Quantum Molecular Resonance Effects on Patients With Dry Eye Disease: A Randomized Controlled Trial

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Purpose: The aim of the study was to evaluate the efficacy and safety of quantum molecular resonance in the treatment of dry eye disease.

Methods: This study was a double-blind randomized control trial in 1 academic medical center, for 2 years. Participants received treatment or a placebo with the Rexon-Eye device, once per week for 4 weeks. The primary outcome was the change in dry eye symptoms assessed by the Ocular Surface Disease Index (OSDI). Secondary outcomes were clinical findings associated with the dry eye such as meibomian gland dysfunction (MGD) score, tear break-up time (TBUT), corneal fluorescein staining, Schirmer test, and bestcorrected visual acuity (BCVA).

Results: Forty patients were recruited, 20 in each arm. The mean age was 63.5 ± 15.1 years and 27 (67.5%) were female. The mean OSDI score significantly improved in the intervention group from 19.15 ± 10.3 to 10.5 ± 7.0 (P < 0.001), whereas the control group showed no significant change (14.4 ± 8.4 to 15.5 ± 8.6 , P = 0.830). MGD scores significantly improved in the intervention group (1.57 ± 1.2 to 0.8 ± 0.9 , P = 0.006), whereas showing no significant change in the control group (1.60 ± 0.9 to 1.99 ± 1.0 , P = 0.244). The corneal staining score also showed significant decline in the placebo group (P = 0.50). No significant difference was seen in TBUT, visual acuity, and Schirmer scores

between groups. No harm resulting from treatment was reported during the duration of the trial.

Conclusions: High-frequency electrotherapy may have a positive effect on symptoms and signs of dry eye. This emerging technology may become part of the arsenal of therapeutic modalities for this condition.

Key Words: dry eye, dry eye disease, quantum molecular resonance, Rexon, Ocular Surface Disease Index

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Dry eye disease (DED) is a highly prevalent and disabling disorder, which affects approximately 9 million persons in the United States alone.¹ Affected individuals can have a considerable reduction in quality of life and suffer from decreased visual function, social and physical functioning, and workplace productivity.² Available treatments include the administration of artificial tear substitutes, suppression of ocular inflammation, eyelid hygiene, and targeted treatment for improving meibomian gland function. However, these therapeutic modalities have limited efficacy and the dry eye remains a chronic and debilitating disorder and an area of unmet medical need.³

The Rexon-Eye device (Resono Ophthalmic Inc, Sandrigo, Italy) is a new device based on quantum molecular resonance (QMR) technology. QMR is a technique in which low-intensity, high-frequency electric currents are administered to a biological tissue through contact electrodes.⁴ The Rexon-Eye device applies stimulation to the epidermis of closed eyelids up to the lid margin through specially designed goggles. Previous studies have shown a favorable safety profile with high patient satisfaction for several QMR devices. Results of several studies suggested that the Rexon device can be an effective tool for accelerating healing in systemic chronic wounds and tissue regeneration.^{5,6} In addition, 2 recent observational, nonrandomized studies reported the device to be both subjectively and objectively effective for treating symptoms of dry eye; however, no control group was evaluated.^{6,7}

Given these results, we set out to evaluate whether the QMR technology is effective for the treatment of dry eye disorder. The purpose of this study was to evaluate the efficacy and safety of the Rexon-Eye device in a randomized, placebo-controlled, double-blind fashion.

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This study was approved by the institutional research committee (Reference number: 0194-20-ASF) and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study involves human participants and was approved by Shamir Medical Center Helsinki Ethics Committee. Reference number: 0194-20-ASF.

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METHODS

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Shamir Medical Center. Informed written consent was granted before enrollment.

Design and Patient Population

The study was conducted at Shamir Medical Center (Assaf-Harofeh), an academic tertiary medical center in central Israel. This was a double-masked, randomized control trial (ClinicalTrials.gov Identifier: NCT05469932).

We included male or female subjects 18 years or older who have the full legal capacity to volunteer on the date the informed consent document is signed. Additional inclusion criteria were subjects who agreed to participate in the study, subjects who can follow the instructions of the clinical staff at the clinical site, can attend examinations on the scheduled examination date, and subjects who meet the applicable criteria for patients suspected of having DED. A diagnosis of DED was obtained after a corneal specialist examination. The definition of DED was defined as having each of the following in OU: 1) Ocular Surface Disease Index (OSDI) score <13, 2) tear break-up time (TBUT) ≤ 10 , and 3) corneal staining ≥ 1 . We excluded subjects who routinely use contact lenses, have active intraocular inflammation, female subjects of childbearing potential who are currently pregnant or nursing, experienced ocular trauma, or subjects who underwent any ophthalmic intervention (surgery, refractive laser surgery, etc) within 6 months before the trial.

Study Protocol

Participants were randomized into 2 groups: intervention and placebo groups. Patients in the intervention group were treated with the Rexon-Eye device 4 times, once per week for a total of 4 weeks at the manufacturer's recommended power setting (power 4). Patients in the control group were treated at identical treatment sessions with the Rexon-Eye device (4 times, once per week for a total of 4 weeks) at identical locations and duration. They were connected to the device; however, the device was set at zero power during treatment. Throughout the trial, we took all measures to ensure that patients had a consistent experience in both groups, making it difficult for them to discern whether they were receiving active treatment or placebo. Treatment sessions were scheduled at varying times, effectively preventing communication between participants in the 2 groups.

All patients were examined by an experienced ophthalmologist before the first treatment and after the last treatment.



FIGURE 1. Diagram showing the flow of participants through each stage of the trial (CONSORT).

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	Intervention Group		Control Group		
Variable	N (%)	SD	N (%)	SD	P
No. of patients	20		20		
Age, mean	62.8	16.5	64.3	14.1	0.769
Female sex	13 (65)		14 (70)		0.736
BMI, kg/m ²	26.6	7.2	26.2	6.0	0.867
Medical history					
Smoking	4 (20)		3 (15)		0.677
Asthma	0 (0)		2 (10)		0.136
Diabetes mellitus	3 (15)		7 (35)		0.118
Hypertension	4 (20)		7 (35)		0.243
History of malignancy*	1 (5)		0 (0)		0.323
Ocular history					
Refractive surgery - LASIK	2 (10)		1 (5)		0.720
Refractive surgery - PRK	3 (15)		2 (10)		0.652
Cataract surgery	6 (30)		9 (45)		0.484
Pars plana vitrectomy	1 (5)		1 (5)		1.0
Anti-VEGF treatment	0 (0)		1 (5)		0.323
Blepharoplasty	4 (20)		3 (15)		0.677
Pterygium	0 (0)		1 (5)		0.323
BCVA (logMAR)	0.141	0.155	0.133	0.11	0.855
Signs and symptoms of dry eye disease (mean \pm SD)					
Baseline OSDI score, mean	19.15	10.3	14.4	8.4	0.119
MGD score, mean	1.57	1.2	1.60	0.9	0.943
Tear break-up time, seconds	6.58	3.1	6.65	2.9	0.941
Corneal staining, mean	2.25	2.3	2.30	2.1	0.943
Schirmer score, mm	8.50	7.5	10.6	7.7	0.379

TABLE 1.	Clinical	Characteristics	of th	e Intervention	and
Control G	roups at	Baseline			

Clinical and demographic characteristics of 40 patients included in the study. *One individual in the intervention group had thyroid cancer. BMI, body mass index.

Each examination was composed of a subjective questionnaire (eg, OSDI) filled out by the subject and clinical assessment that included the following for each eye: meibomian gland dysfunction (MGD) score: we used gentle meibomian gland expression for the lower and upper eyelids using a cotton-tipped applicator. Secretions were graded according to the Bron scale (0 = clear, 1 = cloudy, 2 =cloudy with debris, and 3 = inspissated, toothpaste-like). MGD score was calculated as a mean of both upper and lower lids; TBUT was assessed after placing a drop of fluorescein solution into the eye; and corneal staining was evaluated under cobalt blue filter illumination after fluorescein instillation. The cornea was examined for the presence of discrete "dots" of staining, and the number of dots was counted and assigned a grading score (0 = 0 dots, 1 = 1-5 dots, 2 = 6-30dots, and 3 = >30 dots). Additional extra points are collected for patches of confluent staining (+1 point), staining in the pupillary area (+1 point), and the presence of one or more filaments (+1 point). The total ocular staining score for each eye was determined by adding up the fluorescein score for the cornea. The maximum possible score for each eye was 6.

MGD score, TBUTs, and corneal staining were measured
using a slit-lamp biomicroscope. Schirmer test was conducted
after anesthesia with 1 drop of oxybuprocaine hydrochloride
0.4%. The physician then bend a TearFlo Schirmer test strip
(HUB Pharmaceuticals, LLC) and placed it into the lower
temporal lid margin of each eye of the participant. Subjects
were instructed to close their eyes. After 5 minutes have
elapsed, the Schirmer strip was removed. The length of the
moistened area was recorded (mm) for each eye separately.

Demographics, medical history, concomitant medication, and artificial tear use data were collected. During the trial, the patients were instructed to continue their regular treatment for dry eye (eg, artificial tears, etc).

Masking

Patients and examiners were masked to the allocation. Patients allocated to the placebo group were given the same number and length of treatments performed identically to the intervention group but with the device set to a power of zero in the duration of treatment. During treatment, the electrical current provided by the device is not felt by the patient and no noise or other indication exists for the power setting used. Patients did not have access to the device control panel or display. Ophthalmologists examining the patients at the beginning and end of the trial were also masked to the treatment.

Outcomes

The primary objective of this study was to evaluate the change in dry eye symptoms assessed by the OSDI between patients treated with the Rexon-Eye device and controls. This index has been previously shown to be a valid and reliable instrument for measuring the severity of DED.⁸ It is based on assessing 3 aspects: ocular symptoms, vision-related function, and environmental triggers. The index was assessed twice, at the beginning of the trial and after the last treatment.

Secondary objectives were clinical signs associated with a dry eye disorder, which were assessed by a masked examiner. These included MGD score, TBUT, corneal staining score, Schirmer score, and best-corrected visual acuity (BCVA).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 23.0 by IBM (Armonk, NY). For categorical variables, χ^2 tests were used. Clinical parameter distributions were tested for normality by the Shapiro–Wilk test. Independent and paired t-tests were conducted for continuous variables with a normal distribution and the Mann–Whitney U and Wilcoxon tests were for variables with a nonnormal distribution. For TBUT, a cutoff of 10 seconds was used to indicate normal and abnormal values. *P* values less than 0.05 on a 2-sided test were considered statistically significant. To avoid biases arising from between-eye correlation, a single eye (right eye) of each patient was included in the analysis.⁹

	Intervention Group		Control Group		
Variable	Change	SD	Change	SD	1 P
Main outcome					
Overall OSDI score	-8.6	7.8	0.5	9.4	0.002
1st part*	-3.2	3.7	0	5.7	0.036
2nd part†	-3.0	3.2	0.4	1.9	0.004
3rd part‡	-2.6	3.6	0.9	3.4	0.003
Secondary outcomes					
MGD score	-0.75	1.1	0.37	1.4	0.007
Upper lid	-0.60	1.3	0.35	1.5	0.037
Lower lid	-0.90	1.0	0.41	1.6	0.004
Tear break-up time, sec	1.6	4.1	-0.45	3.3	0.097
Corneal staining	-1.1	2.3	0.30	1.9	0.044
Schirmer score (mm)	0.90	5.0	1.65	6.7	0.693
BCVA (logMAR)	-0.0074	0.06	0.0049	0.04	0.450

Table 2.	Clinical	Outcomes	Between	Groups
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*Symptoms.

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+Limitation in activity.

[†]Environmental triggers.

Clinical outcomes of the 40 patients included in the study according to the group. The change in each parameter after the trial period is compared between groups Data were expressed as mean \pm SD. Significant values are in bold.

We also report the outcomes for the left eye for sensitivity testing.

Sample Size

For sample size calculations, we used the reduction in OSDI as the primary outcome.8 Power calculations showed that a minimum of 14 participants in each group were required to detect a clinically significant difference of 5 points with a 2-sided significance level of 0.05 and a power of 80% using a paired model. The SD of normal values was estimated to be 6 points. To increase power and take into account unexpected variables, we decided on an additional 30% margin and recruitment was set at 20 participants in each group. Calculations were performed using MedCalc software version 16 (Mariakerke, Belgium).

RESULTS

Participant Flow and Baseline Data

Forty patients were recruited and included in the final analysis (20 were randomly allocated to the intervention group and 20 to the control group; Fig. 1). The mean age was 63.5 ± 15.1 years and 27 (67.5%) were female. Eight patients had previously undergone laser refractive surgery (n = 5photorefractive keratectomy (PRK), n = 3 laser-assisted in situ keratomileusis (LASIK)), 16 patients had a history of cataract surgery (14 in OU, 2 in either the left or right eye only), and 2 patients had previously undergone pars plana vitrectomy. No statistically significant difference in any baseline characteristic was seen between the 2 groups. All 40 patients had a known diagnosis of DED. Additional baseline characteristics are available in Table 1.

Main Outcome: OSDI Scores

Baseline OSDI scores were similar between groups (Table 1). The mean OSDI score significantly improved in the intervention group from 19.15 \pm 10.3 to 10.5 \pm 7.0 (P < 0.001), whereas the control group showed no statistically significant change (14.4 \pm 8.4–15.5 \pm 8.6, P = 0.830). The difference between groups was statistically significant $(-8.6 \pm 7.8 \text{ vs. } 0.5 \pm 9.4, \text{ intervention and control groups},$ respectively, P = 0.002). A comparison of clinical outcomes between groups is further detailed in Table 2.

Assessing the individual parts of the OSDI showed consistent results. In all 3 parts individually, a significant improvement was seen in the intervention group but not in the control (Fig. 2 and Table 3).

Secondary Outcomes: Clinical Signs Assessment

MGD scores significantly improved in the intervention group $(1.57 \pm 1.2 - 0.8 \pm 0.9, P = 0.006)$ while showing no significant change in the control group (1.60 \pm 0.9–1.97 \pm 1.0, P = 0.244). The lower eyelids specifically showed the largest amount of improvement (1.50 \pm 1.1–0.60 \pm 0.8, P = 0.001 in the intervention group; $1.60 \pm 1.0-2.0 \pm 1.1$, P = 0.269 in the control group; Table 3).

Further secondary outcomes included corneal staining that showed a significant improvement in the intervention group $(2.25 \pm 2.3 - 1.1 \pm 1.4, P = 0.045)$ while showing a nonsignificant change in the control group (2.3 \pm 2.1–2.6 \pm 2.1, P = 0.500). The difference between groups was also statistically significant (Table 2).

TBUT showed a nonsignificant improvement in the intervention group (6.6 \pm 3.1–8.2 \pm 2.4 seconds, P = 0.112) and a nonsignificant decline in the control group (6.6 \pm $2.9-6.2 \pm 2.2$ seconds, P = 0.549). In the intervention group, 7 patients (35%) improved from below 10 seconds to 10 or more seconds, compared with only 1 (5%) in the control group (P = 0.082, Table 2).

Schirmer scores showed no significant change in either group after the study period, and no significant differences between groups were seen (Table 2). To further assess sensitivity scores, we also analyzed the left eye scores, which demonstrated similar results between groups (Supplemental Table 1, Supplemental Digital Content 1, hiip://links.lww. com/ICO/B608).

Safety and Side Effects

Visual acuity was assessed for safety monitoring. Visual acuity did not change significantly in the duration of the trial (0.141 \pm 0.155 logarithm of the minimum angle of resolution (logMAR) [Snellen equivalent: 20/27.67] to 0.133 ± 0.12 logMAR [Snellen equivalent: 20/27.16], P = 0.578 in the intervention group; 0.133 \pm 0.11 logMAR [Snellen equivalent: 20/27.16] to $0.137 \pm 0.11 \log$ MAR [Snellen equivalent: 20/27.41], P = 0.609 in the control group). No further adverse events were reported during the trial.

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FIGURE 2. Comparison of OSDI scores between groups. (The full color version of this figure is available at www.corneajrnl.com.)

DISCUSSION

In this study, 40 patients with DED were randomly and blindly allocated to either receive treatment with a low-power high-frequency electric stimulation applied to the periocular area in several sessions or a placebo group who attended identical treatment sessions with the device power set to zero. Participants filled out the OSDI questionnaire and were examined by an ophthalmologist, masked to the allocation, before and after the study period. Signs and symptoms of dry eye were recorded. Results show significant improvement in symptoms of dry eye as recorded in all 3 parts of the OSDI questionnaire in the intervention group, whereas no change was seen in the control group. Signs of dry eye were also significantly improved in the intervention group while showing a minimal change in the control group.

To the best of our knowledge, this is the first randomized control trial that evaluated the role of QMR high-frequency electrotherapy for patients with DED. Our results showed a positive effect on both signs and symptoms and demonstrated a good safety profile, with no adverse events reported. These results suggest that this treatment modality might be considered an additional option in the arsenal of treatments for dry eye disease. It should be noted that patients continued their regular treatment with preservative-free artificial tears so the QMR treatment can only be considered an adjunct treatment option based on these results.

QMR uses the principle of tissue regeneration by using a high-frequency, low-intensity alternate electrical current. Several mechanisms of action of QMR-mediated healing have been proposed, including mechanical deformation of the cellular membrane, transient membrane potential modification, and calcium ion release from the sarcoplasmic reticulum; however, the exact physiological mechanism remains known.⁴

QMR technology is in practice in other fields of medicine such as musculoskeletal disorders, neurology, plastic and reconstructive surgery, otorhinolaryngology, and more. It has been shown to positively affect wound healing and postoperative inflammation.^{5,10–13}

QMR has been examined before in the context of DED. One previous study reported the capabilities of QMR in 27 patients with DED. The authors showed improvement in all

Table 3.	Clinical	Outcomes	Before	and After	Treatment in
Both Gro	ups				

	Before Treatment		After Treatment		
Variable	Mean	SD	Mean	SD	Р
Intervention group					
Overall OSDI score	19.15	10.3	10.5	7.0	< 0.001
1st part*	8.15	4.5	4.9	3.4	0.001
2nd part†	5.44	4.6	2.4	3.1	0.001
3rd part‡	5.9	4.1	3.3	2.6	0.005
MGD score	1.57	1.2	0.8	0.9	0.006
Upper lid	1.65	1.2	1.1	1.1	0.055
Lower lid	1.50	1.1	0.6	0.8	0.001
Tear break-up time, sec	6.58	3.1	8.2	2.4	0.112
Corneal staining	2.25	2.3	1.1	1.4	0.045
Schirmer score, mm	8.50	7.5	9.4	5.3	0.433
BCVA (logMAR)	0.141	0.155	0.133	0.12	0.578
Control group					
Overall OSDI score	14.4	8.4	15.5	8.6	0.830
1st part*	7.80	4.1	7.80	5.0	1.0
2nd part†	2.36	2.6	2.00	1.9	0.414
3rd part‡	3.95	3.0	4.85	2.9	0.243
MGD score	1.60	0.9	1.97	1.0	0.244
Upper lid	1.60	1.0	1.95	1.1	0.297
Lower lid	1.60	1.0	2.00	1.1	0.269
Tear break-up time, sec	6.65	2.9	6.20	2.2	0.549
Corneal staining	2.30	2.1	2.60	2.1	0.500
Schirmer score, mm	10.6	7.7	12.3	6.7	0.289
BCVA (logMAR)	0.133	0.11	0.137	0.11	0.609

*Symptoms.

†Limitation in activity.

‡Environmental triggers.

Clinical outcomes of 40 patients before and after the study period according to the group.

Data were expressed as mean \pm SD. Significant values are in bold.

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subjective and objective parameters. OSDI scores improve from 43.0 to 25.3 (P = 0.001), TBUT increased from 4.7 to 7.1 in the right eyes (P = 0.001) and from 4.6 to 6 in the left eyes (P > 0.05), fluorescein staining decreased from 1.2 to 0.4 in OU (P < 0.001), and Schirmer test score increased from 5.8 to 9.9 in the left eyes (P < 0.001) and from 6.7 to 8 in the right eyes (P > 0.05). However, the study was limited by the lack of a control group. Furthermore, results were significant only in part of the parameters, and sometimes for 1 eye only.⁶ A different study specifically addressed a population of 25 patients with evaporative DED and also reported positive outcomes of the QMR high-frequency electrotherapy, with no adverse events.⁷

Recently, Trivli et al tested the effects of QMR on 18 patients with DED. In that study, OSDI improved from 45.46 to 34.45 (P = 0.013), corneal staining (by the Oxford scale) decreased from 1.41 to 0.55 (P = 0.002), TBUT increased from 6.71 to 9.53 (P < 0.001), and Schirmer test results increased from 8.75 to 9.91 (P = 0.675).¹⁴

Yet, while presenting significant improvement in most parameters, all of the above studies did not include a control group and thus are prone to biases. Our results correspond with these of previous studies. They demonstrate an improvement in symptoms and some clinical signs.

This study has limitations. First, we evaluated only 40 patients in 1 center. Our results should be confirmed in a larger multicenterd trial. Second, we included all types of DED, with no subclassification including postrefractive patients. Finally, we mainly assess short-term results, and long-term follow-up data are not yet available.

To conclude, among 40 patients randomly treated with the Rexon-Eye device or placebo treatments, a positive therapeutic effect was seen in the intervention group. This modality can be considered an adjunct option in the arsenal of therapeutic agents for patients with DED.

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