Retina Publish Ahead of Print
DOI: 10.1097/IAE.0000000000003386

‘Transcorneal Electrical Stimulation Therapy May Have A Stabilization Effect on Multifocal Electroretinography for Patients with Retinitis Pigmentosa’

‘Transcorneal Electrical Stimulation’

Didem Dizdar Yigit, MD[1], Mehmet Orkun Sevik, MD[1], Özlem Şahin, MD[1]
[1]Marmara University, School of Medicine, Department of Ophthalmology, Istanbul,Turkey

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

The authors have no financial or proprietary interest in a product, method, or material described herein. The authors declare that there is no conflict of interest.

The abstract of this work contains 238 words. This text contains 3697 words, 5 Tables, 6 Figures, 29 references, and it has previously been presented in Euretina (European Society of Retina Specialists) 2020, Virtual, 2-4 October 2020.

Corresponding Author;

Didem Dizdar Yigit, MD

Summary

This study assesses the effects of Transcorneal Electrical Stimulation (TES) on several objective and subjective measures of visual function in retinitis pigmentosa (RP). TES was applied monocularly, 30 minutes/week for 6 months. The progression in mf-ERG might have been stabilized with TES. Further studies with larger sample sizes are needed.

Corresponding Author;

Didem Dizdar Yigit, MD

Marmara University, School of Medicine, Department of Ophthalmology, Istanbul,Turkey

Address: Fevzi Çakmak, Muhsin Yazıcıoğlu Cd No:10, 34899 Pendik, Istanbul,Turkey

E-mail: drdidemdizdar@gmail.com

Phone Number:+095306600889

Fax Number: +90.216 625 46 39

Contributing Author;

Mehmet Orkun Sevik, MD

Marmara University, School of Medicine, Department of Ophthalmology, Istanbul, Turkey

Email: m.orkunsevik@gmail.com

Phone Number: +905350829028

Contributing Author;

Özlem Şahin, MD, Professor of Ophthalmology

Marmara University, School of Medicine, Department of Ophthalmology, Istanbul,Turkey

Email: ozlem.sahin@marmara.edu.tr

Phone Number: +095324941315

Abstract

Purpose: To assess the effects of Transcorneal Electrical Stimulation (TES) on several measures of visual function in retinitis pigmentosa (RP).

Methods: This prospective, randomized, fellow-eye-controlled study includes 30 eyes of 15 RP patients. Each patient's eyes were randomly selected as treatment(TE) and control eye(CE), and 30 minutes/week TES applied for six months. Patient evaluations were done before and after TES including comprehensive ophthalmological examination, visual fields, full-field and multifocal (mf-) electroretinography (ERG), 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(MSA) in mf-ERG were stabilized in TE. MSA in CE decreased in every ring, reaching significance in fifth ring (847,15±393,94 and 678,77±282,66 nV, p=0.039, before and after TES, respectively). The changes in MSA of TE and CE were -0,38±295,53 and -185,15±332,62nV in second(p=0,046), 36,69±326,4 and -143,38±317,41nV in fourth(p=0,028), -17,46±333,07 and -168.38±297,14nV in fifth

rings(p=0,046), respectively. The decrease in MSA between 2° to 20° midperipheral retina was significantly less in TE (-33,59±225,1nV) than CE (-205,56±345,1nV)(p=0,011). There were no siginificant changes in other parameters.

Conclusions: The progression in mf-ERG might be stabilized with TES. Further studies with larger sample sizes and longer follow-up are needed to conclude that TES reduces RP progression.

Keywords: Retinitis Pigmentosa, Transcorneal Electrical Stimulation, Neuroprotection, Multifocal Electroretinography, Microperimetry

Introduction

Retinitis pigmentosa (RP) is characterized by progressive, peripheral vision loss due to impairment of photoreceptor cells and retina pigment epithelium (RPE).[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]

TES's beneficial effects in amblyopia, amaurosis, chorioretinitis, glaucoma, and optic atrophies have been speculated since 1873.[1] It is a non-invasive 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 security, 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 RP patients after weekly 30-minute stimulation for six 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 (EPT). 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 UK has denoted TES's safety in RP patients after six months of weekly stimulation.[3] The visual function tests like VF and microperimetry (MP) did not reveal any significant difference between the treated and control eyes. TES might still be an attractive potential therapy option due to 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 of the patients or patients' legal guardians.

This prospective, randomized, fellow-eye-controlled study included 30 eyes of 15 RP patients whose diagnosis was confirmed by electrophysiological tests and recruited from the retina department of Marmara University Hospital, Istanbul, between August 2013-March 2019. Inclusion criteria were an age of 10-50 years, best-corrected visual acuity (BCVA) better than 0,7 logMAR (6/30 Snellen), recordable VF and MP results, and patient cooperation. Exclusion criteria were any ocular diseases like 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.

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 control eye (CE). The primary outcome measures were electrophysiological tests and visual function tests as VF and MP. 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. TES was administered weekly for 30 minutes for six months. Subjects were re-evaluated with the same examination procedures in the same order after six months. Any possible adverse effects were explained, and informed consent was signed each week before TES.

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

Electrical Stimulation and Determination of EPT

The stimulation system consisted of 3 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 ms positive and 5 ms negative deflection with a frequency of 20 Hz. The current amplitude was started from 0,02 mA and asked the subject to tell if they ‘feel’ the pulses. The current is slowly augmented by 0,01-0,05 mA until a maximum level of 1,0 mA. When the patient name 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 USB stick, and the same

individual treatment parameters were used in all visits. The delivered current during therapy was 200% of the patient's EPT.

TES therapy was administered in a quiet, dimly lighted room where the patients lay down with their heads positioned at a 45-degree 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 15000 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, USA), and proparacaine hydrochloride 0.5% (Alcaine®, Alcon, USA) ERG jet electrodes were placed. The ff-ERGs were recorded according to ISCEV standards.

Mf-ERGs were recorded after pupil dilatation. The stimulated retinal area was subtended in an area of 60°x55°; 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 ISCEV standards **(Figure 1)**.[13] The amplitude and latencies of P1, N1, and N2 components were recorded for every ring. The mean signal amplitudes (MSA) of mf-ERG in the macula (central 0-2 degrees) and the peripheral (2-20 degrees) signal amplitude changes were evaluated separately**(Figure 2)**.

Microperimetry

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 two, six, and ten-degree concentric visual field 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 two regions as central (16 test points) and peripheral (52 test points), and the changes in those two regions were evaluated separately. Although our device did not have the software needed, the mean of the central 13 points (0-2 degrees) and the mean of the remaining 24 points (2-10 degrees) was calculated arithmetically **(Figure 4)**.

The mean retinal sensitivities in the first ring (central 2 degrees), second ring (6 degrees), and third ring (10 degrees) 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

SD-OCT images were taken after pupil dilatation at the same time of the day by the same technician. 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°x20° area). The scanning was made in radial lines mode. The central foveal thickness (CFT) is defined as the distance between the inner limiting membrane to the outer border of the RPE via the automatic segmentation algorithms of the Spectralis software was recorded.

VF evaluated with the SITA Standard test, with standard Goldmann III stimulus with a background luminance of 10 cd/m2. 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%, false-positive and false-negative responses were less than 15%.

Statistical Analysis

The statistical analysis was performed using Number Cruncher Statistical System 2007 (NCSS 2007; Kaysville, Utah, USA) and Statistical Package for Social Sciences for Windows version 20.0 (SPSSv20.0; IBM, NY, USA). All descriptive data are presented as mean, standard deviation (SD), median, minimum (Min), maximum (Max), and 95% confidence interval (CI). Parametric tests and non-parametric 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 as "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.

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 were given in **Table 1**.

The mean BCVA in TE was 0,16±0,15(Snellen equivalent 20/29)(min-max; 0-0,5), while the mean BCVA in CE was 0,17±0,19(Snellen equivalent 20/30)(min-max; 0-0,7) in LogMAR ($p>0,05$). After TES therapy, the BCVA changed by -0,03±0,09(Snellen equivalent 20/21) and -0,03±0,11(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 D. The patients with a family history have more myopic refraction (-4,04±1,58 D; min-max:-6,00--1,50 D) than the patients who have not a family history (-0,63±2,18 D; min-max:-4,00-2,75 D)($p<0,05$).

The mean EPT of treated eyes was 0,283±0,22 mA. (min-max: 0,16-0,40 mA) There was no correlation between EPTs, VA, and mfERG, MP, and VF changes after therapy.

The mf-ERG MSA of 1st ring (0°-2°), 2nd ring (2°-5°), 3rd ring (5°-10°), 4th ring (10°-15°), and 5th ring (15°-20°) of the TE and CE before and after therapy are given in **Table 2**.

The MSA in the 1st, 2nd, 3rd, and 4th rings did not show statistically significant change after six months in the CE (p>0,05); however, the decrease in the MSA in the 5. ring reached statistical significance (p=0,039). On the other hand, the MSA in the 1st, 2nd, 3rd, 4th, and 5th rings did not show statistically significant change after six 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 2nd ring, the decrease in the CE's MSA showed statistical significance compared to the decrease in the TE (-185,15±332,62 nV vs. -0,38±295,53 nV, respectively, p=0,046). The mean amplitude signal decrease in the CE and TE were -143,38±317,41 nV and 36,69±326,4 nV in the 4th (p=0,028), and -168,38±297,14 nV and -17,46±333,07 nV in the 5th (p=0,046) rings, respectively **(Table 2, Figure 5)**.

After TES therapy, peripheral (2-20°) signal amplitude decrease in mf-ERG of the CE were 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 were 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 3rd ring was noted compared to TE. However, changes in mean retinal sensitivities in the 1st, 2nd, 3rd rings did not reach significance (p>0,05) **(Table 4)**.

In the Spearman correlation analysis, a low positive correlation was found between the peripheral (2 -10°) MP sensitivity and the mf-ERG P1 amplitude in 2 -10° (p=0,013; r=0,404) **(Figure 6)**. Although there was no correlation between the mean sensitivity in MP and BCVA and central foveal thickness (CFT), there was 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 PSD 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 3rd week of the therapy and completely disappeared in one 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 to the other probable treatment

options, TES has the potential to be prevalently used due to its low-risk profile, easy use, and non-invasiveness.[3-5] In this study, the TES's effects on visual functions and its safety profile were evaluated in RP patients.

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 RP patients. [4, 5] They speculated that in a younger population, the therapy might be more beneficial due to 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. TES 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 of the tests constitute major problems in 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 to 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 while the less degenerated retina need less stimulation. [5, 17] It was previously noted that stimulation strategy needs more investigation in order 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 the present study, the ff-ERG responses were undetectable before and after TES, so the ff-ERG results were not included in the statistical analysis.

On the other hand, 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., the different rings in mf-ERG results were not analyzed separately.[4] In the 150% EPT group, the change was -1,54 μV(range:-4,12-1,05); in 66% group, it was -1,49 μV(range:-3,92-0,95), and in the placebo group it was -0,39 μV (range:-3,1-2,32) after six weeks($p>0,05$). In the present study, the mf-ERG results were analyzed and compared according to the topographical rings. After six 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 rings ($p=0,046$). Despite the humble number of the participants and the high standard deviation, compared to 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 RP patient. When the mean N1, P1, and N2 waves were evaluated, no statistically significant difference was found between groups before and after TES. The central 0-2 degrees in mf-ERG showed no

significant change in any groups before and after therapy (p>0,05). While 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). 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 RP patients, the SD of the RP subjects was found to be larger than controls.[20] While the average variability in repeated mf-ERG amplitudes in controls was found to be 1.5 dB, 32% of the RP patients fell out of 99% CI. There were no significant changes in mf-ERG after three 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 six 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, like the analysis protocol in mf-ERG. When the 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 RP patients were followed up for 1-4 years and evaluated with MP and BCVA, and the floor effect is avoided by using two methods.[14] In the first method, the test area is divided into two regions as central (16 points) and peripheral (52 points), which were evaluated separately. In the second method, the test area is divided into two regions as seeing and scotomatous retina. The annual BCVA decrease has not been significant, while 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 to TE, but it did not reach statistical significance, which again might be due to the short follow-up and limited study population.

The MP central retinal sensitivity correlated with BCVA (p=0,03; r=-0,343) and CFT (p=0,012; r=0,438). Additionally, the MP peripheral (2-10°) retinal sensitivity correlated with 2-10° 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 mfERG might be significant because the photoreceptor cells are affected since the earlier stages of the disease. In contrast, the changes in MP retinal sensitivities did not reach significance in the short term, maybe because, unlike mfERG, they are not solely 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 four to fifteen years have to pass to lose half of the functional VF in RP patients.[26, 27] In the present 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., after six weeks, the VF area increased by %17 in the TES group and decreased by %6 in the placebo group (p<0,001).[4] 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 due to 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] Also, it is unknown if there are any effects in the untreated eye due to 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 mfERG 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.

References

1. Evans K. WR, Mark E. Retinitis pigmentosa and allied disorders. Ryan's Retina. 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, Rock 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 Cell Res Ther 2016; 7:178.
8. Arslan U, Ozmert 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. Janaky M, Palffy A, Deak 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, Rock 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 and 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, Schonfisch B, Zrenner E and Jagle H. Long-term follow-up of retinitis pigmentosa patients with multifocal electroretinography. Invest Ophthalmol Vis Sci 2008; 49:4664-4671.
22. Rohrschneider K, Bultmann S and 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 and 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 and 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 and Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet 2013; 84:132-141.
29. Rahmani S, Bogdanowicz L, Thomas J and Hetling JR. Chronic delivery of low-level exogenous current preserves retinal function in pigmented P23H rat. Vision Res 2013; 76:105-113.

Figure Legends

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

Figure 2. The mf-ERG results of one of the treatment eyes before and after six months of TES therapy.

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

Figure 4. The microperimetry test results. The central 13 points (0-2^{o}) and the remaining 24 points (2-10°).

Figure 5. The changes of the mfERG MSA of the study and control eyes in 2nd (a), 4th (b), 5th (c) rings before and after six months of treatment.

Figure 6. Spearman correlation analysis of the peripheral (2-10°) MP sensitivity and the mf-ERG P1 amplitude in 2-10° (p=0,013; r=0,404).

Table *1.* The demographic and clinical features of the patients.

Age, Year	
Median (Min-Max)	28 (13-42)
Mean±SD	25,92 ± 10,25
Gender, 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	
Treatment Eyes	
Median (Min-Max)	0,10 (0-0,5)
(Snellen Equivalent)	(20/25)
Mean±SD	0,16 ± 0,15
(Snellen Equivalent)	(20/29)
Control Eyes	
Median (Min-Max)	0,10 (0-0,7)
(Snellen Equivalent)	(20/25)
Mean±SD	0,17 ± 0,19
(Snellen Equivalent)	(20/30)
p-value	0,655*
Refractive Error, D	
Min-Max	-6,00 - +2,75
Mean±SD	-2,33 ± 2,55

BCVA = best-corrected visual acuity; D = diopters; logMAR = logarithm of the minimum angle of resolution

Sample size, n = 13

*Wilcoxon signed rank test

Table 2. The mf-ERG MSA in the treatment and control eyes before and after TES therapy with the changes after six months of TES therapy.

Signal Amplitude (nV)		Treatment Eyes			Control Eyes			Δ Test Value
		Before	After	Change	Before	After	Change	*p*
1th Ring	*Median (Min, Max)*	1048 (270, 2053)	1078 (227, 2629)	99 (-730, 1281)	1017 (371, 1692)	814 (124, 2301)	114 (-1232, 894)	[a]*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, 1323)	649 (317, 1659)	-20 (-433, 7169)	791 (353, 1682)	752 (267, 1361)	-282 (-665, 495)	[a]*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, 1516)	569 (335, 1496)	-81 (-789, 553)	697 (338, 1762)	690 (232, 1169)	-155 (-771, 522)	[a]*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, 935)	643 (300, 1491)	-89 (-260, 773)	651 (350, 1611)	788 (271, 1063)	-179 (-621, 655)	[a]*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, 1185)	647 (279, 1600)	-87 (-527, 669)	783 (367, 1621)	724 (310, 1186)	-180 (-616, 528)	[a]*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

[a]Wilcoxon Signed Rank Test

*p<0,05

Table 3. The MP values in the treatment and control eyes before and after six months of TES therapy.

Thresholds (dB)		Treatment Eyes			Control Eyes			Δ Test Value
		Before	After	Change	Before	After	Change	*p*
Average	*Median (Min, Max)*	21 (0, 27)	20 (0, 25)	0,45 (-3, 2)	19 (0, 28)	20 (0, 25)	0 (-3, 4)	[a]*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, 28)	25 (18, 27)	0,52 (-4, 3)	22 (20, 29)	24 (19, 27)	0,4 (-1, 4)	[a]*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, 26)	0,41 (-2, 2)	23 (19, 27)	19 (19, 26)	0,25 (-3, 2)	[a]*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, 25)	20 (1, 23)	0,25 (-2, 4)	18 (1, 26)	17 (0, 27)	0,16 (-3, 1)	[a]*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

[a]Wilcoxon Signed Rank Test

Table 4. The changes of peripheral mf-ERG signal amplitudes in the treatment and control eyes after six months of TES therapy.

Peripheral Signal Amplitude (nV)		The Change Before and After TES Therapy		Δ Test Value
		Treatment Eyes	Control Eyes	*p*
N1 Wave	***Median (Min, Max)***	6,20 (-174, 366)	-37,50 (-559, 222)	[a]*p=0,331*
	Mean±SD	2,28±116,4	-61,84±164,4	
P1 Wave	***Median (Min, Max)***	-38,00 (-282, 190)	-92,50 (-677, 340)	[a]*p=0,102*
	Mean±SD	-33,78±101,1	-109,60±178,9	
N2 Wave	***Median (Min, Max)***	-13,35(-461, 492)	-45,50 (-581, 391)	[a]*p=0,089*
	Mean±SD	-2,18±170,8	-52,12±204,5	
Total Amplitude	***Median (Min, Max)***	-15,60 (-461, 492)	-61,50 (-677, 391)	***[a]p=0,019****
	Mean±SD	-33,59±225,1	-205,56±345,1	

Sample size for each group, n=13
[a]Wilcoxon Signed Rank Test
**p<0,05*

Table 5. The results and changes in the VF test values before and after TES therapy.

		Treatment Eyes			Control Eyes			Δ Test Value
		Before	**After**	**Change**	**Before**	**After**	**Change**	***p***
30-2 VF MD (dB)	***Median (Min,Max)***	-21,41 (-32, -2)	-21,01 (-32, -14)	-0,02 (-5, 2)	-22,40 (-31, -14)	-23,30 (-32, -13)	0,12 (-2, 2)	[a]*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 PSD	***Median (Min,Max)***	10,41 (5, 15)	10,94 (4, 15)	0,26 (-1, 1)	9,33 (5, 15)	10,91 (5, 15)	0,09(-1, 2)	[a]*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, -2)	-7,01 (-29, -2)	0,07 (-2, 2)	-8,10 (-27, -2)	-8,52 (-28, -2)	-0,26 (-3, 2)	[a]*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 PSD	***Median (Min,Max)***	3,52 (1, -11)	3,62 (1, 11)	-0,04(-1, 1)	3,27 (1, 11)	3,14 (1, 10)	-0,15 (-1, 2)	[a]*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

[a]Wilcoxon Signed Rank Test