Early Results of Transcorneal Electrical Stimulation Therapy in Three Cases with Cone Dystrophy

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ABSTRACT

We aimed to report the early results of transcorneal electrical stimulation (TES) therapy in three patients with cone dystrophy. A detailed ophthalmic examination including ishihara color vision test, electroretinography (ERG), multifocal ERG (mf-ERG), optical coherence tomography and the quality of life (QoL) of low-vision patients questionnaire was performed before and after the TES therapy. After the TES therapy, favorable outcomes were obtained from the patients. Increase in visual acuity and color vision levels, improvement in photopic ERG and mf-ERG responses were noted. Furthermore, the QoL questionnaire scores increased remarkable in all patients. Objective and subjective promising results obtained with TES in these patients suggest that TES therapy may be a new treatment method in retinal dystrophy cases.

Keywords: Cone dystrophy, Electroretinography, Retinal dystrophy, TES therapy, Transcorneal electrical stimulation.

INTRODUCTION

The cone dystrophies which are characterized by hemeralopia, decreased visual acuity, abnormalities of colour vision and photophobia because of cone photoreceptors damage are rarely seen retinal disorder.[1] There is a wide clinical and genetic heterogeneity. It may has autosomal dominant, autosomal recessive, and X linked recessive inheritance.[1] Unfortunately, the majority of patients with cone dystrophies progress to legal blindness before the age of 50 years, and currently, there is no treatment choice for any of the retinal dystrophies.

Transcorneal electrical stimulation (TES) is a new treatment method that has been investigated in recent years in degenerative and ischemic retinal diseases. Case report in Best vitelliform macular dystrophy has indicated the promising effects of TES therapy.[2] Furthermore, Schatz et al. proved that the TES therapy was safe and beneficial in patients with retinitis pigmentosa (RP) by their prospective, randomized, sham-controlled studies.[3,4]

CASE REPORT

We aimed to present three cases with cone retinal dystrophy whose visual findings and symptoms improved after the TES therapy. It was recommended to these patient since its positive effects on cone photoreceptors which was so recently reported clinical trial on RP patients.[4]

For performing TES therapy, Ocuvision system (CE approved, GmbH, Reutlingen, Germany) consisting of stimulating device (Ocustim), application spectacle (Ocuspex) and electrode (OcuEl) was used as described previously in the literature.[3,4] While an ocular electrode was placed on the cornea, two skin electrodes were placed on temple area bilaterally. After determining the value of electrical phosphene threshold, TES therapy was performed to the patients with an interval of one week for 12 weeks with the following paramaters; 180-240 µA power, 20 Hz frequency, 2 msec biphasic and 30 min duration. Initially, we offered 8 sessions of treatment to all three patients. After that, we applied 4 more doses because of the obtained positive results and high patient satisfaction.

The procedures were performed to the tenets of the Declaration of Helsinki. After explaining the procedures to be applied, written informed consent was obtained from the patients. All of the procedures were performed in the

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consulting room by the same ophthalmologist (MND) or under his supervision. The detailed ophthalmic examination including color vision, full-field electroretinography (ERG), and multifocal ERG (mf-ERG; RetiScan 3.22.0.1; Roland Instruments, Wiesbaden, Germany) tests, optical coherence tomography (OCT, DRI, SS-OCT Atlantis; Topcon, Tokyo, Japan) and the quality of life (QoL) of low-vision patients questionnaire was performed before and after the TES therapy. This questionnaire which has been created to measure the vision targeted health status of patients with chronic eye diseases causing low vision has 25 items and 11 subscales.[5]

Case-1

A 45-year-old male patient presented with the complaints of gradual decreased vision, hemeralopia, photophobia, glare and central scotoma. His complaints began in twenties and he has been diagnosed with cone dystrophy. The best-corrected visual acuity (BCVA) was 0.2 in the right eye and 0.1 in the left eye. Color vision was 5/20 numbers in the right eye and 3/20 numbers in the left eye by ishihara color vision test - 38 plate (Table 1). The temporal of the optic discs were pale and the maculas had atrophic view in the fundoscopic examination (Figure 1). The OCT showed the photoreceptor outer segment band loss in subfoveal area. The central foveal thickness was 140 µm in the both eyes (Figure 1). Photopic b-wave amplitudes were decreased in ERG (Table 2). The QoL of low-vision patients questionnaire was 85/120 points. ABCA4 gene mutation was detected in the patient.

After 12 sessions of TES therapy; the BCVA increased to 0.4 in the right eye and 0.2 in the left eye, and the color vision increased to 18/20 numbers in the right eye and 15/20 numbers in the left eye. An eleven-point increase (from 85/120 points to 96/120 points) in the QoL questionnaire score (Table 1). Mean deviation levels improved from -2.93 dB and -3.23 dB to -1.82 dB and -1.89 dB in the

Table 1: *Best-corrected visual acuity, Color Vision, Foveal Thickness, Quality of life Questionnaire Score and Intraocular pressure of patients before and after Transcorneal Electrical Stimulation therapy.*

	Before TES Therapy					After TES Therapy				
	BCVA (Snellen)	Color Vision (number)	Central Foveal Thicknes (µm)	QoLQS (points)	IOP (mmHg)	BCVA (Snellen)	Color Vision (number)	Central Foveal Thicknes (µm)	QoLQS (points)	IOP (mmHg)
Case 1 OD	0.2	5/20	140	85/120	14	0.4	18/20	143	96/120	13
OS	0.1	3/20	140		14	0.2	15/20	140		14
Case 2 OD	0.5	18/20	198	76/120	14	0.7	20/20	205	90/120	13
OS	0.4	17/20	202		13	0.5	20/20	200		12
Case 3 OD	0.7	20/20	199	70/120	11	0.8	20/20	203	79/120	12
OS	0.5	20/20	201		12	0.7	20/20	206		12

BCVA; Best-corrected Visual Acuity, QoLQS; Quality of life Questionnaire Score, IOP; Intraocular Pressure

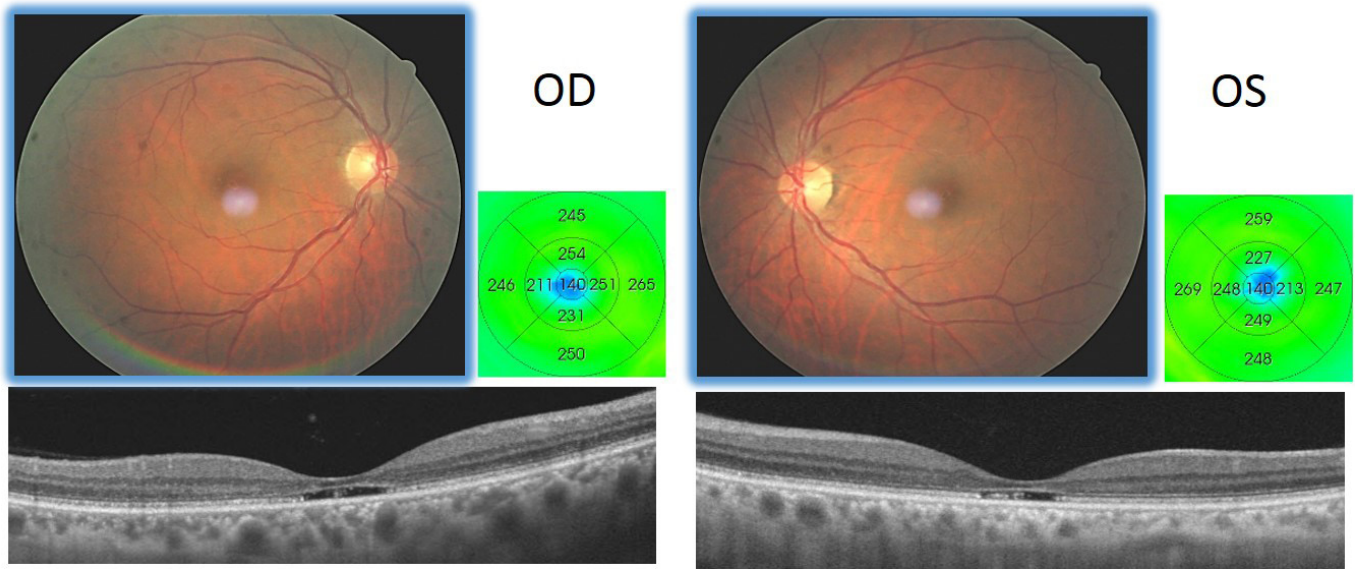

Figure 1: *Fundus photograph and OCT images of case 1.*

right and left eyes respectively in the computerized visual field testing (Figure 2). Amplitudes of b-wave in photopic responses and 1st ring increased, whereas implicit times decreased in ERG and in mf-ERG (Table 2). No ocular and systemic adverse event was observed except the mild and transient punctate epitheliopathy after the TES therapies. The patient stated that he was very pleased that he could especially recognize people's faces better and his complaint of photophobia decreased.

Case-2

A 28-year-old female patient presented with the complaints of decreased vision, hemeralopia and photophobia. Her BCVA was 0.5 in the right eye and 0.4 in the left eye. Color vision was 18/20 numbers in the right eye and 17/20 numbers in the left eye by ishihara color vision test - 38 plate (Table 1). On the fundus examination, a hyperpigmented lesion with a marked margin, reddish colored in the macula was observed. The central foveal thickness was 198 µm in the right eye and 202 µm in the left eye. The QoL of low-vision patients questionnaire was 76/120 points. CNGA1, GUCY2D and PDE6B gene mutations were detected in the patient.

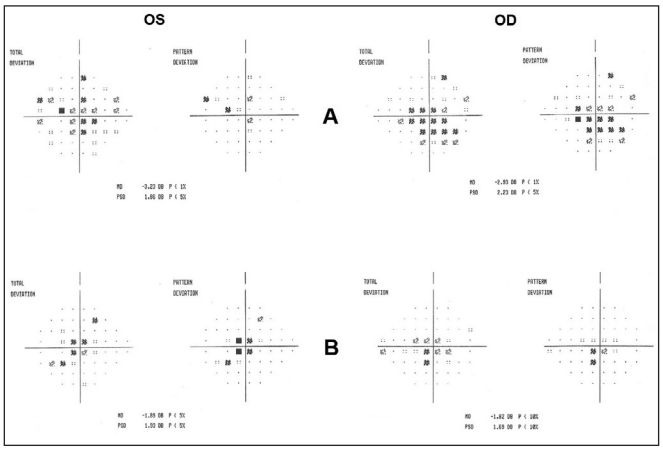

Figure 2: *Computerized visual field tests of case 1; A) before and B) after TES therapy.*

After 12 sessions of TES therapy; the BCVA increased to 0.7 in the right eye and 0.5 in the left eye, and the color vision increased to 20/20 numbers in the both eyes. A fourteen-point increase (from 76/120 points to 90/120 points) in the QoL questionnaire score (Table 1). Amplitudes of b-wave in photopic responses and 1st ring increased, whereas implicit times decreased in ERG and in mf-ERG (Table 2). The patient did not state an ocular or systemic adverse event about the therapy.

Case-3

A 32-year-old male patient presented with the complaints of decreased vision, hemeralopia and photophobia. His BCVA was 0.7 in the right eye and 0.5 in the left eye. Color vision was 20/20 numbers in the both eyes by ishihara color vision test - 38 plate. On the fundus examination, a hyperpigmented lesion with a marked margin, reddish colored in the macula was observed. The central foveal thickness was 199 µm in the right eye and 201 µm in the left eye. The QoL of low-vision patients questionnaire was 70/120 points. ABCA4 and CACNA2D4 gene mutations were detected in the patient.

After 12 sessions of TES therapy; the BCVA increased to 0.8 in the right eye and 0.7 in the left eye. A nine-point increase (from 70/120 points to 79/120 points) in the QoL questionnaire score (Table 1). Amplitudes of b-wave in photopic responses and 1st ring increased, whereas implicit times decreased in ERG and in mf-ERG (Table 2). The patient did not state an ocular or systemic adverse event about the therapy.

Table 2: *Electrophysiological responses of patients before and after Transcorneal Electrical Stimulation therapy.*

	Before TES Therapy						After TES Therapy					
	Photopic ERG				mf-ERG		Photopic ERG				mf-ERG	
	b-wave amplitude (µv)	b-wave implicite time (msec)	3.0 flicker b-wave amplitude (µv)	3.0 flicker b-wave implicite time (msec)	1st ring amplitude (µv)	1st ring implicite time (msec)	b-wave amplitude (µv)	b-wave implicite time (msec)	3.0 flicker b-wave amplitude (µv)	3.0 flicker b-wave implicite time (msec)	1st ring amplitude (µv)	1st ring implicite time (msec)
Case 1 OD	18.3	30.5	14.0	26.4	18.53	32.0	19.8	29.4	14.2	26.1	19.34	30.9
OS	14.0	31.7	12.8	25.8	20.45	35.8	18.4	29.4	15.4	25.5	23.16	33.7
Case 2 OD	14.1	32.3	10.4	34.2	18.55	48.3	19.7	35.8	14.4	32.4	25.07	40.2
OS	11.4	36.7	13.0	35.1	16.82	44.6	15.8	34.1	14.3	31.5	23.62	40.2
Case 3 OD	13.0	34.1	11.4	32.4	27.81	54.1	21.4	33.2	18.6	30.8	47.64	41.1
OS	16.2	34.1	13.9	30.6	26.94	51.3	20.3	29.6	15.0	29.6	36.80	44.3

ERG; full-field electroretinography, mf-ERG; multifocal electroretinography

DISCUSSION

We determined that the TES therapy can improve the visual symptoms of patients with cone retinal dystrophy. To the best our knowledge, this is the first case series who underwent TES therapy for cone dystrophy. The demographic characteristics of our cases are summarized in Table 3.

The outcomes of Schatz et al.'s clinical trial encouraged us to perform the TES therapy to this patient.[4] They investigated the effects of TES on 52 RP patients in a prospective, randomized, sham-controlled, 1 year follow-up study. They found that only the improvement in cone function was statistically significant.[4] We previously reported that TES therapy provided positive visual results in 21 patients with RP, especially in the early stages of disease.[6]

TES therapy is a newer treatment method that is on the agenda in recent years in the treatment of the retinal diseases that can not be treated. Although the exact mechanism of the effects of the TES therapy has not been identified, it is thought that the protective effects of its can be related with vasodilatory, neurotrophic, anti-apoptotic, anti-glutamate and anti-inflammatory mechanisms.[7] Morimoto et al.[8] showed that the TES therapy promoted the survival of photoreceptors in transgenic rabbits by evaluating ERG responses and immunohistochemical analysis. Wang et al.[9] demonstrated that glucose replacement restored the dormant cone electrophysiology in a pig model of autosomal-dominant RP. We think that, TES therapy causes the dormant (but alive) cells to wake up like.[10]

Schatz et al.[3] performed the TES therapy to the 24 RP patients for 6 weeks in their preliminary study, and they observed statistically significant improvements in scotopic b-wave amplitude and CVF test. After these promising outcomes, 52 RP patients performed themselves the TES therapy at home conditions for 52 weeks. The authors observed a statistically significant improvement in light-adapted single flash b-wave amplitude and a statistically insignificant improvement in scotopic b-wave amplitude as in our study.[4] Dizdar Yiğit et al.[11] found statistically significant changes in the mean mf-ERG signal amplitudes of rings 2,4 and 5 in the TES-treated eyes of 15 RP patients compared to the untreated fellow eye. Sinim Kahraman and Oner[12] determined a statistically significant improvement in p1 wave amplitude in rings 1, 2, and 3 at the first month in 101 RP patients who underwent TES therapy for 30 min once a week for 8 consecutive weeks. However, they observed that these improvements partially disappeared at 6-month follow-up.

Contrary to these promising results, Röck et al.[13] declared that they could not determine any positive effect of TES therapy in 12 patients with Stargardt's disease.

However, the optimal parameters of the TES therapy and repetition times have not been determined, yet. The parameters of the TES applications in the literature are different from each other. The experimental study of Morimoto et al.[14] can guide to researchers in this regard. The authors investigated the effects of TES on the survival of axotomized retinal ganglion cells (RGCs) in rats by examining the levels of the mRNA and protein of insulin-like growth factor (IGF-1). They determined that TES increased the survival of axotomized RGCs by increasing the level of IGF-1 production by Muller cells, and the degree of recovery depended on the electrical phosphene strength.[14] They also detected that the IGF-1 elevation started several hours after TES application and reached a peak level on the 7th day and continued at a significant level even on the 10th day.[14]

In conclusion; objective and subjective tests demonstrated that the TES therapy had beneficial effects in patients with cone dystrophy. The lack of microperimetric measurements is the biggest limitation of our case series. Prospective, randomized studies with large sample size, sham-controlled and long follow-up time are absolutely needed to confirm these results.

Table 3: *The demographic data of patients who underwent Transcorneal Electrical Stimulation therapy.*

Patients	Age	Gender	Phosphene Threshold Value (μA)	Session	Symptoms	Genetic Mutation
Case 1	45	Male	OD: 120, OS: 120	12	Hemerolopia, decreased vision, glare, central scotoma	ABCA4
Case 2	28	Female	OD: 90, OS: 100	12	Hemerolopia, decreased vision, photophobia	CNGA1, GUCY2D, PDE6B
Case 3	32	Male	OD: 100, OS: 110	12	Hemerolopia, decreased vision, photophobia	ABCA4, CACNA2D4

REFERENCES

1. Michaelides M, Hunt DM, Moore AT. The cone dysfunction syndromes. Br J Ophthalmol. 2004;88:291-7.
2. Ozeki N, Shinoda K, Ohde H, et al. Improvement of visual acuity after transcorneal electrical stimulation in case of Best vitelliform macular dystrophy. Graefes Arch Clin Exp Ophthalmol. 2013;251:1867-70.
3. 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;52:4485-96.
4. 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;58:257-69.
5. Idil A, Ozen M, Atak N, et al. Validity and reliability study of Turkish version on low vision with quality of life questionnaire. Int J Ophthalmol. 2011;4:546-51.
6. Demir MN, Acar U, Sobaci G, Goksuluk D. Outcomes of transcorneal electrical stimulation therapy in the early stages of retinitis pigmentosa. Turk J Med Sci. 2022;52:741-6.
7. Tao Y, Chen T, Liu B, Wang LQ, 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;9:914-9.
8. Morimoto T, Kanda H, Kondo M, et al. Transcorneal electrical stimulation promotes survival of photoreceptors and improves retinal function in rhodopsin P347L transgenic rabbits. Invest Ophthalmol Vis Sci. 2012;53:4254-61.
9. Wang W, Lee SJ, Scott PA, et al. Two-step reactivation of dormant cones in retinitis pigmentosa. Cell Rep 2016;15:372-85.
10. Koenekoop RK. Why some photoreceptors die, while others remain dormant: lessons from RPE65 and LRAT associated retinal dystrophies. Ophthalmic Genet. 2011;32:126-8.
11. Dizdar Yigit D, Sevik MO, Şahin Ö. Transcorneal Electrical Stimulation Therapy May Have a Stabilization Effect on Multifocal Electroretinography for Patients with Retinitis Pigmentosa. Retina. 2022;42:923-33.
12. Sinim Kahraman N, Oner A. Effect of Transcorneal Electrical Stimulation on Patients with Retinitis Pigmentosa. J Ocul Pharmacol Ther. 2020;36:609-17.
13. Röck T, Schatz A, Naycheva L, et al. [Effects of transcorneal electrical stimulation in patients with Stargardt's disease]. Ophthalmologe. 2013;110:68-73.
14. Morimoto T, Miyoshi T, Matsuda S, et al. Transcorneal electrical stimulation rescues axotomized retinal ganglion cells by activating endogenous retinal IGF-1 system. Invest Ophthalmol Vis Sci. 2005;46:2147-55.