Transcutaneous periorbital electrical stimulation in the treatment of dry eye

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ABSTRACT

Purpose To evaluate efficacy and safety of transcutaneous application of electrical current on symptoms and clinical signs of dry eye (DE).

Methods 27 patients with DE underwent transcutaneous electrostimulation with electrodes placed onto the periorbital region of both eyes and manual stimulation with a hand-piece conductor moved by the operator. Each patient underwent 12 sessions of 22 min spread over 2 months, two sessions per week in the first month and one session per week in the second month. Ocular Surface Disease Index (OSDI) questionnaire, tear break-up time (TBUT), fluorescein staining of the cornea, Schirmer I test and adverse events were evaluated at baseline, at end of treatment and at 6 and 12 months.

Results OSDI improved from 43.0±19.2 at baseline to 25.3±22.1 at end of treatment (mean±SD, p=0.001). These effects were substantially maintained at 6-month and 12-month follow-up evaluations. Improvement of the values of TBUT was recorded for the right eye at the end of treatment (p=0.003) and found in the left eye after 12 months (p=0.02). The Oxford scores changed in both eyes at the end of treatment and at the 6-month evaluation (p<0.001), and in the right eye at the 12-month evaluation (p=0.035). Schirmer I improved significantly at the end of treatment in the left eye (p=0.001) and in both eyes at the 12-month evaluation (p=0.004 and p=0.039 for the left and right eye, respectively). A significant reduction of the use of tear substitutes was found at the end of treatment (p=0.003), and was maintained during the follow-up (p<0.001).

No complications occurred and patients found the treatment satisfying.

Conclusions Transcutaneous electrical stimulation was shown to improve DE, both subjectively and objectively, without any adverse effects and has the potential to enlarge the armamentarium for treating DE.

INTRODUCTION

Aetiology and management of dry eye (DE) challenge ophthalmologists. The International Dry Eye WorkShop in 2007 defined DE as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbances and tears film instability with potential damage to the ocular surface … accompanied by increased osmolarity of tear film and inflammation of the ocular surface'.[1]

Tear dysfunctions leading to DE include primary tear deficiency, tear deficiency associated with systemic connective tissue disorders (eg, Sjögren syndrome), and evaporative loss of water from the tear film in subjects with normal lacrimal secretory function.[2]

All these conditions can lead to the alteration of the tear aqueous, mucin and lipid components that results in the hyperosmolarity of the tear film, a key step in the vicious circle of DE pathology evolving in a chronic inflammatory disease.[3]

Despite the causative mechanisms, tear substitutes to moisten the ocular surface and improve ocular comfort represent the first line in patients with DE. Symptoms rarely completely disappear, while their reduction positively affects patients' quality of life and improves sleep and mood disorders.[4 5]

Since current treatments are substantially palliative, as no one are capable of restoring the physiological lacrimal secretion,[6] a more reliable therapeutic approach could be obtained by the dynamic adaptation of treatment to address every single ocular surface structure involved in the tear film dysfunction.[7]

Consequently, emerging treatments to enlarge the therapeutic armamentarium are currently focused on new drugs that stimulate tear secretion, or on the mechanical stimulation of eyelid and periocular region, by vibration, massage and thermotherapy, or that specifically address the recovering of the meibomian gland function with the thermal pulsation system.[8–10]

No studies have considered the use of electrotherapy to treat DE, although transcutaneous electrical stimulation of nerves and muscles through adhesive pads showed efficacy in different fields of medicine, for example, physiotherapy, pain management, urogenital disorders and obstructive sleep apnoea.[11–13]

Recently, the transpalpebral microcurrent stimulation showed potential efficacy in the treatment of macular degeneration.[14 15]

The application of a frequency-specific electrical current in the range of 4–64 MHz, patented as quantum molecular resonance (QMR) technology by Telea Electronic Engineering (Sandrigo, Italy), showed to be effective in reducing joint effusion in patients undergoing total knee arthroplasty[16] and in skin antiageing treatment (unpublished results).

The QMR was originally employed in an electrosurgical device (VESALIUS, Telea Electronic Engineering, Italy) to achieve both precise cut and coagulation functions, without increasing temperature and damaging the surrounding tissue.[17] According to QMR, the energy is transmitted to the tissue packed into quanta, the energy of each quantum being proportional to the frequency of the current provided. The spectrum of frequencies

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used by QMR produces an amount of energy adequate to break the molecular bonds in the biological tissue, and to obtain a non-traumatic incision of the tissue, without pressure or crashing of the cells, always keep a temperature lower than 50°C, as coagulation results from protein denaturation instead of tissue warming.

In a subsequent and distinct application of QMR at lower current intensities, the effect of incision of the tissue has been replaced by a stimulation effect that leads to a structural and functional improvement, particularly evident in skin, muscles and joints. Again, the electrical field applied through large plate electrodes has no thermal effects, and improvements appear following applications repeated at intervals of one or a few days.

In vitro studies in cultured murine muscle fibres showed that QMR produces (1) a mechanical stimulation, (2) an electrical interaction with the cellular membrane and (3) a biochemical interaction that involves the internal structures of the cells, particularly the sarcoplasmic reticulum.[18] The series of contractions and relaxations that the cells undergo trigger intercellular and intracellular metabolism. Moreover, the increase in the concentration of calcium ions within the cell constitutes an effective activation signal of intracellular calcium-dependent metabolic pathways. We believe that through the series of contractions and relaxations during this peculiar '*cellular massage*', some biochemical stimulation of cellular structures is obtained that can explain the positive effects achieved by QMR in physiotherapy and aesthetic medicine.

In the case of DE, our hypothesis is that QMR can stimulate the lacrimal system, reactivating the lacrimal and meibomian gland tissue and benefit the ocular annexes.

An initial study was performed by J. Schroeter, at the Charité Augenklinik in Berlin, on seven patients with moderate to severe DE and blepharitis. Data from this case series showed that the stimulation with QMR by means of adhesive electrodes on the periorbital area of both eyes improves DE clinically and subjectively in about half of the patients, without side effects (unpublished results).

Based on these encouraging results, the present study was designed to assess QMR in a larger group of patients with DE, with the aim to evaluate safety and potential efficacy, early after treatment and in the long term.

MATERIALS AND METHODS

A prospective, open-label, single-arm pilot study was conducted at the Eye Clinic of the University of Verona, from December 2012 to September 2014, in agreement with the tenets of the Declaration of Helsinki. Institutional Ethical Committee approval and written patients' informed consent were obtained.

Patient selection

We included adult patients with diagnosis of DE in both eyes, regular use of tear substitutes eye drops, complete eyelids occlusion, Ocular Surface Disease Index (OSDI) score >12, Schirmer I test (without anaesthetic) <10 mm/5 min in both eyes and tear break-up time (TBUT) <10 s in both eyes.

We excluded patients requiring anti-inflammatory, antibiotic or glaucoma eye drops; history of ocular surgery in the previous 3 months; who suffered from ocular infection in the previous 6 months; holding a non-removable electrical device (eg, cardiac pacemaker); or with dermatological skin problems (eg, rosacea, acne). We assessed meibomian gland dysfunction (MGD) by slit-lamp evaluation of lid debris and telangiectasias, and collected patients' medical and personal history to evaluate the presence of risk factors for DE.

Patients were allowed to adjust their current tear substitutes during the study period, and other eye drops were not allowed.

Application of electrical stimulation

Electrical stimuli were applied by means of electrodes placed in the periorbital area of both eyes using the REXON-EYE (Telea Electronic Engineering, Sandrigo, Italy; patent pending), a device that generates QMR by high-frequency (4–64 MHz) and low-power (60–120 mJ/cm^2/s) electrical currents. Its function is based on the resonance effect, which is the possibility of maximising the delivery of energy to biological tissues by oscillating electric fields without increasing the temperature and eliciting biological responses, both pathophysiological and potentially therapeutic.[18–20]

Each session of stimulation consisted in two sequential phases: in the first phase, we applied two electrodes close to each eye, one over the temporal area and one under the lower lid, and activated each of them for 60 s in sequence. The cycle was repeated 4 times, for a total stimulation length of 16 min, at a nominal power of 80 mJ/cm^2/s. In the second phase, the operator moved a hand-piece conductor around the periorbital areas of both eyes during two sequential phases of 3 min each, with a 1 min rest, for a total stimulation time of 6 min, at a nominal power of 80 mJ/cm^2/s.

Each patient underwent 12 sessions of stimulation during a 2-month period: two sessions per week in the first month, and one session per week in the second month. Nominal power and number of sessions were chosen based on previous experiences that showed that 80 mJ/cm^2/s is effective without inducing any patients' discomfort, for example, excessive heat. A repetition of treatment every 3 days in the first month appeared adequate to induce an effect, as well as the repetition of treatment every week in the following month to maintain such effect.

Patients laid down on a bed with head elevated and a passive electrode applied under their back (figure 1). Electrical stimulation was perceived as a pleasant sensation, as a mild warmth under the electrodes. In the case of excessive or absence of the warm sensation, the operator could modify the intensity from the nominal value of 80 mJ/cm^2/s to lower or higher values, respectively, in the range of power allowed by the device.

Outcome assessment

We evaluated all patients at baseline, at 1 week after the last treatment session (end of treatment), and at 6 and 12 months after treatment. The following were assessed: (1) OSDI score (primary endpoint),[14] (2) TBUT, (3) corneal staining with fluorescein dye (Oxford grading system)[21] and (4) Schirmer I test.

During the treatment period, patients recorded daily on a diary (1) type and frequency of tear substitutes, (2) additional eye drops or systemic drugs used for DE or any condition other than DE, and (3) ocular symptoms. We assessed safety before and after each session of treatment, and during a further visit 1 week after the end of treatment. Before starting each session, the treating physician examined the occurrence of adverse events, general health status and eye complaints arisen from the previous visit. Recordings in the diary were also examined.

Safety evaluation after each session of treatment included (1) potential side effects, (2) biomicroscopy of the anterior segment, (3) corneal sensitivity (cotton tip) and (4) intraocular pressure (Goldman tonometry). We measured uncorrected and best-corrected visual acuity at baseline and at the end of treatment.

Figure 1 Patient receiving microcurrent treatment. (A) During the first phase of each session of treatment, we applied two adhesive electrodes close to each eye, one over the temporal area and one under the lower lid. (B) During the second phase of each session of treatment, the operator moved a hand-piece conductor around the periorbital areas of both eyes.

Statistical analysis

A sample size of 26 patients achieves 80% power to detect a mean standardised difference (mean of the change of OSDI measured at baseline and at the end of treatment over the SD of the change between baseline and end of treatment) of at least 0.6 at a significant level of 5% using the Wilcoxon test for paired observations. To take into account a dropout rate of 15% we sought to enrol at least 31 patients.

We expressed results of descriptive analyses as a means and SD, median and range for quantitative variables, and as a count and percentage for categorical variables. All observations were analysed together or per eye. The primary endpoint and the clinical outcomes were also analysed with respect to the type of DE. Differences of measurements between two time points were assessed with the Wilcoxon signed rank test, and between groups with Wilcoxon rank sum test. A p value <0.05 was considered statistically significant.

Since the pilot nature of the study, we did not make adjustments for taking into account multiple comparisons. Spearman correlation analysis was performed to investigate the possible correlation between response to treatment and baseline values of OSDI scores. A positive Spearman correlation coefficient (rho) indicates positive correlation between severity of OSDI score and effective response to treatment. Statistical analyses were performed with R 3.2.3 for Windows and with SAS statistical software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Thirty-two patients who met the inclusion criteria were recruited and 27, with a mean age of 57.3 (14.9) years (median 58.0; range 23–82), were included in the analyses (table 1). Five patients were not included because they missed to attend to one or more treatment sessions due to professional or personal reasons.

Table 1 Patients' demographics and baseline characteristics (N=27)

	N (%)
Sex	
Female	21 (77.8)
Male	6 (22.2)
Systemic risk factors for DE	
No	19 (70.4)
Yes	8 (29.6)
Sjögren syndrome	4
Rheumatoid arthritis	2
Sarcoidosis	1
Use of antidepressant drugs	1
Lid margins	
Normal	20 (74.1)
Meibomian gland dysfunction	7 (25.9)
Duration of DE (years)	
Mean (SD)	11.8 (13.4)
Median	10
Range	1–55
Type of DE*	
Evaporative	18 (66.7)
Hyposecretive	9 (33.3)
Ocular Surface Disease Index score	
Mean (SD)	43.0 (19.2)
0–12 normal	0
13–22 mild	3 (11.1)
23–32 moderate	6 (22.2)
33–100 severe	18 (66.7)
Schirmer I test (mm)	
Mean (SD)	6.4 (3.5)
>10	0
5–10	21 (77.8)
<5	6 (22.2)
Tear film break-up time (seconds)	
Mean (SD)	4.7 (2.3)
>10	0
10–5	12 (44.4)
<5	15 (55.6)
Oxford test	
Mean (SD)	1.2 (0.9)
0	2 (7.4)
1–2	21 (77.8)
3–5	4 (14.8)
Tear substitutes (no. of drops/day)	
Mean (SD)	6.0 (3.6)
1–3	8 (29.6)
4–6	10 (37.0)
≥7	9 (33.3)

*Two patients have both hyposecretive and evaporative DE.
DE, dry eye.

Before treatment, 16 (59%) patients showed superficial punctate keratopathy in both eyes, 7 (26%) MGD and 4 (15%) anterior blepharitis. None of the patients had undergone prior refractive surgery or used to wear contact lenses.

Type of DE was differentiated into evaporative or hyposecretive based on the presence of aetiological risk factors (ie, autoimmune diseases, use of medications known to reduce tear production, reduced blinking activity during visual display terminal work, previous refractive surgery or blepharoplasty) and on clinical evaluation of MGD.

Among the patients with evaporative DE, seven had MGD, eight had a reduced blinking, two had undergone blepharoplasty 5 years before and one had undergone various post-traumatic maxillofacial surgeries. Seven patients suffering from hyposecretive DE were affected by an autoimmune disease and one assumed antidepressant drug (paroxetine).

OSDI score

The primary efficacy variable significantly improved from 43.0 ±19.2 at baseline to 25.3±22.1 at the end of treatment (mean ±SD, p=0.001). These effects were substantially maintained at 6-month and 12-month follow-up evaluations. Compared with baseline, OSDI scores showed significant (p<0.01) mean (SD) differences of −17.7 (24.6) at the end of treatment, −15.0 (19.0) at 6 months and of −13.1 (17.6) at 12 months. No statistically significant differences were found in between end of treatment and 6-month and 12-month follow-up (figure 2).

The OSDI scores improved at the end of treatment in 17 (63%) patients, and were unaffected in 10 (37%). In 11 out of 17 patients it improved from severe to normal (N=7), moderate (N=3) and mild (N=1) scores, respectively, and in five out of 17 from moderate to normal (N=3) and mild (N=2) scores, respectively. In one patient, the OSDI score improved from mild to normal. Seven out of 10 unresponsive patients persisted in the category of severe OSDI scores (two of these patients significantly worsened the OSDI scores from 32.2 to 41.7 and from 47.5 to 85.0), one patient in that of moderate and two in that of mild.

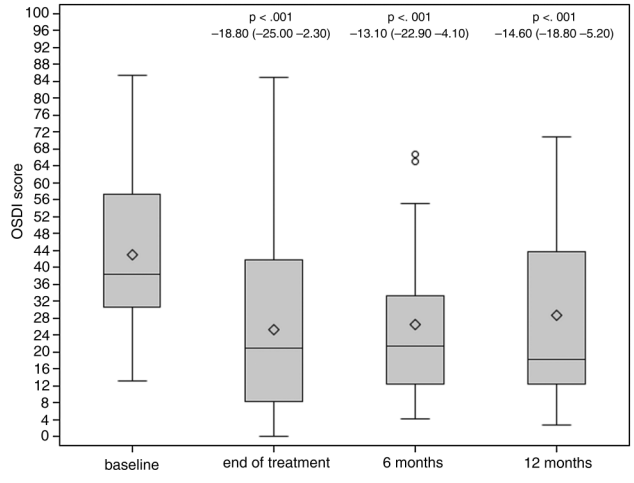

Figure 2 Differences in the Ocular Surface Disease Index (OSDI) scores showed statistically significant reduction from baseline to each evaluation during follow-up, in all patients (N=27). The boxes represent the 25th and 75th percentiles; whiskers are lines extending from each end of the box to the minimum or maximum or the lowest datum within 1.5-fold IQR of the lower quartile or the highest datum within 1.5-fold IQR of the upper quartile. The median value is the line that bisects the boxes, diamond represents the mean and the circles are the outlier values. Data accompanying p values are median and SD.

Patients with evaporative DE reported 31% reduction of OSDI score, from the mean value of 40.5±18.9 at baseline to the 27.7±25.3 value at the end of treatment (– 12.7±24.1; p=0.027).

Patients with hyposecretive DE reported 58% reduction of mean OSDI score, from 48.1±19.8 at baseline (mean±SD) to 20.4±13.8 at the end of treatment (–27.7±23.5; p=0.012).

Compared with baseline, a differential response between evaporative and hyposecretive DE was not significant at all evaluation times (end of treatment p=0.131, 6 months p=0.397, 12 months p=0.066).

Treatment response was unaffected by OSDI severity in patients with evaporative DE at all evaluations, while it was influenced in patients with hyposecretive DE, at the end of treatment and at 6 months (r=−0.63, p=0.067; r=−0.83, p=0.010, respectively).

Tear film break-up time

Significant improvements of the TBUT values were found in the right eye at the end of treatment and in the left eye at 12-month evaluation (table 2). Compared with baseline, 6 (22%) patients worsened TBUT at the end of treatment, in one or both eyes.

Patients with evaporative DE showed higher improvement of TBUT (mean difference±SD) in the right eye than patients with hyposecretive DE, at the end of treatment compared with baseline, 3.7±3.4 and 0.02±3.4 (p=0.007), respectively.

Corneal fluorescein staining

Oxford scores showed statistically significant changes from baseline in both eyes at all evaluations, without statistically differences between end of treatment and the evaluations during follow-up (table 3). Only one patient showed worsened Oxford score value, from 0 to 1 in the left eye, at the end of treatment compared with baseline.

Patients with evaporative DE showed a higher improvement than patients with hyposecretive DE, at the end of treatment compared with baseline, in the right eye (mean difference±SD: −1.0±0.5 and −0.4±0.5, p=0.014).

Schirmer I test

Scores in the Schirmer I test improved significantly after treatment in the left eye and in both eyes at 12 months of evaluation (table 4), while 8 (30%) patients worsened their Schirmer scores

Table 2 TBUT at baseline, end of treatment, and follow-up (N=27)

TBUT (seconds)	Baseline	End of treatment	6 months	12 months
In the left eye				
Mean±SD	4.6±1.8	6.0±4.2	5.3±2.6	7.0±3.8
Median	5.0	4.0	5.0	7.0
Min–max	1.0–8.0	1.0–18.0	1.0–12.0	2.0–15.0
p Value*		n.s.	n.s.	0.01
In the right eye				
Mean (SD)	4.7±2.3	7.1±4.0	5.9±3.2	6.6±2.9
Median	4.5	8.0	5.0	6.0
Min–max	1.0–8.0	1.0–14.0	1.0–13.0	1.0–12.0
p Value*		0.001	n.s.	n.s.

*Between baseline and each evaluation during follow-up.
TBUT, tear break-up time.

Table 3 Corneal fluorescein staining—Oxford score (N=27)

Oxford score	Baseline	End of treatment	6 months	12 months
In the left eye				
Mean±SD	1.2±0.8	0.4±0.9	0.2±0.5	0.8±1.1
Median	1.0	0.0	0.0	0.0
Min–max	0.0–4.0	0.0–4.0	0.0–2.0	0.0–4.0
p Value*		<0.001	<0.001	n.s.
In the right eye				
Mean (SD)	1.2±0.9	0.4±0.9	0.2±0.5	0.6±1.0
Median	1.0	0.0	0.0	0.0
Min–max	0.0–4.0	0.0–4.0	0.0–2.0	0.0–4.0
p Value*		<0.001	<0.001	0.035

*Between baseline and each evaluation during follow-up.

in one or both eyes, at the end of treatment compared with baseline.

Patients with evaporative DE significantly improved Schirmer I scores (mean difference±SD) at the end of treatment compared with baseline in the left eye, 4.1±5.4 (p=0.009), and in both eyes at 12 months, 3.5±4.3 (p=0.007) and 4.4±7.3 (p=0.035), in the left and right eye, respectively. Improvements of Schirmer scores in patients with hyposecretive DE (4.0±5.0 and 0.6±4.2 in the left and right eye at the end of treatment, respectively; 4.4±8.2 and 1.8±7.0 in the left and right eye at 12 months, respectively) did not reach statistical significance (p>0.05).

Use of tear substitutes and long-term subjective evaluation

A significant reduction of the use of tear substitutes was found at the end of treatment, and such a reduction was almost maintained during the follow-up (table 5).

Compared with baseline, at the end of treatment, 19 (70%) patients reduced the daily number of tear substitutes eye drops, 4 (15%) patients completely halted the use of eye drops and 4 (15%) patients increased this number.

Significant reduction in the use of tear substitutes was observed at the end of treatment, compared with baseline, in both evaporative and hyposecretive patients (mean difference ±SD: −1.3±1.2, p=0.021 and −2.6±2.3, p=0.001).

After 12 months, 15 (56%) patients maintained the number of daily tear substitutes eye drops achieved at the end of treatment, 12 were using tear substitutes less than twice daily as rescue therapy and three did not use tear substitutes at all. The remaining 12 (44%) patients reported to use tear substitute eye drops from 3 to 8 times per day.

Table 4 Schirmer I measured at baseline, end of treatment, and follow-up (N=27)

Schirmer test (mm)	Baseline	End of treatment	6 months	12 months
In the left eye				
Mean±SD	5.8±3.1	9.9±6.2	7.3±4.6	10.1±7.0
Median	6.0	11.0	7.5	9.0
Min–max	1.0–10.0	0.0–21.0	0.0–15.0	1.0–27.0
p Value*		<0.001	n.s.	0.002
In the right eye				
Mean (SD)	6.7±3.2	8.0±5.8	9.1±7.5	10.4±8.0
Median	7.0	9.0	8.0	9.0
Min–max	1.0–9.5	0.0–20.0	0.0–30.0	0.0–26.0
p Value*		n.s.	n.s.	0.034

*Between baseline and each evaluation during follow-up.

Table 5 Daily use of tear substitutes (N=27)

No. of drops/day	Baseline	End of treatment	6 months	12 months
Mean±SD	5.5±3.8	3.8±2.8	3.1±2.6	4.0±2.5
Median	4.5	3.0	3.0	3.0
Min–max	1.0–14.5	0.0–12.0	0.0–12.0	0.0–12.0
p Value*		0.003	<0.001	<0.001

*Between baseline and each evaluation during follow-up.

Patients provided a subjective evaluation on the maintenance or loss of the result obtained at the end of treatment in the subsequent months. Eight (30%) patients reported that the results of treatment were maintained up to 12 months, 7 (26%) patients that results decreased in the following months and 12 (44%) patients stated that DE was not affected by treatment or that the improvements were quickly lost within the first 2 months after the end of treatment.

Electrical stimulation power applied during study

All patients started both phases of treatment at the nominal power 80 mJ/cm^2/s, as per protocol criteria. Following the first application of QMR during the first phase of treatment (the adhesive electrodes application), we reduced the power to 75 mJ/cm^2/s in two patients, increased it to 90 mJ/cm^2/s in 24 patients, while in one patient the power was not modified. In the second phase of treatment (the hand-piece conductor application), following the first application the power was increased to 100 mJ/cm^2/s in 25 patients and in two patients it was not modified. These powers were then applied unchanged during all the subsequent application sessions.

Safety evaluation

All patients were compliant with the study procedures and underwent all sessions of treatment scheduled by the study protocol.

Adverse effects related to the use of the REXON-EYE occurred in three cases, two patients showed mild cutaneous transitory erythema following the first application of the treatment and one patient generically felt uncomfortable during the first session of treatment. None of these effects was judged as serious. Erythema resolved spontaneously, without recurrences during the following sessions of treatment.

All patients found the treatment very pleasant and none of them asked to stop treatment during stimulation.

Three patients reported blepharitis, conjunctivitis and anterior uveitis (one event each) within the second month of treatment and one patient suffered from a seasonal allergy during the last 2 weeks of treatment. All these effects were mild in severity and not considered related to the treatment.

Intraocular pressure and corneal sensibility, measured after each session of treatment, and uncorrected and best-corrected visual acuity, measured at baseline and at the end of treatment, showed no changes.

DISCUSSION

DE is a chronic disorder and its management is often inadequate, as no established proper cure is available. Patients need to find the better treatment that suits their own condition, must learn how to prevent triggers, and have to refer to doctors in the case of the condition worsening. Tear substitutes, traditional

warm compresses and heating devices can only help patients to control symptoms to some extent.

In the present study, we show that the periorbital transcutaneous electrical stimulation, with high-frequency low-power microcurrents, significantly affect subjective outcomes and objective measures in patients with DE.

Studies that have investigated the response of cells and tissues to oscillating electrical fields showed that the direct effects of these fields may be attributed to dielectric dispersion, that is, to the variations of the permittivity of a dielectric material in relation to the frequency of the applied electric field.

Although the mechanisms by which the stimulation obtained with high-frequency electrical fields can benefit DE are still unknown, we may offer two possible hypotheses to explain the positive results obtained in the present study, as regards the biological effects induced by this electrical stimulation.

The first hypothesis is that high-frequency low-power microcurrents generated by REXON-EYE could stimulate the self-renewal processes of tissues. A study on cultured muscle fibres[18] showed that QMR determines a change in the membrane potential and increases intracellular free calcium. Therefore, the biological effects of this electric field are strictly related to the cells' biochemistry and the activation of intracellular metabolic pathways.

The second hypothesis is based on the deformation of the cell membranes induced by QMR, which could lead to a cascade of reactions at cellular level capable of increasing the normal metabolism.

It is important to underline that none of these potential mechanisms involves an increase of the tissue temperature to produce a cellular stimulation.

We chose the OSDI score as primary outcome of our study because the main goal of treatment of DE is to improve the symptoms. Moreover, Shiffman[22] showed that OSDI score provides a quantifiable assessment of the frequency of DE symptoms and of their impact on the vision-related function, without the need of a strict correlation between OSDI score and clinical signs. With respect to this, we observed a significant reduction of the OSDI scores at the end of treatment, with a more marked effect on patients with hyposecretive DE.

However, the differential effect in favour of evaporative patients we have found for TBUT, corneal staining and Schirmer test seems to indicate that the evaporative group obtained better objective results.

Whether or not patients with evaporative or hyposecretive DE could differently benefit from the REXON-EYE treatment, and the overall positive effects we have found as well, cannot be proved without a carefully designed randomised clinical trial. Moreover, the difficulties of implementing a placebo group in which the electrodes were placed but not activated, with the risk that patients could easily unmask the mild heat sensation due to the QMR, are another limitation.

However, an important key strength of this study is the long-term follow-up, which allows us to monitor all patients for up to 12 months after the end of treatment and thus appreciate how they were able to basically maintain the improvements over such an extended period of time.

Finally, based on the favourable results provided by this study, scheduling of sessions and the overall duration of treatment should be further evaluated and optimised, in order to shorten and simplify the treatment protocol without affecting its overall efficacy.

In conclusion, this study shows that 2-month treatment with the REXON-EYE is a safe and effective treatment option to improve subjective and objective symptoms in patients with DE, and to reduce the number of applications of tear substitutes eye drops.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Ethics Committee Protocol No. TELEA RE, Prog. No. 2223, 24th October 2012.

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Transcutaneous periorbital electrical stimulation in the treatment of dry eye

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