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The effect of thermo-mechanical device (Tixel) treatment on evaporative dry eye disease – A pilot prospective clinical trial

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ABSTRACT

Purpose: To examine the effects of treatment with a thermomechanical skin device to the eyelid area on the clinical signs and symptoms of patients who suffer from dry eye disease (DED) secondary to meibomian gland dysfunction (MGD).

Methods: Forty patients aged 45 years or older with DED due to MGD were recruited. Both eyes (n = 80) of each patient received three treatments with the Tixel device (Novoxel®, Israel), with each treatment separated by a 2-week period. Treatment was applied across the upper and lower eyelids, with the same intensity, tip protrusion distance, and contact duration. Two additional follow-up visits were performed at 2-week intervals after treatment cessation. DED status was evaluated during each visit via SPEED II questionnaire, tear break-up time (TBUT), corneal staining score (CSS), MGD score, and frequency of lubricant use. Visual acuity (VA) was recorded during first and last visits.

Results: Mean age was 64.3 ± 12.4 years and 72.5 % (n = 29) were female. 45 % (n = 18) had a history of blepharitis, 12.5 % (n = 5) had chalazia, and 17.5 % (n = 7) suffered from allergic conjunctivitis. Mean follow-up time was 2.1 ± 0.6 months. Comparing the first and last visits, all parameters showed significant improvement after Tixel treatment: mean SPEED II scores (16.5 ± 5.9 to 11.8 ± 6.7, $p < 0.001$), CSS (2.0 ± 1.3 to 0.5 ± 0.9, $p < 0.001$), TBUT (2.7 ± 0.8 s to 6.5 ± 2.2 s, $p < 0.001$), MGD score (2.7 ± 0.5 to 1.2 ± 0.4, $p < 0.001$), and rate of lubricant use (3.4 ± 2.4 per day to 1.9 ± 2.0, $p < 0.001$). VA also improved (0.10 ± 0.11 logMAR to 0.08 ± 0.10 logMAR, $p < 0.05$). No major side effects were observed.

Conclusions: In this pilot study Tixel treatment induced significant improvement of signs and symptoms among patients with DED due to MGD. Benefits persisted for at least one month. Further randomized controlled double-blinded studies are needed.

1. Introduction

Dry eye disease (DED) is a common ocular disorder, caused by either impaired tear production, excessive tear film evaporation, or a combination of both mechanisms. DED is a frequent cause of ocular complaints leading patients to seek ophthalmic care [1]. DED severity may range from mild, occasional discomfort to sight-threatening, severely-debilitating disease.

The oily component of the tear film assists in maintaining tear stability by reducing tear evaporation, and contributes to lubrication between ocular surface and the eyelids during blinking [2]. It consists of meibum, a mixture of polar lipids (phospholipids) and nonpolar lipids (cholesterol, wax esters, cholesterol esters) [3]. Meibum is secreted by the meibomian glands, located across the lid margin of the superior and inferior eyelids.

Meibomian gland dysfunction (MGD) is thought to be a key component in evaporative DED [2]. The most common mechanism of MGD is gland obstruction caused by increased meibum viscosity, combined with epithelial hyperkeratinization. This leads to stasis and cystic distention of the glands [4]. The main risk factors for MGD include advanced age [5], extremely dry environment [6], rosacea [2], seborrheic dermatitis [2], and infestation by Demodex species [7]. Ocular surface damage in MGD results from a combination of several mechanisms, including increased tear evaporation, hyperosmolarity, secretion of proinflammatory mediators, and increased friction between the eyelids and globe [2,3].

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The significant impact of this disease on patients' quality of life and visual function has led numerous research studies to seek effective, safe and long-lasting treatment modalities for DED. Local heating of the eyelid margin area has been the mainstay of MGD treatment for many decades [5,8] due to its ability to induce liquification of the meibum at temperatures greater than 40 °C, thus facilitating its expression from the clogged glands [9].

Several devices for the treatment of DED have been introduced in recent years such as Lipiflow and intense pulsed light (IPL) therapy. LipiFlow [10–12] combines heat and mechanical compression to the eyelid margin. IPL therapy incorporates light energy delivered to the lid margin in order to treat MGD [13].

Tixel (Novoxel®, Netanya, Israel) is a thermomechanical system, which transfers heat to the skin by means of a titanium tip heated to a uniform temperature of 397–400 °C, briefly contacting the skin. Application of Tixel dehydrates the stratum corneum and superficial epidermis and creates micropore channels. It has been widely used for skin rejuvenation treatments, including in the periocular region [14]. Recently, this device has also been successfully used for intradermal delivery of various drugs [15–18]. This method of tissue heating is both safe [19,20], and rapid.

The aim of this prospective pilot study was to evaluate the effect of Tixel treatment application to the eyelid skin and meibomian glands in patients with DED secondary to MGD.

2. Methods

2.1. Ethics

Institutional Review Board (IRB)/Ethics Committee approval was obtained (Institutional Review Board of Shamir Medical Center). This study adhered to the tenets of the Declaration of Helsinki and was publicly registered as required at https://my.health.gov.il/CliniTrials/Pages/MOH_2020-02-24_008734.aspx. All patients received detailed explanations, and informed written consent was given prior to enrolment.

2.2. Patient selection

Only patients with wrinkles in the periorbital region and pre-existing DED secondary to MGD were included. Preliminary evaluation was performed in the eye clinic at Shamir Medical Center. Inclusion criteria for the study (described in detail in Fig. 1) were: age older than 45 years, DED with associated MGD, tear break-up time (TBUT) of less than 5 s, and corneal staining score (CSS) of at least 1. Exclusion criteria included an ocular history of graft versus host disease, Sjogren's, previous ocular trauma or surgery, apart from uneventful cataract surgery.

2.3. Tixel treatment technique

Tixel (Novoxel®, Netanya, Israel) technology combines thermal energy with motion (protrusion). The system consists of a handpiece with titanium tip heated to 400 °C (Fig. 2**A-2B**). Each time a button on the handpiece is pushed, the titanium tip advances and contacts the skin. Tip protrusion distance and the duration of tip-to-skin contact (the pulse duration) determine the amount of thermal energy delivered to the tissue. The system provides the user with predefined pulse duration parameters that range from 5 to 18 ms. A second system parameter is protrusion, defined as the distance that the heated tip is advanced into the skin from the edge of the handpiece distance gauge. Larger protrusion acquires better thermal matching (e.g., more heat energy is transferred to the tissue due to firmer contact) between the tip and the treated tissue without skin perforation. Most of the thermal effect is concentrated in the stratum corneum, leading to rapid heat transfer and dehydration of the layer.

All treatments in the current study were performed by one of two ophthalmologists (MS and MH) who had been trained in operating the device. The patients were placed in a supine position, and the titanium tip of the Tixel device was applied on dry, clean eyelid skin in the temporal and central area of the upper and lower eyelids of both eyes. The device emits no radiation so corneal shields were not used. The medial aspect of the eyelid was avoided in order to spare potential damage to the lacrimal ducts and puncti from the heat. Treatment for each eyelid was performed in two overlapping rows: the first row was applied just adjacent to the anterior eyelid margin, and the second row applied 5 mm distally to the margin (Fig. 2**C**). Each eyelid received 15 applications per treatment. Skin contact duration and protrusion distance were kept constant. Skin contact duration for the lower eyelids was 8 ms, and for the upper eyelids 6 ms. Tip protrusion distance was set to 400 μm for all locations. No topical nor systemic analgetic treatment was applied. The treatment of upper and lower eyelids of both eyes took up to 2 min per patient.

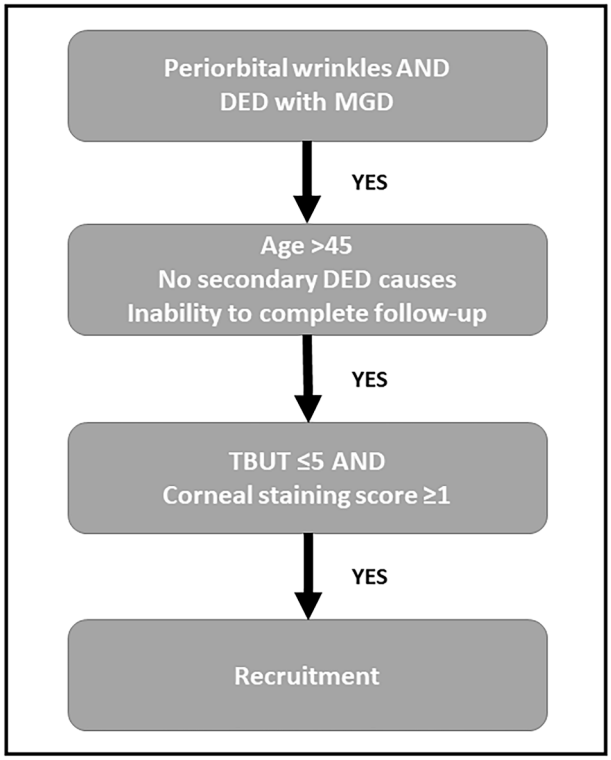

Fig. 1. Inclusion process Patients with periorbital wrinkles with DED and MGD, who were interested in rejuvenation treatment, were screened. Exclusion criteria included: age under 45 years, known secondary causes of DED, very mild DED signs, and inability to complete 2-weekly follow-up for a total of 10–12 weeks. *DED- dry eye disease; MGD- meibomian gland dysfunction; TBUT- tear break-up time.

2.4. Data gathering

Patients were evaluated five times during the study period, at two-week intervals. During the first three appointments, both treatment with Tixel and clinical evaluation were performed. The two last appointments included clinical evaluation only. Each evaluation consisted of DED and MGD quantification, along with slit lamp examination for general pathology. DED was evaluated using TBUT, CSS (based on the SICCA ocular staining score) [21] and SPEED II questionnaire. MGD was graded separately for upper and lower eyelids of each eye based on a 1–4 scale: clear/cloudy to granular/toothpaste/no secretion [22]. The patients were questioned about the frequency of lubricant use and any side effects, noted from the previous treatment. During first and last visits visual acuity (VA) was also documented. All examinations were

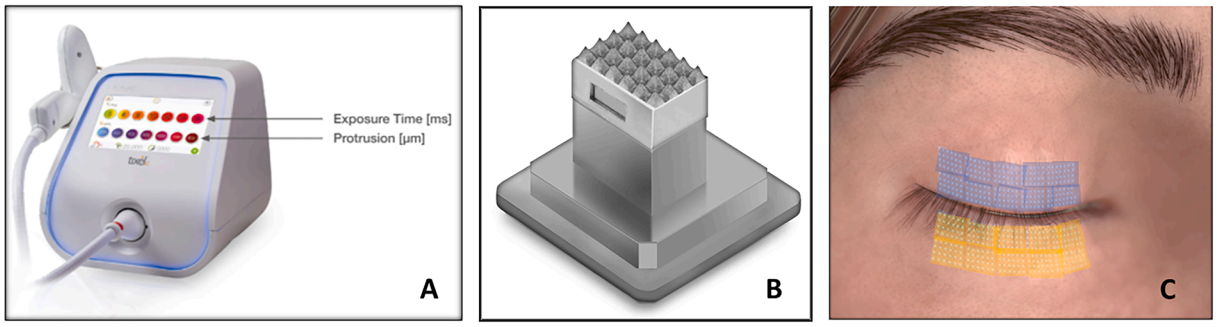

Fig. 2. Treatment with the Tixel device 2A- Tixel console with attached handpiece, and treatment parameters; **2B-** The Tixel tip is a 1 X 1 cm titanium made structure, consisting of 9X9 evenly spaced small pyramids; **2C**- The treatment location for eyelid skin rejuvenation. Overlapping applications were performed with in two rows for each eyelid.

performed by one of two ophthalmologists. In order to prevent possible bias, the examiner did not look at previous evaluations' findings, neither did the examiner ask the patient how he felt until after full slit-lamp examination and recording all objective findings.

2.5. Outcome measures

The main outcome was improvement in DED parameters, including SPEED II questionnaire, TBUT and CSS. A secondary outcome was reduction in frequency of lubricant use.

2.6. Statistical analysis

Statistical analysis was performed using SPSS for windows version 23.0 by IBM (Armonk, NY, USA). For categorical variables $\chi 2$ tests were used. Clinical parameters 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 for variables with a non-normal distribution. P values less than 0.05 on a two-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 main analysis. For meibomian gland dysfunction the mean grade of the lower and upper eyelid was used. For main outcome analyses of SPEEDII, CSS, TBUT, MGD severity score and frequency of lubricant use- the last follow-up visit of each patient was used, i.e., comparison between assessment at first visit prior to treatment initiation, and last visit occurring 4 weeks after treatment termination. Sub- analysis of differences between adjacent study visits were also performed for all measured variables.

3. Results

Eighty eyes of 40 patients were included. The mean age was 64.3 ± 12.4 years (range: 41 – 85 years) and 72.5 % (n = 29) were female. 45 % (n = 18) had a history of blepharitis, 12.5 % (n = 5) previously suffered from chalazia, and 17.5 % (n = 7) had prior history of allergic conjunctivitis. Baseline patient characteristics are further detailed in Table 1.

Table 1
Baseline demographic and clinical characteristics of study population.

Demographic and clinical characteristics	Value
Age, years (mean ± SD)	64.3 ± 12.4
Female sex	72.5 % (29/40)
Blepharitis	45.0 % (18/40)
Chalazia	12.5 % (5/40)
Allergic conjunctivitis	17.5 % (7/40)
Visual acuity at enrolment, logMAR (mean ± SD)	0.10 ± 0.11

Of the 40 enrolled patients, all arrived for the first and second treatment sessions, and all but two arrived for the third treatment session. Two follow-up visits were performed after treatment was concluded, to which 33 and 32 patients arrived respectively. Mean overall follow-up was 2.1 ± 0.6 months.

Mean SPEED II scores improved from 16.5 ± 5.9 to 11.8 ± 6.7 ($p < 0.001$) at the last follow-up visit. A consistent decrease was noted during treatment, which persisted after treatment was discontinued, as illustrated in Fig. 3. Mean SPEED II scores decreased to 13.4 ± 6.4 at the second treatment ($p < 0.001$), 12.6 ± 6.6 at the third treatment ($p < 0.001$), 11.4 ± 6.1 at the first follow-up visit ($p < 0.001$) and to 11.5 ± 6.1 at the second follow-up ($p < 0.001$, all comparisons are to baseline values).

Corneal fluorescein staining score improved from 2.0 ± 1.3 at baseline to 0.5 ± 0.9 ($p < 0.001$) at the last follow-up visit. Again, a consistent decrease in scores was noted during treatment and follow-up, as illustrated in Fig. 4. Mean scores decreased to 0.8 ± 0.9 at the second treatment ($p < 0.001$), and to 0.4 ± 0.9 at the third treatment ($p < 0.001$). During the two follow-up visits staining scores remained low at 0.4 ± 0.8 ($p < 0.001$) and 0.5 ± 0.9 ($p < 0.001$, all comparisons are to baseline values), during the first and second follow-up visits respectively.

TBUT significantly increased during treatment from 2.7 ± 0.8 s at baseline to 6.5 ± 2.2 s at last follow-up ($p < 0.001$). MGD scores also

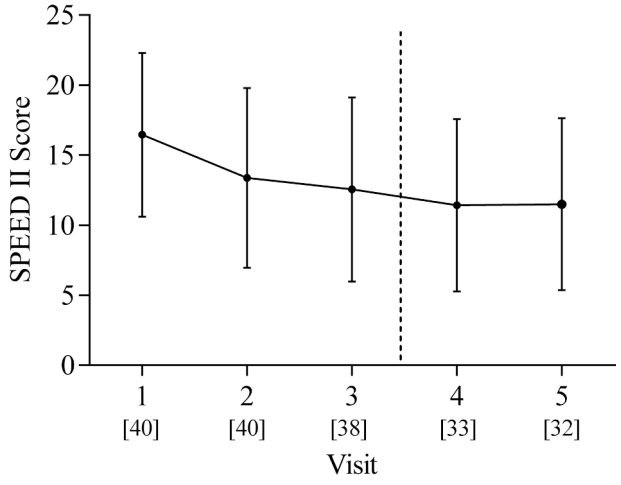

Fig. 3. SPEED II score during treatment and follow-up Mean SPEED II score recorded at each visit. During the first three visits treatment with Tixel was performed, and the two subsequent visits were follow-up visits only. All follow-up visits were $p < 0.001$ compared to baseline. Error bars represent standard deviations (SD). The dashed line separates treatment visits from follow-up visits. Digits under the visit number represent the number of patients included at each visit.

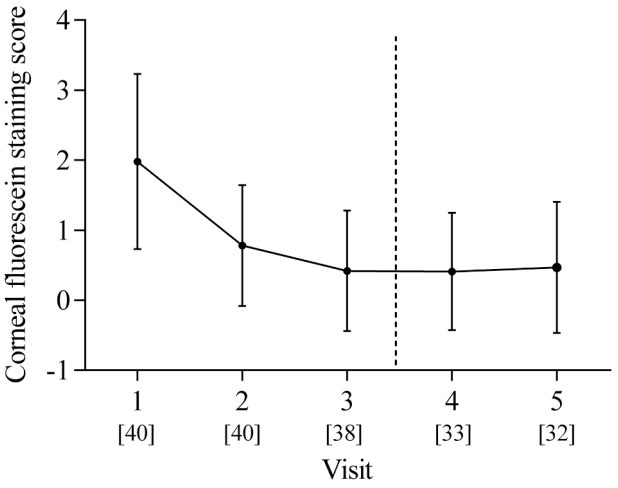

Fig. 4. Corneal fluorescein staining score during treatment and follow-up Corneal fluorescein staining recorded at each visit. During the first three visits treatment with Tixel was performed, and the two subsequent visits were follow-up visits only. All follow-up visits were $p < 0.001$ compared to baseline. Error bars represent standard deviations (SD). The dashed line separates treatment visits from follow-up visits. Digits under the visit number represent the number of patients included at each visit.

improved from 2.7 ± 0.5 to 1.2 ± 0.4 ($p < 0.001$) at the last follow-up visit. Figs. 5 and 6 illustrate the changes in TBUT and MGD scores with the corresponding values at each visit.

Reported daily use of artificial tears decreased from baseline mean of 3.4 ± 2.4 applications per day to 1.9 ± 2.0 at the last follow up visit ($p < 0.001$). The decrease was significant starting from the first follow-up visit after treatment initiation ($p < 0.001$). Visual acuity slightly, but significantly, improved following treatment from 0.10 ± 0.11 logMAR (20/25 Snellen equivalent) at baseline to 0.08 ± 0.10 logMAR (20/24 Snellen equivalent) at the last visit ($p < 0.05$).

The amount of improvement in all measurements following treatment was compared between the different patient groups according to sex, age, and prior history of blepharitis, chalazia or allergic conjunctivitis. For age, the group was divided according to the median of 66 years to two groups of 20 patients each, those aged 66 or younger and

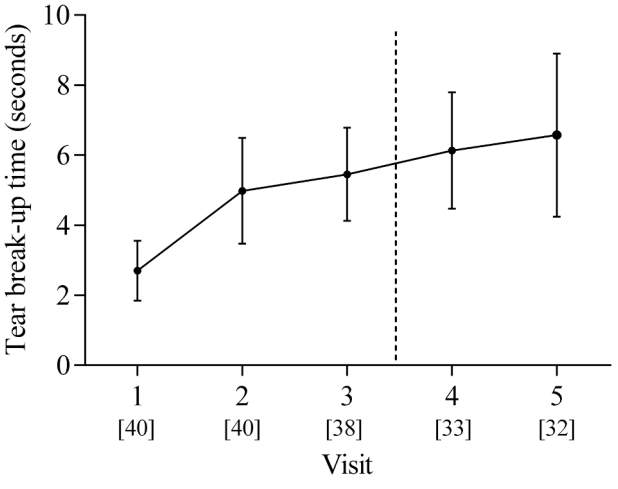

Fig. 5. Tear break-up time during treatment and follow-up Tear break-up time at each visit. During the first three visits treatment with Tixel was performed, and the two subsequent visits were follow-up visits only. All follow-up visits were $p < 0.001$ compared to baseline. Error bars represent standard deviations (SD). The dashed line separates treatment visits from follow-up visits. Digits under the visit number represent the number of patients included at each visit.

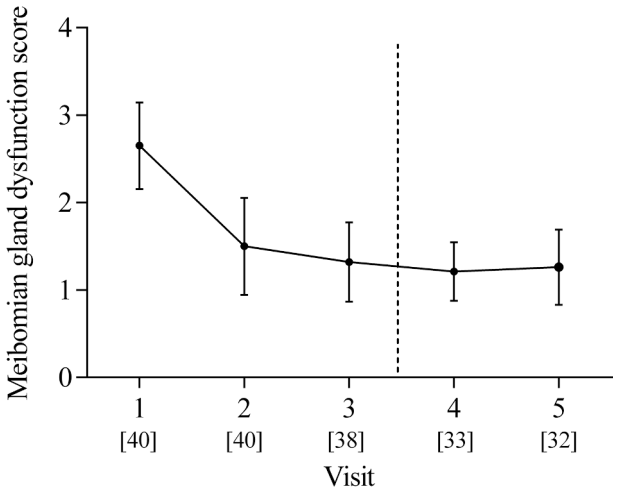

Fig. 6. Meibomian gland dysfunction score during treatment and follow-up Meibomian gland dysfunction score at each visit. Values represent the mean grade of the lower and upper eyelid. During the first three visits treatment with Tixel was performed, and the two subsequent visits were follow-up visits only. All follow-up visits were $p < 0.001$ compared to baseline. Error bars represent standard deviations (SD). The dashed line separates treatment visits from follow-up visits. Digits under the visit number represent the number of patients included at each visit.

those older than 66 years. Upon analysis, no significant difference in response to Tixel treatment was observed between the examined subgroups.

3.1. Adverse events

Of the 40 patients treated, one reported tearing for 24 h after treatment, and one reported a mild burning sensation which lasted for two days. The remaining 38 patients reported no negative side effects. No major adverse events occurred during treatment or follow-up in any patient.

4. Discussion

Meibomian gland dysfunction (MGD) is the leading cause of dry eye disease (DED) worldwide [1,5]. Increased viscosity of meibum is a major component of MGD pathophysiology [4]. Phase transition temperature is defined as the temperature required to induce a change in the lipid physical state from the ordered gel phase, to the disordered liquid crystalline phase. In healthy individuals the transition temperature of the meibum is below the eyelid temperature, ensuring liquid state and good expressibility of the meibum [4,9]. Patients with MGD however, have been shown to have a 4 °C higher than normal transition temperature, making the meibum more viscous, and less prone to spontaneous expression at eyelid temperature [4]. Raising the temperature of a patient's meibum induces its liquification, facilitating spontaneous excretion through the narrowed orifice at the lid margin [8,9].

Local heat application has been the mainstay of treatment for MGD for many years, mainly by asking the patient to apply warm compresses [1,5,8]. Since MGD is a diffuse disorder, involving most of the meibomian glands of the affected patient [5], it is difficult to insure proper application of the compresses, with optimal heat distribution to the entire eyelid margin area. The LipiFlow technology has attempted to overcome this problem by applying heat through a device placed directly onto the eyelids of both eyes, with a protective cover over the cornea and conjunctiva. This method, while at least as effective as two months of simple compresses [11], is accompanied by potential discomfort for the patient due to direct contact with the eye and the long duration of treatment. MGD treatment with IPL technology, while

effective, requires covering the eyes with protective goggles and application of ultrasound gel throughout the treatment, which may cause patient discomfort as well [13]. Additionally, serious adverse effects of IPL, including excessive photophobia and uveitis, have been reported [13]. Low-level light therapy (LLLT) has also been tested, with significant improvement in some but not all DED parameters, and no effect on MGD severity [23].

The Tixel device is a thermo-mechanical system, applying heat of 400 °C through a titanium tip at a preset tip–skin contact duration and tip protrusion. The local heat has dual positive effect on DED due to MGD: meibum liquification [8,9], and eradication of Demodex mites from the eyelid margin [7]. Demodex species are thought to cause DED in several mechanisms. Demodex folliculorum causes direct damage to cells at the base of the hair follicle, causing reactive hyperkeratinization and blepharitis. Demodex brevis physically blocks the meibomian glands, resulting in a granulomatous reaction and predisposing to MGD [8]. Previous studies have demonstrated a correlation between prevalence of DED signs and symptoms in patients with MGD and Demodex eyelid margin infestation [24]. A temperature above 57 °C has been shown to be lethal for Demodex mites, thus making Tixel treatment likely to be effective in Demodex eradication [7], as a previous study has already demonstrated by performing cultures before and after Tixel treatment [15].

Mechanical devices such as LipiFlow [10–12], which combines heat and mechanical compression to the eyelid margin, have been shown to improve DED due to MGD [9]. A recent meta-analysis has shown only a modest improvement in objective DED findings (TBUT mean deviation of 0.4 s) following Lipiflow treatment. Lipiflow treatment also requires direct contact with the eye, and relatively long treatment duration (at least 12 min), which may cause patient discomfort. The intense pulsed light (IPL) therapy incorporates light energy delivered to the lid margin in order to treat MGD [13]. While TBUT improves under this treatment (mean difference of 2.3 s), improvement in subjective complaints varies in the literature, sometimes reported as non-significant [25]. IPL treatment requires the patient to use protective goggles throughout the procedure and is associated with a varying degree of pain and discomfort [13,26].

In this study, all DED grading parameters (TBUT, CSS, SPEED II questionnaire), MGD score and quantity of lubricants' use showed significant improvement with each treatment. As previously described, no major side effects were observed [20]. VA showed a statistically, but not clinically, significant improvement, presumably due to improved tear-film stability [27].

The Tixel device was initially developed for aesthetic use, and allowed for a personalized approach to each patient, avoiding locations where no data exists regarding its effect (eyelid nevi etc.). This study demonstrates that the indications for Tixel treatment may also be expanded to include DED management.

All patients in our study expressed satisfaction with the mode of treatment with Tixel, and no requests were made for topical anesthetic agents, as previously described [14,15]. The accurate treatment location is also responsible for its safety, allowing the setting of minimal intensity parameters. The treatment is also not time consuming, taking up to 2 min for both eyes per patient. Additionally, tissue damage with Tixel (at duration <9 ms and protrusion of 400 μm, as in this treatment protocol) is negligible [28], and tissue healing after Tixel treatment to the facial area has been reported to be extremely fast [14].

This was the first study to evaluate the efficacy of periocular Tixel treatment on DED due to MGD. However, there were some limitations. First, as this was a pilot study, a placebo control group was unavailable, hence placebo effect on subjective improvement could not be assessed. Second, since the examiner was not blinded, some degree of bias may be present in DED severity judgement. Third, the ongoing COVID-19 pandemic made compliance with treatment or follow-up visits more challenging, leading to patient drop-out and precluding the option of a longer follow-up period. Finally, while it is speculated that tissue heating effect of Tixel is responsible for improvement in our patient cohort, the precise mechanism of Tixel's effect on DED with MGD has not yet been fully elucidated. Prospective studies with longer follow-up time, double-blinded, and further evaluation of meibomian gland function and content under Tixel treatment could be helpful.

In conclusion, this pilot study demonstrated that Tixel treatment to the eyelid area may be beneficial to patients with DED and MGD. It had a significant positive effect on DED signs and symptoms in patients with MGD, during a period of 10 weeks' follow-up. These results suggest that treatment with the Tixel device might be a valuable additional tool in the management of DED and MGD. Further randomized controlled double-blinded studies, with sample size determination are needed.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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