OkuStim®: Application and Effect of Transcorneal Electrical Stimulation of the Eye

The OkuStim System (Fig. 1) is designed for electrical stimulation of the retina in patients with retinitis pigmentosa (RP) in an out-patient or home setting.

Using a thin electrode thread (Fig. 2), weak electrical impulses are transmitted to the surface of the eye (conjunctiva, cornea), from where the current enters the eye (transcorneal stimulation) and spreads intraocularly to the retina, thus polarizing it.

Transcorneal electrical stimulation (TcES) is aimed at maintaining the function of photoreceptors as long as possible and to delay their decay and the subsequent degeneration of the retina. As a result, the constriction of the visual field can be slowed down, and the useful visual performance of the affected individuals can be maintained for longer.

Clinical investigations show that regular use triggers a positive effect in the retina against the progression of RP. The safety of TcES therapy with the OkuStim System has been demonstrated in over 140 years of application in clinical trials without serious adverse events.

Fig. 1: Electrical stimulation therapy with the OkuStim® System.

Indications, for which the Application of TcES is Approved

TcES therapy with OkuStim is suitable for the treatment of:

- patients with retinitis pigmentosa (also syndromal, e.g. Usher syndrome)
- patients with similar retinal diseases[1] such as cone-rod dystrophy and choroideremia

[1] According to the work group “Clinical Issues” of the German Patient Organization PRO RETINA there are no objections to treating these diseases with TcES. Source: https://www.pro-retina.de/forschungsfoerderung/wissenschaftliche-beratungsgremien/empfehlungen/bewertung-zur-elektrostimulation-am-auge

© Okuvision 2020 | Rev. 2.0

Fig. 2: OkuStim System. Left: OkuStim device. Centre: OkuSpex frame (top) holder for OkuEl electrodes (bottom). Right: During stimulation, the electrode thread is in contact with the conjunctiva and cornea below the pupil.

Application and Handling of the OkuStim System

- **Medical prescription.** The OkuStim products are only dispensed upon medical prescription, after diagnosis and determination of the eligibility for the therapy, to ensure a regular follow-up.
- **Determination of the individual stimulation level (current).** First, the doctor determines the patient's threshold for electrically generated visual perceptions (phosphenes). Using this phosphene threshold, the doctor sets the individual stimulation level for the therapy and programs it on the USB-memory stick of the device.
- **Therapy procedure.** The patient stimulates his eyes once a week for 30 minutes (home use) and appears regularly (every 6-8 months) in the eye clinic for follow-ups.
- **Stimulation parameters.** Biphasic current pulses, pulse duration 10 ms, frequency 20 Hz
- **Handling of the OkuStim System.** Operation of the OkuStim System is simple and tailored to the needs of the patient. The OkuStim System has an acoustic output of system messages so that patients in advanced stages of visual impairment can use it independently without any problems.

Clinical Results

Clinical studies show that TcES triggers physiological processes in the retina of RP patients. The application immediately causes a significant increase in blood flow to the central retina [1] and increased oxygen consumption of retinal cells [2]. Randomized, controlled studies with weekly application also showed a significant improvement in visual acuity [1], visual field [1,3], and improved b-wave amplitudes in the dark-adapted [3] and light-adapted ERG [4]. The effect of TcES appears to be transient, suggesting long-term application [5].

Although the clinical data from the various studies do not yet provide a consistent picture of clinically relevant long-term effects, they do indicate significant effects of TcES on photoreceptor function and a positive effect on the visual field. In recognition of this, the German Institute for Quality and Efficiency in Health Care (IQWiG) has confirmed that TcES therapy with the OkuStim System has the potential for patient-relevant benefits [6].

Mode of Action

The electrical stimulation on the surface of the eye polarizes the retina, which is directly reflected in the resulting visual impressions (so-called phosphenes [7]). The data of the clinical studies show that regular application elicits a positive effect in the retina against the progression of the retinal disease RP [3,4]. How exactly this neuroprotective effect on the photoreceptors is mediated has not yet been conclusively determined.

The effect of TcES is associated with anti-apoptotic, neurotrophic, vasodilator, anti-inflammatory and anti-glutamate mechanisms. Several TcES-induced protective mechanisms may also act simultaneously and together promote retinal cell survival [8]. Preclinical studies have shown that electrical stimulation activates anti-apoptotic and neuroprotective signalling pathways whilst suppressing inflammatory signalling pathways, thereby producing a cell-preserving effect in the retina (see reviews [9,10]). An important role is attributed to the electrically activatable protective and repair function of Müller cells, the glial cells of the retina [11,12].

Safe Therapy Option for RP

Due to the neuroprotective effect of electrostimulation, TcES is classified in scientific and medical reviews as a promising strategy and non-invasive treatment option for retinal dystrophies [8,9,13-15]. Although TcES is not yet recommended as a treatment option in national and international guidelines, medical circles have no objections to its use. The Arbeitskreis Klinische Fragen (AKF) of the Scientific Medical Advisory Board of PRO RETINA Deutschland e. V. evaluates the use of TcES with the OkuStim device in retinal dystrophies as safe and has no objections to its controlled use in patients with RP and other generalized hereditary retinal dystrophies such as cone-and-rod-dystrophies, choroideremia, Usher syndrome, etc. [16].

All clinical studies conducted with the OkuStim System to date (

Fig. 3) have consistently demonstrated the safety of using TcES therapy in outpatient and home settings. More than 300 patients have participated in the studies and have used the therapy for 130 years, including approximately 50 years in home use. With a total of more than 3,500 hours of stimulation, no serious adverse event related to the device or therapy occurred.

A common side effect is temporary dry eyes, which can be treated with eye drops.

Clinical Investigations with the OkuStim-System

Pilot Study EST I

In the 6-week randomized controlled pilot study, 24 RP patients were treated with TcES (EST I study, clinicaltrials.gov: NCT00804102). The highest stimulated group had a 17% larger visual field ($P<0.001$) and a 13% larger b-wave in the dark-adapted (scotopic) ERG ($P<0.027$) compared to the untreated control group.

Publication: Schatz, et al. [3]

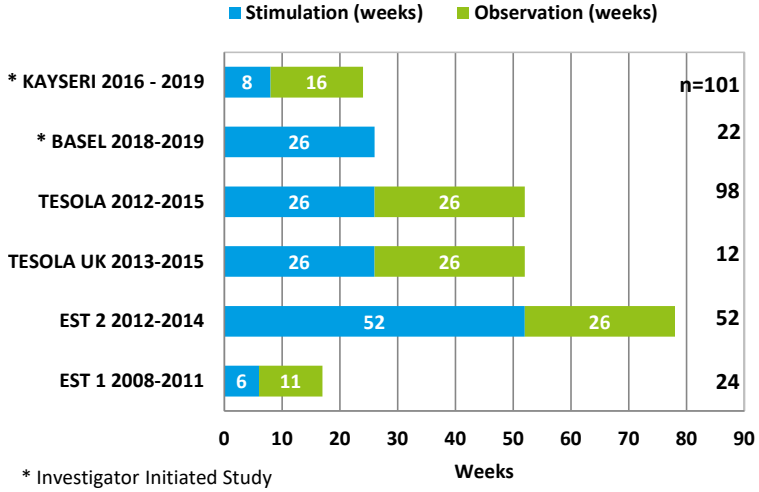

Fig. 3: Clinical trials of the use of transcorneal electrical stimulation (TcES) with the OkuStim System (or with DTL electrodes, EST 1) in retinitis pigmentosa.
Left axis: name and duration of the studies, lower axis: duration of the studies (stimulation with subsequent observation period); right: number of participating patients.

Long Term Study EST II

In the randomized, controlled, long-term study (EST II study, clinicaltrials.gov: NCT01837901) 52 RP patients were treated with the OkuStim system for one year at different stimulation levels. In the group with the strongest TcES stimulation, there was a positive trend in reduction of visual field loss (P=0.24) compared to the non-stimulated eye and a significant improvement (P<0.0001) in b-wave in the light-adapted (photopic) ERG.

Publication: Schatz, et al. [4]

Post-Market Clinical Observation TESOLA (Transkorneal Electrostimulation Open Label)

The safety of the OkuStim System has been clearly demonstrated in the multicentre observational study (TESOLA, clinicaltrials.gov: NCT01835002, NTC01847365) in 11 European eye-hospitals. In the prospective, open-label study, 98 RP patients received weekly home stimulation with the OkuStim System for 6 months and were followed-up for a further 6 months without stimulation. There were no serious adverse events (SAEs) associated with the device or therapy throughout the study. A common side effect was temporary dry eyes that could be treated with eye drops. The visual fields and visual acuity of stimulated and non-stimulated eyes remained stable throughout the observation period.

Publications: Jolly, et al. [17], Wagner, et al. [18]

Observational Study BASEL

In a prospective observational study involving 22 RP patients, an increased oxygen consumption after six months of weekly, 30-minute stimulation with the OkuStim System was shown, while maintaining the same retinal vessel diameter. This demonstrates that TcES induces physiological processes in the retina of RP patients.

Publication: Della Volpe-Waizel, et al. [2]

Retrospective Study KAYSERI

A statistically significant positive effect of TcES on the visual field after two months of treatment was shown in a retrospective study with 101 patients. However, the effect appears to be transient as it was no longer detectable after 6 months without further treatment. This suggests a permanent therapy with TcES.

Publication: Kahraman and Oner [5]

Literature

1 Bittner, A. K. *et al.* Randomized controlled trial of electro-stimulation therapies to modulate retinal blood flow and visual function in retinitis pigmentosa. *Acta Ophthalmol* **96**, e366-e376, doi:10.1111/aos.13581 (2018).

2 Della Volpe-Waizel, M. *et al.* Metabolic monitoring of transcorneal electrical stimulation in retinitis pigmentosa. *Graefes Arch Clin Exp Ophthalmol*, doi:10.1007/s00417-019-04522-9 (2019).

3 Schatz, A. *et al.* Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled exploratory study. *Invest Ophthalmol Vis Sci* **52**, 4485-4496, doi:10.1167/iovs.10-6932 (2011).

4 Schatz, A. *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* **58**, 257-269, doi:10.1167/iovs.16-19906 (2017).

5 Kahraman, N. S. & Oner, A. Effect of Transcorneal Electrical Stimulation on Patients with Retinitis Pigmentosa. *J Ocul Pharmacol Ther*, doi:10.1089/jop.2020.0017 (2020).

6 G-BA. *Erprobungs-Richtlinie Transkorneale Elektrostimulation bei Retinopathia Pigmentosa*, <https://www.g-ba.de/richtlinien/99/> (2017).

7 Naycheva, L. *et al.* Phosphene thresholds elicited by transcorneal electrical stimulation in healthy subjects and patients with retinal diseases. *Invest Ophthalmol Vis Sci* **53**, 7440-7448, doi:10.1167/iovs.12-9612 (2012).

8 Pardue, M. T. & Allen, R. S. Neuroprotective strategies for retinal disease. *Prog Retin Eye Res* **65**, 50-76, doi:10.1016/j.preteyeres.2018.02.002 (2018).

9 Sehic, A. *et al.* Electrical Stimulation as a Means for Improving Vision. *Am J Pathol* **186**, 2783-2797, doi:10.1016/j.ajpath.2016.07.017 (2016).

10 Tao, Y. *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* **9**, 914-919, doi:10.18240/ijo.2016.06.21 (2016).

11 Yu, H. *et al.* Noninvasive Electrical Stimulation Improves Photoreceptor Survival and Retinal Function in Mice with Inherited Photoreceptor Degeneration. *Invest Ophthalmol Vis Sci* **61**, 5, doi:10.1167/iovs.61.4.5 (2020).

12 Enayati, S. *et al.* Electrical Stimulation Induces Retinal Muller Cell Proliferation and Their Progenitor Cell Potential. *Cells* **9**, 18, doi:10.3390/cells9030781 (2020).

13 Fu, L., Lo, A. C., Lai, J. S. & Shih, K. C. The role of electrical stimulation therapy in ophthalmic diseases. *Graefes Arch Clin Exp Ophthalmol* **253**, 171-176, doi:10.1007/s00417-014-2889-7 (2015).

14 Wang, A. L., Knight, D. K., Vu, T. T. & Mehta, M. C. Retinitis Pigmentosa: Review of Current Treatment. *Int Ophthalmol Clin* **59**, 263-280, doi:10.1097/IIO.0000000000000256 (2019).

15 Perin, C. *et al.* Non-invasive current stimulation in vision recovery: a review of the literature. *Restorative Neurology and Neuroscience* **Preprint**, 1-12, doi:10.3233/RNN-190948 (2019).

16 AKF_PRO-RETINA. *Bewertung zur Elektrostimulation am Auge bei Patienten mit retinalen Dystrophien mit Hilfe des Okustim-Gerätes der Firma Okuvision GmbH*, <https://www.pro-retina.de/forschungsfoerderung/wissenschaftliche-beratungsgremien/empfehlungen/bewertung-zur-elektrostimulation-am-auge> (2014).

17 Jolly, J. K. *et al.* Transcorneal Electrical Stimulation for the Treatment of Retinitis Pigmentosa: A Multicenter Safety Study of the OkuStim® System (TESOLA-Study). *Ophthalmic research*, doi:10.1159/000505001 (2019).

18 Wagner, S. K. *et al.* Transcorneal electrical stimulation for the treatment of retinitis pigmentosa: results from the TESOLAUK trial. *BMJ Open Ophthalmol* **2**, e000096, doi:10.1136/bmjophth-2017-000096 (2017).