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Research article

Immediate sequential changes in the tear film lipid layer following eyelid massage in dry eye syndrome: A comparative control study

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ABSTRACT

Background/Purpose: Meibomian glands are sebaceous glands that release meibum onto the ocular surface; enhancing the quality and quantity of meibum secretions has been proven to improve signs and symptoms of evaporative dry eye (EDE) and meibomian gland dysfunction (MGD). This study aimed to evaluate and compare the efficacy of a heated eye mask (HEM) and eyelid massage device EyePeace (EP) in alleviating signs and symptoms of evaporative dry eye.
Methods: Forty dry eye participants were recruited in a prospective, contralateral-eye trial study. After undergoing 10 min of HEM therapy, eyelid massage therapy was applied to one eye by the device. The efficiency was assessed at four time points: baseline (0 min), 5 min (5 min), 15 min (15 min), and 30 min (30 min). Non-invasive breakup time (NITBUT), redness score (RS Score), tear meniscus height (TMH), tear-film lipid layer (TFLL), endothelial cell count (ECC), meibomian gland expressibility (MGEx), meibomian gland quality (MGQ), conjunctivocorneal staining (CS), ocular surface temperature (OST), best corrected visual acuity (BCVA), intraocular pressure (IOP), central corneal thickness (CCT) flat-axis keratometry value (K1), and steep-axis keratometry value (K2), were examined.
Results: Baseline clinical measurements did not have statistically significant differences between the groups (all $p > 0.05$). After 30 min, a comparison was made between the HEM group and EP + HEM group, revealing significant changes only in the primary outcomes, TFLL (2.18 ± 0.45 versus 2.40 ± 0.50; $p < 0.05$), and MGEx grades (0.68 ± 0.53 versus 0.98 ± 0.70; $p < 0.05$). Improvements in NITBUT and TMH were sustained until 5 min and 15 min after using EP + HEM. No significant changes were observed in RS Score, MGQ, OST, CFS, BCVA, IOP, ECC, K1, K2, and CCT (all $p > 0.05$) at all test time points.
Conclusion: The application of a heated eye mask followed by a gentle massage using EyePeace on the eyelids can have a sustained improvement in the tear film lipid layer and meibomian gland expressivity score but not clinically significant, and does not pose any significant immediate impact on the cornea.
Trial registration number: NCT06158997.

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1. Introduction

Meibomian gland dysfunction (MGD) is often characterized by blockage in the ducts and/or irregularities in the quantity or quality of glandular secretions, as described by the International Workshop [1,2]. These glands, which have been modified from sebaceous glands, produce meibum right onto the ocular surface. Enhancing the production of meibum, both in terms of quality and quantity, can help reduce the signs and symptoms of evaporative dry eye (EDE) and MGD [3].

EyePeace (EyePeace, Belfast, UK) is a commercially available eyelid massage device designed to improve the expression of meibum [4]. EyePeace is a flexible silicone handheld gadget. It is used in conjunction with warm compress treatment and exerts controlled vertical pressure on the closed eyelids. The device's relative safety and effectiveness compared to heated eye mask (HEM) has not yet been determined.

Additionally, studies have demonstrated that the use of a HEM can effectively alleviate symptoms of dry eye (DE). The heat generated by the mask stimulates the meibomian glands, leading to enhanced liquefaction and release of meibum [5–7]. Recent

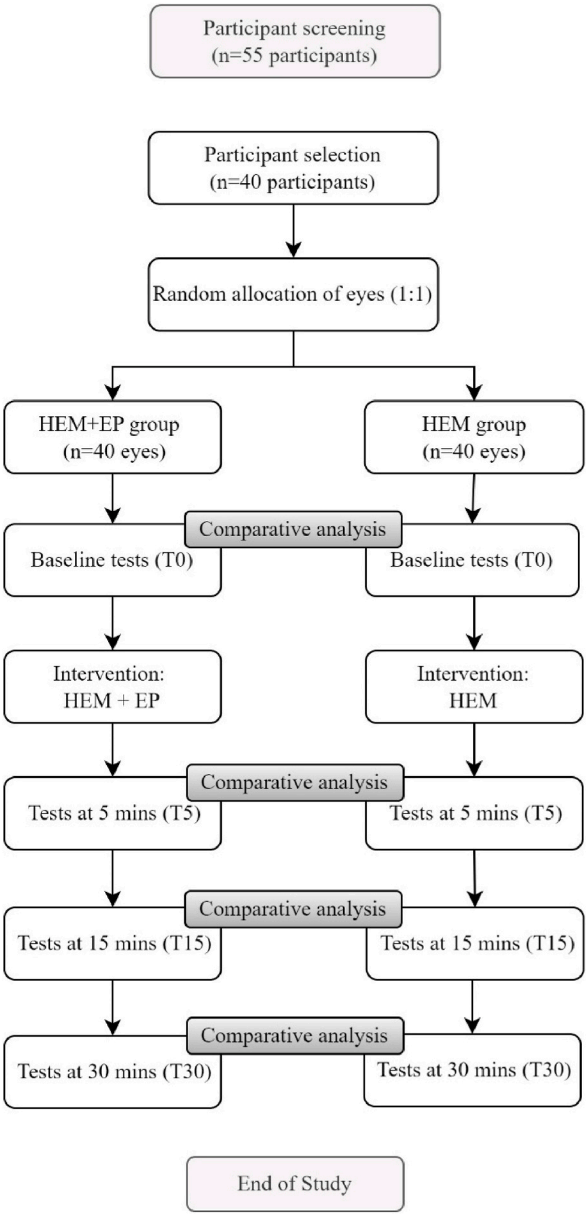

Fig. 1. Study design.
HEM: heated eye mask, EP: EyePeace, T0: pre-treatment baseline, T5: post-treatment 5 min, T15: post-treatment 15 min, T30: post-treatment 30 min.

findings indicate that the melting points of meibomian secretions exhibit variability and tend to rise as the severity of MGD increases, hence impacting the efficacy of HEM [8,9]. Additionally, studies suggested chronic eye rubbing due to co-morbidities such as atopic eczema may reduce corneal hysteresis and resistance factors. McMonnies et al. define chronic habits of aberrant rubbing (CHAR) as the frequent and/or forceful rubbing of the eyes, with extended duration, and occurring consistently over an extended period of time, either throughout the year or during specific seasons [10]. This decreases the corneal hysteresis, and the resistance factor may distort the cornea [10]. The immediate sequential changes in the tear film lipid layer following eyelid massage in dry eye syndrome (DES), using within 30 min, have not been determined. Therefore, the current randomized contralateral-eye study aimed to explore the effects of combining a HEM and subsequent eyelid massage using an EyePeace device on the ocular surface parameters, cornea and tear film measurements for DE patients and to perform a comparison with HEM alone as the control group.

2. Methods

2.1. Study design

This open-label randomized research included a total of 110 eyes from 55 DE patients. The research protocol underwent evaluation and received permission from the ethical review committee (IRB(2023)K029.01) and was registered with clinicaltrials.gov in Nov. 2023 (NCT06158997). During the enrolling phase of the trial, every participant provided written informed consent. Each patient completed the tests four times (T0: pre-treatment baseline, T5: post-treatment 5 min, T15: post-treatment 15 min, T30: post-treatment 30 min) on one day (Fig. 1). The clinical tests also included ocular surface thermography [11], and complete ophthalmological evaluation [12].

The determination of satisfying sample size criteria was computed using the PASS 2021 software. The sample size calculation is based on meibomian gland expression (MGEx) and tear film lipid layer (TFLL). The standard deviation of normal values was estimated to be 1 lipid layer grade [13]. Multiplicity and non-parametric adjusted power calculations were conducted to determine the sample size needed to detect a clinically significant difference of one lipid layer grade in TFLL, with a power of 95 % and a significance threshold of 5 %. The calculations indicated that a total of 38 participants were necessary.

Exclusion criteria were any corneal pathology, with a history of hypersensitivity to EyePeace and HEM therapies, with received treatment for dry eye or used eye drops within the past month, Individuals with systemic immune-mediated diseases, such as secondary Sjögren's syndrome or graft-versus-host disease, may utilize topical medication(s) to treat ocular conditions including glaucoma or allergic conjunctivitis, preceding ocular surgery or trauma. The inclusion criteria for this study were individuals who were at least 18 years or older and had both the capability and desire to adhere to the treatment protocol. The diagnosis of DE is made based on the diagnostic criteria in the TFOS DEWS II report [14]: (i) Ocular Surface Disease Index (OSDI) questionnaire score range (13–100), (ii) Non-invasive tear breakup time (NITBUT) $<$ 10 s, (iii) The corneoconjunctival staining score (CS) indicates the presence of more than 5 spots on the cornea, more than 9 spots on the conjunctiva. A positive diagnosis of DE was established by the presence of two or more criteria [15].

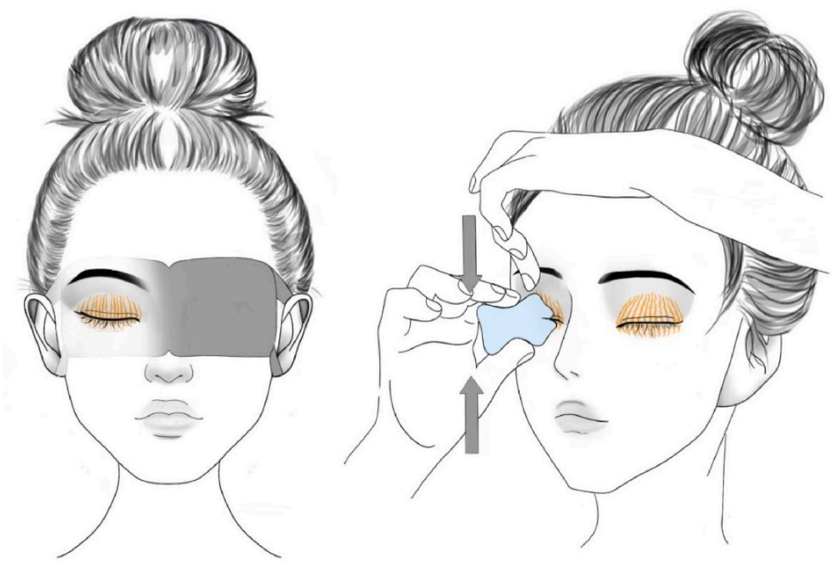

Fig. 2. Treatment diagram.

2.2. Treatment

Eligible participants wore a disposable eye mask on both eyes and were randomized to the eyelid massage device (EyePeace, Belfast, UK) on one eye, for self-administration. The eye mask was air-activated and manufactured by Ocuface Medical Co., Ltd. in Guangzhou, China. The medical device is registered under the number 20192090563 in China [16]. They were initially (1:1) into EP + HEM or HEM groups (Fig. 1). Participants received training on applying the HEM therapy and eyelid massage technique using Eye-Peace. According to the instructions, all participants received the HEM therapy for 10 min. Subsequently, one eye was subjected to 10 consecutive mild squeezes using the eyelid massage equipment. (Fig. 2).

Initially, after participants were enrolled in the trial, subjective and objective ocular surface assessments were performed by trained optometrists on the same test devices for all participants. Meibomian gland assessment and CS were performed at the end of the tests to prevent the physical tests from affecting the signs and symptoms of dry eyes.

2.3. Measurements

OSDI (validated Chinese version) offered a measurable evaluation of DE symptoms [17]. The 12 questionnaire items may be analyzed to calculate an individual score, indicating the severity of symptoms (0 representing no symptoms and 100 representing severe symptoms).

K1, K2, and central corneal thickness (CCT), NITBUT, tear meniscus height (TMH), redness score (RS Score), TFLL, meibomian gland quality (MGQ), MGEx, ocular surface temperature-open eyes (OST Open), ocular surface temperature-closed eyes (OST Closed), were performed at T0, T5, T15, and T30. Best corrected visual acuity (BCVA), endothelial cell count (ECC), intraocular pressure (IOP), and CS were assessed at T0 and T30. The measurements were conducted within the same room (temperature:20–23 °C, humidity: 60–68 %).

TFLL was conducted using DR-1, a device manufactured by Kowa in Nagoya, Japan. The results were categorized as follows: grade 1, somewhat gray color, uniform distribution; grade 2, somewhat gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, presenting many colors with nonuniform distribution; grade 5, indicating that corneal surface is partially exposed [18–20]. A "1″ score represents the “highest score,” while a score of 5 represents the “lowest score."

Keratometry, flat-axis keratometric value (K1) in diopters (D) on the anterior corneal surface, steep-axis keratometric value (K2) in diopters on the anterior corneal surface, as well as central corneal thickness (CCT) were assessed using a Pentacam 70700 (Oculus, Wetzlar, Germany).

NITBUT was assessed using the Keratograph 5M topographer, manufactured by Oculus in Germany. Three consecutive measurements were recorded, and the median value was used in the final analysis [21].

RS Score and TMH were assessed using the S90L WDR+130 Slitlamp (Mediworks, Shanghai, China). TMH was measured in the center of the margin, and the image was 1156*873 pixels. The photograph of the inferior tear meniscus was taken immediately following a complete blink while measuring the TMH [22]. The computer screen indicated the RS value (accurate to 0.1 U) which varied from 0.0 (normal) to 4.0 (severe) [23]. Each test was performed 3 times consecutively.

MGEx and MGQ were evaluated using a slit-lamp [24]. A total of eight meibomian glands in the middle parts of the eyelid were assessed using a rating scale ranging from 0 to 3 for each gland (0 indicated clear meibum; 1 indicated cloudy meibum; 2 indicated cloudy and granular meibum; and 3 indicated thick, toothpaste-like consistency meibum) [25]. Expression of the meibomian glands: five meibomian glands in the middle part were evaluated on a scale of 0–3. A score of 0 indicated that all glands were expressible, a score of 1 indicated that 3–4 glands were expressible, a score of 2 indicated that 1–2 glands were expressible, and a score of 3 indicated that no glands were expressible.

Thermal imaging procedure was conducted on the ocular surface using a high-resolution camera 160 × 120 pixels, ±3 °C (FLIR One Pro, FLIR Systems Inc., USA). According to standard examination technique [11,26,27]. Before doing ocular thermography and other tests, participants were given a 20-min period to adjust to the room environment. The patients were instructed to properly blink and close their eyes for 3 s. The first image was captured soon after the patients' eyelids opened [11,28]. The temperature measurement was obtained at the central cornea, which is specifically defined as a region with a diameter of 4 mm located in the center of the cornea.

CS evaluated corneal and conjunctival epithelial damage. We performed these examinations with S90L WDR+130 Slitlamp (Mediworks, Shanghai, China) [29]· The conjunctival sac was filled with 2 μL of a preservative-free mixture containing 1 % lissamine green and 1 % sodium fluorescein. The cornea, nasal conjunctiva, and temporal conjunctiva were each represented by one of the three equal portions of the eye. Each region received a score ranging from 0 to 3 points. The scores from all three sections were then summed and presented in a range from 0 to 9 (normal-severe) [30–32].

2.4. Safety assessments

The assessment of safety involved the measurement of BCVA, IOP, ECC; K1, K2, and CCT, corneal and conjunctival exams with a slit-lamp microscope during each visit.

BCVA was assessed using a Decimal notation visual acuity chart. The IOP measurement was performed using a non-contact tonometer (NT-510, NIDEK, Japan). The assessment of ECC was measured using a corneal endothelial counter (SP–3000P, TOP-CON, Japan). Three sequential readings were captured.

Meibomian gland assessment and CS were performed at the end of the tests.

2.5. Statistical analysis

Analyzed using the SPSS software for MacOS, version 26 developed by IBM Corp. The significance of different time points was assessed using repeated measures two-way analysis of variance (ANOVA) for continuous variables with normal distributions confirmed by Kolmogorov-Smirnov testing ($p > 0.05$). The mean standard deviation (SD) was used to express descriptive statistics for continuous variables. Post-hoc multiplicity-adjusted was used to evaluate repeated measurements of continuous variables, including IOP, ECC, BCVA, OST open, K1, K2, CCT, OST closed, and NITBUT. Generalized linear mixed model analysis with Bonferroni post-hoc analysis was used for repeated measurements of discrete variables, including the TFLL, CS score, and MG assessments. $p < 0.05$ was shown statistical significance.

3. Results

Based on the specified criteria for inclusion and exclusion, initially, eighty eyes of 40 participants were included in the statistical analysis. The findings indicated that most patients had aqueous-deficient mixed evaporative dry eye. They were initially randomized (1:1) into EP + HEM or HEM groups. The number of right/left eyes randomly allocated in HEM or EP + HEM was the same. Table 1 presents the demographic statistics.

3.1. Efficacy evaluation

The mean NITBUT at T0 for EP + HEM and HEM group was reported to be 5.14 ± 2.75, 4.87 ± 2.37 s, respectively ($p = 0.637$). At T5 for EP + HEM and HEM group was reported to be 9.31 ± 3.21, 7.08 ± 2.66 s, respectively ($p = 0.001$). At T15 for EP + HEM and HEM group was reported to be 8.62 ± 3.60, and 6.91 ± 2.90 s, respectively ($p = 0.021$). At T30 for EP + HEM and HEM group was reported to be 6.72 ± 3.46, and 5.44 ± 2.44 s, respectively ($p = 0.058$)(Table 2, Figs. 3 and 9A).

The mean TMH at T0 assessment was 0.15 ± 0.03 and 0.14 ± 0.03 mm for the EP + HEM and HEM groups, respectively ($p = 0.657$). At T5 for EP + HEM and HEM group was reported to be 0.17 ± 0.04, 0.16 ± 0.04 mm, respectively ($p = 0.031$). At T15 for EP + HEM and HEM group was reported to be 0.17 ± 0.04, 0.15 ± 0.03 mm, respectively ($p = 0.015$). At T30 for EP + HEM and HEM group was reported to be 0.16 ± 0.04, and 0.15 ± 0.04 mm, respectively ($p = 0.139$). (Table 2, Figs. 4 and 9B).

RS Score at T0 for EP + HEM and HEM group was reported to be 1.03 ± 0.29, 1.00 ± 0.33, respectively ($p = 0.665$). At T5 for EP + HEM and HEM group was reported to be 1.15 ± 0.28, 1.11 ± 0.26, respectively ($p = 0.592$). At T15 for EP + HEM and HEM group was reported to be 1.13 ± 0.30, and 1.04 ± 0.27, respectively ($p = 0.160$). At T30 for EP + HEM and HEM group was reported to be 1.06 ± 0.26, and 1.04 ± 0.29, respectively ($p = 0.717$) (Table 2, Figs. 5 and 9C).

The mean TFLL score was not statistically different between the group at T0 ($p = 0.405$). A significant difference between the EP + HEM group and HEM group was found at T5 ($p = 0.001$), T15 ($p = 0.002$), and T30 ($p = 0.036$). TFLL score for the EP + HEM group improved from 2.34 ± 0.47 at T0 to 2.18 ± 0.45 at T30, and the HEM group improved from 2.44 ± 0.59 to 2.40 ± 0.50. (Table 2, Figs. 6 and 9D).

The mean MGQ score at T0 for EP + HEM and HEM group was reported to be 1.30 ± 0.52, 1.43 ± 0.55, respectively ($p = 0.298$). At T5 for EP + HEM and HEM group was reported to be 1.13 ± 0.40, 1.28 ± 0.51, respectively ($p = 0.147$). At T15 for EP + HEM and HEM group was reported to be 1.15 ± 0.36, and 1.33 ± 0.62, respectively ($p = 0.125$). At T30 for EP + HEM and HEM group was reported to be 1.18 ± 0.45, and 1.35 ± 0.48, respectively ($p = 0.096$) (Table 2, Figs. 7 and 9E).

The mean MGEx score was not statistically different between the group at T0 ($p = 0.878$). A significant difference in mean MGEx score between the EP + HEM group and HEM group was found at T5 ($p = 0.017$), T15 ($p = 0.013$), and T30 ($p = 0.033$). MGEx score for the EP + HEM group improved from 1.05 ± 0.75 at T0 to 0.68 ± 0.53 at T30, and the HEM group improved from 1.03 ± 0.70 to 0.98 ± 0.70. (Table 2, Figs. 8 and 9F).

T0 OST Open for EP + HEM and HEM group was reported to be 30.93 ± 3.01, 31.03 ± 3.11 °C, respectively ($p = 0.916$). The T5 OST Open for EP + HEM and HEM group was reported to be 33.19 ± 3.18, 33.19 ± 3.13 °C, respectively ($p = 0.994$). The T15 OST Open for EP + HEM and HEM group was reported to be 32.74 ± 2.71, 32.93 ± 2.80 °C, respectively ($p = 0.765$). The T30 OST Open for EP + HEM and HEM group was reported to be 32.05 ± 2.79, 32.14 ± 2.78 °C, respectively ($p = 0.886$) (Table 2).

The mean OST Closed at T0 for EP + HEM and HEM group was reported to be 30.64 ± 3.00, 30.71 ± 3.08 °C, respectively ($p = 0.924$). At T5 for EP + HEM and HEM group was reported to be 33.12 ± 3.09, 33.13 ± 3.06 °C, respectively ($p = 0.991$). At T15 for EP + HEM and HEM group was reported to be 32.51 ± 2.76, and 32.73 ± 2.78 °C, respectively ($p = 0.726$). At T30 for EP + HEM and HEM group was reported to be 31.97 ± 2.86, and 32.01 ± 2.89 °C, respectively ($p = 0.957$) (Table 2).

At T0, mean CS was 0.50 ± 1.13 and 0.58 ± 1.22 in EP + HEM group and HEM group, respectively ($p = 0.776$). At T30, mean CS

Table 1
Demographic information.

Variable		Range value
No. eyes (patients)	80 (40)	
Sex, female (%)	23 (57.5 %)	
Age, range (years)	27.45 ± 6.32	21,44
OSDI	31.11 ± 3.09	26.4, 36.8

Table 2
Analysis of DE disease metrics.

	EP + HEM (n = 40 eyes)	HEM (n = 40 eyes)	*F*	*p-value*
NITBUT (sec)				
T0	5.14 ± 2.75	4.87 ± 2.37	0.224	0.637
T5	9.31 ± 3.21	7.08 ± 2.66	11.442	0.001[a]
T15	8.62 ± 3.60	6.91 ± 2.90	5.515	0.021[a]
T30	6.72 ± 3.46	5.44 ± 2.44	3.696	0.058
TMH (mm)				
T0	0.15 ± 0.03	0.14 ± 0.03	0.199	0.657
T5	0.17 ± 0.04	0.16 ± 0.04	4.848	0.031[a]
T15	0.17 ± 0.04	0.15 ± 0.03	6.217	0.015[a]
T30	0.16 ± 0.04	0.15 ± 0.04	2.233	0.139
RS Score(0–4)				
T0	1.03 ± 0.29	1.00 ± 0.33	0.189	0.665
T5	1.15 ± 0.28	1.11 ± 0.26	0.289	0.592
T15	1.13 ± 0.30	1.04 ± 0.27	2.010	0.160
T30	1.06 ± 0.26	1.04 ± 0.29	0.132	0.717
TFLL(1–5)				
T0	2.34 ± 0.47	2.44 ± 0.59	0.700	0.405
T5	1.98 ± 0.16	2.28 ± 0.51	12.822	0.001[a]
T15	2.03 ± 0.28	2.30 ± 0.46	10.371	0.002[a]
T30	2.18 ± 0.45	2.40 ± 0.50	4.545	0.036[a]
MGQ (0–3)				
T0	1.30 ± 0.52	1.43 ± 0.55	1.099	0.298
T5	1.13 ± 0.40	1.28 ± 0.51	2.147	0.147
T15	1.15 ± 0.36	1.33 ± 0.62	2.404	0.125
T30	1.18 ± 0.45	1.35 ± 0.48	2.831	0.096
MGEx (0–3)				
T0	1.05 ± 0.75	1.03 ± 0.70	0.024	0.878
T5	0.53 ± 0.51	0.83 ± 0.59	5.912	0.017[a]
T15	0.60 ± 0.55	0.95 ± 0.68	6.478	0.013[a]
T30	0.68 ± 0.53	0.98 ± 0.70	4.719	0.033[a]
OST Open (°C)				
T0	30.93 ± 3.01	31.01 ± 3.11	0.011	0.916
T5	33.19 ± 3.18	33.19 ± 3.13	0	0.994
T15	32.74 ± 2.71	32.93 ± 2.80	0.090	0.765
T30	32.05 ± 2.79	32.14 ± 2.78	0.021	0.886
OST Closed (°C)				
T0	30.64 ± 3.00	30.71 ± 3.08	0.009	0.924
T5	33.12 ± 3.09	33.13 ± 3.06	0	0.991
T15	32.51 ± 2.76	32.73 ± 2.78	0.123	0.726
T30	31.97 ± 2.86	32.01 ± 2.89	0.003	0.957
CS (0–9)				
T0	0.50 ± 1.13	0.58 ± 1.22	0.081	0.776
T30	0.43 ± 1.08	0.53 ± 1.20	0.153	0.696

[a] $p < 0.05$, T0: pre-treatment baseline, T5: post-treatment 5 min, T15: post-treatment 15 min, T30: post-treatment 30 min, SD: Standard Deviation, EP + HEM: EyePeace and heated eye mask, HEM: heated eye mask, NITBUT: non-invasive tear break-up time (units: sec), TMH: tear meniscus height (units: mm), TFLL: tear film lipid layer (range:1–5), MGQ: meibomian gland quality (range:0–3), MGEx: meibomian gland expression (range:0–3), OST Open: ocular surface temperature-open (units: °C), OST Closed: ocular surface temperature-closed (units: °C), CS: conjunctivocorneal staining.

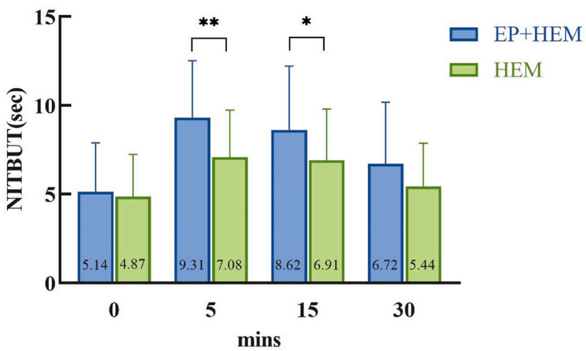

Fig. 3. Mean NITBUT comparison between groups.

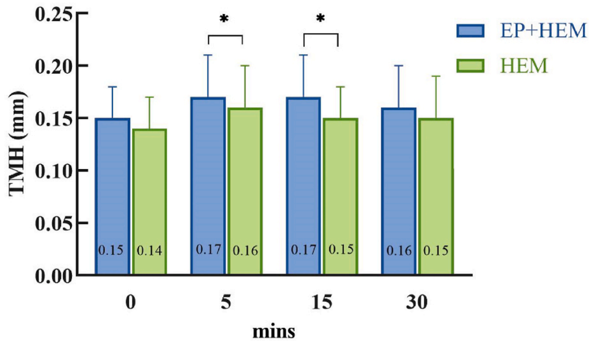

Fig. 4. Mean TMH comparison between groups.

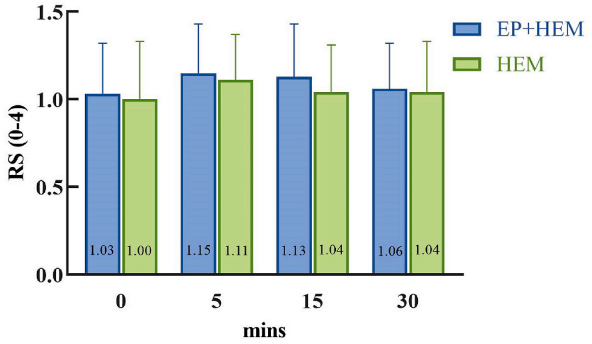

Fig. 5. Mean RS score comparison between groups.

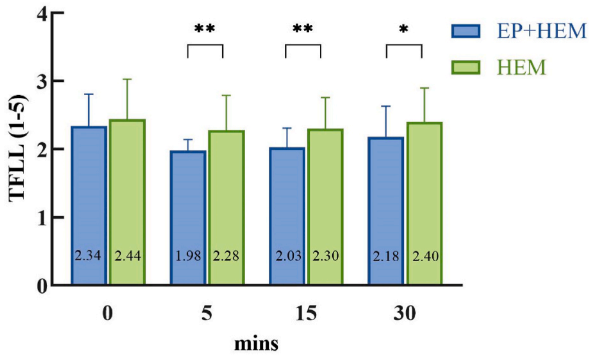

Fig. 6. Mean TFLL comparison between groups.

was 0.43 ± 1.08 and 0.53 ± 1.20 in EP + HEM group and HEM group, respectively ($p = 0.696$). (Table 2).

3.2. Safety data

Throughout the experiment, there were no occurrences of systemic adverse event. There was no not vary substantially between the EP + HEM group and HEM group with regard to BCVA, IOP, ECC, K1, K2, and CCT pre-and post-treatment. (Table 3).

4. Discussion

The current study results indicated that TFLL and MGEx grades in the EP + HEM group improved significantly at T5, T15, and T30 better than the HEM group. TFLL not only supports tear-film homeostasis, but studies suggested that meibum also has antibacterial properties that maintain the health of the lid margin [33]. Studies have demonstrated that having thin and insufficient lipid layers is associated with higher levels of DE symptoms, greater evaporation of the tear film, and reduced stability of the tear film [34–36].

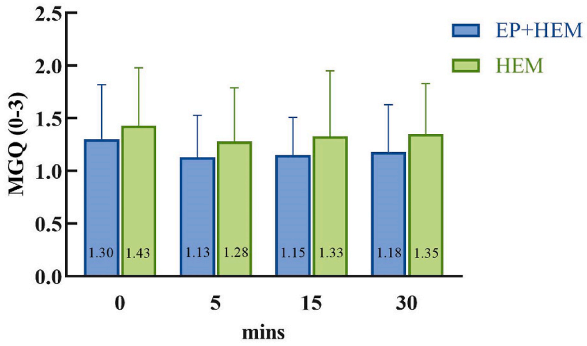

Fig. 7. Mean MGQ comparison between groups.

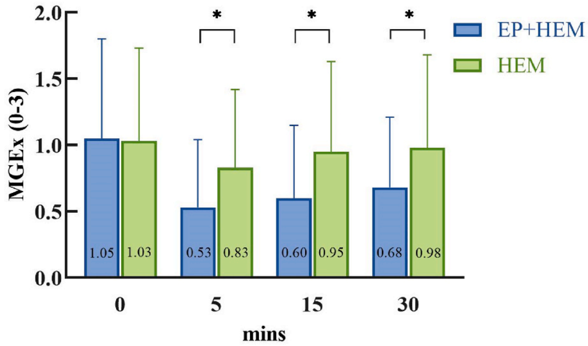

Fig. 8. Mean MGEx comparison between groups.

Additionally, the therapy for DES and MGD focuses on enhancing the production and secretion of meibum to reduce symptoms. Similar to the findings of Wang et al. using the EyePeace, significant improvements were documented in TFLL thickness; however, they warranted a more prolonged study with varying severity of DES [37]. Nonetheless, the scope of the current study was to assess the short-term safety and effectiveness of combining HEM and EyePeace, an eyelid massaging device, and then follow-up with a long-term study.

The study found no changes in corneal eccentricity. Eye rubbing/massage is considered as a major external environmental component that induces a mechanical change in the cornea [38]. Excessive eye rubbing can develop as a result of annoying symptoms. Atopy and allergies are the primary risk factors for the persistent behavior of inappropriate eye rubbing [39]. Studies have shown that eye rubbing caused corneal mechanical damage and the development of progressive ectasia [40–42]. The processes of warm compresses that raise the temperature of the cornea may interact with the temperature rises caused by massage, resulting in a prolonged period of heightened risk for negative outcomes [43]. When prescribing therapeutic massage, it is necessary to consider the risk factors for undesirable alterations that may occur as a result of rubbing or massage. However current findings indicated that using EyePeace combined with HEM did not pose any danger to corneal topographical findings [44].

It has been documented that corneal temperature may increase with lid closure, rapid blinking, increased tearing, ambient temperature, aqueous humor temperature, and blood supply [44]. The temperature of the eyelids' surface varies from 33° to 37 °C [11,45]. One of the primary therapies for controlling MGD in clinical practice is applying heat to the eyelids, followed by a moderate massage to express the glands [46]. The melting range of expressed meibum, falls 31.94 ± 0.54 °C for normal individuals 32.38 ± 0.69 °C for individuals with MGD [47]. It has been reported that temperatures closer 40 °C may be sufficient to liquefy meibum [48]. According to Wu et al. [49], the Ocuface Medical HEM used in this investigation reached a temperature higher than 40 °C, facilitating the melting of meibum, and the eyelid massage device (EyePeace) simultaneously squeezes the meibomian gland, encouraging the outflow of melted meibum similar to the action of LipiFlow®. Compared to LipiFlow, the HEM has some potential advantages. It is less invasive, more cost-effective, and can be conveniently used in domestic settings [50]. In addition, if all gland contents were not liquefied, additional manual eyelid massage device (EyePeace) expression can evacuate all expressible gland contents. This might potentially contribute to maintaining the therapeutic benefits. According to Lane et al.'s [51] findings combining LipiFlow® with compress therapy resulted in mild conjunctival injection, hyperemia or redness, and trace or mild petechial hemorrhages on the eyelid or conjunctiva. These symptoms were present immediately after treatment or at 1 day but had completely gone by the 2-week follow-up appointment without any intervention. However, none of these adverse events were observed in the current study.

It has been reported, that Intensed pulsed light (IPL) treatment significantly enhances TFLL, and improvements in signs and symptoms of DED can be attributed to improved meibomian gland function [52]. Review demonstrated that use of eyelid massage

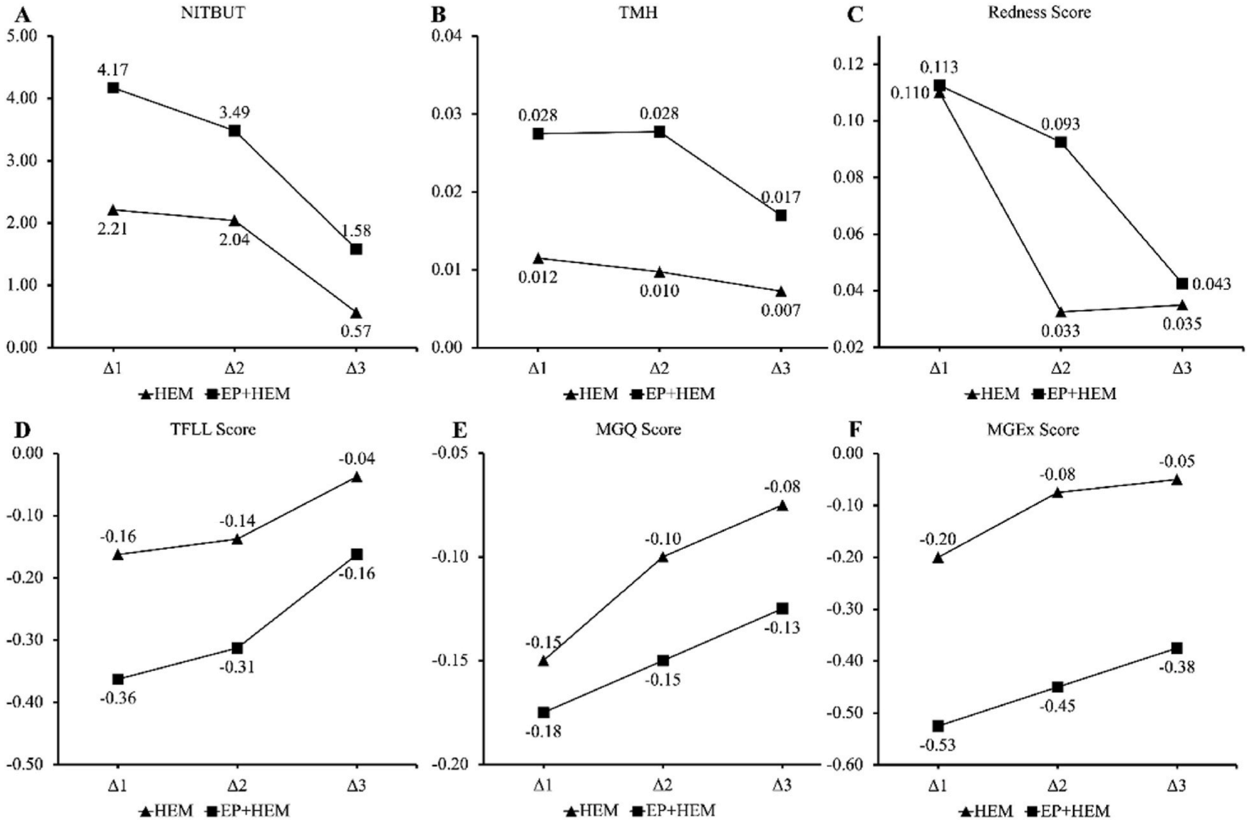

Fig. 9. The magnitude of changes in dry eye parameters.
Panel (A): Within-group non-invasive tear break-up time (NITBUT) comparison(units: sec); (B): Within-group tear meniscus height (TMH) comparison(units: mm); (C): Within-group Redness Score comparison; (D): Within-group tear film lipid layer (TFLL) comparison; (E): Within-group meibomian gland quality (MGQ) comparison; (F): Within-group meibomian gland expression (MGEx) comparison; HEM: heated eye mask, EP + HEM: EyePeace and heated eye mask: EyePeace, Δ1: 5mins - baseline, Δ2: 15 min - baseline, Δ3: 30 min - baseline.

Table 3
Analysis of safety parameters.

	EP + HEM	HEM	*F*	*p-value*
BCVA				
T0	1.00 ± 0.00	1.00 ± 0.00	–	–
T30	1.00 ± 0.00	1.00 ± 0.00	–	–
IOP (mmHg)				
T0	16.53 ± 2.22	16.80 ± 2.07	0.329	0.568
T30	16.45 ± 2.06	16.98 ± 1.99	1.340	0.251
ECC (mm^2)				
T0	2888.64 ± 242.88	2855.99 ± 241.56	0.363	0.548
T30	2862.84 ± 233.40	2878.87 ± 257.63	0.084	0.773
K1 (diopter)				
T0	42.54 ± 1.61	42.68 ± 1.60	0.146	0.703
T30	42.59 ± 1.63	42.64 ± 1.52	0.022	0.882
K2 (diopter)				
T0	43.84 ± 1.49	43.88 ± 1.58	0.010	0.919
T30	43.83 ± 1.55	43.87 ± 1.59	0.018	0.893
CCT (μm)				
T0	545.80 ± 35.81	547.25 ± 39.76	0.029	0.864
T30	548.55 ± 37.55	550.15 ± 39.62	0.034	0.853

*: $p < 0.05$, T0: pre-treatment baseline, T30: post-treatment 30 min, SD: Standard Deviation, EP + HEM: EyePeace and heated eye mask, HEM: heated eye mask, BCVA: best corrected visual acuity, IOP: intraocular pressure, ECC: endothelial cell count, K1: flat-axis keratometry value, K2: steep-axis keratometry value, CCT: central corneal thickness.

device, as an adjunct to warm compress treatment, affected marginally greater improvements in TFLL compared to conventional manual lid massage [4]. Compared with traditional treatments such as IPL, HEM is cheaper and more convenient to use, the patient's compliance is higher.

The study has the following limitations. The open-label design and using the same participant's contralateral eye as the control eye could have introduced participant bias, especially for subjective outcomes. In addition, the follow-up intervals was short, participants had a 10-min break between follow-up tests, and expressing the meibomian glands for assessing expressibility and quality maybe have affected the results. Furthermore, the average age of the participants was 27.45 ± 6.32 years; the dry eye symptoms were not particularly severe, and the meibomian gland atrophy has been reported to be more prevalent in older patients, therefore research will concentrate on a longer follow-up and cover a broader age range in future. Overall, these findings confirm the effectiveness and safety of the eyelid massaging device. Additional research is required to gather data pertaining to various non-pharmaceutical treatment modalities, including their specific indications that are most suitable for various types and severity of DES [53]. Furthermore, it is necessary to investigate the effectiveness of combining these approaches with pharmaceutical-based therapy, as well as to elucidate the mechanisms of action underlying the more advanced technological systems.

5. Conclusion

In summary, the results demonstrated that at 30 min, the combined effect of the eyelid massage device and HEM therapy significantly improved TFLL and meibomian gland expression grade than the HEM alone. Improvements in NITBUT and TMH significantly decreased after 15 min. Heat and gliding motion massage provided by EyePeace to the eyelids appears safe because it does not immediately affect the cornea. In summary, in short-term, combining eyelid massage with HEMwas found to be more effective than using HEM only in alleviating the signs and symptoms experienced by DE patients.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data availability statement

Data will be provided upon request.

CRediT authorship contribution statement

Jiayan Chen: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Sile Yu:** Resources, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Guanghao Qin:** Writing – review & editing. **Salissou Moutari:** Formal analysis. **Jonathan E. Moore:** Writing – review & editing, Supervision, Resources. **Ling Xu:** Writing – review & editing. **Wei He:** Writing – review & editing. **Emmanuel Eric Pazo:** Supervision, Investigation, Formal analysis, Conceptualization. **Xingru He:** Resources, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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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