• Clinical Research •

Efficacy of indirect intense pulsed light irradiation on meibomian gland dysfunction: a randomized controlled study

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Abstract

● **AIM:** To investigate the efficacy and mechanisms of indirect intense pulsed light (IPL) irradiation on meibomian gland dysfunction (MGD).

● **METHODS:** A total of 60 MGD patients was included in this prospective randomized controlled trial. Patients were randomly assigned 1:1 into two groups (3-mm group and 10-mm group) in which IPL was applied at distances from the lower eyelid margin of 3 and 10 mm, respectively. Both groups received three times treatment with 3-week interval. Meibomian gland yield secretion score (MGYSS), standard patient evaluation of eye dryness (SPEED) questionnaire, tear break-up time (TBUT), corneal fluorescein staining (CFS), and *in vivo* confocal microscopy were performed at baseline and after every treatment.

● **RESULTS:** After three IPL treatments, both groups had significant improvement in MGYSS (both $P<0.05$). The non-inferiority test showed that improvement in 10-mm group was not inferior to that in 3-mm group ($P<0.001$). In both groups, temporal regions of both upper and lower eyelids showed significant improvement in MGYSS. Scores of SPEED questionnaire in both groups declined significantly (both $P<0.001$) and changes of SPEED had no difference between two groups ($P=0.57$). Density of central corneal subepithelial nerves and TBUTs showed no statistically significant changes. The 3-mm group had improvement on corneal fluorescein staining ($P=0.048$) and meibomian gland morphology (acini wall thickness $P=0.003$, hyperreflective points $P=0.024$) while the 10-mm group had not.

● **CONCLUSION:** The efficacy of IPL indirect irradiation in improving meibomian gland secretion and alleviating dry eye symptoms remains unchanged with increase in treatment distance. IPL may primarily act on the functional improvement of the meibomian glands and corneal nerves.

● **KEYWORDS:** meibomian gland disfunction; dry eye; intense pulsed light; ocular surface

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INTRODUCTION

Meibomian gland dysfunction (MGD) is the leading cause of evaporative dry eye. It compromises patients' quality of life and can impair visual function in severe cases. MGD is a multifactorial disease characterized primarily by abnormalities in the quality and quantity of meibum[1]. Hormone levels, systemic diseases, skin diseases, and many other factors that disturb the ocular surface or the eyelid margin can contribute to its onset and development[2-4]. Traditional therapies such as warm compresses, lid hygiene, meibomian gland expression, antibiotics, artificial tears, and oral omega-3 fatty acid supplements are usually applied in combination, but still face issues with limited efficacy and lack of durability[5]. In the past two decades, the application of intense pulsed light (IPL) has gradually expanded from dermatology to the treatment of dry eye and eyelid diseases in ophthalmology, showing superior efficacy especially in the treatment of meibomian gland (MG)-related diseases[6].

IPL is a broadband light source with high intensity, consisting of visible polychromatic and incoherent light ranging from 500 to 1200 nm[7]. It can be absorbed by a variety of chromophores in the tissue. The exact mechanism of IPL treatment for

MGD is not yet clear. Current hypotheses primarily evolve from dermatological applications based on the direct irradiation mechanisms of IPL, such as photothermolysis, which is the basal mechanism of IPL therapy[6], can close abnormally dilated blood vessels thereby reducing the release of inflammatory factors[8], and the ability to kill microbes, especially *Demodex* mites, thus minimizing their damage to the glands and meibum[9]. Recently, the hypothesis that photobiomodulation (PBM) might also be a mechanism for IPL treatment of MGD has been proposed[10]. This hypothesis, which moves away from the concept of "direct irradiation" alone, broadens the perspectives for studying the mechanisms of IPL treatment for MGD.

PBM has long been studied and clinically applied in the field of phototherapy[11]; it is considered the primary mechanism for the "systemic effects" of phototherapy. "Systemic effects" manifest as significant benefits to non-irradiated areas of the body *in vivo* experiments, as a result of irradiation on other parts of the body[12-14]. Similarly, in most IPL ophthalmic treatments, the skin area corresponding to the MG is never directly exposed to light due to the protective cover of eye masks, and both the cornea and conjunctiva are further shielded by the additional layer of the eyelid from direct irradiation. Thus, we speculate that among the numerous hypotheses of IPL treatment mechanisms for MGD, the indirect irradiation effect mechanism based on PBM could play a key or even dominant role. In our preliminary animal experiments, IPL irradiation was only applied to the cheek areas of mice with MGD. Compared to the control group, improvements were observed in MG morphology and function, reduced levels of oxidative stress and apoptosis in glandular tissue, improved mitochondrial structure, and decreased inflammation levels[15]. In this clinical trial, we increased the distance of the IPL irradiation site from the eye, using a standard distance 3-mm group as a control, to observe improvements in MG function and other indicators. This aims to confirm the crucial role of indirect IPL irradiation in treating MGD and related dry eye conditions and to analyze its underlying mechanisms.

SUBJECTS AND METHODS

Ethical Approval This prospective, randomized, double-masked clinical trial followed the principles of the Declaration of Helsinki and was registered in the Chinese Clinical Trial Registry (ChiCTR1800019160). Approval from the Human Research and Ethics Committee of Peking University First Hospital was attained before enrollment began (2018 research245). The participants' recruitment, treatment, and follow-ups for this study are all conducted at the Department of Ophthalmology, Peking University First Hospital. All participants signed informed consent before any examinations or treatments were performed.

Trial Design and Subjects Subjects were randomized (1:1) to receive IPL therapy with the emitting head 3 mm or 10 mm from the lower eyelid margin (3-mm group and 10-mm group). Randomization was performed by the IPL therapist using a random number table after subjects met the inclusion and exclusion criteria. The observer and subjects remained masked over the duration of the trial. The inclusion criteria were 1) age≥18y; 2) Fitzpatrick skin type classification 1-4; 3) Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score ≥6; 4) MG secretion function score ≤12; 5) tear break-up time (TBUT) ≤10s; 6) corneal fluorescein staining (CFS) score ≥1 (TBUT≤5s not be considered); 7) The subject voluntarily participates in this study and is willing to comply with the treatment and follow-up. The exclusion criteria were 1) lactating or pregnant women; 2) wearing corneal contact lenses within the past 3mo; 3) presence of acute inflammation or infection in the eyes; 4) obvious scarring or keratinization of the eyelid margin; 5) ocular surgery (including eyelid surgery) within the past 6mo prior to enrollment; 6) neural paralysis in the treatment area within the 6mo before enrollment; 7) currently using punctal plugs; 8) presence of precancerous lesions, skin cancer, or pigmentation in the treatment area; 9) laser-assisted *in situ* keratomileusis surgery within the past 6mo prior to enrollment; 10) suffering from diseases in the treatment area that may be triggered by 560 to 1200 nm light waves, such as herpes simplex virus type 1 and 2, systemic lupus erythematosus, and porphyria; 11) taking photosensitive medications such as isotretinoin, tetracycline, or St. John's Wort; 12) use of eye drops for dry eye (except artificial tears) within 48h before enrollment; 13) history of head and neck radiotherapy within the past year before enrollment, or expected to undergo radiotherapy within 8wk after IPL treatment; 14) chemotherapy within the past 8wk before enrollment, or expected to undergo chemotherapy within 8wk after IPL treatment; 15) history of migraine or epilepsy; 16) underwent facial IPL treatment within the past year before enrollment; 17) excessive sun exposure within 4wk before enrollment; 18) other conditions deemed unsuitable for trial enrollment by the researcher.

Sample Size Calculation According to one of our previous studies, the standard deviation (SD) of meibomian gland yield secretion score (MGYSS) of the lower eyelids (l-MGYSS) at baseline was 3.3. As for the noninferiority threshold, we referred to our previous study that compared change of l-MGYSS between the IPL+meibomian gland expression (MGX) group and the warm compress+MGX group[16]. It was calculated to be 2.8, based on the change in value of the IPL+MGX group minus the change in value of the warm compress+MGX group after three treatments compared to baseline. This noninferiority threshold represented only the

partial of the beneficial effects of IPL that exceeded the effects of warm compress. Therefore, with a smaller noninferiority threshold, a more conservative or larger sample size would be obtained. The sample size was chosen to achieve a statistical power of 80% at a 5% significance level while considering 20% loss to follow-up[16]. The sample size calculation indicated that an enrollment of 27 subjects in each group would meet the above-mentioned design. The sample size was finalized as 30 subjects for each group, 60 in total.

Intervention The M22 system (Lumenis, Tel Aviv, Israel) was used to perform IPL therapy (14-18 overlapping IPL irradiations, 35 mm×15 mm each irradiation area) at the forehead, bilateral temporal area, and 3 or 10 mm from the lower eyelid margin on the cheek (Figure 1). A 590 nm filter was used. Energy densities ranged from 12 to 15 J/cm^2 according to the Fitzpatrick skin type and subjects' tolerance to pain. Eyes were protected with eye shields. Three IPL treatments were performed at 3-week intervals. Three follow-up visits will be scheduled before the second and third treatments (on the same day), as well as 3wk after the third treatment. From entry to the end of the follow-up, the total duration is approximately 2mo. Patients using artificial tears as part of their treatment were allowed to continue.

Measurements All follow-ups were conducted by a fixed, experienced physician, and the follow-up personnel remained blinded. The primary outcome, MGYSS, was measured with a MG evaluator (Tear Science Inc., Morrisville, North Carolina, USA). Lane *et al*'s[17] protocol was used to grade the meibum expressed from each MG: 3, clear liquid secretion; 2, cloudy liquid secretion; 1, inspissated/toothpaste consistency; and 0, no secretion. In each eyelid, a total of 15 MGs from temporal, central and nasal region of the eyelid (5 MGs in each region) were measured. The total MGYSS of each eyelid (15 glands included, with a range from 0 to 45) and MGYSS of each region of the eyelid (5 glands per region, with a range from 0 to 15) were calculated for data analysis. The MGYSS reflects the overall function of meibum secretion by the MGs within the observed range. It is a direct functional assessment index of the MGs with high specificity, unlike comprehensive ocular surface assessment indices such as TBUT.

SPEED questionnaire was used to evaluate the severity and frequency of dry eye symptoms. TBUT was measured with moist fluorescein sodium strips (Jingming New Technological Development Co, Ltd, Tianjin, China). The average TBUT of three repeated measurements were calculated for data analysis. CFS was graded following the protocol forwarded by the Cornea Group of Chinese Ophthalmological Society[18]: the cornea was divided into four quadrants (temporal superior, temporal inferior, nasal superior, and nasal inferior); in each quadrant, grade 0 represented no staining, 1 was assigned for 1–30 points of punctate staining, 2 for over 30 points of punctate staining, and 3 for infused staining or an ulcer; grades of the four quadrants are summed as the CFS score.

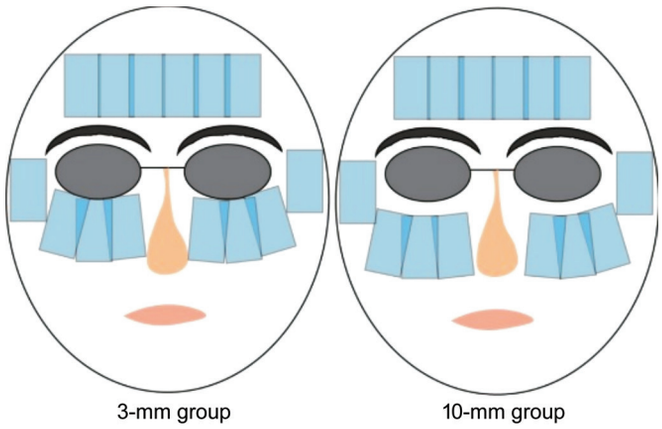

Figure 1 Schematic diagram of the IPL intervention Patients' eyes were protected with goggles. The blue rectangles in the diagram stand for the area where the IPL device was applied and 14-18 overlapping IPL irradiations were applied (35 mm×15 mm each irradiation area) on the forehead, bilateral temporal area, and 3 or 10 mm from the lower eyelid margin on the cheek. IPL: Intense pulsed light.

In vivo confocal microscopy (IVCM; Heidelberg RetinaTomograph II-Rostock Cornea Module: HRTII-RCM; Heidelberg Engineering GmbH, Dossenheim, Germany) was performed to observe the cornea and MG morphology. Image J software (National Institutes of Health, Bethesda, MD, USA) was used to measure the central corneal subepithelial nerves (CCSNs) density, hyperreflective points (points that have high grey level and can be distinguished from the gland tissue) in MG and the wall thickness of MG acini (Figure 2). Each image of IVCM covers a 400×400 μm^2 area. Three representative images were selected for measurement. The average of the three was recorded for analysis.

Statistical Analysis Data from the right eye were used for analyses. The non-inferiority test was performed with SAS 9.4 for Windows software (SAS Institute Inc. Cary, NC, USA). Rest of the data analysis were performed with SPSS 22.0 for Windows software (SPSS Inc., Armonk, New York, USA). Descriptive statistics of continuous variables were reported as the mean±SD. The Kolmogorov-Smirnov test was performed to determine whether the data obeyed a normal distribution. Data of the same group from different timepoints were compared with a paired *t*-test. An independent sample *t*-test was conducted to compare data between the two groups for a normal distribution with equal variance; otherwise, a Mann-Whitney *U* test was conducted. The descriptive statistics of categorical variables are expressed as frequencies or proportions/percentages. Categorical statistics were compared with a Chi-square test. For all tests, $P<0.05$ was considered statistically significant. Intention-to-treat analyses were

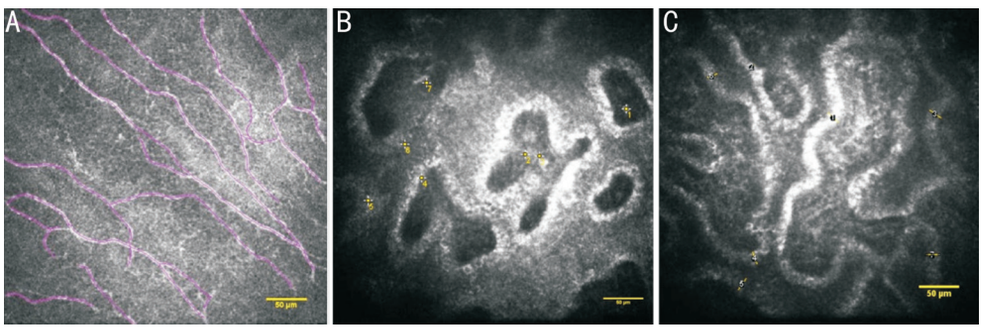

Figure 2 Measurements of parameters from *in vivo* confocal microscopy images Image J software was applied for measurements of parameters from *in vivo* confocal microscopy images. The central corneal subepithelial nerves were tracked and measured by Neuron J plugin (A). Hyperreflective points in meibomian gland tissue were defined as points that have prominent higher reflectivity and can be distinguished from pyknotic meibocytes. Hyperreflective points were marked manually and counted by multicount function of Image J (B). Wall thicknesses of all the acini in one 400×400 μm^2 image were measured and averaged. Each clear acinus was measured at one spot that had good contrast and regular morphology, where the measuring short line was drawn in the direction perpendicular to the tangent of the spot (C). Scale bars: 50 μm.

Table 1 Demographic information of two groups

Parameters	3-mm group	10-mm group	*P*
Subjects, *n*	32	28	-
Age, means±SD (range), y	36.16±12.92 (18-63)	36.50±12.23 (22-61)	0.91
Gender (female/male)	18/14	19/9	0.36
Fitzpatrick type (I/II/III/IV)	0/8/18/6	0/8/18/2	0.42

performed. Missing values were handled by inputting the missing value using the last observation carried forward.

RESULTS

Demographic Features Sixty subjects were enrolled in the study and randomly allocated to two treatment groups: 32 in 3-mm group and 28 in 10-mm group. In 3-mm group, two subjects withdrew before the first treatment and three subjects were lost to follow-ups. In 10-mm group, one subject withdrew before treatment and two subjects were lost to follow-ups. Demographic features did not differ between the two groups (all P>0.05; Table 1).

Primary Outcome and Non-inferiority Test After three IPL treatments, both groups had significant improvement in l-MGYSS compared to baseline (3-mm group: 2.5±4.2; 10-mm group: 3.1±3.8). The non-inferiority test performed by SAS 9.4 software showed that improvement in 10-mm group is not inferior to that in 3-mm group (P<0.001).

Variation of MGYSS in Different Regions After the IPL treatment, improvement in MGYSS of both upper and lower eyelids were observed in both groups and had already emerged after the second IPL treatment (Figure 3). In both groups, temporal regions of both upper and lower eyelids showed significant improvement in MGYSS (Figure 4). In general, consistent growth in MGYSS observed during the whole three IPL treatments.

Parameters of Symptomatology and Ocular Surface After three IPL treatments, scores of SPEED questionnaire in both groups declined significantly (P<0.001 in both groups; Figure 5). Change values of SPEED in 3-mm group (-3.4±4.9) and 10-mm group (-4.0±3.9) had no statistically significant difference (P=0.57).

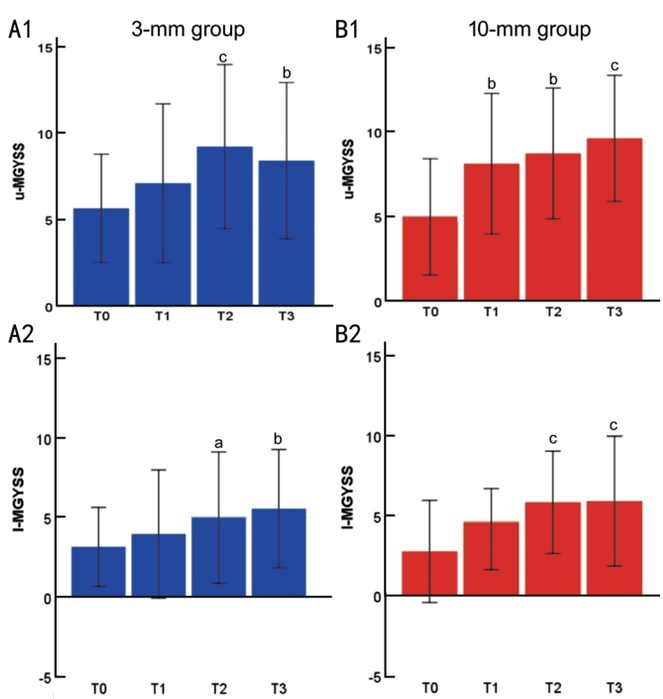

Figure 3 MGYSS at different timepoints MGYSSs of upper (A1, B1) and lower (A2, B2) eyelids at different timepoints. MGYSSs were evaluated at baseline (T0) and at 3wk after each treatment (T1-T3). [a]P<0.05, [b]P<0.01, [c]P<0.001 compared to baseline. MGYSS: Meibomian gland yield secretion score; u-MGYSS: MGYSS of upper eyelid; l-MGYSS: MGYSS of lower eyelid.

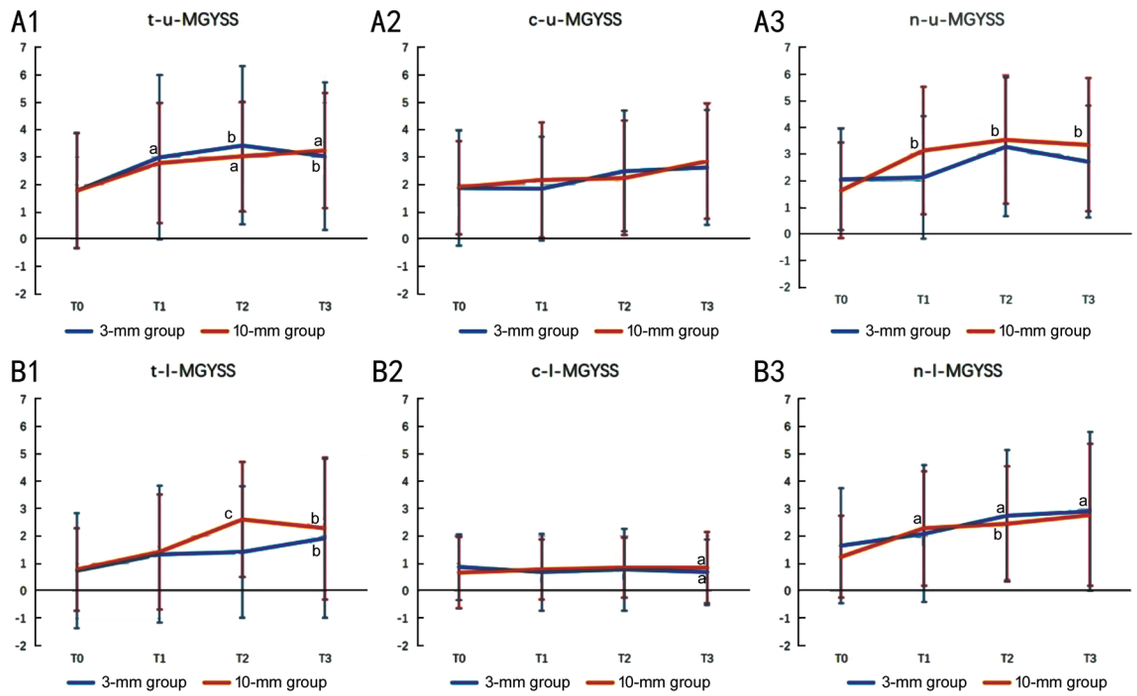

Figure 4 MGYSS trends in different regions of the eyelid MGYSS trends (from T0 to T3) in different regions of the eyelids. A1-A3: MGYSS of upper eyelids; B1-B3: MGYSS of lower eyelids. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001 compared to baseline. MGYSS: Meibomian gland yield secretion score; u-MGYSS: MGYSS of upper eyelid; l-MGYSS: MGYSS of lower eyelid; t-MGYSS: MGYSS of temporal region of the eyelid; c-MGYSS: MGYSS of central region of the eyelid; n-MGYSS: MGYSS of nasal region of the eyelid; T0: Baseline; T1-T3: 3wk after each treatment.

TBUT did not differ between 3-mm group (3.4±1.3) and 10-mm group (3.3±1.9) at baseline (*P*=0.63). Subtle improvements in TBUT were observed in both groups after three IPL treatments (0.3±1.9 in 3-mm group, 0.6±2.1 in 10-mm group), however were not statistically significant in both groups. Distribution of TBUT subgroups (TBUT<2s, 2s≤TBUT<5s, and TBUT≥5s) did not differ between groups (9.7%, 80.6%, and 9.7% in 3-mm group, 23.1%, 69.2%, and 7.7% in 10-mm group, *P*=0.38). After three IPL treatments, the distribution data of TBUT subgroups were 6.5%, 87.1%, and 6.5% in 3-mm group, and 11.5%, 76.9%, and 11.5% in 10-mm group (*P*=0.60, Chi-square test). After three IPL treatments, numbers of subjects with TBUT less than 2s had decreased in both groups (Figure 6), however these changes in TBUT distribution after the treatments were still not statistically significant.

CFS did not differ between 3-mm group (1.1±1.5) and 10-mm group (1.1±1.3) at baseline (*P*=0.83). After three IPL treatments, both groups showed decreases in CFS (-0.5±1.3 in 3-mm group, -0.2±1.7 in 10-mm group). Change in CFS was statistically significant in 3-mm group (*P*=0.048), while not in 10-mm group (*P*=0.552).

Density of CCSNs did not differ between 3-mm group (16.2±4.3 mm/mm^2) and 10-mm group (16.2±4.6 mm/mm^2) at baseline (*P*=0.965). After three IPL treatments, densities of 3-mm group and 10-mm group showed no statistically significant change (3-mm group: *P*=0.728, 10-mm group: *P*=0.644).

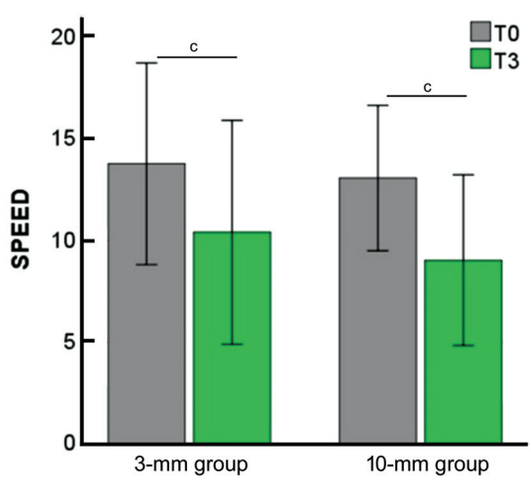

Figure 5 Symptomatology scoring before and after IPL treatments Both groups had significant decrease in scores of SPEED questionnaire (*P*<0.001 in both groups). [c]*P*<0.001 between groups. IPL: Intense pulsed light; SPEED: Standard patient evaluation of eye dryness; T0: Baseline; T3: 3wk after the 3rd treatment.

Morphological Features of Meibomian Gland Wall thickness of MG acini of the upper eyelid in 3-mm group increased after three IPL treatments (*P*=0.003). Figure 7 showed a typical case of wall thickness increase after the treatments. Wall thickness of lower eyelids in 3-mm group and of both lower and upper eyelids in 10-mm group did not show statistically significant change (Table 2).

Amounts of hyperreflective points in meibomian gland tissue of the upper eyelid in 3-mm group decreased after

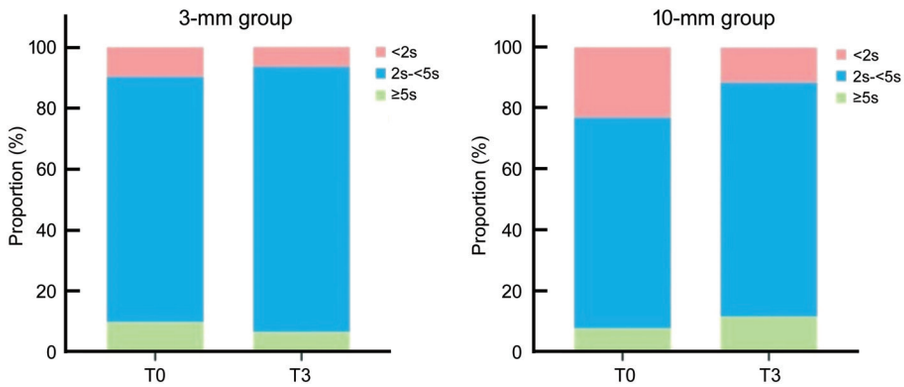

Figure 6 Distribution of TBUTs at baseline and after the third IPL treatment TBUTs at baseline (T0) and after the last IPL treatment (T3) were divided into three subgroups (TBUT<2s, 2s≤TBUT<5s, and TBUT≥5s). At baseline, most TBUT in both groups were under 5s. After the IPL treatments, numbers of TBUTs under 2s decreased, however this change was not statistically significant. IPL: Intense pulsed light; TBUT: Tear break-up time; T0: Baseline; T3: 3wk after the 3rd treatment.

Table 2 Meibomian gland morphology in IVCM images mean±SD

Parameters	3-mm group			10-mm group		
	T0	T3	*P*	T0	T3	*P*
u-WT (pixel)	14.2±3.1	15.8±2.2	0.003	14.1±2.6	14.4±2.5	0.158
l-WT (pixel)	14.6±2.3	14.9±2.1	0.282	14.9±12.6	14.4±2.5	0.146
u-HP (point)	4.6±2.1	3.9±1.5	0.024	4.3±1.4	4.0±1.0	0.371
l-HP (point)	5.2±2.6	4.5±1.9	0.055	4.2±1.7	4.3±1.4	0.720

IVCM: *In vivo* cofocal microscopy; T0: Baseline; T3: 3wk after the 3rd treatment; u-: Upper eyelid; l-: Lower eyelid; WT: Wall thicknesses of meibomian gland acini; HP: Hyperreflective points in meibomian gland tissue.

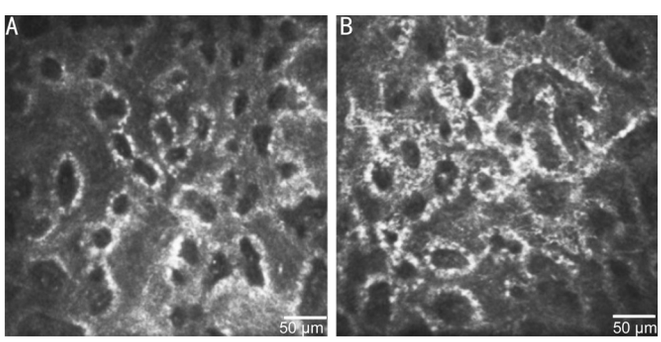

Figure 7 Typical case of wall thickness increase after IPL treatment A: IVCM image of a patient's MG tissue at baseline; B: IVCM image of the same patient's 3wk after the third IPL treatment. Scale bars: 50 μm. IPL: Intense pulsed light; IVCM: *In vivo* cofocal microscopy; MG: Meibomian gland.

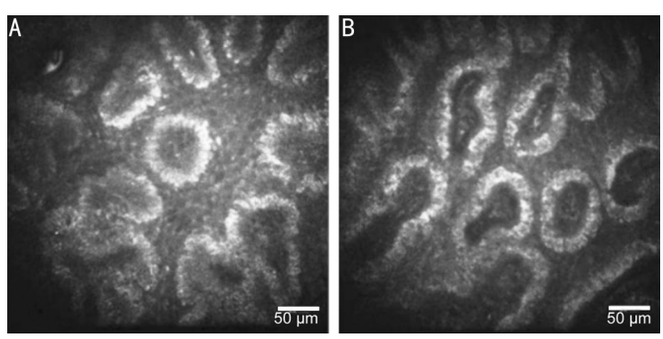

Figure 8 Typical case of hyperreflective points decrease after IPL treatment A: IVCM image of a patient's MG tissue at baseline; B: IVCM image of the same patient's 3wk after the third IPL treatment. Scale bars: 50 μm. IPL: Intense pulsed light; IVCM: *In vivo* cofocal microscopy; MG: Meibomian gland.

three IPL treatments (P=0.024). Figure 8 showed a typical case of hyperreflective points decrease after the treatments. Hyperreflective points of lower eyelids in 3-mm group and of both lower and upper eyelids in 10-mm group did not show statistically significant change (Table 2).

DISCUSSION

IPL, a mature technology in dermatology, has recently become an important therapy in MGD management. The mechanism of IPL for MGD remains unclear. This randomized, double-masked, controlled non-inferiority trial confirmed the therapeutic effects of IPL indirect application, demonstrating that a longer distance from the irradiation area to the eye did not diminish IPL effectiveness on MG secretory function and related dry eye symptoms. In addition, this result provided a possibility to move the IPL device out of the orbital area and to apply it at spots where dermatologists routinely apply it. Since the energy density used in dermatology are much higher than in ophthalmology[19], this potential new treating location allows a safer space for ophthalmologists to increase the energy density to magnify the therapeutic effects of IPL for MGD. The various observational indicators designed in this study can assist us in further dissecting and reasoning the therapeutic mechanism of MGD through indirect IPL irradiation.

IPL indirect application may improve the overall secretory function of the MGs in an eyelid by stimulating dormant glands into an activated state. According to Norn's[20] study, only about 45% of adult glands were active at any given time. Glands in the nasal region are the most active, followed by the central region, and then the temporal region[21]. By analyzing the nasal, central, and temporal regions of the eyelid separately, we found that the temporal parts of the eyelids in both groups showed significant improvement in MG secretion after IPL treatment. Additionally, the PBM effect in phototherapy, produced by infrared and near-infrared light included within the IPL spectrum, involves the absorption of photons that carry energy by photoreceptors or chromophores in the target tissue, leading to various photochemical and photobiological reactions[22]. The most fundamental mechanism is the modulation of cytochrome C oxidase activity, which stimulates the mitochondria, subsequently upregulating ATP production, metabolic levels, and promoting transcription, translation, and other vital activities[23-24]. Therefore, IPL indirect irradiation may stimulate the metabolic activities of dormant glands through the PBM effect, enhancing the secretory function of the temporal glands. Moreover, the effectiveness of PBM decreases with an increase in temperature at the treatment site[25]; thus, increasing the distance from the treatment site within a certain range may have a protective effect.

For glands with degenerated meibum and obstructive changes, the efficacy of IPL may still primarily derive from the photothermal effects at the site of direct irradiation. As mentioned previously, the overall improvement in the secretory function of MGs in this study may mainly stem from the activation of dormant glands in the temporal region. In cases where IPL is applied indirectly without combining with MGX or warm compresses, the improvement in glands that have already undergone obstructive changes may be limited. This study conducted IVCM observations of the MGs in the central part of the eyelids, finding that improvements in gland wall thickness and tissue hyperreflectivity points occurred only in the lower eyelids of the standard distance group, the nearest part to the direct irradiation site among both upper and lower eyelids in the two groups. Gland wall thickness of MG acini is a parameter that only suitable for images captured by IVCM. Histologically, it only shows the basal cell layer of the acinus[26]. When MGD happens, meibum degenerates and stagnates in the gland, and can harm the meibocytes in the basal cell layer. On the other hand, tissue hyperreflectivity points in IVCM images were considered to be representative of inflammation in MG tissue[27-28]. Under closer distance to the application site, the eyelid can still benefit from the direct photothermal effects of IPL, which can help melt degenerated meibum and coagulate abnormally dilated vessels nearby, so that the stagnation of meibum can be relieved and inflammatory factors released from the vessels be reduced[8].

The independent effect of IPL (without combining with MGX or warm compresses) on improving dry eye symptoms may primarily derive from the suppression of neuralgia through PBM. On one hand, baseline data showed that the study population had short TBUT but not severe CFS, suggesting that their dry eye symptoms may be more related to neuralgia[29]. On the other hand, after treatment, there was no significant improvement in TBUT in either group, but symptoms relieved significantly, and increasing the treatment distance did not weaken the symptom relief effect. Furthermore, the occurrence of pain is due to action potentials that spread rapidly along nerve cells induced by stimulation, namely the efflux of sodium (Na^+) and influx of potassium (K^+) in nerve cells[30]; in the mechanism of PBM, photons are directly absorbed by the receptors within the lipid bilayer of the nerve cell membrane (with absorption peaks between 905 nm and 910 nm); once absorbed, PBM light increases the permeability of the cell membrane, allowing the reabsorption of Na^+ and the efflux of K^+, thereby rebalancing the sodium-potassium pump through the cell membrane and eliminating pain signals from the source[23,31]. Thus, indirect IPL irradiation can suppress corneal neuralgia through the action of PBM, thereby significantly alleviating symptoms of dry eye.

The independent effect of IPL on the treatment of dry eye might initially begin with functional improvements, such as enhancing MG secretion and alleviating neuralgia. It might be only after a certain period of treatment and follow-up that improvements in structure (such as glandular and nerve micro-morphology) and the overall condition of the ocular surface can be observed. TBUT is a comprehensive indicator of ocular surface tear film condition, determined by the quality of mucin, aqueous, and lipid components[32]. In the short follow-up period of this study, although lipid secretion improved, the other two damaged components in moderate to severe dry eye may still be recovering, hence no significant improvement in TBUT was observed yet; in IVCM observations, there were no noticeable changes in corneal nerve density or glandular morphology. Such structural changes, compared to functional recovery, require a longer observation time.

There were limitations in this study. First, we used moist fluorescein sodium strips for the TBUT measurements. The components of fluorescein sodium strips may change the characteristics of the tear film, although this is a small effect. Second, only the short-term outcomes were observed; we believe longer observation is necessary, especially in terms of TBUT and corneal nerves. Then with more adequate funding, multi-center studies and systematic research into the molecular mechanism of indirect effects of IPL are necessary and meaningful.

In conclusion, in the treatment of MGD with indirect IPL irradiation, the effect of improving MG secretion and alleviating dry eye symptoms is not weakened when the treatment distance from the eye is appropriately increased. These therapeutic effects are likely primarily achieved through PBM. In regular treatment distances, MGD and related dry eye can still benefit from the photothermal effects at the directly irradiated sites. When IPL is used alone, without combining with other treatments, its efficacy may initially act on the functional improvement of the glands and corneal nerves, while structural improvements and enhancements in the overall condition of the ocular surface may require a longer treatment period.

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