudes between 2° and 20° midperipheral retina was significantly less in TE (−33.59 ± 225,1 nV) than CE (−205.56 ± 345.1 nV) ($P = 0.011$). There were no significant changes in other parameters.

Conclusion: The progression in multifocal electroretinography might be stabilized with TES. Further studies with larger sample sizes and a longer follow-up are needed to conclude that TES reduces retinitis pigmentosa progression.

RETINA 42:923–933, 2022

Retinitis pigmentosa (RP) is characterized by progressive, peripheral vision loss because of impairment of photoreceptor cells and retinal pigment epithelium.[1] There is no established therapy; therefore, even legal blindness might be seen in advanced cases. Several studies assessing gene and stem cell therapies, various supplements, platelet-rich plasma therapy, retinal prosthesis, and transcorneal electrical stimulation (TES) therapy were conducted for halting or slowing the disease process.[2–8]

Transcorneal electrical stimulation's beneficial effects in amblyopia, amaurosis, chorioretinitis, glaucoma, and optic atrophies have been speculated since 1873.[1] It is a noninvasive method to activate retinal "dormant" cells. The mechanism has not been clarified, yet several hypotheses are suggested: growth factor release and photoreceptor survival, neuroprotection through retinal blood flow regulation, and regulation of voltage-gated ion channel activity.[9–11]

The safety, tolerability, and effectiveness of TES therapy were assessed for several clinical entities.[3–6] An initial study has shown that TES was safe in 16 patients with RP after weekly 30-minute stimulation for 6 months.[4] There was a significant improvement in the visual field (VF) area and scotopic b-wave amplitude of the patients stimulated with 150% of their electrical phosphene thresholds (EPTs). The same study group's follow-up study did not reach the same

results but revealed improvement in photopic b-wave amplitudes.[5] Another open-label, multicenter research in the United Kingdom has denoted TES's safety in patients with RP after 6 months of weekly stimulation.[3] The visual function tests, such as VF and microperimetry (MP), did not reveal any significant difference between the treated and control eyes (CEs). Transcorneal electrical stimulation might still be an attractive potential therapy option because of its safety and relative ease of application.

This study aimed to assess TES's effects on several subjective and objective measures of visual function and its safety when used as a treatment modality for patients with RP.

Material and Methods

Patient Selection

The study protocol was approved by the Institutional Review Board of Marmara University School of Medicine, and it was financially supported by the Scientific Research Project Commission of Marmara University School of Medicine, Istanbul, Turkey (project no: SAG-A-120418-0151). The study was conducted within the tenets of the Declaration of Helsinki, and written informed consent was provided from all the patients or patients' legal guardians.

This prospective, randomized, fellow-eye–controlled study included 30 eyes of 15 patients with RP whose diagnosis was confirmed by electrophysiological tests and recruited from the retina department of Marmara University Hospital, Istanbul, between August 2013 and March 2019. The inclusion criteria were an age from 10 years to 50 years, best-corrected visual acuity (BCVA) better than 0.7 logarithm of the minimum angle of resolution (6/30 Snellen), recordable VF and MP results, and patient cooperation. The exclusion criteria were any ocular diseases such as diabetic retinopathy, choroidal neovascularization, exudative age-related macular degeneration, corneal opacity, dense cataract, glaucoma, dry eye disease, history of any ocular surgery, and history of systemic diseases causing retinopathy.

From the Department of Ophthalmology, School of Medicine, Marmara University, Istanbul, Turkey.

Supported by the Scientific Research Project Commission of Marmara University School of Medicine, Istanbul, Turkey (Project No: SAG-A-120418-0151).

Paper presented at Euretina (European Society of Retina Specialists) 2020, Virtual, October 2–4, 2020.

None of the authors has any conflicting interests to disclose.

M. Orkun Sevik and Ö. Şahin contributed equally.

Reprint requests: Didem Dizdar Yigit, MD, Department of Ophthalmology, School of Medicine, Marmara University, Fevzi Çakmak, Muhsin Yazıcıoğlu Cd No:10, Pendik, Istanbul 34899, Turkey; e-mail: drdidemdizdar@gmail.com

Study Design

Patients' eyes were randomly selected into the treatment eye (TE) group by an online random integer generator (www.random.org/integers), and the fellow eyes were taken as the CE. The primary outcome measures were electrophysiological tests and visual function tests as VF and MP. The places of the parentheses are mixed. The sentence should be as written below: At baseline, various procedures including a comprehensive ophthalmologic examination, spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Germany), 30-2 and 10-2 VF (HFA II; Carl Zeiss, USA), MP (MAIA, Centervue, Italy), full-field (ff-), and multifocal (mf-) electroretinography (ERG; Metrovision, MonPackOne, France) were performed in order. At the second visit, EPT determination and the first TES session were performed. Transcorneal electrical stimulation was administered weekly for 30 minutes for 6 months. Subjects were reevaluated with the same examination procedures in the same order after 6 months. Any possible adverse effects were explained, and informed consent was obtained each week before TES.

The technicians who performed autorefractometry, SD-OCT, VFs, MP, ff-ERG, and mf-ERG were masked. The doctor evaluating ophthalmologic examination and EPT was not blinded.

Electrical Stimulation and Determination of Electrical Phosphene Thresholds

The stimulation system consisted of three elements: OkuStim, OkuEl, and OkuSpex (Okuvision GmbH, Reutlingen, Germany). After 20 minutes of dark adaptation, a single-use Dawson–Trick–Litzkow electrode OkuEl was placed onto a metallic spectacle-like frame, OkuSpex. The electrode was then put into the inferior fornix, and the counter electrode was placed onto the patient's forehead after being cleaned with 70% isopropyl alcohol. For the assessment of EPTs, an alternative forced-choice method was used.[12] A complete dark environment during EPT assessment is essential to perceive very slight phosphenes and the accuracy of the procedure. The subject was given a prompt when beginning. The stimulation parameters were pulses of 5 milliseconds positive and 5 milliseconds negative deflection with a frequency of 20 Hz. The current amplitude was started from 0.02 mA and asked the subject to tell whether they "feel" the pulses. The current is slowly augmented by 0.01 mA to 0.05 mA until a maximum level of 1.0 mA. When the patient names correctly the number of pulses

at least three times, the individual threshold was determined. The threshold was rechecked three times using OkuStim software (V.1.4.4.0), and the mean was obtained. Every patient's EPT was recorded on a Universal Serial Bus stick, and the same individual treatment parameters were used in all visits. The delivered current during therapy was 200% of the patient's EPT.

Transcorneal electrical stimulation therapy was administered in a quiet, dimly lighted room where the patients lay down with their heads positioned at a 45° angle. The stabilization of the system was easily maintained in this position. During therapy, the device measured real-time resistance in the electrode and gave a warning sign if it exceeded 15,000 Ω. In this case, the electrodes and positioning were checked.

Electroretinography

After 30 minutes of dark adaptation and pupil dilatation with the application of one drop of tropicamide 1% (Tropamid, Bilim İlaç, Turkey), phenylephrine 2.5% (Mydfrin, Alcon), and proparacaine hydrochloride 0.5% (Alcaine, Alcon), ERG jet electrodes were placed. The ff-ERGs were recorded according to International Society for Clinical Electrophysiology of Vision standards.

Multifocal electroretinographies were recorded after pupil dilatation. The stimulated retinal area was subtended in an area of 60° × 55°; 61 hexagon stimulants were used with alternating black (5 cd/m^2) and white (100 cd/m^2) stimulants. The concentric rings were analyzed according to International Society for Clinical Electrophysiology of Vision standards (Figure 1).[13] The amplitude and latencies of P1, N1, and N2 components were recorded for every ring. The mean signal amplitudes (MSAs) of mf-ERG in the macula (central 0°–2°) and the peripheral (2°–20°) signal amplitude changes were evaluated separately (Figure 2).

Microperimetry

The MP test, combining scanning laser ophthalmoscopy and automatized perimeter with eye-tracking technology, was recorded without pupil dilatation after 30 minutes of dark adaptation. During the test protocol, 37 retinal points were stimulated according to the stairway strategy, and the mean threshold sensitivities were noted in 2°, 6°, and 10° concentric VF areas (Figure 3).

The regional sensitivity was assessed with the topographical method used by Iftikhar et al.[14] In this method, the test area is divided into 2 regions as central (16 test points) and peripheral (52 test points), and the changes in those 2 regions were evaluated separately. Although our device did not have the software needed, the mean of the central 13 points (0°–2°) and the mean of the remaining 24 points (2°–10°) were calculated arithmetically (Figure 4).

The mean retinal sensitivities in the first ring (central 2°), second ring (6°), and third ring (10°) were obtained by calculating every ring's arithmetical mean for TE and CE. The changes in these sensitivities after therapy were also compared.

Optical Coherence Tomography and Visual Field Testing

Spectral domain optical coherence tomography images were taken after pupil dilatation at the same time of the day by the same technician. The fast macula protocol was used to obtain the retinal scans, with an automatic real-time mean value of 9, which acquires 25 horizontal lines (20° × 20° area). The scanning was made in radial line mode. The central foveal thickness (CFT) is defined as the distance from the inner limiting membrane to the outer border of the retinal pigment epithelium through the automatic segmentation algorithms of the Spectralis software. The visual field evaluated with the SITA standard test, with standard Goldmann III stimulus with a background luminance of 10 cd/m^2. The test was conducted from a 33-cm distance with spectacle correction, without pupil dilatation. The test results were evaluated as acceptable if fixation losses were less than 25% and false-positive and false-negative responses were less than 15%.

Statistical Analysis

The statistical analysis was performed using the Number Cruncher Statistical System 2007 (NCSS 2007; Kaysville, UT) and Statistical Package for Social Sciences for Windows version 20.0 (SPSSv20.0; IBM, NY). All descriptive data are presented as mean, SD, median, minimum (min), maximum (max), and 95% confidence interval. Parametric tests and nonparametric tests were applied depending on the distribution of the data. The change within one group was marked as "Δ," and the significance of the differences evaluated with the Wilcoxon signed-rank test between the change within groups was labeled "Δ test value *P*." The Mann–Whitney *U* test was used to assess the significance of differences among groups. The correlations were evaluated by Spearman correlation analysis. Statistical significance was regarded as a *P* value of less than 0.05.

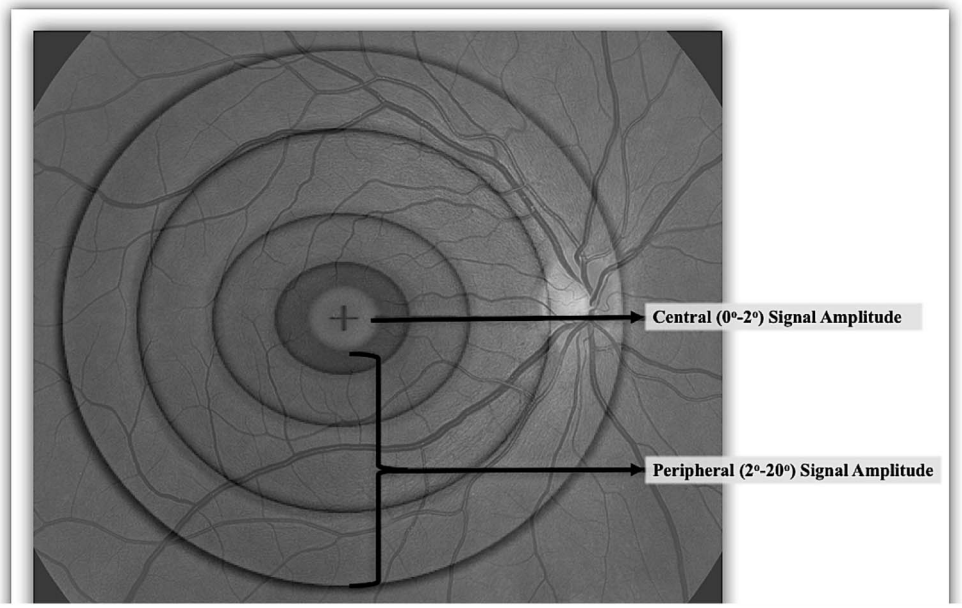

Fig. 1. The schematic view of mf-ERG rings and related fundus areas.

Results

Thirteen of 15 patients (87%) completed the TES therapy and the follow-up period. The mean age of the patients was 25.92 ± 10.25 (min–max, 13–42) years. The demographic and clinical characteristics of the patients are given in Table 1.

The mean BCVA in TE was 0.16 ± 0.15 (Snellen equivalent 20/29) (min–max; 0–0.5), whereas the mean BCVA in CE was 0.17 ± 0.19 (Snellen equivalent 20/30) (min–max; 0–0.7) in logarithm of the minimum angle of resolution ($P > 0.05$). After TES therapy, the BCVA changed by −0.03 ± 0.09 (Snellen equivalent 20/21) and −0.03 ± 0.11 logarithm of the minimum angle of resolution (Snellen equivalent 20/21) in the TE and CE, respectively ($P > 0.05$).

The mean spherical equivalent of the patients was −2.33 ± 2.55 diopters (D). The patients with a family history have more myopic refraction (−4.04 ± 1.58 D; min–max:−6.00 to 1.50 D) than the patients who not have a family history (−0.63 ± 2.18 D; min–max:−4.00–2.75 D) ($P < 0.05$).

The mean EPT of the treated eyes was 0.283 ± 0.22 mA (min–max: 0.16–0.40 mA). There was no correlation between EPTs, BCVA, mfERG, MP, and VF changes after therapy.

The mf-ERG MSA of the first ring (0°–2°), second ring (2°–5°), third ring (5°–10°), fourth ring (10°–15°),

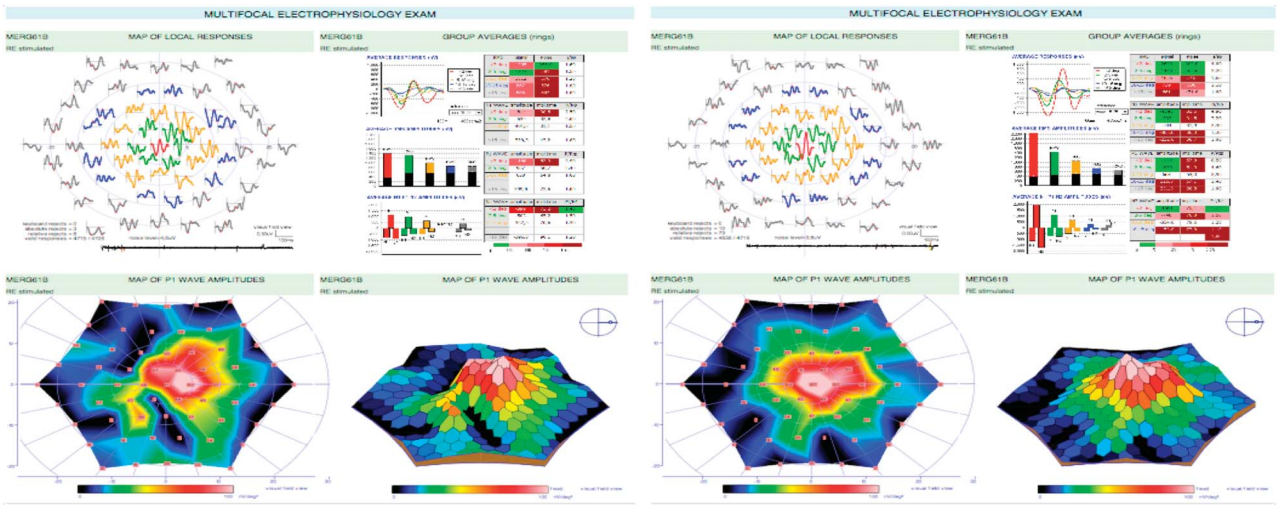

Fig. 2. The mf-ERG results of one of the TEs before and after 6 months of TES therapy.

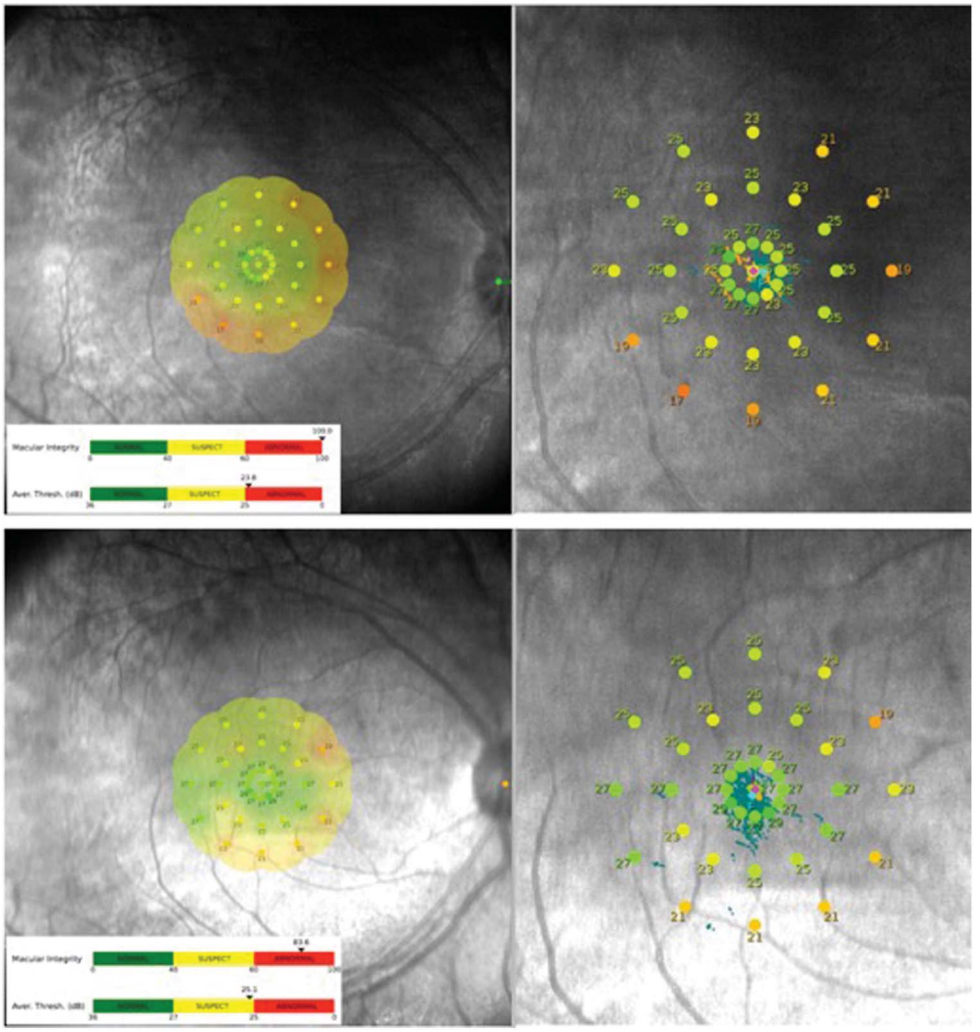

Fig. 3. The MP results of the same patient in Figure 2, before and after 6 months of TES therapy.

and fifth ring (15°–20°) of the TE and CE before and after therapy is given in Table 2.

The MSA in the first, second, third, and fourth rings did not show statistically significant changes after 6 months in the CE ($P > 0.05$); however, the decrease in the MSA in the fifth ring reached statistical significance ($P = 0.039$). Conversely, the MSA in the first, second, third, fourth, and fifth rings did not show statistically significant changes after 6 months in the TE ($P > 0.05$).

When the changes of mf-ERG results in the CE evaluated, it was seen that the MSA in all rings were decreased. In the second ring, the decrease in the CE's MSA showed statistical significance compared with the decrease in the TE (−185.15 ± 332.62 nV vs. −0.38 ± 295.53 nV, respectively, $P = 0.046$). The mean signal amplitude decrease in the CE and TE was −143.38 ± 317.41 nV and 36.69 ± 326.4 nV in the fourth ($P = 0.028$) and −168.38 ± 297.14 nV and −17.46 ± 333.07 nV in the fifth ($P = 0.046$) rings, respectively (Table 2, Figure 5).

After TES therapy, peripheral (2°–20°) signal amplitude decrease in mfERG of the CE was greater than the decrease of the TE in the total signal amplitude (−205.56 ± 345.1 nV vs. −33.59 ± 225.1 nV, respectively, $P = 0.019$). Peripheral total and N1, P1, and N2 wave signal amplitude decrease of the TE and CE are given in Table 3.

The mean sensitivity in MP test before and after TES therapy did not change significantly in TE (19.35 ± 7.84 and 19.13 ± 6.95 dB, respectively, $P > 0.05$) and CE (18.41 ± 7.47 and 18.3 ± 6.76 dB, respectively, $P > 0.05$).

The mean central area sensitivity in MP was higher than the peripheral area sensitivity in the TE and CE. The central and peripheral sensitivity changes did not reach significance in both groups. When the results were evaluated in rings in CE, a decreasing trend in the third ring was noted compared with TE. However, changes in mean retinal sensitivities in the first, second, and third rings did not reach significance ($P > 0.05$) (Table 4).

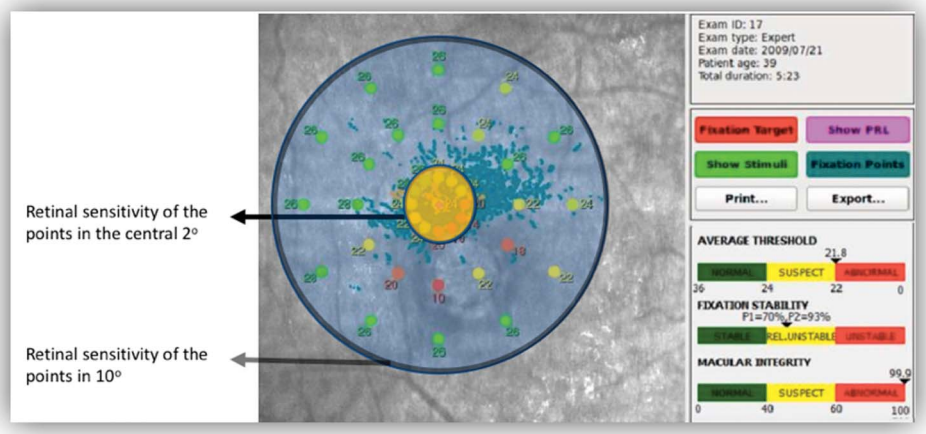

Fig. 4. The microperimetry test results. The central 13 points (0°–2°) and the remaining 24 points (2°–10°).

In the Spearman correlation analysis, a low positive correlation was found between the peripheral (2°–10°) MP sensitivity and the mf-ERG P1 amplitude from 2° to 10° ($P = 0.013$; r = 0.404) (Figure 6). Although there was no correlation between the mean sensitivity in MP and BCVA and CFT, there were a low negative correlation between central area sensitivity and BCVA ($P = 0.03$; r = −0.343) and a low positive correlation between central area sensitivity and CFT ($P = 0.012$; r = 0.438).

The CFT before and after TES did not change significantly in TE (232.64 ± 53.43 and 231.82 ± 52.41 μm, respectively, $P > 0.05$) and CE (227.45 ± 57.38 and 226.36 ± 55.57 μm, respectively, $P > 0.05$).

The analysis of MD and Pattern standard deviation of the 30-2 and 10-2 VFs between TE and CE and before and after TES showed no statistical significance (Table 5).

TES therapy was tolerated well. Two patients reported a mild foreign body and stinging sensation, which resolved 24 hours after the prescription of artificial tears. It was noted that the patients did not develop epitheliopathy. One patient defined mild electrical sensation during the therapy, radiating to the incisors on the therapy side. This effect started on the third week of the therapy and completely disappeared in 1 month. This complication did not appear again, so the therapy was not interrupted. No other adverse events were encountered.

Discussion

The main objective in therapeutical research for RP is to find new ways to function instead of the degenerated cells or to slow down apoptosis. Compared with the other probable treatment options, TES has the potential to be prevalently used because of its low-risk profile, easy use, and noninvasiveness.[3–5] In this study, the TES's effects on visual functions and its safety profile were evaluated in patients with RP.

Table 1. The Demographic and Clinical Features of the Patients

Age, year	
Median (min–max)	28 (13–42)
Mean ± SD	25.92 ± 10.25
Sex, n (%)	
Female	4 (30.8)
Male	9 (69.2)
Family history, n (%)	
Positive	5 (38.5)
Negative	8 (61.5)
Consanguineous marriage, n (%)	
Positive	5 (38.5)
Negative	8 (61.5)
Inheritance pattern, n (%)	
Autosomal recessive	5 (38.5)
Sporadic	8 (61.5)
BCVA, LogMAR	
TEs	
Median (min–max) (Snellen equivalent)	0.10 (0–0.5) (20/25)
Mean ± SD (Snellen equivalent)	0.16 ± 0.15 (20/29)
CEs	
Median (min–max) (Snellen equivalent)	0.10 (0–0.7) (20/25)
Mean ± SD (Snellen equivalent)	0.17 ± 0.19 (20/30)
P-value	0.655*
Refractive error, D	
Min–max	−6.00 ± 2.75
Mean ± SD	−2.33 ± 2.55

Sample size, n = 13.
*Wilcoxon signed-rank test.
logMAR, logarithm of the minimum angle of resolution.

Table 2. The mf-ERG MSA in the Treatment and CEs Before and After TES Therapy With the Changes After 6 Months of TES Therapy

Signal Amplitude (nV)	TEs			CEs			Δ Test Value
	Before	After	Change	Before	After	Change	*P*
1st ring							
Median (min–max)	1,048 (270 to 2053)	1,078 (227 to 2,629)	99 (−730 to 1,281)	1,017 (371 to 1,692)	814 (124 to 2,301)	114 (−1,232 to 894)	*0.173
Mean ± SD	1066.92 ± 502.23	1242.92 ± 735.62	176 ± 595.13	1055.69 ± 475.37	965.69 ± 704.04	−90 ± 634.91	
2nd ring							
Median (min–max)	804 (276 to 1,323)	649 (317 to 1,659)	−20 (−433 to 7,169)	791 (353 to 1,682)	752 (267 to 1,361)	−282 (−665 to 495)	*0.046†
Mean ± SD	812.23 ± 267.88	811.85±436.11	−0.38 ± 295.53	956.46 ± 431.73	771.31 ± 370.27	−185.15 ± 332.62	
3rd ring							
Median (min–max)	702 (397 to 1,516)	569 (335 to 1,496)	−81 (−789 to 553)	697 (338 to 1762)	690 (232 to 1,169)	−155 (−771 to 522)	*0.133
Mean ± SD	760.38 ± 282.22	733.85 ± 364.27	−26.54 ± 340.57	856.77 ± 439.55	706.69 ± 319.39	−150.08 ± 355.89	
4th ring							
Median (min–max)	680 (429 to 935)	643 (300 to 1,491)	−89 (−260 to 773)	651 (350 to 1,611)	788 (271 to 1,063)	−179 (−621 to 655)	*0.028†
Mean ± SD	696.15 ± 146.43	732.85 ± 360.67	36.69 ± 326.4	833.15 ± 419.85	689.77 ± 303.13	−143.38 ± 317.41	
5th ring							
Median (min–max)	713 (322 to 1,185)	647 (279 to 1,600)	−87 (−527 to 669)	783 (367 to 1,621)	724 (310 to 1,186)	−180 (−616 to 528)	*0.046†
Mean ± SD	714.62 ± 225.97	697.15 ± 378.81	−17.46 ± 333.07	847.15 ± 393.94	678.77 ± 282.66	−168.38 ± 297.14	

Sample size for each group, n = 13.
*Wilcoxon signed-rank test.
†$P < 0.05$

The mean age of our patients was 25.9 ± 10.0 years. There was no statistically significant correlation with age and BCVA, mf-ERG, VF, and MP results, before and after TES ($P > 0.05$). In the long-term study of Schatz et al, the mean age was younger (46 ± 15 years) than their previous study (54 ± 12 years) about TES's effects on patients with RP.[4,5] They speculated that in a younger population, the therapy might be more beneficial because of the survival of the peripheral rods, yet their results did not support this hypothesis. It might be misleading to explain the severity of degeneration with age, even within families with common genetic backgrounds. Transcorneal electrical stimulation studies have heterogenic populations regarding genetic background. Therefore, among factors affecting the rate of benefit from therapy, age might not be a supportable one.

RP is a heterogeneous group of diseases. Several electrophysiological, psychophysical, and morphologic studies were conducted to reveal the nature of the disease. However, the variability of nature of the disease and the tests constitutes major problems in the progression follow-up.[15]

The EPTs of patients with retinal dystrophies are shown to be higher than those of healthy volunteers.[16] In this study, the mean EPT of TE (0.283 ± 0.22 mA) was comparable with previous works.[5,16] As suggested before, in this study, a tendency in EPT was noted to be higher in patients with lower visual acuity.[16] However, no statistically significant correlation was noted. There was no significant correlation between EPTs and the effects of TES. The stimulation current was set to 200% of participants' individual EPT at 20 Hz as suggested to have beneficial effects and tolerability in previous studies.[5] The primary aim was to use individualized stimulation as previously hypothesized; the more degenerated cells would necessitate more stimulation, whereas the less degenerated retina need less stimulation.[5,17] It was previously noted that stimulation strategy needs more investigation to find the best approach to have a maximal therapeutic effect.

The ff-ERG is considered the gold standard in RP diagnosis.[18] Unfortunately, in this study, the ff-ERG responses were undetectable before and after TES, so the ff-ERG results were not included in the statistical analysis.

Conversely, the mf-ERG gives retinal cells' sensitivity topographically.[13] As RP progresses centripetally, a topographic evaluation might detect progression more sensitively. Some studies claim that the amplitude decrease in mf-ERG indicates the reduction in photoreceptor number and the prolongation of latency indicates the loss of photoreceptor cell function.[19] In the study of Schatz et al,[4] the different rings in mf-ERG results were not analyzed

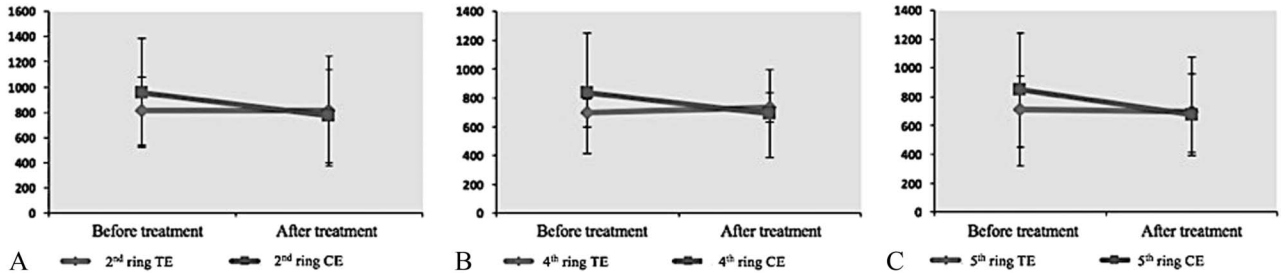

Fig. 5. The changes of the mf-ERG MSA of the treatment and CEs in second (**A**), fourth (**B**), and fifth (**C**) rings before and after 6 months of treatment.

separately. In the 150% EPT group, the change was −1.54 μV (range:−4.12 to 1.05); in 66% group, it was −1.49 μV (range:−3.92 to 0.95), and in the placebo group, it was −0.39 μV (range:−3.1 to 2.32) after 6 weeks ($P > 0.05$). In this study, the mf-ERG results were analyzed and compared according to the topographical rings. After 6 months, the MSA in mf-ERG has decreased in all of the rings in CE. Meanwhile, the amplitudes in TE have decreased less; in fact, in some rings, the amplitudes have increased. This difference between groups reached statistical significance in the second ($P = 0.046$), the fourth ($P = 0.028$), and the fifth ($P = 0.046$) rings. Despite the humble number of the participants and the high SD, compared with CE, a stabilization trend was noted in the results of TE. This trend might be implicating the arrest of the insidious loss of peripheral photoreceptor function, eventually causing VF narrowing which is crucial for the quality of life of a patient with RP. When the mean N1, P1, and N2 waves were evaluated, no statistically significant difference was found between groups before and after TES. The central 0° to 2° in mf-ERG showed no significant change in any groups before and after therapy ($P > 0.05$). Although in the peripheral area (2°–10°), where the progression of the disease process is first detected, the amplitude loss in TE was significantly less than CE ($P = 0.019$). The test–retest reliability is a necessity while assessing the natural history or effects of therapy. In a study comparing the reliability of repeated VF and mf-ERG tests in controls and patients with RP, the SD of the RP subjects was found to be larger than controls.[20] Although the average variability in repeated mf-ERG amplitudes in controls was found to be 1.5 dB, 32% of the patients with RP fell of 99% confidence interval. There were no significant changes in mf-ERG after 3 months. It was indicated that even the test–retest reliability might change among patients, mf-ERG may provide reproducible results as VF.[21]

The MP integrates the real-time fundus images with VF.[22] Studies are supporting that the MP is more reliable than VF in repeated measurements and more sensitive in RP progression detection.[23,24]

After 6 months of TES, the mean retinal sensitivity decrease in MP in the TE was 0.21 ± 1.49 dB and the reduction in the CE was 0.35 ± 1.65 dB. There were no statistically significant differences between groups ($P > 0.05$).

MP results might be interpreted topographically, such as the analysis protocol in mf-ERG. When the

Table 3. The Changes of Peripheral Mf-ERG Signal Amplitudes in the Treatment and CEs After 6 Months of TES Therapy

	The Change Before and After TES Therapy		Δ Test Value
Peripheral Signal Amplitude (nV)	TEs	CEs	*P*
N1 Wave			
Median (min–max)	6.20 (−174 to 366)	−37.50 (−559 to 222)	*0.331
Mean ± SD	2.28 ± 116.4	−61.84 ± 164.4	
P1 wave			
Median (min–max)	−38.00 (−282 to 190)	−92.50 (−677 to 340)	*0.102
Mean ± SD	−33.78 ± 101.1	−109.60 ± 178.9	
N2 wave			
Median (min–max)	−13.35(−461 to 492)	−45.50 (−581 to 391)	*0.089
Mean ± SD	−2.18 ± 170.8	−52.12 ± 204.5	
Total amplitude			
Median (min–max)	−15.60 (−461 to 492)	−61.50 (−677 to 391)	*0.019†
Mean ± SD	−33.59 ± 225.1	−205.56 ± 345.1	

Sample size for each group, n = 13.
*Wilcoxon signed-rank test.
†$P < 0.05$

Table 4. The MP Values in the Treatment and CEs Before and After 6 Months of TES Therapy

	TEs			CEs			Δ Test Value
Thresholds (dB)	Before	After	Change	Before	After	Change	*P*
Average							
Median (min–max)	21 (0 to 27)	20 (0 to 25)	0.45 (−3 to 2)	19 (0 to 28)	20 (0 to 25)	0 (−3 to 4)	*0.859
Mean ± SD	19.35 ± 7.84	19.13 ± 6.95	0.21 ± 1.49	18.41 ± 7.47	18.3 ± 6.76	0.35 ± 1.65	
1st ring							
Median (min–max)	25 (17 to 28)	25 (18 to 27)	0.52 (−4 to 3)	22 (20 to 29)	24 (19 to 27)	0.4 (−1 to 4)	*0.575
Mean ± SD	24.79 ± 3.15	24.65 ± 2.77	0.42 ± 2.08	23.75 ± 2.77	23.64 ± 2.20	0.71 ± 1.66	
2nd ring							
Median (min–max)	24 (19.26)	23 (18 to 26)	0.41 (−2 to 2)	23 (19 to 27)	19 (19 to 26)	0.25 (−3 to 2)	*0.933
Mean ± SD	23.5 ± 2.95	22.85 ± 2.56	0.22 ± 1.28	22.18 ± 2.84	21.42 ± 2.67	0.15 ± 1.68	
3rd ring							
Median (min–max)	19 (1 to 25)	20 (1 to 23)	0.25 (−2 to 4)	18 (1 to 26)	17 (0 to 27)	0.16 (−3 to 1)	*0.092
Mean ± SD	15.47 ± 9.53	15.69 ± 9.29	0.22 ± 1.48	15.06 ± 9.47	14.75 ± 9.53	−0.31 ± 1.35	

Sample size for each group, n = 13.
*Wilcoxon signed-rank test.

visual functions are deeply affected, the basal measurements might be too low and small changes might be missed, which is called the "floor effect."[14,23,24] In a study, 75 eyes of 39 patients with RP were followed up for 1 to 4 years and evaluated with MP and BCVA, and the floor effect is avoided by using 2 methods.[14] In the first method, the test area is divided into 2 regions as central (16 points) and peripheral (52 points), which were evaluated separately. In the second method, the test area is divided into 2 regions as seeing and scotomatous retina. The annual BCVA decrease has not been significant, whereas the mean retinal sensitivity reduction has reached statistical significance ($P < 0.001$). The change of retinal sensitivity was found statistically significant with both methods ($P < 0.001$).

In this study, the retinal sensitivity changes were evaluated with the topographical method. The changes between the TE and the CE were not significant, which might be due to the short follow-up of our study. The peripheral third ring showed a decrease in CE compared with TE, but it did not reach statistical significance, which again might be due to the short follow-up and limited study population.

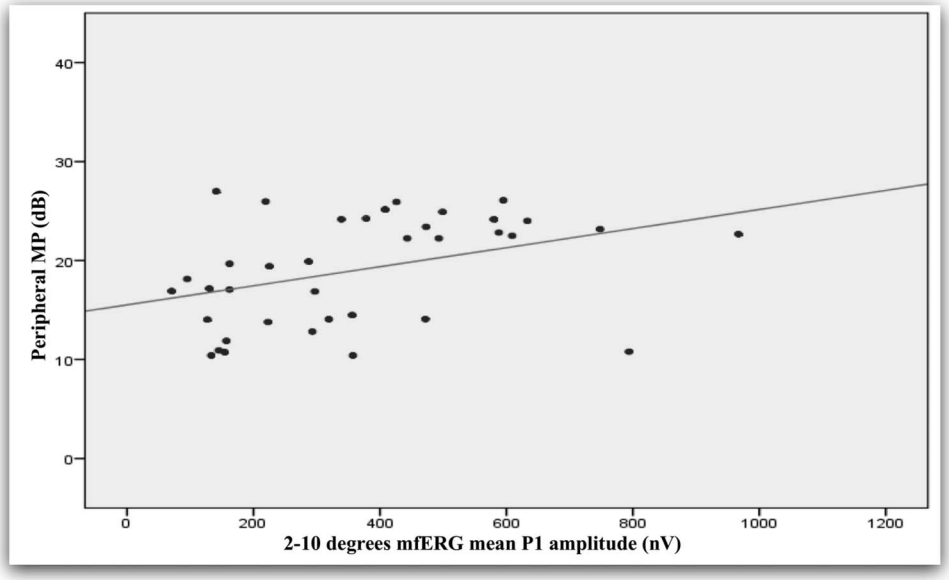

Fig. 6. Spearman correlation analysis of the peripheral (2°–10°) MP sensitivity and the mf-ERG P1 amplitude from 2° to 10° ($P = 0.013$; r = 0.404).

Table 5. The Results and Changes in the VF Test Values Before and After TES Therapy

	TEs			CEs			Δ Test Value
	Before	After	Change	Before	After	Change	*P*
30–2 VF MD (dB)							
Median (min–max)	−21.41 (−32 to −2)	−21.01 (−32 to −14)	−0.02 (−5 to 2)	−22.40 (−31 to −14)	−23.30 (−32 to −13)	0.12 (−2 to 2)	*0.343
Mean ± SD	−20.40 ± 9.04	−22.48 ± 5.83	−0.10 ± 1.98	−22.05 ± 6.25	−22.62 ± 5.62	0.32 ± 1.24	
30–2 VF Pattern standard deviation							
Median (min–max)	10.41 (5 to 15)	10.94 (4 to 15)	0.26 (−1 to 1)	9.33 (5 to 15)	10.91 (5 to 15)	0.09 (−1 to 2)	*0.553
Mean ± SD	10.22 ± 3.60	10.68 ± 3.87	0.40 ± 0.75	9.39 ± 3.62	10.48 ± 3.91	0.25 ± 1.01	
10–2 VF MD (dB)							
Median (min, max)	−8.40 (−28 to −2)	−7.01 (−29 to −2)	0.07 (−2 to 2)	−8.10 (−27 to −2)	−8.52 (−28 to −2)	−0.26 (−3 to 2)	*0.110
Mean ± SD	−10.48 ± 9.56	−10.49 ± 9.48	−0.01 ± 1.34	−10.76 ± 8.41	−11.34 ± 8.61	−0.59 ± 1.51	
10–2 VF Pattern standard deviation							
Median (min–max)	3.52 (1 to −11)	3.62 (1 to 11)	−0.04 (−1 to 1)	3.27 (1 to 11)	3.14 (1 to 10)	−0.15 (−1 to 2)	*0.678
Mean ± SD	4.23 ± 3.48	4.34 ± 3.22	0.11 ± 0.59	4.29 ± 3.47	4.29 ± 3.25	0.01 ± 0.91	

Sample size for each group, n = 13.
*Wilcoxon signed-rank test.

The MP central retinal sensitivity correlated with BCVA ($P = 0.03$; r = −0.343) and CFT ($P = 0.012$; r = 0.438). In addition, the MP peripheral (2°–10°) retinal sensitivity correlated with 2° to 10° mf-ERG amplitudes ($P = 0.013$; r = 0.404). The correlation between the MP sensitivity and the ganglion cell layer has been shown before.[25] The peripheral changes in mf-ERG might be significant because the photoreceptor cells are affected since the earlier stages of the disease. By contrast, the changes in MP retinal sensitivities did not reach significance in the short term may be because, unlike mf-ERG, they are not only influenced by the condition of the retina but also by other elements of the visual pathway.

As in the previous studies, the CFT was found similar in both groups.[3,4] The changes in groups were not statistically significant ($P > 0.05$).

Several studies claimed that 4 to 15 years have to pass to lose half of the functional VF in patients with RP.[26,27] In this study, there were no significant changes in 30-2 and 10-2 VF in any group ($P > 0.05$). In the study of Schatz et al,[4] after 6 weeks, the VF area increased by %17 in the TES group and decreased by 6% in the placebo group ($P < 0.001$). In the long-term study, the VF area decreased in the TES group by 2% and decreased in the placebo group by 8% ($P = 0.24$).

There are more than 50 identified genes in RP pathogenesis.[28] Animal studies showed that some mutations might benefit more from the therapy.[29] If there was a subgroup of patients that benefits more, this group might have been missed because of lack of genetic analysis.

In this study, therapy was applied monocularly, and the fellow eye was taken as control. Even both eyes are considered to be affected, the speed of progression may not be similar.[1] In addition, it is unknown whether there are any effects in the untreated eye because of retrograde transmission.[3–5]

This study has several other limitations as a limited study population and follow-up period. This study's advantage is that the progression has been evaluated in detail with subjective and objective tests performed by a masked practitioner.

In conclusion, the progression rate in mf-ERG was found to be stabilized with TES in this fellow-eye comparative study. Especially in the peripheral retinal areas, the disease progression rate was statistically lower in TE. No serious adverse effects were noted during TES. Further studies with larger sample sizes and more extended follow-up periods are needed to conclude that TES reduces the RP progression.

Key words: retinitis pigmentosa, transcorneal electrical stimulation, neuroprotection, multifocal electroretinography, microperimetry.

References

1. Evans KWR, Mark E. Retinitis Pigmentosa and Allied Disorders In: Schachat AP, Sadda SR (eds). Ryan's Retina, 6th ed. Elsevier; 2018:861–934.
2. Ramsden CM, Powner MB, Carr AJ, et al. Stem cells in retinal regeneration: past, present and future. Development 2013;140: 2576–2585.
3. Wagner SK, Jolly JK, Pefkianaki M, et al. Transcorneal electrical stimulation for the treatment of retinitis pigmentosa: results from the TESOLAUK trial. BMJ Open Ophthalmol 2017;2:e000096.
4. Schatz A, Röck T, Naycheva L, et al. Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled exploratory study. Invest Ophthalmol Vis Sci 2011;52:4485–4496.
5. Schatz A, Pach J, Gosheva M, et al. Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled follow-up study over 1 year. Invest Ophthalmol Vis Sci 2017;58:257–269.
6. Tao Y, Chen T, Liu B, et al. The transcorneal electrical stimulation as a novel therapeutic strategy against retinal and optic neuropathy: a review of experimental and clinical trials. Int J Ophthalmol 2016;9:914–919.
7. Oner A, Gonen ZB, Sinim N, et al. Subretinal adipose tissue-derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: a phase I clinical safety study. Stem Cel Res Ther 2016;7:178.
8. Arslan U, Özmert E, Demirel S, et al. Effects of subtenon-injected autologous platelet-rich plasma on visual functions in eyes with retinitis pigmentosa: preliminary clinical results. Graefes Arch Clin Exp Ophthalmol 2018;256:893–908.
9. Morimoto T, Fujikado T, Choi JS, et al. Transcorneal electrical stimulation promotes the survival of photoreceptors and preserves retinal function in royal college of surgeons rats. Invest Ophthalmol Vis Sci 2007;48:4725–4732.
10. Kurimoto T, Oono S, Oku H, et al. Transcorneal electrical stimulation increases chorioretinal blood flow in normal human subjects. Clin Ophthalmol 2010;4:1441–1446.
11. Ni YQ, Gan DK, Xu HD, et al. Neuroprotective effect of transcorneal electrical stimulation on light-induced photoreceptor degeneration. Exp Neurol 2009;219:439–452.
12. Gekeler F, Messias A, Ottinger M, et al. Phosphenes electrically evoked with DTL electrodes: a study in patients with retinitis pigmentosa, glaucoma, and homonymous visual field loss and normal subjects. Invest Ophthalmol Vis Sci 2006;47: 4966–4974.
13. Hood DC, Bach M, Brigell M, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol 2012;124:1–13.
14. Iftikhar M, Kherani S, Kaur R, et al. Progression of retinitis pigmentosa as measured on microperimetry: the PREP-1 study. Ophthalmol Retina 2018;2:502–507.
15. Janáky M, Pálffy A, Deák A, et al. Multifocal ERG reveals several patterns of cone degeneration in retinitis pigmentosa with concentric narrowing of the visual field. Invest Ophthalmol Vis Sci 2007;48:383–389.
16. Naycheva L, Schatz A, Röck T, et al. Phosphene thresholds elicited by transcorneal electrical stimulation in healthy subjects and patients with retinal diseases. Invest Ophthalmol Vis Sci 2012;53:7440–7448.
17. Jolly JK, Wagner SK, Martus P, et al. Transcorneal electrical stimulation for the treatment of retinitis pigmentosa: a multicenter safety study of the OkuStim(R) system (TESOLA-Study). Ophthalmic Res 2020;63:234–243.
18. Smith HB, Chandra A, Zambarakji H. Grading severity in retinitis pigmentosa using clinical assessment, visual acuity, perimetry and optical coherence tomography. Int Ophthalmol 2013;33:237–244.
19. Wolsley CJ, Silvestri G, O'Neill J, et al. The association between multifocal electroretinograms and OCT retinal thickness in retinitis pigmentosa patients with good visual acuity. Eye (Lond) 2009;23:1524–1531.
20. Seiple W, Clemens CJ, Greenstein VC, et al. Test-retest reliability of the multifocal electroretinogram and humphrey visual fields in patients with retinitis pigmentosa. Doc Ophthalmol 2004;109:255–272.
21. Nagy D, Schönfisch B, Zrenner E, Jägle H. Long-term follow-up of retinitis pigmentosa patients with multifocal electroretinography. Invest Ophthalmol Vis Sci 2008;49:4664–4671.
22. Rohrschneider K, Bültmann S, Springer C. Use of fundus perimetry (microperimetry) to quantify macular sensitivity. Prog Retin Eye Res 2008;27:536–548.
23. Chen FK, Patel PJ, Xing W, et al. Test-retest variability of microperimetry using the Nidek MP1 in patients with macular disease. Invest Ophthalmol Vis Sci 2009;50:3464–3472.
24. Acton JH, Smith RT, Greenberg JP, Greenstein VC. Comparison between MP-1 and Humphrey visual field defects in glaucoma and retinitis pigmentosa. Optom Vis Sci 2012;89:1050–1058.
25. Sato S, Hirooka K, Baba T, et al. Correlation between the ganglion cell-inner plexiform layer thickness measured with cirrus HD-OCT and macular visual field sensitivity measured with microperimetry. Invest Ophthalmol Vis Sci 2013;54: 3046–3051.
26. Grover S, Fishman GA, Anderson RJ, et al. Rate of visual field loss in retinitis pigmentosa. Ophthalmology 1997;104:460–465.
27. Holopigian K, Greenstein V, Seiple W, Carr RE. Rates of change differ among measures of visual function in patients with retinitis pigmentosa. Ophthalmology 1996;103:398–405.
28. Daiger SP, Sullivan LS, Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet 2013;84:132–141.
29. Rahmani S, Bogdanowicz L, Thomas J, Hetling JR. Chronic delivery of low-level exogenous current preserves retinal function in pigmented P23H rat. Vis Res 2013;76:105–113.