CLINICAL STUDIES BOOK

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RESEARCH ARTICLE

Intense pulsed light improves signs and symptoms of dry eye disease due to meibomian gland dysfunction: A randomized controlled study

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Abstract

Purpose

To compare the safety and efficacy of intense pulsed light (IPL) followed by meibomian gland expression (MGX), against monotherapy of MGX.

Methods

Patients with moderate to severe meibomian gland dysfunction (MGD) were 1:1 randomized to 4 sessions of intense pulse light + MGX at 2-week intervals, or 4 sessions of Sham + MGX at 2-week intervals. Both patients and examiners were blinded to the allocation. Outcome measures, evaluated at the baseline (BL) and at a follow-up (FU) conducted 4 weeks after the last IPL session, included fluorescein tear breakup time (TBUT) as the primary outcome measure, OSDI (Ocular Surface Disease Index) questionnaire, Eye Dryness Score (EDS, a visual analog scale (VAS)-based questionnaire), Meibomian gland score (MGS, a score of meibum expressibility and quality in 15 glands on the lower eyelid), daily use of artificial tears, and daily use of warm compresses. In addition, during each treatment session, the number of expressible glands was counted in both eyelids, the predominant quality of meibum was estimated in both eyelids, and the level of pain/discomfort due to MGX and IPL was recorded.

Results

TBUT increased from 3.8±0.2 (μ±standard error of mean (SEM)) to 4.5±0.3 seconds in the control arm, and from 4.0±0.2 to 6.0±0.3 in the study arm. The difference between arms was statistically significant (P < .01). Other signs/symptoms which improved in both arms but were greater in the study arm included MGS (P < .001), EDS (P < .01), the number of expressible glands in the lower eyelids (P < .0001) and upper eyelid (P < .0001), the predominant meibum quality in the lower eyelid (P < .0001) and upper eyelid (P < .0001), and

randomization sequence. The funders had no role in data collection or decision to publish.

Competing interests: Dr. Rolando Toyos - speaks, consult, research for Lumenis Dr. Steven Dell - speaks, consult, research for Lumenis Dr. Neel Desai - speaks, consult, research for Lumenis Dr. Melissa Toyos - research for Lumenis These competing interests do not alter our adherence to PLOS ONE policies on sharing data and materials.

the level of pain due to MGX (P < .0001). Outcome measures which improved in both arms with no significant differences between the two were OSDI (P = .9984), and the daily use of artificial tears (P = .8216). Meibography, daily use of warm compresses, and severity of skin rosacea did not show statistically significant changes in either arm. No serious adverse events were observed. There was a slight tendency for more adverse events in the control group (P = 0.06).

Conclusions

The results of this study suggest that, in patients with moderate to severe symptoms, combination therapy of intense pulse light (IPL) and meibomian gland expression (MGX) could be a safe and useful approach for improving signs of dry eye disease (DED) due to meibomian gland dysfunction (MGD). Future studies are needed to elucidate if and how such improvements can be generalized to different severity levels of MGD.

Introduction

Background

Dry eye disease (DED) is a multifactorial disease of the ocular surface, characterized by a loss of homeostasis of the tear film, tear film instability and ocular surface inflammation [1, 2]. The prevalence of DED is between 5% and 50%, depending on geographical region [3]. The condition occurs in two main forms, aqueous-deficiency and evaporative, although both types often co-exist [4]. The major cause of evaporative dry eye disease is meibomian gland dysfunction (MGD), defined by the international workshop on MGD as "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion" [5]. MGD leads to poor quality of the meibum, destabilization of the tear film, exposure of the ocular surface and, eventually, the development of dry eye symptoms [6]. It was estimated that between 60% [7] and 86% [8] of DED cases are due to MGD. According to Tear Film & Ocular Society's Dry Eye Workshop II (TFOS DEWS II), over the age of 40 the prevalence rate of MGD ranges between 38% to 68% [3].

Many treatments for MGD include lid hygiene [6], thermal pulsation [9], artificial tear substitutes [10], artificial lubricants [6], topical or systemic antibiotics [10], FDA-approved anti-inflammatory medicines like cyclosporine [11], autologous serum eye drops [12], immunosuppressant agents [6], Lymphocyte function-associated antigen-1antagonists [13], and meibomian gland expression [14–16].

Another therapeutic approach, which has gained popularity in the past 5 years, is administration of intense pulse light (IPL) to the skin of the periocular area. IPL technology consists of brief pulses of non-coherent and polychromatic light, with wavelengths ranging from 500 to 1200 nm. IPL was found to be useful in a range of dermatological applications, including capillary and venous malformations [17], telangiectasia [18], and erythema of rosacea [19]. The latter condition is especially relevant for dry eye disease, as it is estimated that about 80% of patients with skin rosacea suffer from MGD [20]. It is therefore reasonable to expect that IPL, which is extremely effective for improving rosacea, could be useful for management of MGD as well. Indeed, although the mechanism of action is still not well understood [21], since the pioneering work of Toyos and colleagues [22] a large number of studies have indicated that

IPL can reduce both signs and symptoms of dry eye [23–26]. In its staged management algorithm, the TFOS DEWS II recommended this technology as a second step for treatment of DED, after lid hygiene and ocular lubricants of various types [10]. In 2020, Cote and colleagues performed a systematic review of the clinical literature and concluded that, due to the scarcity of randomized controlled trials (RCTs), the therapeutic value of IPL is still uncertain [27]. These authors also pointed out that the safety profile of IPL was not sufficiently reported.

Objectives

The purpose of the current prospective multi-center RCT study is to further demonstrate the merits of IPL treatment for DED due to MGD, in a multi-site study performed on a North American population. The main objective was to demonstrate that IPL combined with meibomian gland expression is superior to meibomian gland expression alone, in terms of improvement of signs and symptoms of DED due to MGD. The null hypothesis was that there is no statistically significant difference between the change in tear-break up time in patients treated with IPL combined with MGX, and patients treated with MGX alone.

Materials and methods

This research was approved by an Institutional Review Board (Sterling IRB, # 6051), and registered in ClinicalTrials.gov (NTC03396913).

Trial design

This was a prospective, interventional, multi-site, parallel-group, two-arms, randomized, active-controlled with a 1:1 allocation ratio. The trial is set to assess the superiority of the study arm versus the control arm. The study was conducted in the Unites States (3 sites).

Changes to trial design

In the original design, the sample size was planned for a power of 80%. The primary outcome measure was to be collected in both eyes, but the primary study hypothesis was to be evaluated for the study eye only, where the study eye was defined as the eye with the worst primary outcome measure at baseline (BL). After study commencement (but before any data was unmasked), it was found that 8 patients in one site were not treated in accordance with the treatment protocol. The study was paused in this site, until the treating physician in this site was re-trained to conform with the treatment protocol. To maintain a power of 80% the study statistician recommended to increase the sample size (see below). Following this recommendation, the protocol was amended and approved by the IRB.

Participants

Eligible participants were adults aged 22 to 85 years of age with signs and symptoms of dry eye disease due to MGD, who met all inclusion and exclusion criteria. The inclusion criteria included patients with a tear break-up time (TBUT) $\leq$ 7 seconds in the study eye; patients with a meibomian gland secretion (MGS) $\leq$ 12 in the study eye (where MGS is a score evaluating the quality of meibum along the lower eyelid, as described by Lane and colleagues [9]: sum of 5 nasal + 5 central + 5 temporal meibomian glands along the lower eyelid, where each gland is graded 0 if blocked, or 1, 2, 3 if expressing an inspissated meibum, cloudy liquid meibum, a clear liquid meibum, respectively); patients with at least 5 non-atrophied meibomian glands in the lower eyelid of the study eye; and patients with an OSDI questionnaire score $\geq$ 23 (moderate to severe symptoms of dry eye, as defined by Miller et al., 2010 [28]). The main exclusion

criteria included Fitzpatrick skin type V or VI; use of prescription eye drops within 7 days (excluding artificial tears or glaucoma drops) of recruitment; facial IPL treatment within the past 12 months; any thermal treatment of the eyelids or meibomian gland expression within the past 6 months; ocular surface and eyelid abnormalities, any systemic condition that may cause dry eye; use of photosensitive drugs within the past 3 months; pre-cancerous lesions, skin cancer or pigmented lesions within the treatment area; over exposure to sun within the past 1 month; ocular infections within the past 6 months; uncontrolled infections or immuno-suppressive diseases; and unwillingness or inability to abstain from the use of medications known to cause dryness. An informed consent was obtained from all subjects enrolled in the study.

Study settings

The study took place from January 2018 to July 2019, at 3 clinics in the USA (Dell Laser Consultants in Austin, Texas; Toyos Clinic in Nashville, Tennessee; Eye Institute of West Florida in Largo, Florida).

Interventions

Patients were randomly assigned to receive IPL treatment followed by meibomian gland expression (the study arm) or sham IPL followed by meibomian gland expression (the control arm). Each patient underwent a series of 4 treatment sessions, 2 weeks apart. In each session, the eyes of the patient were occluded with eye protection (adhesive eye patches + Lumenis opaque goggles). In the study arm, IPL was generated by a Lumenis M22 system, with a 560 nm or 590 nm cut-off filter that blocked all wavelengths below 560 nm or 590 nm, respectively. In the control arm, IPL was generated by the same system, but all light signals were blocked with an aluminum plate instead of the 560/590 cut-off filter. based on the double-pass protocol described in a previous publication by Toyos and colleagues [22]. The treatment area included the malar region (from tragus to tragus, including the nose) and the peri-ocular area up to the lower edge of the eye protection, positioned along the lower lid margin inferior to the lash line. IPL treatment was administered in two passes. For patients with the study arm, fluence was adjusted based on the Fitzpatrick skin type (from 11 to 15 J/cm^2, for Fitzpatrick skin types of IV to I, respectively). In all patients, a single follow-up (FU) session was scheduled 4 weeks after the fourth treatment session.

Participants were allowed to continue using artificial tears or warm compresses during the study.

Outcomes

The primary endpoint was the change in tear break-up time (TBUT). Measurement of TBUT followed the same protocol in all sites: a FUL-GLO® fluorescein sodium ophthalmic strip (0.6 mg) was applied to the inferior tarsal conjunctiva. The subject was asked to blink a few times to distribute the dye over the ocular surface. Once positioned at the slit lamp, the subject closed his/her eyelids completely. The examiner viewed the eye of the subject through a slit lamp using broad beam cobalt blue illumination and a yellow barrier filter. Then, the subject was asked to open his/her eyelids without blinking. A stopwatch was started as soon as the subject opened the eyelids, and was stopped at the first sign of breakup (first dark spot or discontinuity in the precorneal fluorescein-stained tear layer). For each eye, 3 consecutive readings were taken, and the average value was recorded. The change in TBUT, (ΔTBUT, was defined as the difference in the value of the outcome measure at baseline and at the follow-up (TBUT(FU)—TBUT(BL)).

Secondary endpoints included the change in OSDI (a validated questionnaire for self-assessment of symptoms, ranging from 0–100, where 0 indicated no symptoms and 100 was consistent with the most severe and frequent symptoms); and the change in EDS (a VAS questionnaire for self-assessment of symptoms, range from 0 to 100, where 0 coded for "No symptoms", 50 for "Moderate symptoms", and 100 for "Unbearable symptoms").

Exploratory endpoints included: (1) the change in percentage of area loss of meibomian glands, as evaluated with infra-red meibography performed with the Antares topographer and Phoenix software analysis (CSO) or the Keratograph 5M and Meiboscan software (Oculus). A 5-point scale (no gland loss, $<$ 25% loss, 2 = 25%—50%, 51–75%, and $>$ 75%), was used to score the severity of area loss of meibomian glands; (2) the change in meibomian gland score or MGS as described by Lane and colleagues [9] (the sum of grades of 15 meibomian glands (5 nasal + 5 central + 5 temporal) along the lower eyelid, where each gland was graded 0 if blocked, or 1, 2, 3 if the expressed meibum was inspissated, cloudy liquid, or clear liquid, respectively); and (3) change (Normal versus Abnormal) in eyelid appearance in biomicroscopy evaluation with the slit lamp, including lid margin thickening, conjunctival injection, and loss of eye lashes.

The change in the severity of rosacea, from baseline to follow-up, was a post-hoc outcome measure. Skin rosacea was evaluated in the malar region. Severity was graded using the standard classification method proposed by the National Rosacea Society Expert Committee (2004). Additional post-hoc analyses were conducted for parameters collected after each treatment session, including the number of expressible glands along the upper and lower eyelids; the predominant quality of meibomian gland secretions along the upper and lower eyelids; the daily use of artificial tear drops and warm compresses (as reported by the participants); and the level of pain/discomfort due to IPL and MGX (each, self-assessed with a VAS ranging from 0 to 100, where 0 implied no pain and 100 implied most severe and intolerable pain).

Change to outcomes

In the original design of the study, outcome measures were to be collected in both eyes but the primary study hypothesis was to be evaluated for the study eye only. Following the finding that 8 patients in one site were not treated in accordance with the treatment protocol (see "Changes to trial design"), the study statistician recommended to include both eyes in the statistical analysis. Correspondingly, the protocol was amended and approved by the IRB.

Sample size

To detect a statistically significant difference in the change of TBUT between the study and control arms, it was assumed that the changes in TBUT are expected to be 5±5 sec and 1±5 sec in the study arm and control arm, respectively (based on preliminary results obtained in a pilot study [24]), and on the literature on the effect of meibomian gland expression). With a two-sided 5% significance and a power of 80%, the study statistician determined that a minimal sample size of 50 evaluable subjects (100 evaluable eyes) would be required. Following the finding that several patients in one site were not treated in accordance with the treatment protocol (see Changes to trial design), the study statistician recommended to increase the sample size to 166 evaluable eyes (83 evaluable subjects).

Interim analyses and stopping guidelines

There were no interim analyses, and no stopping rules were defined.

Randomization: Type

The randomization process adopted a blocked randomization strategy, using random block size of 2 and 4. Prior to study commencement a randomization sequence was created, per site, by the study statistician.

Randomization: Allocation concealment mechanism

A clinical research associate (Sierra Clinical) provided each site with a set of sealed and opaque envelopes, each containing a randomized assignment as prepared by the study statistician. Each envelope was labeled with a unique and consecutive number.

Randomization: Implementation

Following enrollment of a participant, the site study coordinator opened the envelope and determined the allocation. This information was conveyed to the treating physician only. The site examiners remained blinded.

Blinding

Allocation was not disclosed to the patients. Since the eyes were occluded and the patient did not know what level of discomfort to expect, the patient was effectively blinded to the allocation. Allocation was also concealed from the examiners who assessed the outcome measures at baseline, the follow-up, and at each treatment session. Due to the nature of treatment, it was impossible to mask the individuals who delivered the IPL treatment itself. However, the individuals who performed MGX were also blinded to the allocation.

Similarity of interventions

Except for the blocking of IPL energy in the control arm, versus active IPL in the study arm, interventions in the two arms were identical.

Statistical methods

Statistical planning and analysis of the primary, secondary and exploratory endpoints was done by the study statistician, using the R software. Sub-analyses and analyses of post-hoc outcomes were performed by the sponsor with JMP 16.0.0.0 (SAS Institute, Inc.). Imputation of missing data was carried out with excel simulations.

OSDI, rosacea severity, use of warm compresses, and use of artificial tears were collected per subject. All other outcome measures were collected per eye.

For continuous variables, descriptive statistics were expressed as median, mean (μ) ± standard deviation (σ), μ ± standard error of the mean (SEM), or 95% confidence intervals (95% CI: low, high). Within study arm, the change (ΔX_{arm}) of a continuous outcome measure X was calculated as X(FU)-X(BL), averaged across all subjects in that specific arm, where X(FU) and X(BL) are the values of the outcome measure at the follow up and the baseline, respectively. The statistical significance of ΔX was estimated with a paired two-tails t-test and the resulting p-value was noted with a small p. Between study arms, the statistical significance of the mean difference ($MD_{X} = \Delta X_{study} - \Delta X_{control}$) was estimated with a least squares fit model, where the change ΔX was the dependent variable, and the allocation (study arm versus control arm) was the independent variable. Results of a test evaluating the statistical significance of the difference between arms were represented with a large P. In outcome measures for which a statistically significant difference between the two arms was identified, an additional analysis was performed utilizing a more conservative approach. First, the inter-eye correlation was

removed by using a linear mixed effect (LME) model with random intercept, with the change ΔX as the dependent variable, the allocation as an independent variable, and the subject identity as an independent variable with a random effect. Running this LME model is equivalent to defining the "average eye" (the arithmetic average between the value of the outcome measured in the left and right eye of a subject) as the dependent variable, and the application as the sole independent variable. Second, missing values were handled by implementing a multiple imputation technique: for each patient with a missing value at the follow-up, the missing value was imputed with the average result of 1000 simulations, where in each simulation the missing value of an outcome measure was replaced with $N^{-}(p_i, \mu_{FU}, \sigma_{FU})$, where N^{-} is the inverse of a normal cumulative distribution with a mean μ_{FU} and a standard deviation μ_{FU} (the mean and standard deviation of the outcome measure at the follow-up, for the entire sample with available values at follow-up), and p_i is a random probability taken from a uniform distribution between 0 and 1. For simplicity, when applicable, results of this conservative analysis are mentioned in the text, but not in the Tables.

For ordinal categorical variables, descriptive statistics were expressed as frequencies and percentages; within arms, the statistical significance of the change from baseline to follow-up was examined with a Pearson's chi-square test, or with a Fisher's exact test (the latter, when $>$ 20% of the cells in the contingency table had expected frequencies of less than 5); between arms, the statistical significance of the difference in number of eyes which improved/remained the same/deteriorated was estimated with an ordinal logistic regression.

Results

Participant flow

Fig 1 shows the flow diagram according to the CONSORT guidelines. One hundred eleven (111) subjects were screened between January 2018 and May 2019. Twelve subjects (12) were not eligible due to failure to meet all inclusion criteria (MGS $>$ 12: n = 5; OSDI $<$ 23: n = 4; TBUT $>$ 7 seconds n = 3); Eleven (11) additional subjects were excluded due to use of photosensitive medications within 3 months prior to screening (n = 4), history or migraines, seizures or epilepsy (n = 2); ocular surface abnormality compromising corneal integrity (n = 2), use of prescription eyes drops for dry eye within 7 days prior to screening (n = 1), facial IPL within 12 months prior to screening (n = 1), and a combination of *Herpes simplex*, current use of punctal plugs, and precancerous lesions in the area of treatment (n = 1). Of the 88 eligible subjects, 43 and 45 were randomized to the sham treatment plus MGX (the control arm) and IPL plus MGX (the study arm), respectively. These 88 subjects constituted the safety set.

Losses and exclusions

Of the 88 randomized subjects, 6 subjects (all assigned to the study arm) did not complete the full schedule of treatment: 3 withdrew after a single treatment session, 1 after two sessions, 1 after three sessions, and 1 after four sessions. Reasons for discontinuing the study were: subject did not want to continue due to pain of procedure (n = 1); subject did not want to abstain from anti-histamines (n = 1); and subject did not want to continue and gave no reason (n = 1). Three subjects were lost to follow-up without the possibility to inquire about their reasons to withdraw. None of the randomized subjects were excluded after randomization, The 82 subjects who completed all treatments sessions and the follow-up (43 and 39 subjects in the control and study arm, respectively) constituted the efficacy set.

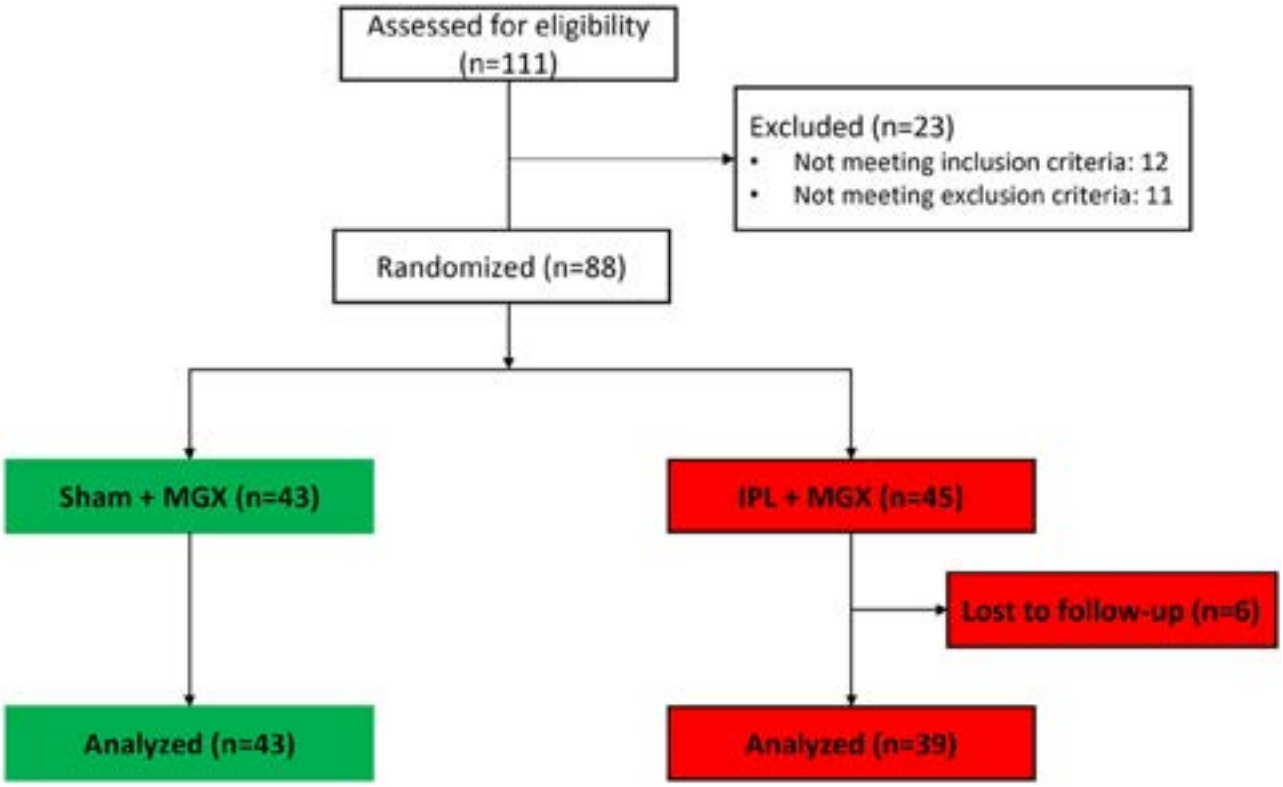

Fig 1. Flow diagram. n: number of subjects.

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Recruitment

Patients were recruited between Jan 2018 and May 2019. Study duration per each patient was 10 weeks (4 treatment sessions at 2 weeks intervals + a follow-up at 4 weeks after the 4th treatment session).

Reason for stopped trial

Study ended when 82 subjects completed the study.

Baseline data

Baseline data in the efficacy set are summarized in Table 1. Between the two arms, there were no differences in demographics (age: P = 0.3396; ethnicity: P = 0.7781; skin type: P = 0.9056). There was a trend form more women in the control arm (60% of women, versus 37% of men), but the difference was not statistically significant (P = 0.0503). The primary and secondary outcome measures were similar between the two arms (TBUT: P = 0.5253; OSDI: P = 0.1380; EDS: P = 0.1437). In the exploratory outcome measures, MGS and Meibography were more severe in the control arm, compared to the study arm (MGS: P = 0.0478; Meibography in lower lids: P = 0.0092; Meibography in upper lids: P = 0.0447).

With respect to the post-hoc outcome measures, at baseline there were no differences between the two arms in the number of expressible glands in the lower lids (P = 0.3201), the number of expressible glands in the upper lids (P = 0.7753), the predominant quality of meibomian gland secretion in the lower lids (P = 0.1389), the predominant quality of meibomian gland secretion in the upper lids (P = 0.1384), the severity of skin rosacea (P = 0.1418), the

Table 1. Baseline values.

		Level	Control (43 pts, 86 eyes)	Study (39 pts, 78 eyes)	P
Demographics					
Age (years) (Continuous)		Patient	56.8 [52.9, 60.7]	54.3 [49.8, 58.7]	0.3793
Gender (Nominal)		Patient	Women: 33 (76.7%)	Women: 22 (56.4%)	0.0503
			Men: 10 (23.3%)	Men: 17 (43.6%)	
Fitzpatrick skin type (Ordinal)		Patient	I: 4 (9.3%)	I: 5 (12.8%)	0.6340
			II: 19 (44.2%)	II: 18 (46.2%)	
			III: 15 (34.9%)	III: 11 (28.2%)	
			IV: 5 (11.6%)	IV: 5 (12.8%)	
Ethnicity (Nominal)		Patient	Caucasian: 37 (86.1%)	Caucasian: 32 (82.1%)	0.7781
			Hispanic: 5 (11.6%)	Hispanic: 5 (12.8%)	
			Asian/Pacific: 1 (2.3%)	Asian/Pacific: 2 (5.1%)	
Primary outcome					
TBUT (sec) (Continuous)		Eye	3.8 [3.4, 4.1]	4.0 [3.6, 4.4]	0.5253
Secondary outcomes					
OSDI (Continuous)		Patient	60.2 [54.6, 65.9]	53.8 [47.1, 60.5]	0.1380
EDS (Continuous)		Eye	71.0 [67.7, 74.3]	67.0 [62.6, 71.4]	0.1437
Exploratory outcomes					
MGS		Eye	8.4 [7.6, 9.2]	9.6 [8.9, 10.4]	0.0478 *
Meibography (%Loss of meibomian glands)	Lower lids (Ordinal)	Eye	None: 10 (11.6%)	None: 13 (16.7%)	0.0092 **
			< 25%: 47 (54.7%)	< 25%: 52 (66.6%)	
			25–50%: 16 (18.6%)	25–50%: 13 (16.7%)	
			51–75%: 9 (10.5%)	51–75%: 0 (0%)	
			>75%: 4 (4.6%)	>75%: 0 (0%)	
	Upper lids (Ordinal)	Eye	None: 14 (16.3%)	None: 15 (19.2%)	0.0447 *
			< 25%: 42 (48.8%)	< 25%: 47 (60.3%)	
			25–50%: 18 (20.9%)	25–50%: 15 (19.2%)	
			51–75%: 8 (9.3%)	51–75%: 1 (1.3%)	
			>75%: 4 (4.7%)	>75%: 0 (0%)	
Post-hoc outcomes					
Number of Expressible glands	Lower lids (Continuous)	Eye	10.6 [9.3, 11.9]	11.5 [10.2, 12.8]	0.3201
	Upper lids (Continuous)	Eye	10.7 [8.9, 12.5]	10.3 [8,7, 12.0]	0.7753
Predominant quality of meibomian gland secretion	Lower lids (Ordinal)	Eye	0 (Blocked): 10 (11.6%)	0 (Blocked): 5 (6.4%)	0.1389
			1 (Inspissated): 49 (57.0%)	1 (Inspissated): 41 (52.6%)	
			2 (Cloudy): 24 (27.9%)	2 (Cloudy): 32 (41.0%)	
			3 (Clear): 3 (3.5%)	3 (Clear): 0 (0%)	
	Upper lids (Ordinal)	Eye	0 (Blocked): 17 (19.8%)	0 (Blocked): 10 (12.8%)	0.1384
			1 (Inspissated): 39 (45.3%)	1 (Inspissated): 33 (42.3%)	
			2 (Cloudy): 28 (32.6%)	2 (Cloudy): 28 (35.9%)	
			3 (Clear): 2 (2.3%)	3 (Clear): 7 (9.0%)	
Skin Rosacea (Ordinal)		Patient	0 (None): 3 (7.0%)	0 (None): 6 (15.4%)	0.1418
			1 (Mild): 21 (48.8%)	1 (Mild): 22 (56.4%)	
			2 (Moderate): 16 (37.2%)	2 (Moderate): 7 (17.9%)	
			3 (Severe): 3 (7%)	3 (Severe): 4 (10.3%)	
Artificial tears (daily use) (Continuous)		Patient	2.7 [1.9, 3.6]	2.5 [1.8, 3.2]	0.6484
Warm compresses (daily use) (Continuous)		Patient	0.6 [0.2, 1.0]	0.41 [0.2, 0.6]	0.4625
Lid Margin thickening in biomicroscopy (Nominal)		Eye	Abnormal: 69 (80.2%)	Abnormal: 55 (70.5%)	0.1477
			Normal: 17 (19.8%)	Normal: 23 (29.5%)	

(*Continued*)

Table 1. (Continued)

	Level	Control (43 pts, 86 eyes)	Study (39 pts, 78 eyes)	P
Conjunctival injection in biomicroscopy (Nominal)	Eye	Abnormal: 63 (73.3%)	Abnormal: 55 (70.5%)	0.6962
		Normal: 23 (26.7%)	Normal: 23 (29.5%)	
Loss of eye lashes in biomicroscopy (Biomicroscopy) (Nominal)	Eye	Abnormal: 26 (30.2%)	Abnormal: 19 (24.4%)	0.3999
		Normal: 60 (69.8%)	Normal: 59 (75.6%)	

Continuous variables: Mean and 95% confidence interval (μ [Low 95%, High 95%]). Categorical variables: frequency and percentage per category (n (%)); Statistical significance (P) was calculated with a two-sided t-test for continuous variables, ordinal logistic regression for ordinal variables, or Pearson's chi-square test for nominal variables;

*: P<0.05;

**:P<0.01;

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number of daily artificial tears (P = 0.6484), the number of daily warm compresses (P = 0.4625), abnormal biomicroscopy findings in lid margin (P = 0.1477), abnormal biomicroscopy findings in the conjunctiva (P = 0.6962), and abnormal biomicroscopy findings in the eye lashes (P = 0.3999.

Number analyzed

The primary analysis was intention-to-treat (ITT). Of the 88 randomized participants, 6 (all in the study group) were lost to follow-up. Thus, data from 82 patients were available for the ITT analysis. The final number of participants in the control and study groups were 43 patients (86 eyes) and 39 patients (78 eyes), respectively.

Outcome measures tested at BL and FU

Tables 2 and 3 summarize the change in outcome measures tested at BL and FU.

TBUT (primary outcome measure). TBUT improved (increased) in both arms, but the improvement was more pronounced in the study arm (compare Tables 1 & 2, and Fig 2). In the control arm, the mean TBUT increased from 3.8 [95% CI: 3.4, 4.1] to 4.6 [95% CI: 4.0, 5.1] seconds; the median TBUT increased from 3.7 to 3.85 seconds; and ΔTBUT (the difference of TBUT at FU and BL) was 0.75 [95% CI: 0.3–1.2] seconds ($p < 0.01$). In the study arm, the mean TBUT improved from 4.0 [95% CI: 3.6, 4.4] to 6.0 [95% CI: 5.4, 6.6] seconds, the median TBUT improved from 4.0 to 5.85 seconds, and ΔTBUT was 2.0 [95% CI: 1.4, 2.6] seconds ($p < 0.0001$). The mean difference between ΔTBUT of the two arms (MD_{TBUT} =) was 1.24 ±0.37 seconds (mean ± SEM), in favor of the study arm (P = 0.001). When the inter-eye correlation was taken into account, MD_{TBUT} was 1.24 ±0.50 seconds in favor of the study arm (unadjusted: p = 0.0147; adjusted by TBUT at baseline: p = 0.0076). Since this difference was statistically significant, a more conservative analysis (which handled missing values, as described in Methods), was also performed. In this conservative analysis, MD_{TBUT} slightly decreased to 1.20 ±0.48 seconds in favor of the study arm. This difference remained statistically significant, although to a lesser degree of certainty (P = 0.0136).

The minimal clinically important difference (MCID) for TBUT change was not previously characterized or defined in the literature. Hence, in a post-hoc analysis we examined several different possibilities for threshold values (2, 3, 4, and 5 seconds). We found that the proportions of eyes which exceeded these thresholds were twice or more in the study arm, compared to the control: 2 seconds- 90% vs. 44% (P = 0.00001); 3 seconds- 56% vs. 26% (P = 0.004); 4 seconds- 38% vs. 19% (P = 0.045); and 5 seconds- 26% vs. 9% (P = 0.049).

Table 2. Change of continuous outcome measures tested at BL and FU. Adjusted: by value of the variable at baseline.

Outcome measure	Arm	FU		Change from BL (FU-B)		p (within arms)	P (Between arms)
		Mean [95%CI: low, high] (n)	Median	Mean [95%CI: low, high] (n)	Median		
TBUT (sec)	Control	4.5 [4.0, 5.1] (86)	3.85	0.7 [0.3, 1.2] (86)	0.4	0.0021** ↑	0.0147* Adjusted: 0.0076**
	Study	6.0 [5.4, 6.6] (78)	5.85	2.0 [1.4, 2.6] (78)	2	<.0001**** ↑	
OSDI (0–100)	Control	34.3 [27.5, 41.1] (43)	33.3	-25.9 [-33.5, -18.3] (43)	-27.1	<.0001**** ↑	0.9984 Adjusted: 0.3518
	Study	27.9 [21.5, 34.3] (39)	20.4	-25.9 [-33.1, -18.6] (39)	-25.5	<.0001**** ↑	
EDS (0–100)	Control	48.9 [43.5, 54.3] (86)	50	-22.1 [-28.0, -16.2] (86)	-15.5	<.0001**** ↑	0.0072** Adjusted: 0.0001***
	Study	34.0 [29.6, 38.5] (78)	32	-33.0[-38.1, -27.8] (78)	-31	<.0001**** ↑	
MGS (0–45)	Control	13.6 [12.1, 15.1] (86)	13	5.2 [3.8, 6.6] (86)	5	<.0001**** ↑	<.0001**** Adjusted by MGS at baseline: <0.0001****
	Study	28.2 [25.5, 30.9] (78)	26	18.5 [15.8, 21.2] (78)	16.5	<.0001**** ↑	
Artificial tears (daily use)	Control	2.1 [1.2, 3.0] (43)	1	-0.65 [-1.3, -0.05] (43)	0	0.0176* ↑	0.8216 Adjusted: 0.6248
	Study	1.7 [1.2, 2.3] (39)	2	-0.74 [-1.3, -0.19] (39)	0	0.0050** ↑	
Warm compresses (daily use)	Control	0.3 [0.1, 0.5] (43)	0	-0.3 [-0.7, 0.1] (43)	0	0.0566	0.3525 Adjusted: 0.5706
	Study	0.31 [0.1, 0.5] (39)	0	-0.1 [-0.3, 0.1] (39)	0	0.1267	

For all variables, the value at FU and the change from BL to FU are represented with Mean and the 95% confidence interval (μ [Low 95%, High 95%]), and the median. Within each arm, p tests the null hypothesis that there is no change between BL (Table 1) and FU (two-sided paired t-test). P tests the null hypothesis that the change is similar between the two arms (least squares fit). For eye level variables (TBUT, EDS and MGS), correlation between eyes was removed as explained in Methods.

*: P<0.05;

**: P<0.01;

***: P<0.001;

****: P<0.0001;

↑: Variable improved from BL to FU;

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OSDI (secondary outcome measure). OSDI improved (decreased) in both arms (Compare Tables 1 & 2, and Fig 3). In the control arm, OSDI decreased from 60.2 ± 2.8 (μ±SEM) to 34.3 ± 3.4, with a ΔOSDI of -25.9 ± 3.6 points [95%CI: -33.5 to -18.3] (p<0.0001). In the study arm, OSDI decreased from 53.8 ± 3.3 to 27.9 ± 3.2, with a ΔOSDI of -25.9 ± 3.8 points [95%CI: -33.1 to -18.5] (p<0.0001). There were no significant differences between the two arms (unadjusted: P = 0.9984; adjusted by OSDI at baseline: P = 0.3518).

EDS (Secondary outcome measure)). EDS improved (decreased) in both arms (Compare Tables 1 & 2). In the control arm, ΔEDS decreased by -22.1±3.0 (mean±SEM) points [95%CI: -28 to -16.2] (p<0.0001). In the study arm, ΔEDS decreased by -33.0±2.6 points [95%CI: -38.1 to -27.8] (p<0.0001). The difference between ΔEDS of the two arms (MD_{EDS}) was -10.8±4.0 (μ ±SEM), in favor of the study arm (unadjusted: P = 0.0072; adjusted by EDS value at baseline: P = 0.0001). With a conservative analysis, this difference remained statistically significant (MD_{EDS} = -11.6 ± 5.2, mean ± SEM, in favor of the study arm; P = 0.0274).

MGS (Exploratory outcome measure). MGS improved (increased) in both arms, but the improvement was more pronounced in the study arm (Compare Tables 1 & 2, and Fig 4). ΔMGS increased by 5.2±0.7 (μ±SEM) points [95%CI: 3.8 to 6.6] and by 18.5±1.3 points [95% CI: 15.8 to 21.2] in the control and study arm, respectively. The difference between ΔMGS of the two arms (MD_{MGS}) was 13.3 ± 1.5 (μ±SEM), in favor of the study arm (unadjusted: P<0.0001; adjusted by MGS value at baseline: P<0.0001). With a conservative analysis that hand, this difference remained statistically significant (MD_{MGS} = 12.8 ± 1.9, mean ± SEM, in favor of the study arm; P < 0.0001).

Table 3. Change of categorical outcome measures tested at BL and FU.

Outcome measure		Arm	FU Category n (%)	Change of Category from BL to FU: n (%)	p	P
Biomicroscopy	**Lid Margin thickening**	Control	Abnormal: 62 (72%) Normal: 24 (28%)	-1 (Deteriorated): 0 0 (Did not change): 79 (92%) +1 (Improved): 7 (8%)	0.2103	0.0605
		Study	Abnormal: 41 (52%) Normal: 37 (46%)	-1 (Deteriorated): 0 0 (Did not change): 64 (82%) +1 (Improved): 14 (18%)	0.0212*	
	Conjunctival injection	Control	Abnormal: 70 (81%) Normal: 16 (19%)	-1 (Deteriorated): 9 (11%) 0 (Did not change): 75 (87%) +1 (Improved): 2 (2%)	0.2024	0.0002***
		Study	Abnormal: 38 (49%) Normal: 40 (51%)	-1 (Deteriorated): 0 0 (Did not change): 61 (78%) +1 (Improved): 17 (22%)	0.0055**	
	Loss of eyelashes	Control	Abnormal: 25 (29%) Normal: 61 (71%)	-1 (Deteriorated): 5 (6%) 0 (Did not change): 75 (87%) +1 (Improved): 6 (7%)	0.8674	0.3594
		Study	Abnormal: 14 (18%) Normal: 64 (82%)	-1 (Deteriorated): 3 (4%) 0 (Did not change): 67 (86%) +1 (Improved): 8 (10%)	0.3267	
Meibography (area loss)	**Lower Lids**	Control	Normal: 10 (12%) < 25%: 45 (53%) 25–50%: 16 (19%) 51%-75%: 9 (11%) >75%: 4 (5%)	-1 (Deteriorated): 1 (1%) 0 (Did not change): 83 (99%) +1 (Improved): 0	1.000	0.1315
		Study	Normal: 15 (19.2%) < 25%: 51 (65.4%) 25–50%: 12 (15.4%) 51%-75%: 0 >75%: 0	-1 (Deteriorated): 1 (1%) 0 (Did not change): 73 (94%) +1 (Improved): 4 (5%)	0.9082	
	Upper Lids	Control	Normal: 14 (16%) < 25%: 38 (45%) 25–50%: 20 (24%) 51%-75%: 7 (8%) >75%: 5 (6%)	-1 (Deteriorated): 5 (6%) 0 (Did not change): 79 (94%) +1 (Improved): 0	0.9773	0.0699
		Study	Normal: 13 (16.7%) < 25%: 52 (66.6%) 25–50%: 13 (16.7%) 51–75%: 0 >75%: 0	-1 (Deteriorated): 3 (4%) 0 (Did not change): 70 (90%) +1 (Improved): 5 (6%)	0.5645	
Rosacea		Control	Normal: 4 (9%) Mild: 21 (49%) Moderate: 14 (33%) Severe: 4 (9%)	-1 (Deteriorated): 3 (6%) 0 (Did not change): 35 (81%) +1 (Improved): 5 (11%)	0.9397	0.0506
		Study	Normal: 9 (23.1%) Mild: 25 (64.1%) Moderate: 4 (10.2%) Severe: 1 (2.6%)	-1 (Deteriorated): 0 0 (Did not change): 30 (77%) +1 (Improved): 9 (23%)	0.3327	

For all variables, the frequency and percentage are represented per category at FU. Also represented are the number and percentage of patients/eyes which improved, did not change, or improved from BL. Within each arm, p tests the null hypothesis that there is no change in the number of patients across categories, between BL (Table 1) and FU (Chi-test). Between arms, P tests the null hypothesis that there is no difference in the number of patients who improved, remained the same, or deteriorated between the two arms (Ordinal logistic regression);

*: <0.05;

**: <0.01;

***: <0.001.

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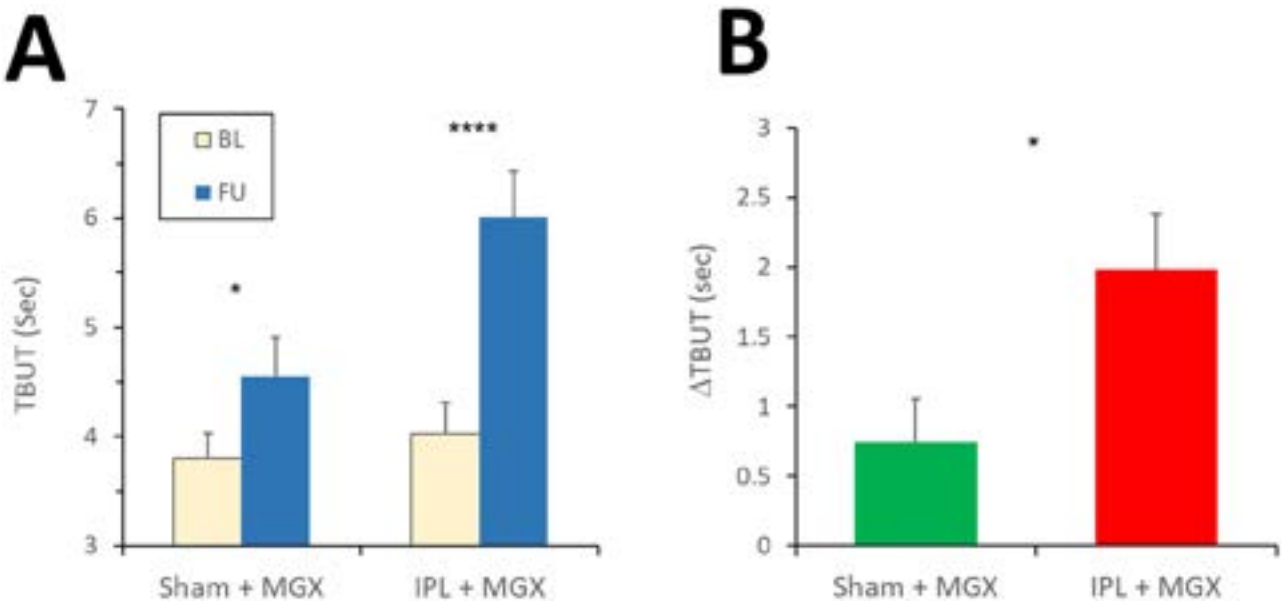

Fig 2. Change of primary outcome (TBUT). A. Absolute values of TBUT. Statistical tests within arms: paired two-sided t-test; **: $p < 0.01$; ****: $p < 0.0001$. B. ΔTBUT (the change of TBUT from BL to FU). Statistical test between arms: least squares fit of ΔTBUT. **: $P<0.01$.

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Meibography (Exploratory outcome measure). Area loss of meibomian glands, as assessed with Meibography, was an exploratory outcome measure categorized in 5 levels, in each eyelid separately (Normal, less than 25%, between 25 and 50%, between 51% and 75%, and more than 75%). An improvement is defined as a switch from one level to a lower level. Within each arm, most eyelids did not change (lower lids: p = 1.000 for the control arm, and

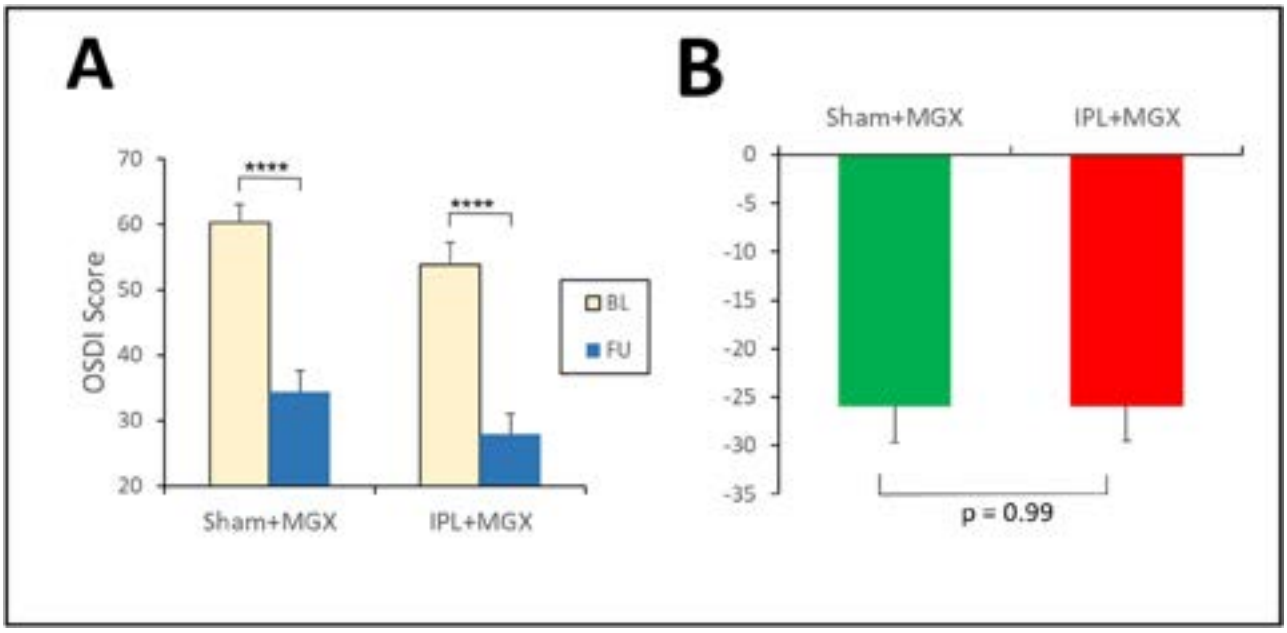

Fig 3. Change of symptoms (OSDI). A. Absolute values of OSDI; Statistical tests: 2-sided paired t-test of FU versus BL (within each arm); ****: $p<0.0001$. **B**. ΔTBUT; Statistical test: 2 sided least squares fit of ΔOSDI (between arms).

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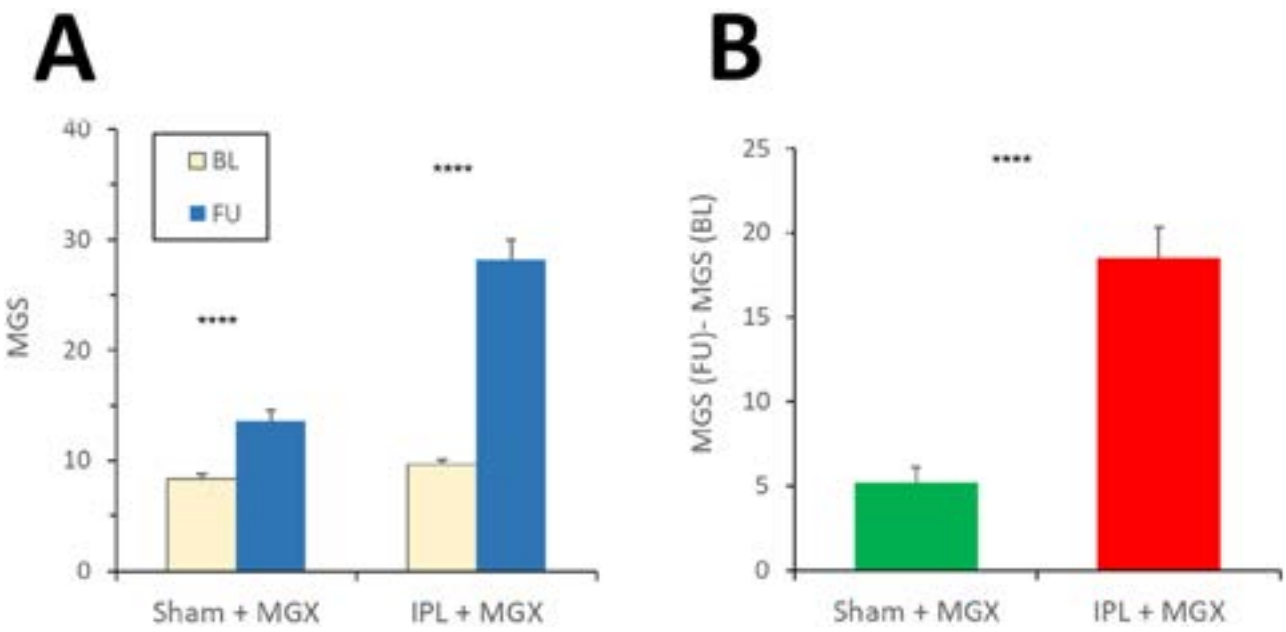

Fig 4. Change of MGS. A. Absolute values of MGS at BL and FU; ****: p (within arms) <0.0001. **B**. Change of MGS from BL to FU (ΔMGS); ****: P (between arms) <0.0001.

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p = 0.9082 for the study arm; upper lids: p = 0.9773 for the control arm, and p = 0.5645 for the study arm). Between the two arms, in the lower lids there were no differences in the proportion of eyes which improved, deteriorated, or didn't change (P = 0.1315); in the upper lids, there was a small tendency for more improvement in the study arm, but the difference was not statistically significant (P = 0.07).

Skin rosacea (Post-hoc outcome measure). The severity of skin rosacea was defined as normal, mild, moderate, or severe. Within arms, there were no significant changes in the severity of skin rosacea (Control arm: p = 0.9397; Study arm: p = 0.3327). Between the two arms there was a tendency for more improvement in study patients compared to control patients, but the difference was not statistically significant (P = 0.0506).

Daily use of artificial tears (Post-hoc outcome measure). In both arms, there was a statistically significant decrease the number of artificial tear drops used per day (Control arm: p = 0.0176; Study arm: p = 0.005). The difference between the two arms was not statistically significant (P = 0.8216).

Daily use of use of warm compresses (Post-hoc outcome measure). Neither arm showed a significant decrease in the number of warm compresses used (Control arm: p = 0.0566; Study arm: p = 0.1267). There was no difference between the two arms (P = 0.3525).

Biomicroscopy (Post-hoc outcome measures). For each of the examined features (lid margin thickening, conjunctival injection, and loss of eye lashes), an improvement is defined as an increase in the number of eyes which switched from abnormal to normal (Compare Tables 1 & 3).

Lid margin thickening. In the control arm, the percentage of normal eyelids increased from 19.8% to 28% (p = 0.2103). In the study arm, the percentage of eyes with normal lid margin increased from 20% to 46% (p = 0.0212). Between the two arms, there were no differences in the number of eyes which improved, deteriorated, of remained the same: more eyes improved

in the study arm when compared to the control arm, but the difference was not statistically significant (18% vs 8%, P = 0.065).

Conjunctival injection. In the control arm, the percentage of normal eyelids *decreased* from 26.7% to 19% (p = 0.2024). In the study arm, the percentage of eyes with normal conjunctiva increased from 29.5% to 51% (p = 0.0055). More eyes improved in the study arm when compared to the control arm (22% vs 2%, P = 0.0002).

Loss of eyelashes. In the control arm, the percentage of normal eyelids remained stable (69.8% at BL, compared to 71% at FU; p = 0.8674). In the study arm, the percentage of eyes with normal eye lashes slightly increased from 75.6% to 82%, but the change was not significant (p = 0.3267). No differences were observed between the two arms (P = 0.3594).

Outcome measures tested after each treatment session

Tables 4 and 5 summarize results of outcome measures tested after every treatment.

Number of expressible glands (Post-hoc outcome measure). The number of expressible glands, as function of time, is illustrated in Fig 5A. In the lower lids, in both arms the number of expressible glands increased: From Tx1 to Tx4, there was a change of 1.7 glands [95% CI: 0.59 to 2.86] in the control arm, versus a change of 8.0 glands [95% CI: 6.6 to 9.4]) in the study arm (Fig $5A_1$). At Tx4, the number of expressible glands in the lower lid was 19.9 [95% CI: 18.2, 21.5]) in the study arm, compared to 12.3 [95% CI: 11.0, 13.6] in the control arm (P<0.0001). Recall that at the baseline (Tx1) there was no statistically significant difference between the two arms (P = 0.3201, Table 1).

In the upper lids, there number of expressible glands in the control arm remained stable, while it increased in the study arm (Fig 5A2). From Tx1 to Tx4, there was an increase of 0.53 glands [95% CI: -0.78 to 1.85] in the control arm, compared an increase of 5.1 glands [95% CI: 3.52 to 6.73] in the study arm. At Tx4, the number of expressible glands in the upper lid was 15.7 [95% CI: 13.6, 17.9] in the study arm, compared to 11.2 [95% CI: 9.6, 12.8] in the control arm (P < 0.001). At Tx1, however, there was no difference between the arms (P = 0.7753, Table 1).

Pain due to MGX (post-hoc outcome measure). In the control arm, pain decreased from 43 [95% CI: 37.8, 48.2] at Tx1 to 36.7 [95% CI 30.9, 42.4] at Tx4. In the study arm, pain

Table 4. Continuous outcome measures tested after every treatment session.

		Arm	Time = 0 (Tx1)	Time = 2 weeks (Tx2)	Time = 4 weeks (Tx3)	Time = 6 weeks (Tx4)	P
			Mean [95%CI: low, high] (n)	Mean [95%CI: low, high] (n)	Mean [95%CI: low, high] (n)	Mean [95%CI: low, high] (n)	
#Expressible glands	LL	Control	10.6 [9.3, 11.9] (86)	11.4 [104, 12.6] (86)	12.3 [10.9, 13.6] (86)	12.3 [11.0, 13.5] (86)	<0.0001****
		Study	1.5 [10.2, 12.8] (90)	15.7 [14.0, 17.4] (84)	18.1 [16.3, 19.9] (82)	20.0 [18.2, 21.5] (80)	
	UL	Control	10.7 [8,9, 12.5] (86)	9.8 [8.3, 11.3] (86)	10.5 [9.0, 12.0] (86)	11.2 [9.6, 12.8] (86)	<0.0001****
		Study	10.3 [8.7, 12.0] (90)	13.0 [11.0, 15.0] (84)	15.4 [13.2, 17.5] (82)	15.7 [13.6, 17.9] (82)	
Pain due to MGX		Control	43.0 [37.8, 48.2] (86)	40.5 [34.9, 46.1] (86)	39.9 [34.0, 45.9] (86)	36.7 [30.9, 42.4] (86)	0.0438*
		Study	48.8 [43.4, 54.1] (90)	43.4 [37.7, 43.4] (84)	39.0 [33.5, 44.5] (82)	34.7 [29.2, 40.2] (80)	
Pain due to IPL		Control	2.9 [1.6, 4.2] (86)	4.4 [2.0, 6.8] (86)	3.8 [2.6, 5.2] (86)	4.2 [2.6, 5.8] (86)	<0.0001****
		Study	50.0 [44.1, 55.6] (90)	45.4 [40.6, 50.2] (84)	42.2 [36.9, 47.6] (82)	40.7 [35.2, 46.1] (80)	

LL = Lower lids; UL = Upper lids; For all variables, the values at Tx1, Tx2, Tx3 and Tx4 are represented with Mean and 95% confidence interval (μ [Low 95%, High 95%]). P (least squares fit) tests the null hypothesis that the change from Tx1 to Tx4 is similar between the two arms.

*: P<0.05;

****: P<0.0001;

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Table 5. Categorical outcome measures tested after every treatment session.

		Arm	Time = 0 (Tx1)	Time = 2 weeks (Tx2)	Time = 4 weeks (Tx3)	Time = 6 weeks (Tx4)	Change	P
			N (%)	N (%)	N (%)	N (%)		
Meibum Quality (0 = Blocked to 3 = clear liquid)	LL	Control	Blocked: 10 (12%) Inspissated: 49 (57%) Cloudy: 24 (28%) Clear: 3 (3%)	Blocked: 3 (3.5%) Inspissated: 45 (52.3%) Cloudy: 38 (44.2%) Clear: 0 (0%)	Blocked: 4 (5%) Inspissated: 54 (63%) Cloudy: 28 (32%) Clear: 0 (0%)	Blocked: 3 (3.5%) Inspissated: 52 (60.4%) Cloudy: 31 (36.1%) Clear: 0 (0%)	-1: 17 (20%) 0: 42 (49%) +1: 27 (31%)	P<0.0001****
		Study	Blocked: 6 (7%) Inspissated: 46 (51%) Cloudy: 38 (42%) Clear: 0 (0%)	Blocked: 0 (0%) Inspissated: 21 (25%) Cloudy: 52 (62%) Clear: 11 (13%)	Blocked: 1 (1%) Inspissated: 13 (16%) Cloudy: 37 (45%) Clear: 31 (38%)	Blocked: 0 (0%) Inspissated: 10 (12.5%) Cloudy: 38 (47.5%) Clear: 32 (40%)	-1: 1 (1%) 0: 31 (39%) +1: 48 (60%)	
	UL	Control	Blocked: 17 (20%) Inspissated: 39 (45%) Cloudy: 28 (33%) Clear: 2 (2%)	Blocked: 11 (13%) Inspissated: 38 (44%) Cloudy: 36 (42%) Clear: 1 (1%)	Blocked: 12 14%) Inspissated: 32 (37%) Cloudy: 41 (48%) Clear: 1 (1%)	Blocked: 7 (8%) Inspissated: 36 (42%) Cloudy: 39 (45%) Clear: 4 (5%)	-1: 9 (10%) 0: 30 (35%) +1: 47 (55%)	P = 0.0009***
		Study	Blocked: 14 (17%) Inspissated: 34 (40%) Cloudy: 29 (35%) Clear: 7 (8%)	Blocked: 10 (12%) Inspissated: 20 (24%) Cloudy: 25 (30%) Clear: 28 (34%)	Blocked: 6 (7.3%) Inspissated: 9 (11%) Cloudy: 29 (35.4%) Clear: 38 (46.3%)	Blocked: 4 (5%) Inspissated: 13 (16%) Cloudy: 22 (28%) Clear: 41 (51%)	-1: 9 (11%) 0: 19 (24%) +1: 52 (65%)	

LL = Lower lids, UL = Upper lids; -1 = Deteriorated, 0 = No change, +1 = Improved; The frequency and percentage of each meibum quality level are represented at Tx1, Tx2, Tx3 and Tx4. P tests the null hypothesis that the percentage of eyelids which improved, remained the same or deteriorated are similar between the two arms (ordinal logistic regression).

**: P<0.01;

****: P<0.0001;

https://doi.org/10.1371/journal.pone.0270268.t005

decreased from 48.8 [95% CI: 43.3, 54.2] at Tx1 to 34.8 [95%CI: 29.3, 40.2] at Tx4. At Tx4, the difference between the two arms was statistically significant (P < 0.0001).

Pain due to IPL (post-hoc outcome measure). In the control arm, pain due to IPL remained low, with 2.9 [95%CI: 1.7, 4.2] at Tx1 and 4.2 [95%CI: 2.6, 5.8] at Tx4. In the study arm, pain due to IPL decreased from 49.8 [95%CI: 44.1, 55.6] at Tx1 to 40.7 [95%CI: 35.3, 46.1] at Tx4. The difference between the arms was statistically significant (P < 0.0001).

Predominant quality of meibum (post-hoc outcome measure). The predominant quality of meibum, as function of time, is illustrated in Fig 5B.

For the lower lids (Fig $5B_1$), in the control arm there was no significant change in the predominant quality of the meibum. For example, in the control arm the proportions of eyelids with predominantly dysfunctional meibomian glands was 69% (12% blocked + 57% inspissated) at Tx1, and 63.9% (3.5% blocked + 60.4% inspissated) at Tx4. In contrast, in the study arm the predominant quality of the meibum improved, with 58% dysfunctional glands at Tx1 (7% blocked + 51% inspissated) decreasing to 12.5% (0% blocked + 12.5% inspissated) at Tx4. The percentage of eyelids which deteriorated, remained the same, or improved was 20%, 49% and 31% in the control arm, compared to 1%, 39%, and 60% in the study arm. This difference was statistically significant (P<0.0001).

Similar results were observed for the upper lids. In the control arm, the proportions of eyelids with predominantly dysfunctional meibomian glands was 65% (20% blocked + 45% inspissated) at Tx1, and 50% (8% blocked + 42% inspissated) at Tx4. In contrast, in the study arm

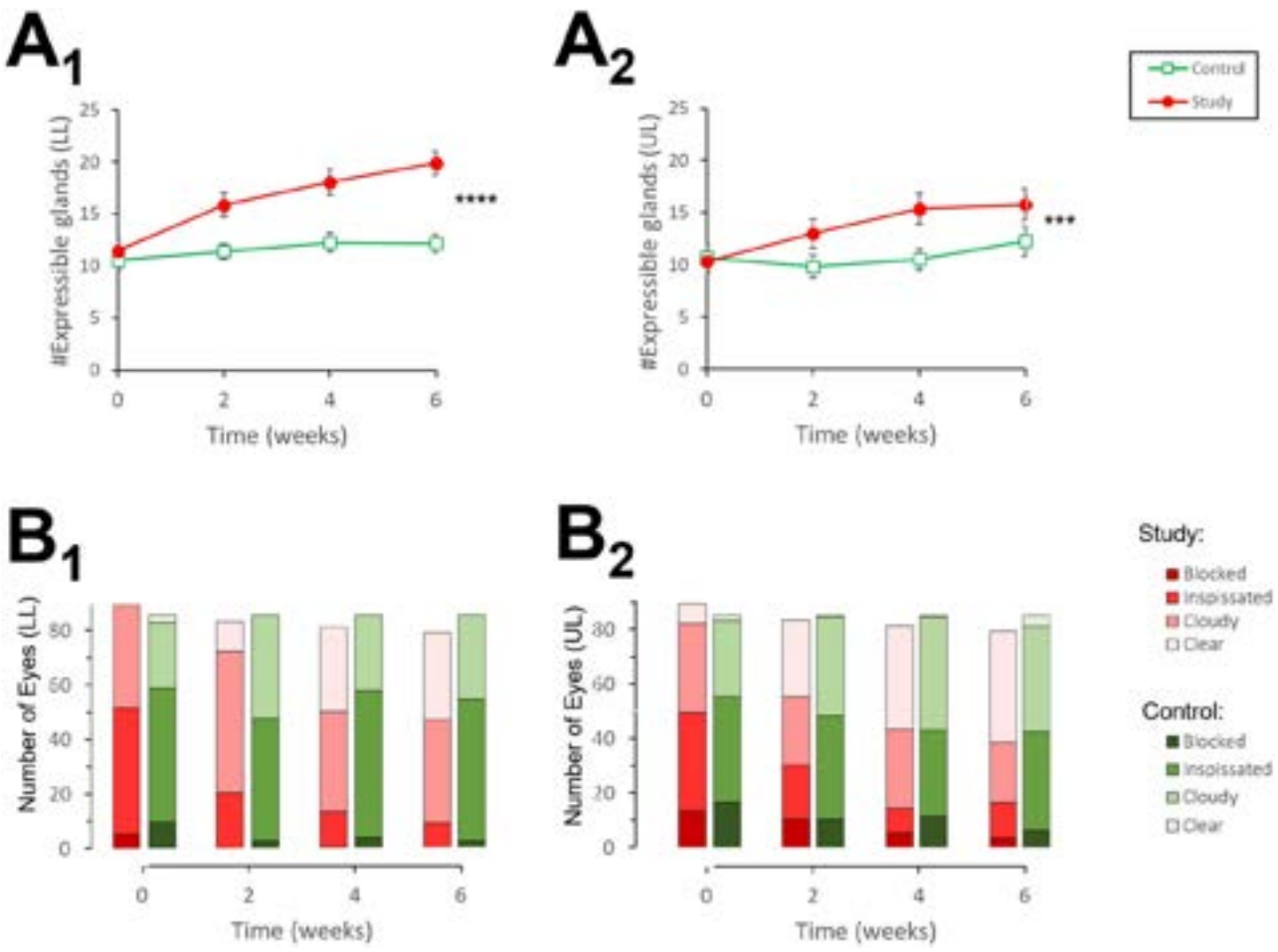

Fig 5. Number of expressible glands and meibum quality as function of time. Time: 0 = Tx 1, 2 weeks = Tx 2, 4 weeks = Tx 3, 6 weeks = Tx 4; A. Number of expressible gland in lower lids (A1) and upper lids (A2). Error bars: SEM; ***: P (between arms) < 0.001; ****: P (between arms) <0.0001. B. Distribution of predominant quality of meibum (blocked, inspissated, cloudy liquid, clear liquid) in study and control eyes. B1: lower lids. B2: upper lids.

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the predominant quality of the meibum decreased from 57% at Tx1 (17% blocked + 40% inspissated) to 21% (5% blocked + 16% inspissated) at Tx4. The percentage of eyelids which deteriorated, remained the same, or improved was 10%, 35% and 55% in the control arm, compared to 11%, 24%, and 65% in the study arm. This difference was statistically significant (P = 0.0009).

Adverse events

The safety population included 88 randomized subjects. There were no serious adverse events reported. The incidence of adverse events was 8.9% in the study arm (mild: n = 1; moderate: n = 3), and 20.9% in the control arm (mild: n = 5; moderate: n = 3; severe: n = 1). Although there was a tendency for more adverse events in the control arm, the difference between the two arms was not statistically significant (P = 0.06).

In the study arm, 1 subject experienced 2 ocular-related adverse events (moderate allergic conjunctivitis and moderate bacterial conjunctivitis). The treating physician determined that the seasonal allergic conjunctivitis (detected first) was not related to the procedure nor the

device, but the bacterial allergic conjunctivitis (detected two weeks later) was possibly related to the procedure (i.e., the meibomian gland expression). As a result of this adverse event, this subject was discontinued from the study. Another subject experienced mild skin pain (possibly related to the procedure). A third subject experienced moderate blepharitis (unrelated to both procedure and device). No subjects experienced systemic adverse events.

In the control arm, one subject experienced a severe conjunctival telangiectasia (unrelated to both procedure and device); one subject experienced a mild chalazion (unrelated) skin-related adverse events (mild chalazion, mild stye), and 6 subjects experienced systemic adverse events (mild bronchitis, mild sinus infection, moderate sinus infection, mild hyperlipidemia, and 2 cases of seasonal allergy worsening).

Except for the mild pain and the moderate bacterial conjunctivitis which were both possibly related to the procedure, none of the other reported adverse events were related to either the procedure or the device.

Discussion

Interpretation of results

Results of this study show that, in comparison with monotherapy of meibomian gland expression, the combination of IPL and meibomian gland expression was more effective in reducing signs of DED due to MGD. With respect to the primary outcome measure, TBUT increased in both arms but on average the change was 1.2 seconds longer in study eyes, compared to control eyes. The between-arms difference was statistically significant. The minimal clinically important difference (MCID) for TBUT change was not previously characterized or defined in the literature. Hence, in a post-hoc analysis we examined several different possibilities. We found that for cutoff values of 2,3,4,or 5 seconds, the proportion of eyes which exceeded these thresholds was twice or more in the study arm, compared to the control arm. For example, 56% vs. 26% of study vs. control eyes exceeded a TBUT change of 3 seconds, and 26% vs. 9% of study vs control eyes exceeded a TBUT change of 5 seconds. If one accepts that such TBUT changes are clinically meaningful, this finding suggests that, at least for some of the patients, IPL could be beneficial. IPL was particularly effective in improving signs related to the functionality of meibomian glands, such as MGS, the number of expressible glands, and the predominant quality of meibum. With respect to symptoms, there was a difference between several methods of evaluating symptoms. Using the OSDI questionnaire and the subject's report of daily use of artificial tears, both study and control subjects improved but the difference between the two arms was mostly negligible. These results are in agreement with other studies with similar designs [25, 29]. Using the EDS questionnaire, in contrast, there was more improvement in study compared to control subjects. One possibility to explain the difference between these two types of questionnaires is that OSDI asks about the symptoms during the last week, whereas EDS is more general and does not restrict the subject to relate to any specific time range. The difference between OSDI and EDS results could reflect, for example, some added value that IPL has in the first few days after a treatment session, but would then fade out.

Why, between the two arms, significant differences in signs were not translated to significant differences in symptoms evaluated with the OSDI questionnaire? This is a key question. First, it is important to reiterate that dry eye disease is characterized by a poor correlation between signs and symptoms, perhaps due to the heterogeneity of DED itself [30], or because of a lack of well-defined diagnostic criteria commonly in use [3]. Moreover, MGX, which was described 100 years ago [31], is well-known for eliciting symptomatic relief for DED patients, as was observed in the current study, and also reported by others [14, 15, 16, 23]. Hence, it

should not be surprising to find that symptoms were reduced not only in the study group, but also in the control. However, the lack of difference in OSDI, between the two arms, requires additional research for better understanding. This could reflect a flooring effect specific to this type of questionnaire: in responders, MGX would be sufficient to transiently reduce the OSDI score to a minimal level and, in those patients, the addition of IPL combined with MGX would not result in further improvement in OSDI.

Mechanisms of action

The mechanism of action of IPL, with respect to DED due to MGD, is not yet fully understood. One possibility is that IPL closes abnormal telangiectasia and blocks the inflammatory mediators they secrete [22]. As a result, a major source of inflammation of the peri-orbital area is removed. Support for this mechanism is the finding that IPL significantly reduces the levels of key cytokines in tear samples [32]. Another possibility is that IPL activates cells by photobiomodulation (PBM). In PBM, light (especially in the red and near infra-red range) is absorbed within cytochrome C oxidase of mitochondria, resulting in a boost in ATP production and modulation of intracellular calcium levels [33]. Previous studies have shown that PBM can up-regulate anti-oxidant defenses, reduce reactive oxygen species in oxidative stressed cells, reduce the levels of pro-inflammatory cytokines in activated inflammatory cells, and even change the phenotype of macrophages (from a form specialized in killing bacteria and pathogens, to a form involved in removal of protein debris and stimulation of healing) [34]. In addition, IPL may also attenuate melanogenic gene overexpression, and suppress UVB-induced cytokine expression [35]. All of these could contribute to reduce inflammation and trigger healing mechanisms at the ocular surface and meibomian gland levels. A third possibility is that IPL could induce heat-shock production, as was demonstrated in skin cells [36, 37]. It is also possible that IPL reduces the population of Demodex mites, another significant risk factor in DED due to MGD [38, 39]. Other researchers proposed that meibomian gland health depends on relative hypoxia [40]. According to these researchers, loss of hypoxic conditions leads to MGD, and the thrombotic effects of IPL are useful for closing excessive blood vessels, thus restoring the hypoxic conditions necessary for normal function of the meibomian glands. Finally, there is the possibility that IPL generates heat which softens abnormally inspissated secretions of dysfunctional meibomian glands. This last explanation is, however, controversial. Some researchers proposed that even brief pulses of IPL are sufficient to transfer heat to the eyelids, melt an abnormally inspissated meibum within the meibomian glands, and thus facilitate their expression [41]. Other researchers argued that IPL can induce only short term thermal effects, with minimal changes in skin surface temperature [26]. According to this line of reasoning, IPL pulses are too brief to induce sustained changes of the meibum.

Several of our results bring further support to some of these potential mechanisms. First, although IPL was applied below the lower eyelids, the upper eyelids also responded positively to IPL: about one third of the increase in the number of expressible eyelids was observed in the upper lids. This result suggests that some factor, or some factors, is or are propagating some distance away from the site of IPL application, whether it is circulation of beneficial molecules (anti-inflammatory agents, anti-oxidants, heat shock proteins, etc.) via the orbital vasculature, or heat transfer through skin and connective tissues. Another interesting result is that patients in the study arm reported less pain associated with MGX, compared to patients in the control arm. Indeed, MGX is a forceful procedure which can be uncomfortable. With some patients, the procedure is not well-tolerated, even under the influence of local anesthetics [23]. For such patients, thus, monotherapy MGX may not be a practical option. Arita and colleagues reported that 3 of their study subjects (7%) refused to be treated with MGX alone, because of such pain,

whereas none of the subjects treated with IPL and MGX complained of unacceptable discomfort. To explain these results, Arita and colleagues adopted the temperature increase as the mechanism of action at work, suggesting that IPL warms the meibomian glands, thereby melting the meibum, decreasing the pressure required for expression and, thus, reducing the pain associated with MGX. As we mentioned earlier, this explanation is not accepted by all. An alternative explanation is that from treatment to treatment the quality of meibum improves due to the PBM processes mentioned earlier. This would be reflected in reduced pain associated with MGX not at the current IPL session, but at the *following* one.

Limitations of the study

The current study has several limitations. First, despite our efforts to mask the allocation and to include only patients naïve to IPL, it was not possible to completely ensure participant blinding. Since IPL is normally felt as a sensation ranging from mild discomfort to moderate pain, some patients could have correctly guessed their group assignment, based on their preliminary expectations and their sensations during the IPL treatment. Second, since study patients were treated with both MGX and IPL, it is difficult to isolate the contribution of IPL. In the design of the control arm, who were treated with MGX alone, we implicitly assumed that the two components are compounded, and therefore simple subtraction of the changes in the two arms should have given us a good estimation of the effect size. However, it is possible that the two components combine in a more complex way than simple linear addition. Another limitation of the study was that the follow-up period was relatively short. Further studies are necessary to elaborate on the durability of IPL's long-term effectiveness. Next, this study was not designed to determine the efficacy of IPL in groups with different severity levels of MGD. Although between-group differences in baseline values of individual outcome measures were neutralized with statistical methods, it is possible that the baseline severity of MGD is not well defined by any of these outcome measures alone, but depends on complex interactions involving several such outcome measures. In such a case, between-group differences in the baseline severity of MGD could have biased the results. Future studies are required to determine the efficacy of IPL as function of MGD severity, so that clinicians may be better informed who of their patients are more likely to benefit from this technology. Finally, findings from this study is based on a specific population, namely patients with mild to moderate MGD, predominantly Caucasian, age 22–85, and with Fiztpatrick skin types I-IV (predominantly II to III). Future studies are warranted to justify the group differences in the more general population.

Conclusions

The current study suggests that IPL, when combined with MGX, may be useful to improve signs and symptoms of MGD in a North American population. With respect to at least some of the signs, patients treated with IPL and MGX could benefit more than patients treated with MGX alone. Based on the results of this study, in February 2021 the US FDA issued an approval for the Lumenis device, for the use of IPL in management of DED due to MGD.

Supporting information

S1 Dataset. Data presented in this paper.
(XLSX)

S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial*.
(DOC)

S1 File. Clinical study protocol.
(DOCX)

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Data collection and study management was performed by a Clinical Research Organization. Statistical planning, randomization, and statistical analyses of the primary, secondary and exploratory endpoints were conducted by the study statistician (Gerry Gray, Phd; Clinreg Consulting). Statistical analysis of post-hoc outcome measures was conducted by the sponsor.

Author Contributions

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Project administration: Rolando Toyos.

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REVIEW

Intense pulsed light for evaporative dry eye disease

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Abstract: There is a clear association between dry eye disease (DED) and skin inflammatory diseases occurring in close proximity to the eyelids, such as facial skin rosacea. Intense pulsed light (IPL) is widely accepted as a treatment for skin rosacea. A number of recent studies demonstrated that, in patients suffering from meibomian gland dysfunction (MGD), IPL therapy also reduces signs and symptoms of DED. Despite these encouraging results, in the context of DED and MGD, the mechanisms of action of IPL are not well understood. The purpose of this review was to raise the potential mechanisms of action and to discuss their plausibility.

Keywords: intense pulsed light, dry eye disease, meibomian gland dysfunction, skin rosacea

Introduction

Dry eye disease (DED) is "a multifactorial disease of the tears and ocular surface…" that afflicts hundreds of millions around the world.[1] In the US alone, 40 million people are estimated to suffer from, or to be predisposed to, this debilitating condition.[2] DED is mostly age related,[1] but can also be triggered by refractive[3,4] or cataract surgery.[5–7] In addition, preexisting DED significantly increases the risk of prolonged or severe post-op signs and symptoms of dry eye.[8,9] Refractive and cataract surgery patients have high visual expectations, and increasingly sophisticated intraocular lens and corneal ablation designs heighten the importance of good ocular surface health. Success of refractive and cataract surgeries is therefore, in many cases, fundamentally dependent on effectively addressing preexisting or iatrogenic DED. The most common form of DED is evaporative, which is mainly due to meibomian gland dysfunction (MGD).[10] Current standard of care of MGD includes anti-inflammatory drugs, warm compresses, and meibomian gland expression.[11–13]

There is a clear association between MGD and skin inflammatory diseases occurring in close proximity to the eyelids. A common example is facial skin rosacea. One in ten people are affected by this skin condition, with >80% of these patients having concomitant MGD.[14] In 20% of the cases, ocular signs precede skin rosacea[15] – possibly suggesting that skin rosacea could already exist in a subclinical form.

Intense pulsed light (IPL) is widely accepted as a treatment for skin rosacea.[16] More than a decade ago, Toyos et al noticed that facial skin rosacea patients treated with IPL reported a significant improvement in their dry eye symptoms.[17] Since then, a number of studies confirmed that IPL therapy reduces both signs and symptoms of dry eye.[18–23] In these studies, IPL therapy comprised several sessions given several weeks apart. Each session consisted of IPL pulses applied from tragus to tragus, just below the lower eyelids and including the nose, as illustrated in Figure 1.

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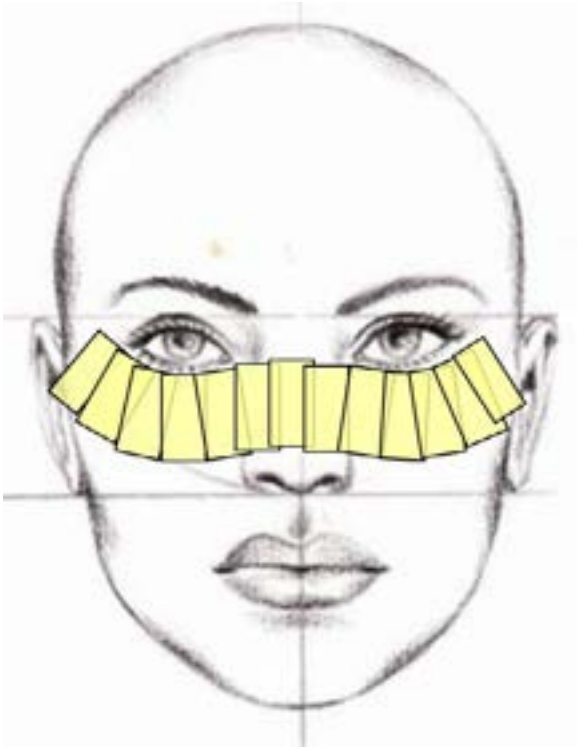

Figure 1 Treatment area in IPL therapy of MGD.
Note: Each yellow rectangle schematically represents the site of a single IPL pulse application.
Abbreviations: IPL, intense pulsed light; MGD, meibomian gland dysfunction.

Despite these encouraging results, the mechanism of action is not well understood. The purpose of this review is to raise the potential mechanisms of action and to discuss their plausibility.

Thrombosis of abnormal blood vessels

Facial skin rosacea is a chronic disorder presenting with vascular and inflammatory signs. The overwhelming majority of patients afflicted with this condition also suffer from MGD.[14] Although the causal relationship is not entirely clear, it seems reasonable that MGD patients might benefit from treatment of their concomitant skin condition. One of the primary features of rosacea is skin erythema and telangiectasia. It has been proposed that these abnormal blood vessels release inflammatory mediators.[18] Via the facial artery and orbital vasculature, these molecules could easily propagate to the eyelids, subsequently triggering the inflammation of meibomian glands and leading to their dysfunction and atrophy.

The beneficial effect of IPL on erythema and telangiectasia has been extensively studied and reported.[16] Light energy absorbed by hemoglobin transforms to heat and causes the localized destruction of superficial blood vessels (thrombosis). In the case of patients affected with MGD, destruction of abnormal erythematous blood vessels reduces a key reservoir of inflammatory mediators, thus removing a major source of inflammation from the eyelids and meibomian glands.

Heating and liquefying the meibum

Eyelid temperature significantly influences the physical properties of meibomian gland secretions, also known as meibum.[24] At higher temperatures, meibum becomes less viscous, which more easily allows its normal distribution over the cornea. At room temperature, the temperature at the eyelids is ~33°C.[25] In patients with MGD, lipid composition may be altered, reflecting changes in the configuration of hydrocarbon chain and lipid–lipid interaction strength. As a result, the phase-transition temperature (the temperature at which the meibomian lipids switch from an ordered and gel-like phase to a disordered and fluid-like phase) may increase, compared to healthy subjects.

In a study that analyzed the physical properties of meibum, the phase-transition temperature was ~28°C for meibum from healthy donors (below eyelid temperature), and just above 32°C for meibum from donors afflicted with MGD (above eyelid temperature).[26] Because the phase-transition temperature of human meibum is near physiological body temperature, a small increase of 4°C is sufficient to change the meibum from gel like to fluid.

Indeed, warming the eyelids (with warm compresses or more sophisticated and automated devices) has some therapeutic value, as it facilitates meibomian gland expression.[27] Craig et al[19] noted that IPL application could induce an increase in skin temperature. However, these authors argued that any increase is modest and short lived: immediately after IPL application, the skin temperature increased by <1°C.[19] However, it should be noted that in their study, skin temperature was measured with infrared thermography a few seconds after treatment and only after removal of the conducting gel. During these few seconds, the skin could cool down considerably and lose heat. It is therefore difficult to infer from this measurement what the temperature of the eyelids would be during IPL treatment itself.

However, whether or not IPL energy is sufficient to warm the skin is less important than its thermal effect on blood vessels under the surface. The eyelids are extensively fed by capillaries and arterioles branching off the facial artery. A mathematical model demonstrates that in medium and large blood vessels (>150 μm), a single IPL pulse of 30 ms duration raises the temperature at the center of the vessel to 80°C–90°C, above the temperature required to cause coagulation and

thrombosis as discussed above.[28] In contrast, in small (60 μm) blood vessels, the temperature may reach only 45°C–70°C, depending on fluence.[28] This temperature elevation is insufficient to cause the destruction of blood vessels, but it is probably enough to raise the temperature of eyelid skin (and meibomian glands) by a few degrees, possibly above the phase-transition temperature. Even if brief, this thermal response could be enough to unclog the meibomian glands and restore their ability to excrete meibum during blinking.

Reducing the epithelial turnover and decreasing the risk for gland obstruction

As often occurs in skin diseases, cutaneous rosacea is accompanied by a dramatic increase in epithelial skin turnover. In a mechanism similar to dandruff production, large amounts of dead epithelial skin cells detach from the epidermal surface and create debris. Since the ducts of meibomian glands are paved with the same type of epithelial cells, accumulation of debris on the lid margin is likely to occur. This, in combination with poor lid hygiene, could potentially clog the orifices of meibomian glands.[29] IPL treatment of rosacea could, thus, decrease the epithelial turnover and reduce the risk factor for obstruction.

Photomodulation

Photomodulation is a process by which light in the visible and infrared portions of the electromagnetic spectrum induces intracellular changes at the gene and protein levels. The biological basis of this process is not well understood. According to the Karu model, red (~630 nm) photons are absorbed in cytochrome C oxidase (Cox), a key enzyme in the electron transport chain embedded within the membrane of mitochondria. Photoexcitation of Cox prompts a photochemical cascade, inducing changes in the redox properties of components along this mitochondrial respiratory chain, leading to quickened electron transfer and, hence, to an increase in ATP production.[30,31] The cytoplasmic rise of ATP activates various intracellular/extracellular exchange mechanisms (pumps and transporters), resulting in an increase in intracellular free calcium concentration.

Smith proposes a complementary model, by which the absorption of infrared photons (~810 nm) induces molecular rotations and vibrations of various molecules.[32] When such physical forces are exerted on calcium channels, the permeability of these channels is altered such that the influx of calcium ions increases. Here as well, the end result is an abrupt surge in intracellular calcium concentration.

This calcium signal activates cellular responses in a variety of ways. In the case of fibroblasts, cell proliferation is enhanced and collagen synthesis is increased;[33] skin-homing T cells are recruited;[34] local blood flow is increased; macrophages cells are activated;[35] epidermal keratinocytes increase the secretion of proinflammatory or anti-inflammatory cytokines and chemokines, depending on the context.

Activating fibroblasts and enhancing collagen synthesis

The extracellular matrix comprises three types of fibers: collagen, reticular, and elastin.[36] With age, all the three types of fibers relax to some extent, thus compromising the natural rigidity and elasticity of tissues. At the eyelid skin level, this process can lead to poor apposition of the lid margins and incomplete blinks, resulting in reduced meibum pumping out of the meibomian glands. This can lead in turn to increased tear evaporation.

Fibroblast cells are responsible for the production of collagen fibers in wound healing and tissue repair. As mentioned earlier, photomodulation can prompt the proliferation of fibroblasts and upregulate the synthesis of collagen fibers.[33] An in vitro study showed that a pulsed 660 nm (LED) light enhanced collagen production in a tissue-engineered reconstructed skin model.[37] In another in vitro study, irradiation of skin fibroblasts with IPL (800–1,200 nm) increased the proliferation rate of fibroblasts and increased the expression of collagen genes.[38] These results are also supported by clinical studies.[39]

Eradicating *Demodex*

One of the potential mediators of blepharitis and MGD are *Demodex folliculum* mites, a type of ectoparasite that normally burrows deep into sebaceous and meibomian glands to feed on their sebum/meibum secretions.[40] In healthy skin, the degree of infestation with *Demodex* mites is controlled. *Demodex* mites are normally colonized with *Bacillus olerinus.*[41,42] Rosacea patients present with increased *Demodex* population on the face, high serum reactivity to *B. olerinus* proteins, and reduced levels of sebum.[43]

The causal relationship between rosacea and *Demodex* is not clear. Some researchers argue that rosacea is fundamentally an infectious disease resulting from *Demodex* thriving on skin damaged by a combination of age, adverse weathering, and changes in sebum composition.[44] Others claim that erythema and superficial telangiectasia (which are characteristics of rosacea) induce edema of the dermis, which in turn increases skin colonization of *Demodex*.[45]

A direct consequence of *Demodex* proliferation is the dramatic increase in bacterial load on the eyelids,[46] particularly *B. olerinus.* The excessive presence of *B. olerinus* near the eyelids triggers a cascade of events that may degenerate into chronic inflammation of the ocular surface. First, the immune system responds by orchestrating an army of proinflammatory agents, including antimicrobial peptides, toll-like receptors, cytokines, chemokines, and matrix metalloproteinases (MMPs).[47,48] In small quantities, these agents may perform well. But an acute inflammatory response may turn into a chronic, self-perpetuating condition. Second, *B. olerinus* releases toxic substances, including lipases which enzymatically alter lipid composition. A change in the ratio of saturated to unsaturated fats of the meibum could raise its melting point, increase its viscosity, and impede its secretion. In addition, one by-product of lipase activity on sebum/meibum is oleic acid, which could play a role in the keratinization of the lid margin, and plugging of the meibomian gland orifices.[13] All of these events could aggravate and perpetuate inflammation inside the meibomian glands.

The pigmented exoskeleton of *Demodex* contains chromophore that absorbs IPL energy. Histologic analysis demonstrated that IPL treatment induces coagulation and necrosis of *Demodex*.[49,50] By eradication of *Demodex*, IPL could decrease the microbial load on eyelids and potentially break the vicious cycle of inflammation.

Modulating the secretion of pro- and anti-inflammatory molecules

Inflammation has a pivotal role in the development and propagation of evaporative DED in early as well as advanced phases of the disease.[51] Factors that adversely affect tear film stability and osmolarity can induce ocular damage and initiate an inflammatory cascade that generates a powerful immunological response which, in turn, may cause further damage at the ocular surface, creating a self-perpetuating inflammatory cycle. Clinical studies consistently report elevated levels of inflammatory molecules in the tears and ocular surface of patients with DED.[52] The levels of these cytokines/chemokines are often correlated with pain, tear instability, tear production, and/or ocular surface integrity.[51]

IPL has the potential to interfere with this inflammatory cycle, by upregulation of anti-inflammatory cytokines, or downregulation of proinflammatory cytokines, or both. A few examples are noteworthy:

1. In cultured keratinocytes, IPL treatment led to a fivefold increase in the levels of interleukin-10 (IL-10), an anti-inflammatory protein that inhibits cytokine production in T cells.[53] In fibroblasts, IPL has a bidirectional effect on the secretion of transforming growth factor-β1 (TGF-β1): inhibition at low fluences, but enhancement at high fluences.[54] TFG-β is an interesting example, because it has both pro- and anti-inflammatory effects, depending on the context and the cellular environment. As an anti-inflammatory agent, TGF-β modulates the proliferation of T cells after encountering ocular surface epithelium, prevents their migration to the conjunctiva,[55] and suppresses natural killer (NK) cells.
2. A third example is the proinflammatory cytokine IL-6, which is downregulated subsequent to LED phototherapy.[56]
3. Yet another example is the effect of IPL on the skin of acne patients: IPL significantly reduces inflammatory lesions, presumably by downregulation of tumor necrosis factor-α (TNF-α) (one of the cytokines which make up the acute phase of inflammation).[57]

The inflammatory cascade in dry eye is extremely complex and incompletely understood. However, it is plausible that at least part of the beneficial effect of IPL on DED patients occurs by interfering with the positive feedback loop underlying the inflammatory cycle of this pathology.

Suppressing MMPs

Another type of proteins involved in the pathogenesis of dry eye are MMPs. These enzymes participate in extracellular matrix remodeling and are both directly and indirectly affected by IPL. For example, in skin fibroblasts, IPL treatment decreases the concentration of MMPs, by downregulation at the mRNA level.[58] In corneal epithelia cells, TNF-α and IL-1 upregulate several types of MMPs.[59] Recall that TNF-α is downregulated by IPL.[57] Therefore, IPL indirectly diminishes the levels of these MMPs. It is interesting to note that corticosteroids relieve dry eye symptoms by similar pathways: they interfere with the inflammatory cycle by lowering the cellular levels of cytokines, chemokines, and MMPs.[60–62]

Reactive oxidative species (ROS)

In rosacea, inflammation is associated with the generation of ROS released by neutrophils and other inflammatory cells.[63] ROS are highly reactive molecules containing oxygen, also widely referred to as free radicals. Examples of ROS include superoxide anions (O_2^-) and hydroxyl radicals (OH–). Abnormally high levels of ROS may result in oxidative stress, as was identified in the tear film of dry eye patients.[64]

There are conflicting reports regarding the effect of visible light irradiation on the levels of ROS. For example, absorption of visible light in mitochondrial and cell membrane

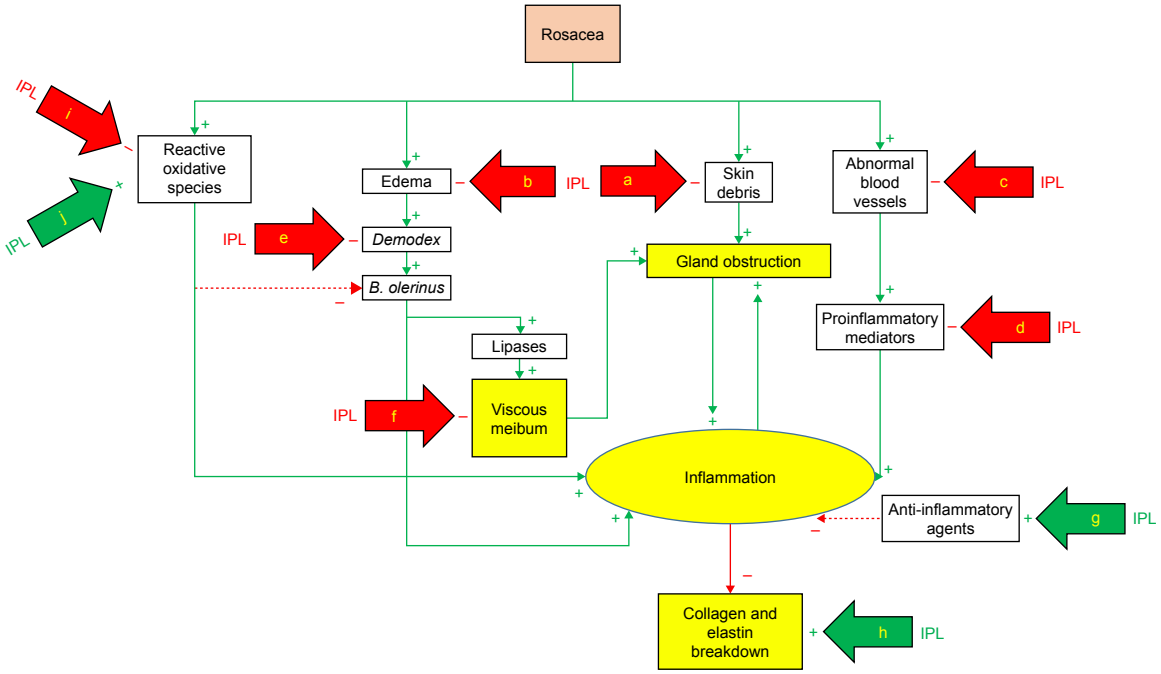

Figure 2 Mechanisms of action of IPL (simplified model).
Notes: Green arrows (+) represent effects that increase the level of the target; red arrows (–) represent effects that decrease the level of the target.
Abbreviations: IPL, intense pulsed light; a, skin rejuvenation; b, rosacea treatment; c, thrombosis; d, down-regulation; e, coagulation; f, warming and liquefying; g, up-regulation; h, fibroblasts activation; i, attenuation; j, production.

cytochromes generate ROS and thus could induce oxidative stress.[65] One report shows that application of light results in reduced levels of ROS.[66] Several researchers have proposed that the effect of light on ROS levels follows a biphasic dose response, also known as the Arndt–Schultz curve.[67,68]

Separately, either one of these contradictory effects could have a beneficial effect on dry eye patients. Following low-level light irradiation, an increase in ROS is described by the ascending part of the Arndt–Schultz curve. In this situation, light irradiation would result in excessive production of ROS and antimicrobial activity, thus reducing the bacterial load on eyelids. At higher doses, the descending part of the Arndt–Schultz curve could describe the antioxidant roles of light irradiation. In this part of the dose–response curve, light irradiation would result in the attenuation of ROS levels, thus diminishing oxidative stress and inflammation.

Conclusion

Dry eye is a multifactorial disease. Potential mechanisms whereby IPL could achieve clinical improvement include thrombosis of abnormal blood vessels below the skin surrounding the eyes, heating the meibomian glands and liquefying the meibum, activation of fibroblasts and enhancing the synthesis of new collagen fibers, eradication of *Demodex* and decreasing the bacterial load on the eyelids, interference with the inflammatory cycle by regulation of anti-inflammatory agents and MMPs, reducing the turnover of skin epithelial cells and decreasing the risk of physical obstruction of the meibomian glands, and changes in the levels of ROS (Figure 2). While any one of these mechanisms of action has the potential to explain the effect of IPL on DED, it is also possible that multiple mechanisms of action are at play. As IPL becomes more commonly used in the treatment of DED, the specific contribution of each of these modes of action will be further elucidated.

Disclosure

SJD is a consultant for Lumenis Ltd. The author reports no other conflicts of interest in this work.

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CLINICAL TRIAL REPORT

Prospective evaluation of intense pulsed light and meibomian gland expression efficacy on relieving signs and symptoms of dry eye disease due to meibomian gland dysfunction

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Video abstract

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Purpose: The aim of this study was to estimate the efficacy of intense pulsed light (IPL), followed by meibomian gland expression (MGX), for reducing the number and severity of signs and symptoms of dry eye disease (DED) secondary to meibomian gland dysfunction (MGD).

Patients and methods: In a prospective study conducted in two sites, 40 subjects (80 eyes) with moderate to severe MGD were enrolled. Major inclusion criteria consisted of at least two of the following measures being compatible with DED in both eyes: tear breakup time (TBUT), meibomian gland score (MGS), corneal fluorescein staining (CFS), Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, and tear film osmolarity (TFO). Enrolled patients underwent four treatment sessions, 3 weeks apart. Each treatment included the administration of 10–15 pulses of IPL on the cheeks and nose, followed by MGX of the upper and lower eyelids. TBUT, MGS, CFS, SPEED, TFO, and lipid layer thickness (LLT) were measured at baseline (BL) and at 9, 12, and 15 weeks after BL.

Results: Due to different staining methods used for TBUT measurements, TBUT and CFS were analyzed separately for each site. From BL to the final follow-up, the number of signs compatible with DED decreased from 3.3±0.1 to 1.4±0.1. TBUT improved by +93% (n=38; $P<0.0001$) and +425% (n=42; $P<0.0001$) for sites 1 and 2, respectively. SPEED, MGS, and CFS improved by −55% (n=80; $P<0.0001$), −36% (n=80; $P<0.0001$), and −58% (n=38; $P<0.0001$), respectively. In 20 eyes with abnormally elevated TFO at BL, TFO improved by −7% (n=20; $P<0.005$). LLT did not change (n=38; $P=0.88$).

Conclusion: In subjects with moderate to severe MGD, IPL combined with MGX reduced the number and severity of symptoms and signs of DED. Except for LLT, all examined outcome measures significantly improved after 15 weeks. These results support the efficacy of IPL + MGX in relieving both signs and symptoms of DED secondary to MGD.

Keywords: dry eye, meibomian gland dysfunction, intense pulsed light

Introduction

Dry eye disease (DED) affects the quality of life of hundreds of millions of people around the globe. The most common form of DED is the evaporative form of the disease.[1] By far, the most common cause of evaporative DED is meibomian gland dysfunction (MGD), with a prevalence of 5%–20% in western countries and 45%–70% in Asian populations.[2] MGD is one of the most common disorders encountered by ophthalmologists. The pathogenesis of both conditions, MGD and DED, was recently described as two vicious cycles linked by inflammation:[3] the MGD vicious

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cycle is triggered by various factors (eg, skin disorders, eyelid inflammation, and microbial infections), resulting in increased melting temperature of the meibum, blockage of the meibomian gland orifices, and, subsequently, inflammation and atrophy of the meibomian glands. As a result, tear film stability is compromised, exposing the cornea and triggering the DED vicious cycle, where inflammation of the ocular surface propagates to the lid margin and feeds back into the MGD cycle.

The current standard of care includes a variety of therapeutic strategies, including corticosteroids and other anti-inflammatory drugs to control the inflammation, antibiotics to suppress bacterial infections, oral supplementations to change the composition of the meibum, warm compresses or thermal devices to soften the meibum, artificial tears and punctal plugs to keep the ocular surface moist and lid hygiene, blinking exercises, and mechanical expression of the meibomian glands.[4] These therapies frequently provide only partial and temporary relief, perhaps because of our incomplete understanding of this complex pathology and perhaps because treatment has focused on addressing the symptoms, rather than the root cause.

Another approach is inspired by the well-known correlation between facial skin rosacea and MGD. A large proportion of patients with skin rosacea, ~80%, suffer also from ocular symptoms, the most prominent of them being MGD.[5–8] Subjects with this skin disorder are three to four times more likely to suffer from symptomatic MGD.[9] Given the correlation between facial skin rosacea and MGD, it seems plausible that treatment of skin rosacea might also improve MGD. Intense pulsed light (IPL) has demonstrated good clinical efficacy in skin rosacea.[10,11] Could that type of treatment somehow benefit MGD as well? The first suggestion that IPL might improve MGD came from Toyos, who observed that rosacea subjects treated with IPL reported an improvement in their DED symptoms.[12] Since then, several studies have shown that IPL therapy has a beneficial effect on MGD in patients with and without rosacea.[13–17]

In this prospective study, we present further evidence that IPL combined with meibomian gland expression (MGX) is effective in treating MGD. The IPL used in this study is based on Optima technology, which ensures uniform delivery of energy and therefore avoids under- or overtreatment.

Patients and methods

Patients

Patients were recruited from, and treated at, two sites in the USA (site 1: Dell Laser Consultants, Austin, TX, USA; site 2: Gaster Eye Center, Beverly Hills, CA, USA).

General health and current/recent use of medications were screened to exclude patients for whom intense pulse light was contraindicated. Contact lens wear, recent ocular surgery, recent thermal treatment for DED (eg, LipiFlow), current use of punctal plugs, or recent expression of the meibomian glands also resulted in exclusion. Patients on standard of care such as warm compresses, lid hygiene, and artificial tears were allowed to continue these treatments.

Study enrollment consisted of consecutive patients who passed all exclusion criteria and satisfied the following inclusion criteria: able to read, understand, and sign an informed consent form; aged 18–80 years; Fitzpatrick skin type I–IV; at least five nonatrophied meibomian glands on each lower eyelid; and a current diagnosis of moderate to severe MGD in both eyes. This latter criterion was defined as two or more of the following conditions: 1) a tear breakup time (TBUT) $\leq$10 s; 2) a meibomian gland score (MGS; using the abbreviated MGD grading system for clinical trials) $>$10; 3) a corneal fluorescein staining (CFS; using the Baylor grading scheme) $\geq$10; 4) a subjective symptom score (using the Standard Patient Evaluation of Eye Dryness [SPEED] questionnaire) $\geq$10; and 5) a tear film osmolarity (TFO) $\geq$310 mOsm/L, or a TFO difference between the eye and its fellow eye (ΔTFO) $\geq$8 mOsm/L. The presence of skin rosacea was not a requirement for inclusion in the study.

This study adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by an Institutional Review Board (Schulman, LUM-VBU-M22-15-01). All participants signed an informed consent form before enrollment.

Study design

This trial was conducted as a prospective, multisite, interventional, single-arm, exploratory, before–after study (NCT 02621593).

Enrolled patients underwent a series of four treatment sessions, 3 weeks apart. IPL was administered with the M22™ Optima™ IPL (Lumenis, Yokneam, Israel). Optima™ IPL technology ensures that fluence is constant and reproducible throughout each pulse, minimizing the risk of overtreatment (spikes) or undertreatment. To minimize the sensation of "snapping rubber band" that subjects treated with IPL occasionally feel, the treatment area was numbed with a topical anesthetic compound (eg, benzocaine 20%–lidocaine 7%–tetracaine 7% compound gel). After protection of the eyes with disposable eye shields (Derm-Aid; Honeywell, Smithfield, RI, USA), Optima™ IPL was applied on a band of skin that extended from tragus to tragus (coronal axis) and on the cheeks from the maxillary process of the zygomatic bone up to the inferior orbital rim below the lower eyelids (longitudinal axis). Settings

of the IPL, such as fluence and pulse interval, were dependent on skin type. Immediately after the IPL treatment, meibomian glands were expressed on both upper and lower eyelids of each eye. To minimize pain during this procedure, the eye was numbed with a solution of proparacaine HCl 0.5%.

MGX was then performed by squeezing the meibomian glands with a meibomian gland expressor forceps, or with the aid of two Q-tips positioned on either sides of the meibomian glands.

Outcome measures were tested at the following four time points: on the same day and just before the first treatment session (hereafter referred to as the baseline [BL]); immediately before the fourth and final treatment sessions (first follow-up [FU1]); 3 weeks after the final treatment session (second follow-up [FU2]); and 6 weeks after the final treatment session (final follow-up [FU3]). From BL to the FU3, each patient was treated and followed up for a total of 15 weeks.

Clinical tests

At the BL and each of the three follow-ups, a series of clinical tests were performed to evaluate the TBUT (primary outcome measure) and secondary outcome measures, including subjective symptoms with the SPEED questionnaire, MGS, CFS, and TFO. Lipid layer thickness (LLT) was also measured in one of the sites, but it was not defined as a secondary outcome measure.

TBUT

After instillation of fluorescein on the ocular surface, the patient was asked to blink a few times to distribute the dye and then to close the eye once positioned at the slit lamp. A timer started when the patient opened his eye and stopped at the first sign of breakup. TBUT was evaluated as the average of three consecutive measurements. The following two sites used different methods of instillation: in site 1, the bulbar conjunctiva was touched with a Fluorescein Sodium Strip (Ful-Glo 0.6 mg; Akorn, Lake Forest, IL, USA); in site 2, a drop (~50 µL) of fluorescein sodium and benonixate hydrochloride ophthalmic solution (0.25%/0.4%; Bausch & Lomb, Rochester, NY, USA) was applied to the bulbar conjunctiva and any excess fluid was blotted off gently with a tissue.

TBUT ≤10 s is traditionally considered abnormal and consistent with DED.[18] In this study, we used this criterion to distinguish between normal and abnormal TBUT values.

Subjective symptoms

Subjective symptoms were assessed with the validated SPEED questionnaire.[19] The patient was asked to grade the severity and frequency of the following four symptoms, separately for each of his/her eyes: dryness/grittiness/scratchiness, soreness/irritation, burning/watering, and eye fatigue. For each of these symptoms, the patient scored the severity (from 0= no symptom to 4= intolerable) and the frequency (from 0= never to 3= constant). SPEED was calculated as the sum of these eight subscores.

A SPEED value of ≥10 is often considered consistent with moderate to severe DED symptoms.[20] This is the cutoff value used in the study to distinguish between no/mild and moderate/severe dry eyes.

MGS

MGS was evaluated using the abbreviated MGD grading system for clinical trials.[21] This compound score is a sum of subscores, including thickening of the upper lid margin (from 0= normal to 3= severe), vascularity of the upper lid margin (from 0= normal to 3= severe), telangiectasia of the upper lid margin (from 0= none to 3= more than 5), number of plugged glands of the 10 central glands in the upper eyelid, quality of the meibum (from 0= clear to 3= solid), expressibility (from 0= minimal pressure to 3= heavy pressure), and gland dropout from the central two-thirds of the lower eyelid. In our study, we used a score of >10 for categorizing DED as moderate to severe.[21]

CFS

Following instillation of fluorescein on the ocular surface, the cornea was examined under blue light illumination and a yellow filter. CFS was estimated using the Baylor grading scheme:[22] staining of each of five zones of the cornea (central, temporal, nasal, superior, and inferior) was scored using the following 5-point scale: 0 dots =0, 1–5 dots =1, 6–15 dots =2, 16–30 dots =3, and >30 dots =4. One point was added if there was a single area of confluent staining. Two points were added if there were at least two areas of confluent staining. According to Fenner and Tong,[23] in evaporative dry eye, the mean Baylor score of each corneal zone ranges between 1.0 and 2.5. In our study, we used cutoff >10 for categorizing DED as moderate to severe.

TFO

TFO was evaluated by measuring the electrical impedance of a 50 nL sample collected from the lower meniscus, using an osmolarity measurement device (TearLan, San Diego, CA, USA). Different studies use slightly different cutoff values to distinguish between normal TFO and TFO consistent with DED, depending on the severity of dry eye and the preferred trade-off between sensitivity and specificity.[24,25] The accepted values range from 305 to 318 mOsm/L.

In our study, we used a cutoff value of 310 mOsm/L. In addition, an intereye difference of ≥8 mOsm/L is also considered as a characteristic signature of DED.[24]

LLT

LLT was measured using the LipiView interferometer (TearScience, Morrisville, NC, USA). LLT measurements were conducted in site 1 only, since site 2 did not have the device. The accepted cutoff values range between 60 and 75 nm.[26] In this study, we used a cutoff value of 60 nm.

Statistical analysis

All statistical analyses were done using JMP 12.2.0 (SAS statistical software). Only eyes that completed all follow-ups were taken for the analysis. In 12 of 320 osmolarity measurements, values were missing due to malfunction of the device or other technical issues. In these cases, values were completed using a "last observation carried forward" strategy.

Descriptive statistics included proportions for categorical variables, mean ± standard deviation (SD) or mean ± standard error of the mean (SEM) for continuous variables. Continuous variables were tested for normality with the Shapiro–Wilk test. Paired analysis allowed comparison of data before treatment and at each of the individual follow-ups. Except where mentioned, all paired analyses assumed nonparametric distributions and were performed with Wilcoxon signed rank test. Paired analyses for parametric distributions were done with two-tail paired *t*-test assuming equal variance. Longitudinal analysis was performed using a within-subjects multivariate analysis of variance (*F*-test).

For categorical analysis, outcome measures were dichotomized according to the cutoff and conditions listed earlier. Odds ratios (ORs) were calculated using logistic regression. Differences were defined as statistically significant at the α=0.05 level.

Results

Flow

Between September 2015 and July 2016, 46 patients were enrolled from two sites (site 1: 24 patients; site 2: 22 patients). One patient in site 2 was withdrawn after receiving a first treatment, due to the history of migraines that was not identified at screening. One patient in site 1 missed FU3 and is considered lost to follow-up. At the time of writing, four patients were still in various stages of the study and were not included in the analysis. Forty patients (80 eyes) completed all treatments and follow-up sessions and formed the statistical database for this article. Figure 1 is a flowchart that summarizes progress through the various phases of the

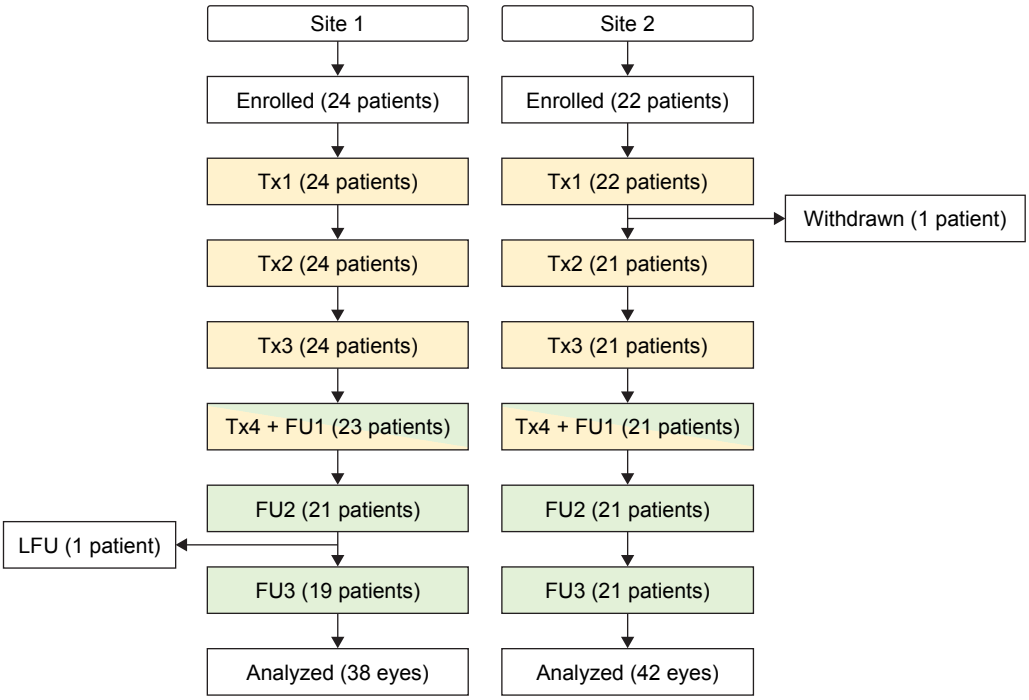

Figure 1 Study flow diagram.
Notes: Withdrawn case in site 2 received one IPL treatment but was withdrawn because it was discovered, after the treatment, that the patient has a history of migraines.
Abbreviations: FU, follow-up; LFU, lost to follow-up; Tx, treatment session.

Table 1 Demographic information

	N	Age (μ ± SD)	Gender (male)	Skin type (Fitzpatrick scale)	Baseline rosacea (0= none; 3= severe)
Site 1	19	53.6±15.7	58%	2.8±0.5	1.36±0.67
Site 2	21	61.0±13.9	43%	2.6±0.7	0.57±0.67
Sites 1+2	40	57.5±15.1	50%	2.7±0.6	0.95±0.78
Site 1 vs site 2 (*P*-value)		0.08	0.41	0.38	<0.0001

Notes: Site 1 vs Site 2 were compared with two-tail *t*-test. A *P*-value less than the α level (0.05) implies that the two sites are different.
Abbreviation: SD, standard deviation.

study (enrollment, withdrawal, treatments, follow-ups, lost to follow-ups, and analysis).

Demographics

Patients in the two sites had similar characteristics, except for BL rosacea, which was on average slightly more severe in site 1 than in site 2 (Table 1). The mean age was 57.5±15.1 years (SD) and ranged between 23 and 77 years. More than 90% of the patients had a Fitzpatrick skin type of II or III. The vast majority of the patients (90%) were Caucasian, with the rest distributed among Hispanic, Asian, or other minorities. Most patients (70%) had no or mild signs of ocular rosacea at BL. Severity of skin rosacea at BL was distributed as follows: 12 (30%), 19 (48%), 8 (20%), and 1 (3%) had no rosacea, mild rosacea, moderate rosacea, and severe rosacea, respectively.

Previous management of DED included none (52.5%), punctal plugs (27.5%), LipiFlow (3%), artificial tears (17.5%), Restasis (10%), and warm compresses (3%). Some of the patients were managed with more than one method of treatment.

TBUT (primary outcome measure)

Because of the different staining methods used for TBUT measurements in the two sites, TBUT results were analyzed separately for each of the two sites (Figure 2). The difference between the two sites is discussed in the "Discussion" section.

In both sites, the average TBUT gradually increased from BL to the FU3, improving by +93% in site 1 ($P<0.0001$) and by +425% in site 2 ($P<0.0001$) (Table 2). The proportion of eyes with normal TBUT values (>10 s) also increased in both sites, from 2.6% to 53% in site 1 and from 36% to 100% in site 2 (Table 3).

In site 1, the OR indicates that a treated eye was 41 times more likely to end up with a normal TBUT value (TBUT >10 s) at the FU3 than at the BL (Figure 3). OR was even larger when adjusted for age (OR =51). In site 2, ORs could not be calculated for the FU3, because at this time point, all eyes had a TBUT value above the cutoff.

In a set of subgroup analyses performed for data collected in site 1, the effects of age, BL rosacea, BL TBUT, and gender on TBUT were examined (Figure 4). Thirty-eight eyes were divided to subgroups according to age group (young vs old, using the median age of 58 years as cutoff), the severity of BL rosacea (none/mild vs moderate/severe), BL TBUT (using the median TBUT of 6 s as cutoff), and gender. All subgroups reached similar TBUT values at the FU3 (young vs old: $P=0.31$; none/mild vs moderate/severe BL rosacea: $P=0.57$; low BL TBUT [≤6 s] vs high BL TBUT [>6 s]: $P=0.91$; male vs female: $P=0.69$).

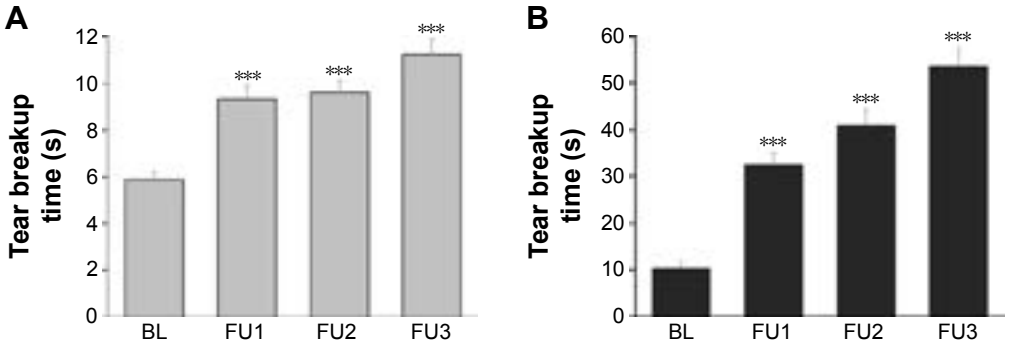

Figure 2 Longitudinal analysis of tear breakup time.
Notes: Error bars: standard error of the mean values. ***Wilcoxon signed rank test against BL ($P<0.001$). (**A**) Site 1 and (**B**) site 2.
Abbreviations: BL, baseline; FU, follow-up.

Table 2 Numerical analysis

Outcome measure	Sites	N	BL	FU1			FU2			FU3			P_{within_pt}
			Mean (SD)	Mean (SD)	Change vs BL (%)	P	Mean (SD)	Change vs BL (%)	P	Mean (SD)	Change vs BL (%)	P	
TBUT (s)	1	38	5.8 (2.3)	9.3 (3.5)	60	<0.0001	9.6 (3.2)	66	<0.0001	11.2 (4.2)	93	<0.0001	<0.0001
	2	42	10.2 (10)	32 (17)	218	<0.0001	41 (22)	300	<0.0001	54 (26)	425	<0.0001	<0.0001
SPEED	1+2	80	12.9 (4.9)	6.6 (4.4)	−49	<0.005	6.3 (4.3)	−51	<0.005	5.8 (4.2)	−55	<0.001	<0.0001
MGS	1+2	80	20.3 (7.2)	13.4 (5.5)	−34	<0.01	12.4 (5.2)	−39	<0.01	12.9 (6.0)	−36	<0.05	<0.0001
CFS	1	38	7.8 (4.6)	3.3 (2.9)	−57	<0.0001	4.5 (3.5)	−43	<0.0001	3.3 (3.3)	−58	<0.0001	<0.0001
	2	42	0.2 (0.9)	1.0 (4.7)	340	0.32	0.1 (0.4)	−50	0.74	0.5 (0.2)	100	0.35	0.07
TFO (mOsm/L)	1+2	20	322.2 (19)	298.5 (12)	−7	<0.0001	297.9 (11)	−7.5	<0.0001	297.8 (9)	−8	<0.0001	<0.005
ΔTFO (mOsm/L)	1+2	24	17.8 (19)	8.6 (5.4)	−52	<0.0001	8.8 (6.9)	−51	<0.005	6.3 (4.2)	−65	<0.0001	0.06
LLT (nm)	1	38	79.3 (19)	80.7 (20)	1.8	0.89	81.1 (22)	2.3	0.73	79.4 (21)	0.2	0.93	0.88

Notes: Change vs BL was calculated by subtracting the BL from the FU means and dividing by the BL mean. *P* = probability that FU and BL are similar (two-tail Wilcoxon signed rank test): $P<0.05$ suggests that the distributions are different. P_{within_pt} = probability that there was no change within subjects (repeated measures, MANOVA test). TBUT and CFS were analyzed per each site separately. TFO was analyzed only for eyes with an abnormally elevated TFO value (≥310 mOsm/L) at BL. ΔTFO, the difference of osmolarity between both eyes of a patient, was analyzed for patients with an abnormally elevated ΔTFO (≥8 mOsm/L) at BL.

Abbreviations: BL, baseline; CFS, corneal fluorescein staining; FU, follow-up; LLT, lipid layer thickness; MANOVA, multivariate analysis of variance; MGS, meibomian gland score; SD, standard deviation; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear breakup time; TFO, tear film osmolarity.

Table 3 Categorical analysis

Outcome measure	Normality criterion	Sites	N	BL, n (%)	FU1, n (%)	FU2, n (%)	FU3, n (%)
TBUT (s)	>10	1	38	1 (2.6)	11 (29)	15 (39)	20 (53)
		2	42	15 (36)	39 (93)	40 (95)	42 (100)
SPEED	<10	1+2	80	18 (22)	65 (81)	61 (76)	67 (84)
MGS	≤10	1+2	80	7 (8.8)	24 (30)	31 (39)	28 (35)
CFS	<10	1	38	24 (63)	38 (100)	34 (89)	36 (95)
		2	42	42 (100)	40 (95)	42 (100)	42 (100)
TFO (mOsm/L)	<310	1+2	20	0 (0)	17 (85)	17 (85)	17 (85)
ΔTFO (mOsm/L)	<8	1+2	24	0 (0)	13 (54)	14 (58)	16 (67)
LLT (nm)	<60	1	38	29 (76)	31 (82)	31 (76)	28 (74)

Notes: In this analysis, outcome measures were dichotomized to "normal" or "consistent with DED", according to the criteria listed under the column "Normality criterion". n, number of eyes with normal values.

Abbreviations: BL, baseline; CFS, corneal fluorescein staining; DED, dry eye disease; FU, follow-up; LLT, lipid layer thickness; MGS, meibomian gland score; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear breakup time; TFO, tear film osmolarity.

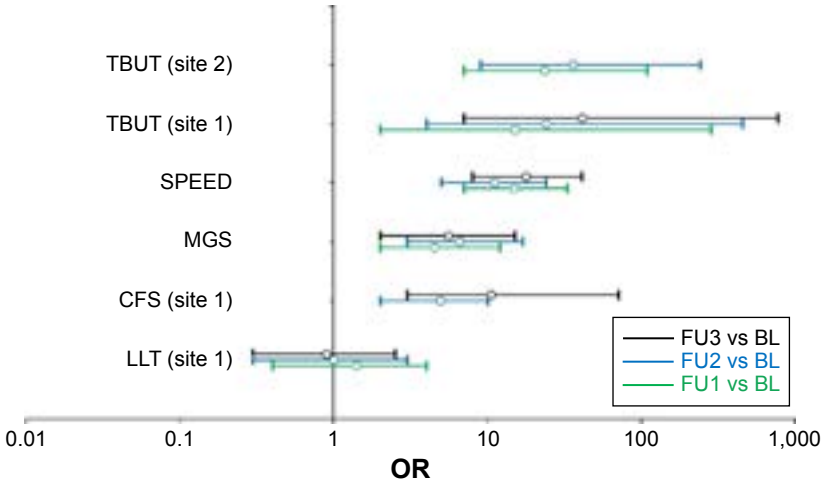

Figure 3 Forest plot of odds ratios for study measures.

Notes: Outcome measures were dichotomized as detailed in Table 3. Open circles and bars represent ORs and 95% confidence intervals, respectively. Green, blue, and black symbols show FU1 vs BL, FU2 vs BL, and FU3 vs BL, respectively. ORs for which the 95% confidence interval do not cross OR =1 are statistically significant. Undefined ORs are missing from this plot.

Abbreviations: BL, baseline; CFS, corneal fluorescein staining; FU, follow-up; LLT, lipid layer thickness; MGS, meibomian gland score; ORs, odds ratios; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear breakup time.

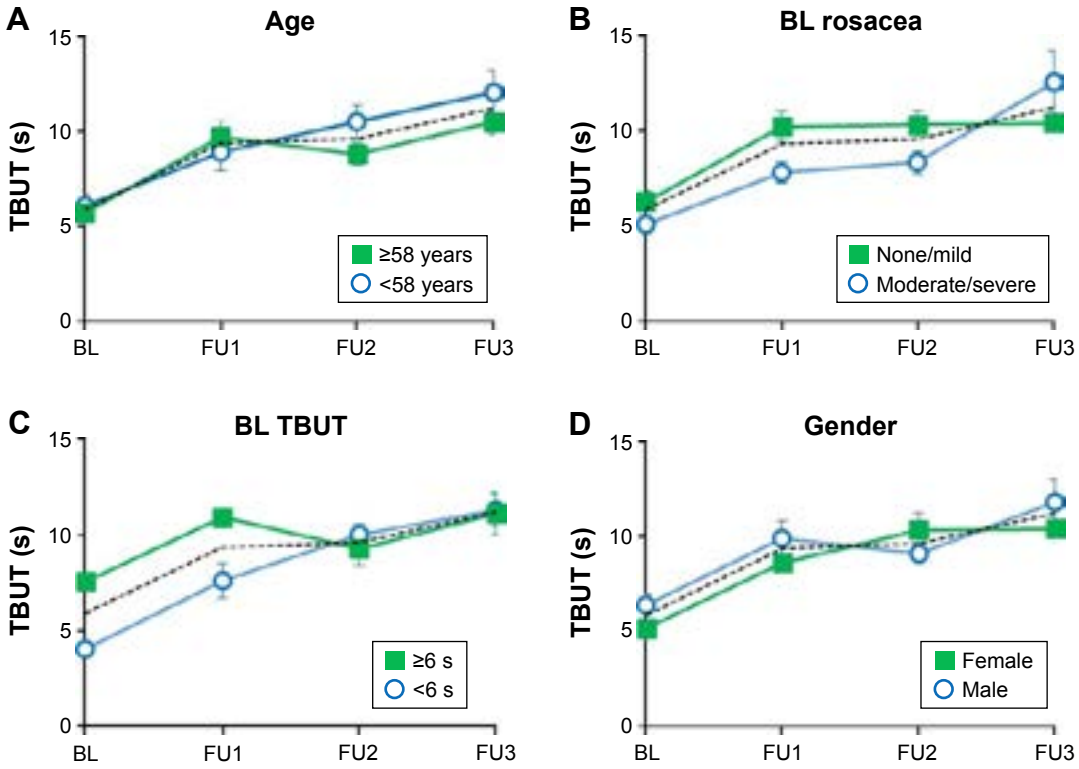

Figure 4 Subgroup analysis of TBUT (site 1).
Notes: In each panel, the dotted line shows the TBUT data for the complete cohort (38 eyes). (**A**) Effect of age. Solid squares: patients aged <58 years (n=18); open circles: patients aged >58 years (n=20). (**B**) Effect of baseline skin rosacea. Solid squares: patients with no or mild skin rosacea at BL (n=24); open circles: patients with moderate or severe skin rosacea at BL (n=14). (**C**) Effect of BL TBUT. Solid squares: eyes with TBUT ≥6 s (n=20); open circles: eyes with TBUT <6 s (n=18). (**D**) Effect of gender. Solid squares: females (n=16); open circles: males (n=22).
Abbreviations: BL, baseline; FU, follow-up; TBUT, tear breakup time.

Subjective symptoms (SPEED)

Subjective symptoms were evaluated using the SPEED questionnaires, performed for each eye separately. From BL to each of the three successive follow-ups, the average SPEED score decreased by –49%, –51%, and –55% ($P<0.0001$) (Table 2). The proportion of eyes with normal SPEED values (<10) increased from 22% at the BL to 84% at the FU3 (Table 3). ORs indicate that a normal SPEED value was 18 times more likely at the FU3 than at the BL (Figure 3).

All eight individual components of the SPEED score, including the severity and frequency of each of the four tested symptoms (dryness/scratchiness, soreness/irritation, burning/watering, and eye fatigue), followed similar changes in time (not shown).

MGS

The MGS is a compound score of the components outlined below. The overall MGS decreased from BL by –34%, –39%, and –36% at the FU1, FU2, and FU3, respectively (Table 2). The proportion of eyes with normal (<10) MGS quadrupled, from 9% at BL to 35% at the FU3 (Table 3). The ORs indicate that, compared to the BL, a normal MGS was 5.6 times more likely at the FU3, compared to prior to treatment (Figure 3). All nine individual components of MGS improved from BL to the FU3.

In the upper lid margin, the proportion of eyes with no telangiectasia doubled (from 31% to 64%) and the average number of telangiectasia decreased by 65% ($P<0.0001$); the proportion of eyes with no vascularity increased from 15% to 25%, and the average change was from mild/moderate to mild (–29%, $P<0.0001$); and the proportion of eyes with no thickening increased from 7.5% to 14%, while the average thickening decreased by 16% ($P<0.01$).

In the 10 central glands of the upper eye lid, the number of plugged glands decreased from 6.2% to 3.2% (–46% $P<0.0001$); the proportion of eyes with a clear meibum more than doubled (from 7.5% to 16%), the proportion of eyes with a solid meibum more than halved (from 33% to 14%), and the average quality of the secretion changed from 1.7 (close to granular) to 1.3 (closer to cloudy) (–24%, $P<0.001$); the number of glands that could not be expressed decreased from 4.7 to 2.8 (–39%, $P<0.0001$); the proportion of eyes for which expressibility (the pressure required for expression) was heavy decreased from 30% to 22%, and the proportion

for which expressibility was minimal or mild increased from 9% to 20%, while the average change modestly declined by 10% ($P<0.01$).

In the central two-thirds of the lower eyelid, the proportion of eyes with no gland dropout doubled (from 12% to 25%) and the proportion of eyes with >66% dropout decreased from 7.5% to 1.2%. On average, this component decreased by 35% ($P<0.0001$).

An unexpected result was the number of nonatrophied glands, which is not a part of the MGS score. Interestingly, this number increased after treatment with Optima™ IPL + MGX: on average, the number of nonatrophied glands increased by 2.5 glands, from 17.2±1.1 at BL to 19.8±1.3 at FU3 ($P<0.0001$). This result is intriguing, as the resuscitation of atrophied glands is highly unlikely – if not impossible. It is possible that some of the glands that were considered atrophied at BL were not completely atrophic but recovered at FU3.

CFS

CFS was evaluated using the Baylor grading scheme.

In site 1, the average CFS decreased from BL by −57%, −43%, and −58% at the FU1, FU2, and FU3, respectively (Table 2). The proportion of eyes with CFS scores below the cutoff (CFS <10) increased from 63% at BL to 95% at the FU3 (Table 3). The proportion of eyes with CFS =0 (no dots or areas of confluence) increased from 0% at BL to 24% at the FU3. With respect to OR, a normal CSF score was 10 times more likely to be observed at the FU3 than at the BL (Figure 3).

In site 2, corneal abrasions or scratches were rarely observed by the investigator and most of the CFS values reported by the investigator were null. Hence, analysis of CFS was omitted for this site. It is possible that the staining method used in site 2 impaired this investigator's ability to detect corneal defects.

TFO

An eye was considered as abnormal with respect to tear osmolarity if at least one of the following conditions held: if TFO was ≥310 mOsm/L, or if ΔTFO, the difference between this eye and the fellow eye, was ≥8 mOsm/L. At BL, 51 eyes (64%) satisfied this requirement. This number declined to 37 (46%), 37 (46%), and 34 (43%) at the FU1, FU2, and FU3, respectively. Next, we examined how Optima™ IPL combined with MGX affected each of these two conditions separately.

For the analysis of TFO, we considered only 20 eyes for which the BL TFO was ≥310 mOsm/L. In the other 60 eyes, TFO was normal and therefore – with respect to their TFO – these eyes were not candidates for improvement. In the 20 eyes included in the analysis, the mean TFO decreased from 322±19 to 298±12 mOsm/L at the FU1. Similar means were obtained at the second and third follow-ups as well (Table 2). While a 7% reduction in TFO may seem modest, according to Versura et al,[25] a change from 322 to 298 mOsm/L, a 7.5% reduction, corresponds to a change from severe to mild DED. Moreover, TFO decreased below the cutoff value in 17 (85%) of the 20 eyes (Table 3). By definition, all eyes taken for this analysis had abnormal TFO at BL. Hence, ORs could not be calculated.

For the analysis of ΔTFO, only patients for whom the ΔTFO was ≥8 mOsm/L were examined. Again, patients with a smaller BL ΔTFO were excluded from this analysis, as by definition these patients were not candidates for improvement. Since all patients satisfying the requirement for analysis had abnormal ΔTFO at BL, ORs were undefined. For patients included in this analysis, on average, ΔTFO decreased from 17.8 mOsm/L at BL to 6.3 mOsm/L at the FU3 (Table 2). Of the 24 patients who satisfied ΔTFO ≥8 mOsm/L at the BL, 16 (67%) patients presented to the FU3 with a normal ΔTFO (Table 3).

LLT

LLT was measured with the interferometer LipiView at site 1 only. No change in LLT was observed (Tables 2 and 3 and Figure 3).

Number of signs and symptoms

To summarize these results, we examined the following question: of the five defining measures, ie, the measures used for inclusion of an eye in the study, how many switched from abnormal to normal as a result of treatment with Optima™ IPL followed by MGX? For TBUT, SPEED, MGS, and CFS, the measure was defined as abnormal if it was ≤10 s, ≥10, >10, and ≥10, respectively. For TFO, the measure was considered abnormal if either TFO ≥310 mOsm/L or ΔTFO (the difference between its TFO and the TFO of the fellow eye) ≥8 mOsm/L.

It is important to recall that the condition for inclusion in the study was that at least two of these measures were compatible with DED. In this study, the median number of signs/symptoms decreased from 3 at the BL to 1 at the FU3. On average, the number of signs/symptoms decreased

from 3.3±0.1 at the BL to 1.4±0.1 at the FU3 (paired *t*-test, $P<0.001$).

Discussion

In this prospective study, we evaluated the effect of Optima™ IPL combined with MGX on eyes affected with moderate to severe MGD. All five defining signs/symptoms responded positively to the treatment, both in terms of average values (numerical analysis) and in terms of the proportion of eyes with signs or symptoms consistent with DED (categorical analysis). The average patient improved from a moderate/severe state to a mild state of DED. A subgroup analysis suggested that the treatment was equally effective for patients with moderate/severe rosacea and for patients with no or a mild form of rosacea.

It is widely accepted that a thicker lipid layer increases the stability of the tear film, thus better preventing the evaporation of the aqueous component.[20] Our study, however, did not show any change in LLT, in contrast with clinically significant changes in TBUT and all other outcome measures. Why were not these improvements accompanied with a corresponding increase in LLT? Our result corroborates with other studies, which found no correlation between TBUT and LLT.[27] The importance of LLT is, indeed, increasingly challenged. King-Smith et al[28] found that a thicker lipid layer does not necessarily imply slower evaporation, if the lipid layer is deficient in composition and/or structure, as is indeed the case in MGD.[29] It is plausible that in our study, improvements in TBUT and other outcome measures are related to qualitative changes in the composition or structure of the meibum rather than merely quantitative changes in its thickness.

Our results are in agreement with several trials, which have demonstrated the efficacy of IPL for the treatment of MGD.[13–17] The mechanism of action is, however, not known. One possibility is that IPL acts by treating the cutaneous forms of rosacea, in patients clinically (or even subclinically) affected with this inflammatory disease. The beneficial effects of IPL on acne rosacea are well known and have been extensively documented:[10,11,30–32] the IPL energy is absorbed in abnormal blood vessels and causes their destruction by thrombolysis. Abnormal blood vessels release chemokines, cytokines, and other proinflammatory agents. By destroying these blood vessels, a major source of inflammatory mediators is reduced.[14] In addition, skin diseases such as rosacea are characterized by an increased epithelial turnover. Large scales can detach from the epidermal surface and may obstruct the meibomian glands.[33] By treating rosacea, this obstruction can be considerably reduced. Other explanations include facilitating expression by softening the meibum as a result of heat transfer to the eyelids and meibomian glands;[13] upregulating anti-inflammatory molecules, such as interleukins;[34] augmenting the production of collagen by stimulating fibroblasts;[35] and eradicating Demodex mites,[36] which thrive on rosacea skin and are infested with *Bacillus olerinus*.[37] This would have the indirect effect on decreasing the bacterial load on the eyelids.

Whatever the mechanism of action, this study and others support the notion that IPL is efficacious in treating MGD and DED.

Limitations

There were several limitations to this study. One limitation was that, in the two sites, different methods were used to stain the ocular surface. In site 1, the ocular surface was stained by touching the conjunctiva with a fluorescein sodium strip, and in site 2, the ocular surface was stained by instilling one drop of Fluess solution. As a result, the TBUT values measured in site 2 were considerably elevated in comparison with the TBUT values measured in site 1. CSF data were affected as well. Consequently, the TBUT and CFS data from the two sites could not be pooled, and the TBUT and CSF analyses had to be conducted separately for each site.

Another limitation of this study was the design. Because the trial was single arm and not randomized controlled, changes observed during the study could be attributed to placebo or Hawthorne effects (the latter, being the process by which a subject is aware of being followed and observed and, as a result, changes his/her routine behavior or hygiene habits, thereby affecting the clinical outcome). Another confounder is that patients generally seek solutions when their symptoms become difficult to tolerate. Hence, it is possible that participants in this study enrolled when their symptoms were at their very worst. If so, improvement during the study is expected – not necessarily because of treatment, but simply due to regression to the mean.

The third limitation was that the treatment included Optima™ IPL sessions immediately followed by MGX, as was done in other studies.[13,15,16] Although expression does not address the root cause, it may help reduce the severity of the condition, by clearing clogged meibomian glands and allowing them to heal and function more properly. It is, therefore, unclear whether the observed improvements in signs and symptoms of DED in our study result from the Optima™ IPL itself, from the expression of meibomian glands, or from a combination of both.

Finally, the fourth limitation was that among the five inclusion criteria, of which two were required for inclusion, only one was specific to MGD (the MGS). This means that a small proportion of eyes included in the study could have signs or symptoms of dry eye but not necessarily due to MGD. Retrospective exclusion of these eyes, however, did not have a significant effect on the results.

Furthermore, randomized controlled studies are required to address these limitations and shed light on these questions and, in particular, the clean effect of monotherapy IPL for relieving the signs and symptoms of MGD.

Conclusion

In subjects with moderate to severe MGD, IPL combined with MGX reduced the number and severity of symptoms and signs of DED. Except for LLT, all examined outcome measures significantly improved after 15 weeks. These results support the efficacy of IPL + MGX in relieving both signs and symptoms of DED secondary to MGD.

Disclosure

SJD, RNG, SCB, and DNC are consultants to Lumenis. The authors report no other conflicts of interest in this work.

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Analysis of Cytokine Levels in Tears and Clinical Correlations After Intense Pulsed Light Treating Meibomian Gland Dysfunction

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• PURPOSE: To investigate the change from baseline of inflammatory markers in tears of dry eye disease (DED) subjects owing to meibomian gland dysfunction (MGD) after intense pulsed light (IPL) treatment and meibomian gland expression (MGE) compared to sham treatment, and the correlations with ocular surface parameters.

• DESIGN: Randomized, double-masked, controlled study.

• METHODS: Those randomized into the active treatment arm received 3 consecutive treatments (14∼16 J/cm^2) approximately 4 weeks apart in the periocular region. Control eyes received 3 treatments in the same intervals of 0 J/cm^2. Tear samples in all eyes were collected and analyzed at baseline, week 12, and/or week 4 for interleukin (IL)-17A, IL-6, and prostaglandin E2 (PGE2). The correlations between cytokines and ocular surface parameters were analyzed before and after IPL treatment.

• RESULTS: All of the inflammatory markers declined in value compared to baselines. IL-17A and IL-6 showed statistically significant decreases compared to sham treatment at each measured time point. PGE2 showed statistically significant decreases compared to sham at week 12. Results showed that the expressions of IL-17A and IL-6 correlated well with ocular surface parameters of the lower eyelid before IPL. The changed values of IL-6 and PGE2 in tears correlated with the changed values of partial ocular surface parameters after IPL treatment in study eyes, respectively.

• CONCLUSIONS: The study results suggest that IPL can significantly reduce inflammatory markers in tears of patients suffering with DED owing to MGD after IPL treatment. These findings indicate that IL-17A and IL-6 play roles in the pathogenesis of DED owing to MGD, and the reduction of the inflammatory factors is consistent with the improvement of partial clinical symptoms and signs. (Am J Ophthalmol 2017;183:81–90. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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DRY EYE DISEASE (DED) ATTRIBUTABLE TO MEIBOmian gland dysfunction (MGD) represents a common and growing public health issue, particularly in older adults. MGD is a common cause of evaporative dry eye, affecting almost 70% of the population in some parts of the world, especially in Asia.[1] Meibomian glands are the largest sebaceous glands in the human body. Meibomian glands synthesize and secrete a mixture of lipids, termed meibomian oil or meibum,[2,3] which is delivered as a clear liquid via orifices located directly in front of the mucocutaneous junction. MGD produces an abnormal meibum that becomes more stagnant than the usual clear liquid secretions.[4,5] MGD and associated evaporative tear loss is followed by increasing inflammation on the surface of the eye and bacterial overgrowth, as abnormal lipids can provide a rich substrate for the resident bacterial microbiota. The subsequent release of toxic bacterial products, such as lipases, and the production and release of proinflammatory cytokines are pathogenic. This malfunction leads to worsening of abnormal meibum, discomfort, and further derangements of the ocular surface and tear film. Although there are different pathogenic mechanisms responsible for DED owing to MGD, evidence increasingly suggests that all forms of MGD are characterized by varying ocular surface inflammation.[6,7] Many investigators have reported that the chronic inflammatory status in patients with MGD is associated with high concentrations of tear cytokines.[8–12] Currently approved topical medications for dry eye, such as cyclosporine and lifitegrast, target inflammation on the ocular surface.[13,14]

Intense pulsed light (IPL) therapy uses light energy to affect the skin surface, and is widely used in dermatology to treat a variety of conditions, including facial rosacea, port wine stains, seborrheic keratosis, and hypertrophic scar.[15] In addition, the IPL device emits energy in a band from a base of the visible spectrum (580 nm) to near-infrared (1200 nm).[16] Concurrent ocular surface health improvements have been observed serendipitously in

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patients undergoing IPL for the dermatologic manifestations of rosacea, leading to interest in evaluating IPL as a potential therapy for DED owing to MGD. There has been a growing number of physicians across the world that use IPL to treat MGD and dry eye.[17,18] Recently, researchers demonstrated that IPL with multiple sculpted pulses showed therapeutic potential for DED owing to MGD, improving tear film quality and reducing symptoms of dry eye.[19,20]

There are several related speculative mechanisms whereby IPL treatment is believed to improve signs and symptoms of DED owing to MGD. First, IPL produces heat that is transferred to the thin periocular skin, which allows the softening of meibum, aids expression, and melts pathologically dysfunctional secretions.[17] Second, the IPL device emits energy that is preferentially absorbed by chromophores in hemoglobin, closing abnormal vasculature in the eyelid margin and adjacent conjunctiva and preventing abnormal vessels from local release of inflammatory factors.[16,21] Third, IPL therapy may exert an effect in relief of inflammatory and neurogenic pain,[22] which is highly related to the improvement of clinical symptoms of DED owing to MGD. Lastly, the IPL treatment can immediately reduce bacteria loads of the eyelid margin and the surrounding adnexa and the associated inflammation caused by them.[23] Despite the many anecdotal case reports outlining efficacy of IPL treatments in dry eye,[17] research quantifying the reduction in specific inflammatory markers during and after IPL treatment is still sparse.

There is mounting evidence that inflammation plays a key role in the pathogenesis of the ocular surface disease that develops in dry eye.[24] Interleukin (IL)-17A is a proinflammatory cytokine produced by T-helper cells and the most commonly investigated member of the IL-17 family.[9] There is an important role for IL-17 in dry eye inflammation processes.[25] IL-17 and IL-6 have both been studied as a possible connection between inflammation and ocular surface parameters in DED.[11,12,25] Further, prostaglandin E2 (PGE2) levels were shown to be higher in tears of MGD patients than in the normal controls.[26] In this study, we compared the levels of all 3 inflammatory markers—IL-17A, IL-6, and PGE2—in tears of subjects suffering with DED owing to MGD before, during, and after MGE combined with either IPL or sham treatments so as to evaluate the efficacy of IPL in reducing tear film cytokines. Additionally, we analyzed inflammatory factor levels in tears and clinical correlations after IPL treating DED owing to MGD.

METHODS

• **SUBJECTS:** This randomized, double-masked, controlled clinical trial was conducted in compliance with the principles of the Declaration of Helsinki for the protection of human subjects in medical research and was approved by the Human Research and Ethics Committee of Peking University First Hospital before the study began. All participants signed written informed consent forms before enrollment. The study was registered at http://www.chictr.org.cn (Study no ChiCTR-INR-16010256).

Subjects were recruited from the outpatient department of the Department of Ophthalmology of Peking University First Hospital from February 2016 to March 2016, and the study was conducted in April 2016. The eyes of subjects were randomized into study or control arms. The inclusion criteria[17,27–29] for this study were (1) adult patients over the age of 18; (2) evidence of meibomian gland obstruction (based on a meibomian gland secretion score of ≤12 for 15 glands of the lower lid); (3) Standard Patient Evaluation of Eye Dryness (SPEED) ≥ 6 in both eyes; (4) Fitzpatrick skin type 1–4. Meibomian gland secretion score was measured using the meibomian gland evaluator (Tear Science Inc., Morrisville, North Carolina, USA). The procedure was performed following Lane protocol,[27]; 15 glands, in both upper and lower eyelids, were evaluated. For each of these glands, the secretion was graded as follows: 0 = no secretion; 1 = inspissated/toothpaste consistency; 2 = cloudy liquid secretion; and 3 = clear liquid secretion. The scores were then summed to a single meibomian gland yield secretion score (MGYSS). The SPEED questionnaire was used to evaluate the severity and frequency of dry eye symptoms.[28] Exclusion criteria included (1) patients with any intraocular inflammatory condition, ocular surgery, or trauma in the past 6 months; (2) patients with present ocular infection or allergy; (3) patients with any eyelid structural abnormality; (4) patients with any systemic disease that could lead to DED; (5) if subjects were unable to stop using medication that may lead to DED; (6) patients currently being treated with punctual plugs; (7) patients who tanned in the past 4 weeks; (8) patients with skin cancer or pigment lesion in the treatment zone; (9) subjects who were pregnant/nursing; (10) any systemic or local conditions that researcher considered inappropriate for the trial. Qualifying subjects stopped all topical or oral dry eye medications, artificial tears, and interventions 2 weeks before the baseline examination.

Eighty-eight eyes of 44 patients with DED owing to MGD (12 male and 32 female) were enrolled into this prospective study, with a mean age of 46.3 ± 16.9 years (range 23–86 years).

• **INTERVENTION PROCEDURE:** The study and control eyes of subjects were randomized according to the random number table by the dermatologist (P.T.), who completed the IPL treatments with the M22 system (Lumenis, Tel Aviv, Israel). Before treatment, the subjects received topical tetracaine/lidocaine cream (compound lidocaine cream; Ziguang Pharmaceutical Co, Ltd, Beijing, China) to periocular treatment areas for 30 minutes (surface

anesthesia) and topical ophthalmic oxybuprocaine hydrochloride eye drops (Benoxil; Santen Pharmaceutical Co, Ltd, Osaka, Japan) into the conjunctival sac 5 minutes before treatment. The study eyes received IPL treatment (14∼16 J/cm^2) depending on the Fitzpatrick skin type per the Toyos protocol, followed by MGE on both the upper and lower eyelids using the Arita meibomian gland compressor (Katena Products, Inc, Denville, New Jersey, USA) with no heat. Control eyes received sham IPL treatment (0 J/cm^2), followed by the same MGE. Handheld flashlights were used to simulate light flicker during IPL therapy in the treatment of the control eyes. IPL treatment was administered to the periocular tissues in 6 treatment areas from the nasal to the temporal side on each eyelid, for a total of 3 treatments approximately every 4 weeks.[19] Patients received a total of 12 overlapping IPL pulses in the periocular areas (8 mm × 15 mm each) on the upper and lower eyelids (Figure 1). Subjects received 1 full pass with overlapping flashes to ensure treatment of the entire area. All treatment areas were identical within different subjects. Prior to light treatment, protective metal shields were placed over the cornea and sclera. During the follow-up period of IPL treatment, all subjects used polyethylene glycol eye drops 3 times a day (Systane ULTRA, Alcon Company, Fort Worth, Texas, USA).

• **OCULAR SURFACE PARAMETERS:** The primary outcome measure was meibomian gland assessment (MGA), measured using the meibomian gland evaluator. Evaluation indicators were the number of meibomian glands yielding liquid secretion (MGYLS) and the number of meibomian glands yielding clear secretion (MGYCS). The scores were then then summed to a single-score MGYSS according to the above grading standards, termed u-MGYLS/MGYCS/MGYSS for the upper lid and d-MGYLS/MGYCS/MGYSS for the lower lid.[27]

SPEED questionnaire and ocular surface disease index (OSDI) were used to evaluate the severity and frequency of dry eye symptoms. Tear breakup time (TBUT) was measured using moist fluorescein sodium strips (Jingming New Technological Development Co, Ltd, Tianjin, China). After the fluorescein was instilled into the conjunctival sac, the patient was asked to blink several times. Then the tear film was observed under the cobalt blue filter during biomicroscopy. The average TBUT of 3 repeated measurements was recorded for each eye. Following the TBUT measurement, the corneal fluorescent staining (CFS) was measured. The cornea was divided into 4 quadrants. Each quadrant was graded on a scale of 0 to 3[30] (0 = no punctate staining, 1 = 1–30 instances of punctate staining, 2 = punctate staining >30 but no infused lesions, 3 = infused lesions or ulcer). Total CFS of 4 quadrants ranged from 0 to 12.

• **TEAR SAMPLE COLLECTION AND ANALYSIS:** Tear samples were collected by instilling 60 μL of phosphate-buffered saline into the inferior fornix without topical anesthetic, followed by movement of the eyes to mix the tear fluid content.[31] A total of approximately 30 μL of unstimulated tear fluid and buffer were collected from the inferior tear meniscus of each eye using a glass capillary micropipette at the lateral canthus. Samples were placed into a 200-μL Eppendorf tube and immediately transported in an insulated cooler to a −80 C freezer, where they remained frozen until further examination.

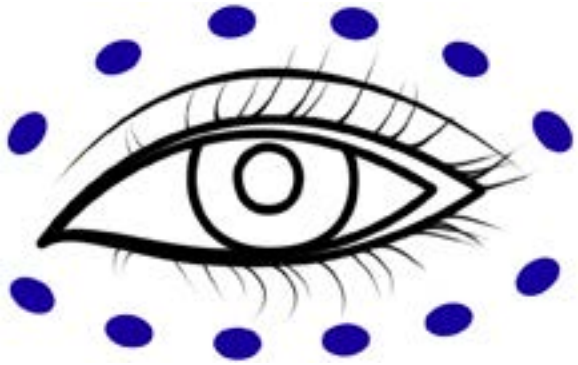

FIGURE 1. Intense pulsed light treatment zone included 6 overlapping periocular areas (8 mm × 15 mm each) on each eyelid.

Tear cytokines IL-17A and IL-6 concentrations were measured using a multiplex immunobead assay (BDTM Cytometric Bead Array Human Soluble Protein Flex Set; BD Biosciences, San Jose, California, USA) and flow cytometry (BD LSRFortessa; BD Biosciences). The measurements were performed according to protocol.[32] Briefly, 10 μL tear fluid was thawed and added to a 50-μL mixture containing each capture antibody–bead reagent and 50 μL detector antibody–phycoerythrin reagent. The mixture was subsequently incubated for 3 hours at room temperature and washed to remove unbound detector antibody–phycoerythrin reagent before flow cytometry. Data were acquired and analyzed using BD Cytometric Bead Array software to calculate the cytokine concentration based on the standard curves and a 5-parameter logistic curve-fitting model with FCAP Array software v3. Flow cytometry was performed using the BD LSRFortessa system (BD Bioscience). The lower limits of detection were the following: IL-17A, 0.3 pg/mL (Human IL-17A Flexset, 560383; BD Biosciences); IL-6, 1.6 pg/mL (Human IL-6 Flexset, 558276; BD Biosciences). The lowest cytokine concentration in the linear portion of the standard curve was used for statistical comparison of tear samples with concentrations of less than this level.

Tear concentrations of PGE2 were measured using a PGE2 ELISA kit (ab133021; Abcam Inc, Cambridge, Massachusetts, USA) according to the manufacturer's instructions. The diluted tear samples (100 μL) was placed in a 96-well goat anti-mouse IgG-coated plate and incubated for 2 hours. After incubation, the plate was washed using the provided washing buffer, and the color was developed

by adding PNPP (200 μL) substrate after 45 minutes. The amount of PGE2 was acquired and calculated using Gen5 2.04.11 software, which calculates the cytokine concentration based on the standard curves, and a 4-parameter logistic curve-fitting model with ELISACalc. ELISA was performed using the BioTekEpoch (1311227; BioTek Instruments, Inc, Winooski, Vermont, USA). According to the manufacturer, the assay's lower limit of detection was 13.4 pg/mL.

We collected tear samples of both eyes at baseline prior to treatment, on week 4, and on week 12 for each subject. Then, we selected the baseline, week 4, and week 12 points to analyze the levels of cytokines IL-17A and IL-6 in the tear samples; the baseline and week 12 points were selected for analysis of the PGE2 concentration.

• **STATISTICAL ANALYSIS:** Data are expressed as mean ± standard error of the mean (SEM). Analysis between 2 different time points (week 4 and week 12) for single variable data was performed using a paired-samples test with SPSS 17.0 for Windows software (SPSS Inc, Armonk, New York, USA). To compare the change in cytokine concentration in tears of study eyes with control eyes at individual time points, a paired-samples test was used. Correlations between the expressions of cytokines and ocular surface parameters, and between their changed values after IPL treatment, were analyzed by Spearman correlation coefficient, respectively. For all tests, $P < .05$ was considered to be statistically significant.

RESULTS

• **INTENSE PULSED LIGHT DOWNREGULATES THE LEVEL OF INTERLEUKIN 17A IN TEARS OF PATIENTS WITH DRY EYE DISEASE OWING TO MEIBOMIAN GLAND DYSFUNCTION:** The changed values of cytokine IL-17A level in tears on week 4 and week 12 after IPL treatment in the study eyes were −173.49 ± 32.26 and −211.75 ± 33.78 pg/mL, respectively (n = 44, mean ± SEM). The IL-17A levels of the control eyes were −64.64 ± 24.12 and −89.61 ± 22.21 pg/mL, respectively. All values represent a decrease from the pretreatment baselines. As shown in Figure 2, IL-17A was more significantly reduced in the IPL treatment arm than in the control after both week 4 and week 12 of IPL treatment (both $P < .001$). The value of IL-17A was most significantly decreased at the final study time point after 3 IPL treatments at week 12 compared to week 4 of IPL treatment in the treatment arm (Figure 2, $P < .001$). However, in the control eyes, no significant differences were found between the measured values of IL-17A at week 4 and week 12 of IPL treatment (Figure 2, $P = .068$).

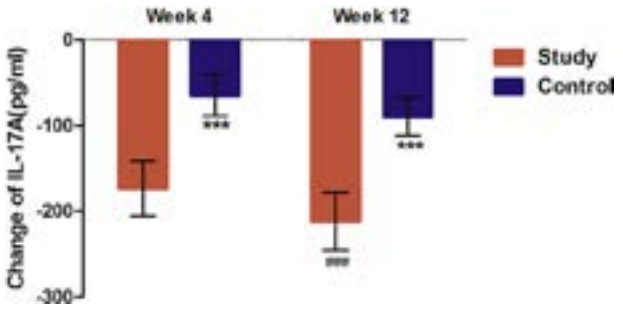

FIGURE 2. Intense pulsed light (IPL) downregulates the level of interleukin (IL)-17A in tears of patients with dry eye disease owing to meibomian gland dysfunction (MGD). IL-17A change to baseline. Baseline corrected change of the level of IL-17A (week 4 minus baseline; week 12 minus baseline). The mean changed value of tear IL-17A level (pg/mL) after week 4 and week 12 of IPL treatment in the study eyes and the control eyes (mean ± SEM, n = 44) is shown. ***$P < .001$ compared to the study eyes at the same time point including week 4 and week 12. ###$P < .001$ compared to week 4 in the study eyes. Bars designate the means with 95% confidence intervals. Week 4: difference value between pretreatment and week 4 after IPL treatment; Week 12: difference value between pretreatment and week 12 after IPL treatment.

• **INTENSE PULSED LIGHT DOWNREGULATES THE LEVEL OF INTERLEUKIN 6 IN TEARS OF PATIENTS WITH DRY EYE DISEASE OWING TO MEIBOMIAN GLAND DYSFUNCTION:** The changed values of cytokine IL-6 level in tears at week 4 and week 12 after IPL treatment in the study eyes were −308.35 ± 58.59 and −405.62 ± 65.61 pg/mL, respectively (n = 44, mean ± SEM). The IL-6 levels of the control eyes were −50.61 ± 22.08 and −143.46 ± 25.99 pg/mL (in the order designated above). These numbers represented a decrease from the pretreatment baselines. Compared to the control eyes, the value of IL-6 was significantly more decreased in the study eyes after week 4 and week 12 of IPL treatment (Figure 3, both $P < .01$). Like IL-17A, IL-6 levels were most significantly lowered after week 12 compared to week 4 (Figure 3, $P < .01$).

• **INTENSE PULSED LIGHT DOWNREGULATES THE LEVEL OF PROSTAGLANDIN E2 IN TEARS OF PATIENTS WITH DRY EYE DISEASE OWING TO MEIBOMIAN GLAND DYSFUNCTION:** The changed concentration of PGE2 in tears at week 12 after IPL treatment in the study eyes was −1.64 ± 0.14 ng/mL (n = 44, mean ± SEM). The PGE2 level of the control eyes at the same time point was −0.73 ± 0.13 ng/mL (n = 44, mean ± SEM). Both numbers represent a decrease from the pretreatment baselines. Compared to the control eyes, the mean concentration of PGE2 was more significantly decreased in the study eyes after week 12 of IPL treatment (Figure 4, $P < .001$).

• **CORRELATIONS BETWEEN CYTOKINES AND OCULAR SURFACE PARAMETERS IN PATIENTS WITH DRY EYE DISEASE OWING TO MGD BEFORE INTENSE PULSED LIGHT**

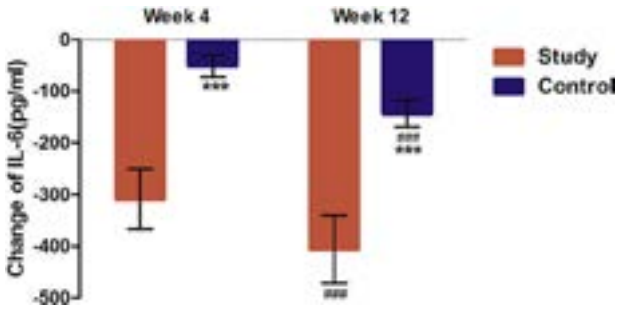

FIGURE 3. Intense pulsed light (IPL) downregulates the level of interleukin (IL)-6 in tears of patients with dry eye disease owing to meibomian gland dysfunction. IL-6 change to baseline. Baseline corrected change of the level of IL-6 (week 4 minus baseline; week 12 minus baseline). The mean changed value of IL-6 (pg/mL) after week 4 and week 12 of IPL treatment in the study eyes and the control eyes (mean ± SEM, n = 44) is shown. ***$P < .001$ compared to the study eyes at the same time point including week 4 and week 12. ###$P < .001$ compared to week 4 in both eyes. Values are expressed as picograms (means ± SEM pg/mL). Bars designate the means with 95% confidence intervals. Week 4: difference value between pretreatment and week 4 after IPL treatment; Week 12: difference value between pretreatment and week 12 after IPL treatment.

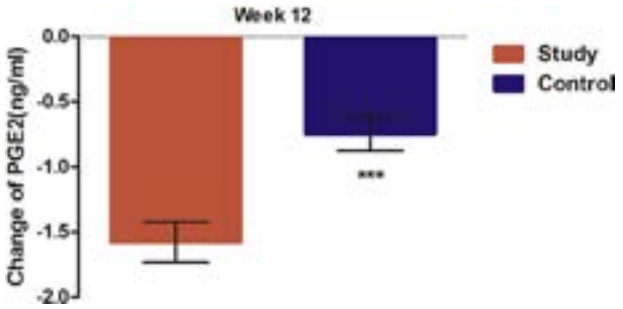

FIGURE 4. Intense pulsed light (IPL) downregulates the level of prostaglandin E2 (PGE2) in tears of patients with dry eye disease owing to meibomian gland dysfunction. PGE2 change to baseline. Baseline corrected change of the level of PGE2 (week 12 minus baseline). The mean changed value of PGE2 (ng/mL) after week 12 (in the IPL treatment endpoint) of IPL treatment in the study eyes and the control eyes (mean ± SEM, n = 44) is shown. ***$P < .001$ compared to the study eyes in the IPL treatment endpoint. Values are expressed as nanograms (means ± SEM, ng/mL). Bars designate the means with 95% confidence intervals. Week 12: difference value between pretreatment and week 12 after IPL treatment.

TREATMENT: The correlations between the expressions of IL-17A, IL-6, and PGE2 and ocular surface parameters of 44 subjects were evaluated in protein levels. One eye was randomly selected for statistical analysis. The correlation analysis between the expression of IL-17A and IL-6 in protein levels and some ocular surface parameters (SPEED, OSDI, BUT, and CFS) showed no statistical significance (all $P > .05$). The correlation analysis between the expression of PGE2 in protein levels and any ocular surface parameter showed no statistical significance (all $P > .05$). On the other hand, the levels of IL-17A in tears correlated well with d-MGYLS ($R = -0.680$, $P < .001$; Figure 5, Top left), d-MGYCS ($R = -0.44$, $P = .003$; Figure 5, Top center), and d-MGYSS ($R = -0.692$, $P < .001$; Figure 5, Top right) at the pretreatment baselines. The levels of IL-6 in tears correlated well with d-MGYLS ($R = -0.839$, $P < .001$; Figure 5, Bottom left), d-MGYCS ($R = -0.446$, $P = .002$; Figure 5, Bottom center), and d-MGYSS ($R = -0.845$, $P < .001$, Figure 5, Bottom right) at the pretreatment baselines.

• **CORRELATIONS BETWEEN THE CHANGED VALUES OF CYTOKINES AND THE CHANGED VALUES OF OCULAR SURFACE PARAMETERS AFTER INTENSE PULSED LIGHT TREATING PATIENTS WITH DRY EYE DISEASE OWING TO MEIBOMIAN GLAND DYSFUNCTION:** Baseline corrected change of the levels of cytokines and ocular surface parameters (week 12 minus baseline) represented a decrease from the pretreatment baselines. The correlations between the changed values of IL-17A, IL-6, PGE2, and ocular surface parameters of 44 subjects were evaluated in protein levels. The correlation analysis between the changed values of IL-17A, IL-6, and PGE2 in protein levels and the changed values of any ocular surface parameter showed no statistical significance (all $P > .05$) in control eyes. On the other hand, the changed value of IL-6 in tears correlated with the changed value of d-MGYCS ($R = -0.411$, $P = .006$; Figure 6, Left) after IPL treatment in study eyes. The changed level of PGE2 in tears correlated with that of CFS ($R = 0.311$, $P = .040$; Figure 6, Right) after IPL treatment in study eyes.

DISCUSSION

MEIBOMIAN GLAND DYSFUNCTION IS A HIGHLY PREVALENT and growing ocular surface condition with potential to create long-term damage to the ocular surface. Current therapies for DED with or without MGD remain nonpermanent and many patients experience side effects or incomplete resolution, prompting researchers to continue exploration of more effective therapeutic approaches. IPL therapy, which has been used extensively in dermatology to treat chronic skin conditions including rosacea, is a relatively new treatment in ophthalmology for patients with evaporative DED.[15] Although there are very few studies published on the use of IPL in patients to reduce the signs and symptoms of DED owing to MGD, IPL therapy has promising results for these patients. Previous reports outline statistically significant improvements in symptoms and clinical examination findings of dry eye owing to MGD.[18] It is helpful to continue to build knowledge in

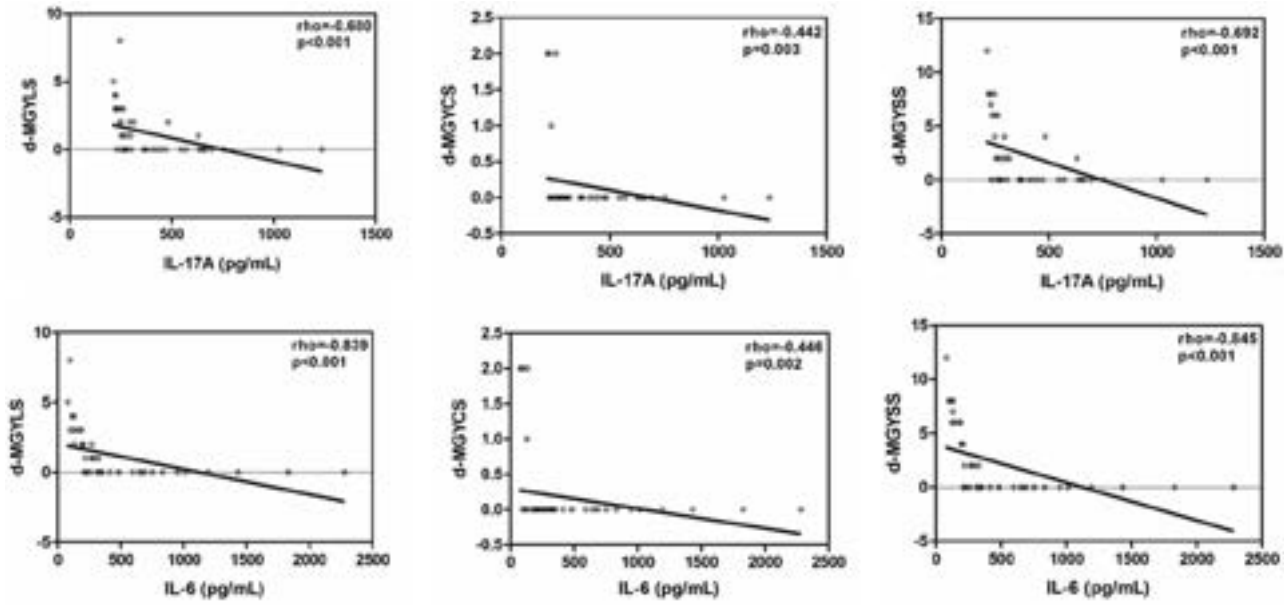

FIGURE 5. Correlations between cytokines (interleukin [IL]-17A and IL-6) and ocular surface parameters in patients with dry eye disease owing to meibomian gland dysfunction before intense pulsed light treatment. Correlation between levels of IL-17A and IL-6 in tears and ocular surface parameters including (at lower lid) number of meibomian glands yielding liquid secretion (d-MGYLS; Top left, Bottom left), number of meibomian glands yielding clear secretion (d-MGYCS; Top center, Bottom center), and single meibomian gland yield secretion score (d-MGYSS; Top right, Bottom right). The R and *P* values were determined with Spearman correlation coefficient.

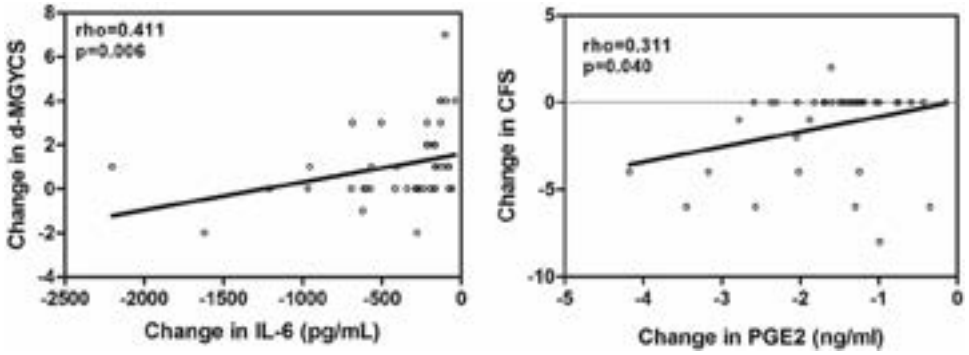

FIGURE 6. Correlations between the changed values of cytokines (interleukin [IL]-6 and prostaglandin E2 [PGE2]) and the changed values of ocular surface parameters after intense pulsed light (IPL) treating patients with dry eye disease owing to meibomian gland disease. (Left) Correlations between the changed values of IL-6 and the changed values of number of meibomian glands yielding clear secretion of the lower eyelid (d-MGYCS). (Right) Correlations between the changed values of PGE2 and the changed values of corneal fluorescent staining (CFS). The R and *P* values were determined with Spearman correlation coefficient.

this area by reporting the change in common ocular surface inflammatory markers owing to MGE alone and also combined with IPL.

Our study showed that IL-17A and IL-6 were significantly decreased in tears from patients with DED owing to MGD after IPL treatment in the study eyes. IL-17A is the most commonly studied member of the IL-17 family, which consists of 6 related proteins, from IL-17A to IL-17F. Th-17 cells are the major source of IL-17A and F, while other cell populations express IL-17A to a lesser extent. As a result, assessment of IL-17A indicates that Th-17 cells are more likely to be the source cells than other cell populations.[9] Several reports previously highlighted increased tear inflammatory cytokines such as IL-17 and IL-6 in patients with DED owing to MGD.[9,11,12,24]

Normal meibum contains antimicrobial properties that keep the lid margin clear from overgrowth.[17] Abnormal blood vessel growth from chronic inflammation (telangiectasias) surround the meibomian glands and leak inflammatory mediators that cause malfunction of the glands.[33] This

dysfunction leads to formation of an abnormal meibum. Eyelid margin telangiectasias are often seen clinically in patients with DED owing to MGD and ocular rosacea. The pathophysiology of rosacea involves thinning of connective tissues, allowing passive dilation of blood vessels (erythema and telangiectasias) and extravasation of inflammatory mediators (causing papules and pustules).[18] IPL allows for selective ablation of these superficial vessels by targeting chromophores in hemoglobin, which not only reduces telangiectasias and erythema but also presumably decreases inflammatory marker access to the meibomian glands.[23] In this research, both IL-17A and IL-6 cytokines were found to be decreased in tears from patients with DED owing to MGD after IPL treatment. Potentially, IPL near the lid should cause closing of the abnormal blood vessels secreting inflammatory mediators, reducing the amount of cytokines IL-17A and IL-6 found in the tears, and also decreasing bacterial overgrowth by disrupting bacterial cell walls with targeted wavelengths of light. Based on this evidence, our data suggest that the decrease of tear IL-17A and IL-6 may correlate with the reduction of signs and symptoms of patients seen in other studies.[17]

In our study, the levels of both IL-17A and IL-6 in tears correlated well with d-MGYLS, d-MGYCS, and d-MGYSS at the pretreatment baselines. But, the correlation analysis between the expression of IL-17A and IL-6 in protein levels and SPEED/OSDI showed no statistical significance. Associations between DED signs and symptoms are low and inconsistent, which is consistent with the systematic literature review of the available evidence on associations between clinical signs and symptoms in DED.[34] The results of the study found that the indicators of the lower eyelid and inflammation were more related. This suggests that the lower eyelid may be more sensitive to inflammation, compared with the upper eyelid index. The MGA of the lower eyelid as an observation indicator in patients with DED owing to MGD is more meaningful and, combined with the upper eyelid, can be used as screening indicators.

There are some related speculative mechanisms whereby the inflammatory factors in tears are more related to the lower eyelid indexes in patients with DED owing to MGD. First, there are about 25–40 glands (average 31), the length of the central tarsal gland is about 5.5 mm, and the capacity is 26 μL in the upper eyelid tarsal gland, whereas there are about 20–30 glands (average 26), the length of the central tarsal gland is about 2 mm, and the capacity is 13 μL in the lower eyelid tarsal gland. The secretion lipid capacity of the upper eyelid is 2 times that of the lower eyelid. Meibomian glands are anatomically different between upper and lower eyelids and may differ functionally, given that upper eyelids move more prominently than do the lower eyelids during blinking.[35] Second, Eom and associates[36] mentioned that gravity may lead to meibum stagnancy in the ducts and orifices, with the result that meibum is more difficult and discontinuous to secrete in the lower eyelid than in the upper eyelid. In our study, we noticed that gland secretion function in the lower eyelids was damaged more seriously than in the upper eyelids (2.3 ± 3.2 vs 9.3 ± 7.5 at the baseline of the study) in study eyes, which is consistent with previous studies.[37,38] It is presumed that the content of inflammatory factors in tears may be more related to the indexes of the lower eyelid. Third, the upper meniscus filled out fully, and the excess tears were distributed to the lower tear meniscus. Also, tear meniscus height and area of the lower eyelid are greater and wider than the upper eyelid.[39,40] Coupled with the role of gravity, the lower eyelid may contact the inflammatory factors in the tears for a longer time and in a wider area, and thus lower eyelid damage is more serious. In other words, inflammatory factors can affect the function of the lower eyelid, resulting in the content of inflammatory factors in tears and lower eyelid indexes being more relevant. It is further explained that lower eyelid damage is more serious in patients with DED owing to MGD. So MGA of the lower eyelid as a measure of DED owing to MGD indicators is more meaningful.

The changed value of IL-6 in tears correlated with the changed values of d-MGYCS after IPL treatment in study eyes. This change suggests that the improvement of d-MGYCS is likely to result in a change in the concentration of IL-6 after IPL treatment. The improvement of the lower eyelid gland clear secretion is particularly associated with the level of IL-6. IPL treatment is more relevant to the change in IL-6. In our study, we noticed that the lowered rate of IL-6 changes was greater than that of IL-17A (-84% vs -52% at the end of the study) in study eyes. IL-6 may be associated with an improvement in eyelid gland signs after IPL treatment. This may be because the decline in IL-17A is not large enough and the sample size of the study is too small.

Reductions in the levels of IL-6 and IL-17A were seen at each study time point in both arms of the study. Chauhan and associates showed that blockade of IL-17 significantly reduced the severity and progression of DED in vivo, which was paralleled by a reduction in the expansion of Th17 cells.[41] Assessment of IL-17A indicates that Th-17 cells are more likely to be the source cells than the other cell populations above.[9] IL-6 also plays a critical role in Th17 cell differentiation.[42] Further research is needed to determine which marker may be most critical and whether Th17 cells are also changed when DED owing to MGD is treated with IPL.

The data showed that levels of PGE2 were lowered in both the control and the study arms and were lowest in the study group receiving IPL. The changed level of PGE2 in tears correlated with that of CFS after IPL treatment in study eyes. PGE2 is a prostaglandin with a significant role in inflammation.[43,44] A small amount of PGE2 is likely to be sufficient to elicit and maintain the inflammatory pain state. PGE2 is a key mediator of pain in inflammation,[44] and its reduction may be responsible for improvement of symptoms in patients receiving IPL

for dry eye. Commonly detectable signs of DED owing to MGD, including tear film instability, evaporative dry eye, and eyelid inflammation, are caused by modified and deficient meibum lipids.[45] Lipid synthesis processes of the meibomian glands are known to be affected by hormonal (mostly androgen), vascular, and neuronal influences.[46] PGE2 may be produced by damaged ocular surface cells, induced by microbes present on the surface, or a result of acute and chronic inflammation on the surface of the eye and within abnormal meibomian glands.[47] The elevated PGE2 in DED patients may aggravate ocular surface inflammation by inducing other inflammatory mediators. The elevated PGE2 may stimulate tear production to overcome surface dryness as well as to elicit irritation symptoms. Reduction in PGE2 levels was also found in the tears of all study patients, but was lowest in the active comparator group receiving IPL. The mechanism by which PGE2 levels are reduced by MGE and IPL is unclear but may be related to reduction in bacterial loads, improvement in meibum quality, decrease in skin inflammation, closure of telangiectasias, and photomodulation of meibomian glands. Further study is warranted to determine the role of PGE2 as a marker in DED owing to MGD.

It is interesting that the lowered levels of IL-17A, IL-6, and PGE2 were seen in the control group at all time points. MGE is known to improve symptoms of dry eye disease.[48] MGE could increase the meibum secretions, reduce the inflammation reaction of meibomian glands, and then lower the level of the molecules in tear samples. The study results also indicate that IPL treatment combined with MGE is more effective than expression alone. Expression would be expected to initially increase the levels of ocular surface inflammation as abnormal gland secretions are expressed onto the surface and then would be expected to decrease as abnormal secretions make way for healthier oils.

The improved outcomes in inflammatory markers with IPL treatment are likely owing to several mechanisms of action. The wavelength of light used in IPL for patients with DED owing to MGD is partially infrared, which can penetrate skin to the meibomian glands, generating enough heat to melt the solid secretions in the dysfunctional glands.[49] The M22 model uses the cooling sapphire crystal tip to cool the skin, allowing higher-temperature pulses without epidermal burning.[50] Secondly, optimized pulse technology (OPT) is a feature on the fifth-generation M22 unit that may confer outcome advantages. The OPT can eliminate energy peak at the beginning of the pulse and increase energy at the end of the pulse, so that the entire energy output can safely and effectively heat the target tissue to the therapeutic temperature. Homogeneous "squared off" energy distribution provides more reproducible treatments for patients, which is also a feature not in other technologies. Thirdly, the IPL is known to close abnormal telangiectasia in skin rosacea, including ocular rosacea, preventing the continued leakage of cytokines that can perpetuate inflammation. Lastly, and possibly most importantly, the specific wavelengths of light provided by the IPL may also stimulate mitochondria of meibomian glands to function normally through a process known as photomodulation.[51] This is the first published work outlining the study of these inflammatory markers over a typical clinical treatment course.

There are several limitations in this study. The volume of tear samples taken was not enough to analyze more than these 3 inflammatory markers. Many hundreds of inflammatory markers are present in acute and chronic dry eye, and some of these markers may prove to be even more important as markers in this disease. Another limitation is the female preponderance (73%) in our enrolled patients, although it reflects the sex divisions seen in clinical practice. The subjects were also asked to provide a subjective assessment of their eyes one to the other, which could introduce some variability. Lastly, it is possible that the subjects could discern whether and how much light/thermal energy was imparted to them, as there is no practical way to present IPL as a true sham treatment. In future studies, clinicians could potentially test larger volumes of tear samples at more time points and enlarge the sample size to optimize the power of the study.

In conclusion, this research demonstrates the reduction of 3 important ocular surface inflammatory factors—IL-17A, IL-6, and PGE2—indicating that IPL combined with MGE is more effective than MGE alone in reducing inflammation of patients with DED owing to MGD. The expressions of IL-17A and IL-6 in protein levels are consistent with ocular surface parameters of the lower eyelid before IPL treatment. Also, the reduction of the inflammatory factors is consistent with the improvement of partial clinical symptoms and signs (d-MGYCS and CFS). These findings indicate that IL-17A and IL-6 play roles in the pathogenesis of DED owing to MGD, and the IL-6 and PGE2 in tears have potential to be a sign of symptom improvement for IPL treatment in patients with DED owing to MGD. In addition, these data present the possibility of an important new approach for treatment of DED owing to MGD. More studies are required to elucidate other issues related to DED, IPL, and its treatment, including the best inflammatory marker to follow, ideal treatment energies, and number of treatments.

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Changes in the Meibomian Gland After Exposure to Intense Pulsed Light in Meibomian Gland Dysfunction (MGD) Patients

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ABSTRACT

Purpose: To observe (1) changes in meibomian gland (MG) after exposure to intense pulsed light (IPL) and (2) to understand the mechanism by which IPL treats meibomian gland dysfunction (MGD) in patients.

Methods: A cohort study, including 35 MGD patients, was conducted. IPL treatment was administered in one group (IPL group; $n = 18$), and eyelid hygiene in another (control group; $n = 17$) for 3 months. All patients were given artificial tears during the treatment period. Associated ocular-surface indexes (ocular surface disease index, OSDI; tear breakup time, TBUT, Schirmer 1Test, corneal staining, and conjunctival staining), MG function, MG macro-morphology, and MG micro-morphology were examined before and after treatment. The relationships between the change in symptom score and the change in the other indexes (related ocular-surface indexes, MG functional indexes, and MG morphological indexes) were evaluated.

Results: There was no statistical difference in pretreatment between the IPL and the control groups in terms of age, gender, related medical history, MGD stage, and all examined indexes, with the exception of conjunctival staining. OSDI, TBUT, meibum quality, MG expressibility, and MG dropout improved after treatment in both of the two groups (all $P < 0.05$). The MG microstructure indexes, including the MG acinar longest diameter (ALD), MG acinar unit density (AUD), and the positive rate of inflammatory cells (ICs) around glandular structures were significantly improved in the IPL group. No improvements of microstructure were found in the control group.

Conclusion: IPL treatment improves the symptom score of patients, associated ocular-surface indexes, MG function, and MG macrostructure as well as eyelid hygiene. And IPL treatment particularly improves MG microstructure and decreases MG inflammation in MGD patients.

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Intense pulsed light; meibomian gland dysfunction; eyelid hygiene; meibomian gland; photomodulation

Introduction

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian gland that is characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion.[1] Intense pulsed light (IPL) treatment is an emerging therapy for MGD. IPL is a noncoherent polychromatic light source with a broad wavelength spectrum of 500–1200 nm.[2] As an established commercial technology, IPL treatment is broadly used in diseases involving facial sebaceous glands[3], and it has been proven that IPL treatment is effective for treatment of the eyelid sebaceous gland, also known as the meibomian gland (MG).[2,4–7] Compared to routine physical therapy (such as eyelid hygiene) for MGD, IPL treatment is more time-efficient and has better efficacy, lasting more than 6 months.[2] Thus, IPL is a promising new therapy for MGD, though the mechanism by which IPL works in the MG and improves MGD is still unclear. The photothermal effect, a decrease in inflammation, and MG activity stimulated by photomodulation are all the hypotheses under discussion.[2,4–7]

Although MGD is commonly characterized by the dysfunction of the MG[1], patients with MGD suffer from both abnormalities of MG function and morphology.[8] MG functional and morphological abnormalities are closely related to each other. MG dysfunction induces MG atrophy, and severe MG atrophy leads to a complete loss of MG function.[8] In fact, in MGD patients, remarkable gland dropout can be observed via noncontact infrared meibography[8] (Figure 1). In addition, changes of microstructure, such as an enlarged MG acinar diameter and a decreased MG acinar unit density, have also been discovered via *in vivo* laser scanning confocal microscopy-[9,10] (Figure 1). Evaluation of MG morphology is as important as evaluation of MG function, and the potential reversibility of MG morphology has recently attracted attention.[11–13]

Eyelid hygiene is a routine physical MGD treatment conducted by doctors or patients themselves, including warming and massage.[1] In this study, a comprehensive evaluation of MG function and morphology was conducted in MGD patients after exposure to IPL. A comparison of MG function and morphology was also done between patients treated with IPL and those treated using eyelid hygiene. The results obtained in this study will be helpful for understanding the mechanisms by which IPL works to

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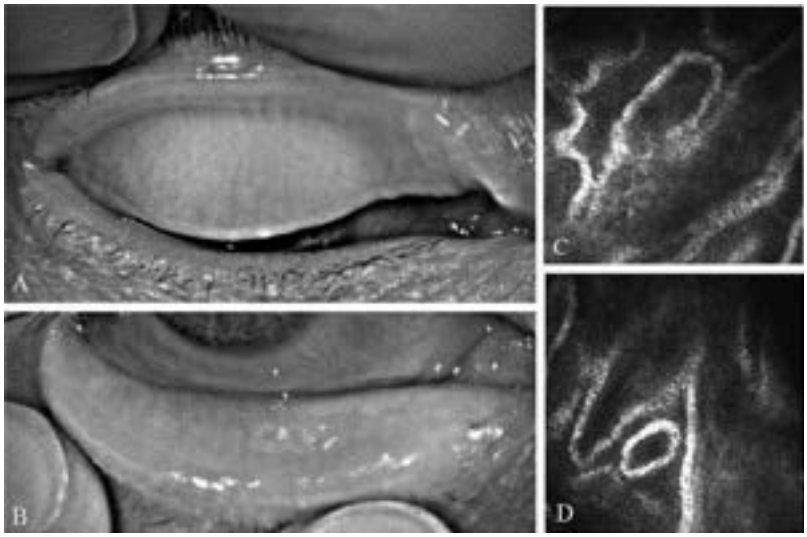

Figure 1. A 50-year-old male patient with severe obstructive MGD. The meibography examination (A: meibography image of upper eyelid; B: meibography image of lower eyelid) showed that the MGs of this patient were vague and difficult to identify in both the upper and lower eyelids; the acinar units were extremely enlarged as seen with confocal microscopy (C, D: confocal microscope images of meibomian acinar structure in upper eyelid).

treat MGD and will provide data for future studies involving IPL treatment for MGD.

Material and methods

Subjects

Adult Asian subjects (IPL group, n = 18; control group, n = 17), who were diagnosed with MGD (>stage1, according to the 2011 International Workshop on MGD[1]) and had not conducted eyelid hygiene or undergone any alternative treatments for at least 3 months, were enrolled consecutively in the study. The study was conducted in the ophthalmology clinic of the Eye & ENT Hospital of Fudan University. The eyes with MGD (in cases where only one eye was affected) or the eyes with more severe MGD (according to stage) were assessed in the study. Diagnostic criteria: [1] symptoms of ocular discomfort, such as eye irritation that limited activities; [2] clinical signs: meibum quality grade ≥4(1) or MG expressibility ≥ 1 (1). Exclusion criteria: [1] previous ocular surgery or trauma (excluding chalazion section); [2] blepharal dysraphism; [3] a history of blepharal and periorbital skin disease in 1 month; [4] acute inflammation; [5] rheumatic immune systemic diseases. Patients with excessive sun exposure in 1 month, a history of herpes zoster infection, pregnancy, use of photosensitive drugs/foods, or skin Fitzpatrick scale V/VI were excluded from the IPL group. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. The sample size was sufficient for statistical calculation. This study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University and was registered with Chinese Clinical Trial Registry prior to the first subject being enrolled. This study adhered to the tenets of the Declaration of Helsinki. All examiners were blinded to the treatment group.

Treatment

(1) Drug

All patients were given artificial lubricant four times a day for 3 months (Tears Naturale, Alcon, America).

(2) Eyelid hygiene

Control group subjects were required to perform an eyelid hygiene regimen at home once daily for 3 months as follows: (1) warming: closed eyelids were warmed for 10 min at about 40°C; (2) massage: traction was applied on the lateral canthus to immobilize the upper and lower eyelids, and then the eyelids were mildly compressed downward or upward with fingers (5 times per hygiene regimen). Warming and massage were performed consecutively.

(3) IPL treatment

Three IPL treatments were administered once a month for 3 months. A modular laser multi-application platform (M22, Lumenis, America) was used to administer treatment to the periorbital area (Figure 2). IPL treatment intensity was chosen based on the Fitzpatrick scale as follows: Fitzpatrick scale III, 17 J/cm^2 with a 560-nm filter; and Fitzpatrick scale IV, 16 J/cm^2 with a 590-nm filter. Patients were required to wear opaque goggles during the IPL procedure. Makeup and contact lenses were removed before treatment. To prevent facial pigmentation secondary to IPL, patients were urged to avoid sun exposure for 1 month after each IPL treatment.

Assessments

(1) Associated ocular-surface indexes

Ocular surface disease index (OSDI), tear breakup time (TBUT), Schirmer 1Test (S1T), corneal staining, and conjunctival staining were assessed. (1) OSDI: a self-administered questionnaire containing 12 items, gives a range of zero (no

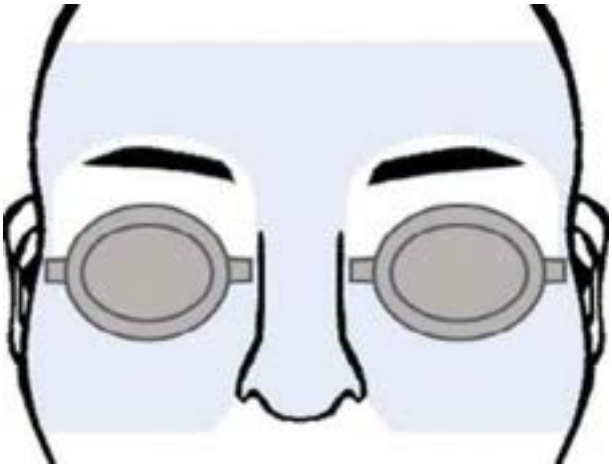

Figure 2. IPL treatment area (marked in blue). To avoid hair loss and eye injury, eyebrow and eyelid were excluded from the treatment area.

symptoms) to 100 (severe symptoms) points. (2) TBUT: TBUT was measured three times consecutively after fluorescein delivery, and the median value was recorded. (3) The S1T was performed for 5 min without topical anesthesia, using a sterile Schirmer test strip. (4) Corneal staining[14]: Five areas (upper, lower, nasal, temporal, and optical-diameter) were evaluated after the instillation of fluorescein. Superficial punctate keratopathy of the cornea was scored between 0 and 3 in each area. (4) Conjunctival staining[14]: Four areas (upper, lower, nasal, temporal) were evaluated after the instillation of lissamine green and scored between 0 and 3 in each area.

(2) MG function indexes

Meibum quality and MG expressibility of the upper eyelid were assessed. (1) Meibum quality[1]: Eight MG glands in the nasal and middle parts of the eyelid were assessed using a scale of 0–3 for each gland: 0, clear; 1, cloudy; 2, cloudy with debris (granular); and 3, thick, like toothpaste. The scores were added to calculate the total score. (2) Expressibility[1]: Five MG glands in the nasal part were evaluated on a scale of 0–3: 0, all glands expressible; 1, 3–4 glands expressible; 2, 1–2 glands expressible; and 3, no glands expressible.

(3) MG morphological indexes

MG dropout and MG acini parameters of the upper eyelids were assessed. (1) MG macrostructure index: MG dropout. After the upper eyelids were everted, the MG dropouts were observed via a noncontact infrared meibography system (Keratograph, OCULUS, German), according to a published method.[15] The whole area of the tarsal plate was limited to the four boundaries[15]: the proximal border, the distal border, the nasal border (tear punctum), and the temporal border (the most visible tarsal conjunctiva of everted eyelid). The examiner defined the array of "string-like" structures traversing palpebral surface vertically as MGs.[15] Partial loss or truncation of these structures was regarded as MG dropout.[15] With ImageJ V1.49 software (provided in the public domain by Bethesda, MD, USA, http://imagej.nih.gov), the MG dropouts were calculated. (2) MG microstructure indexes: confocal microscopy parameters. An *in vivo* laser scanning confocal microscope (HRT II Corneal Rostock Module, Heidelberg Engineering GmbH, Germany) was used to observe MG histological structure. The examiner first everted the upper eyelid and moved the center of the Tomo-Cap onto the palpebral conjunctiva.[9] After the first superficial conjunctival cells were visualized, the focal plane was gradually moved to the subconjunctival tissue until the glandular structures were visualized.[9] MGs were scanned with vertical movements. Images (in a 400 × 400-μm frame) of the nasal, middle, and temporal parts were obtained and used to calculate the confocal microscopy parameters (MG microstructure indexes): MG acinar longest diameter (ALD), MG acinar shortest diameter (ASD), and MG acinar unit density (AUD). Inflammatory cells (ICs) around the glandular structures were also noted.

Statistical methods

Data were analyzed using SPSS 22.0 (IBM Corp, America). Continuous intergroup variables were analyzed using an independent *t*-test, and pretreatment and continuous intragroup variables were tested with a paired *t*-test. Categorical intergroup variables were analyzed with the nonparametric Kruskal–Wallis test, and categorical variables intragroup were analyzed with the nonparametric Wilcoxon signed-rank test. Correlations between normally distributed values and non-normally distributed values were analyzed with the linear Pearson correlation coefficient and the Spearman correlation coefficient respectively. Statistical significance level was <0.05.

Results

Population characteristics

As shown in Table 1, no intergroup differences were found in age, gender, and related medical history (dry eye, blepharokeratoconjunctivitis (BKC), chalazion, chalazion section, and disease duration). MGD stages in the IPL group (age 41.56 ± 9.7 years, 9 female and 9 male) were not statistically different compared with the control group (age 40.76 ± 13.93 years, 8 female and 9 male).

Associated ocular-surface indexes

There was no statistical difference in pretreatment regarding OSDI, S1T, TBUT, and corneal staining between the IPL and control groups (all $P > 0.05$). As shown in Table 2, OSDI and TBUT improved significantly after treatment in both the IPL

Table 1. Characteristics of MGD patients.

Variables	IPL Group n = 18	Control Group n = 17	P-value
Age (Mean ± SD, year)	41.56 ± 9.67	40.76 ± 13.93	0.846
Gender (female/male, n)	9/9	8/9	0.864
Dry eye (%)	94.4	82.4	0.268
BKC* (%)	27.8	29.4	0.916
Eyelid Surgery† (%)	38.9	11.8	0.092
Chalazion (%)	50.0	47.1	0.797
Duration (Mean ± SD, year)	3.4 ± 2.8	3.3 ± 3.5	0.909
Fitzpatrick scale (III/IV, n)	4/14	-	-
MGD stage (Mean ± SD)	2.33 ± 0.49	2.06 ± 0.66	0.208

*BKC, blepharokeratoconjunctivitis.† Eyelid surgery referred to chalazion section. Statistical significance level was $P < 0.05$. There was no statistical difference in characteristics between two groups.

Table 2. Clinical indexes of IPL group and control group before and after treatment.

Variables	Group	Pretreatment	Posttreatment	P Value	Δ*
OSDI*	IPL Group	38.02 ± 26.86	21.76 ± 21.44	*0.001†*	16.26 ± 18.23
(Mean ± SD)	Control Group	45.32 ± 23.39	24.72 ± 21.30	*0.001†*	20.60 ± 20.17
S1T*	IPL Group	10.44 ± 8.74	7.61 ± 7.35	*0.190*	−2.83 ± 8.80
(Mean ± SD)	Control Group	12.00 ± 9.24	10.94 ± 7.98	*0.635*	−1.06 ± 8.78
TBUT*	IPL Group	2.94 ± 2.10	5.78 ± 4.17	*0.002†*	2.83 ± 3.38
(Mean ± SD, s)	Control Group	3.53 ± 2.04	7.00 ± 3.69	*0.002†*	3.47 ± 3.86
Corneal Staining	IPL Group	0.83 ± 0.96	0.89 ± 1.08	*0.834*	−0.06 ± 1.11
(Mean ± SD)	Control Group	1.35 ± 2.57	0.53 ± 1.37	*0.249*	0.82 ± 1.81
Conjunctival Staining	IPL Group	2.33 ± 1.41	1.06 ± 1.06	*0.001†*	1.28 ± 1.27
(Mean ± SD)	Control Group	1.24 ± 1.60	0.53 ± 0.80	*0.079*	0.71 ± 1.65
Quality	IPL Group	2.78 ± 2.34	1.17 ± 1.86	*0.014†*	1.61 ± 2.50
(Mean ± SD)	Control Group	2.00 ± 2.12	0.47 ± 0.94	*0.023†*	1.53 ± 2.50
Expressibility	IPL Group	1/11/6	13/3/2	*0.000†*	4/12/2
(0/1/2, *n*)	Control Group	3/11/3	10/6/1	*0.014†*	10/5/2
Dropout	IPL Group	45.72 ± 12.93	40.28 ± 13.15	*0.002†*	5.44 ± 6.18
(Mean ± SD, %)	Control Group	39.27 ± 13.65	35.22 ± 11.93	*0.008†*	4.05 ± 5.04
ALD*	IPL Group	101.89 ± 21.44	84.67 ± 20.25	*0.006†*	17.22 ± 23.36
(Mean ± SD, μm)	Control Group	98.00 ± 29.01	97.86 ± 25.39	*0.985*	0.13 ± 26.09
ASD*	IPL Group	43.44 ± 12.41	45.17 ± 13.37	*0.562*	1.71 ± 12.36
(Mean ± SD, μm)	Control Group	50.79 ± 19.85	45.50 ± 16.64	*0.345*	−4.90 ± 19.46
AUD*	IPL Group	91.50 ± 37.42	113.11 ± 40.12	*0.006†*	21.61 ± 29.10
(Mean ± SD,/mm^2)	Control Group	88.57 ± 34.24	103.71 ± 27.43	*0.071*	14.13 ± 28.03
IC*	IPL Group	44.44	16.67	*0.025†*	27.77
(positive%)	Control Group	50.00	50.00	*1.000*	0.00

*OSDI, ocular surface disease index; S1T, Schirmer 1 Test; TBUT, tear breakup time; ALD, acinar longest diameter; ASD, acinar shortest diameter; AUD, acinar unit density; IC, inflammatory cell; Δ, the difference value between pretreatment and posttreatment indexes; the difference value had been adjusted, and the positivity of it represented that the index was improved; †, *P*-value <0.05.

and control groups. There was no significant change in S1T or corneal staining after treatment in either IPL or control group (all $P > 0.05$, Table 2). Pretreatment conjunctival staining in the IPL group was slightly higher than that in the control group ($P = 0.040$) and accordingly decreased in the IPL group after treatment ($P = 0.001$, Table 2).

MG function indexes

There was no statistical difference in MG quality or expressibility between the IPL and the control groups prior to treatment (all $P > 0.05$). Meibum quality and MG expressibility improved in two groups with statistical significance after treatment (all $P < 0.05$, Table 2).

MG morphological indexes

There was no statistical difference between the IPL and the control groups in MG dropout, MGALD, MGASD, MGAUD, and IC (all $P > 0.05$). As shown in Table 2, there was mild improvement in MG dropout in both the IPL (5.44 ± 6.18%, $P = 0.002$) and the control groups (4.05 ± 5.04%, $P = 0.008$). Pretreatment MGALD (101.89 ± 21.44 μm to 84.67 ± 20.25 μm), MGAUD (91.50 ± 37.42/mm^2 to 113.11 ± 40.12/mm^2), and the positive rate of IC (44.44% to 16.67%) significantly improved after treatment (all $P < 0.05$) in the IPL group, but not in the control group (all $P > 0.05$). MGASD in both the IPL and the control groups had no statistical change after treatment.

Factors related to the change in OSDI after treatment

Relationships between the change in OSDI and the change in other indexes (related ocular-surface indexes, MG functional indexes, and MG morphological indexes) were evaluated in the IPL and the control groups. In the IPL group, the improvement in OSDI was positively related to the improvement in MGAUD. In the control group, the improvement in OSDI had no correlation with the other indexes.

Discussion

IPL treating MGD was first reported in an article in. 2015[4] Since then, four studies have been published that confirm the efficacy of IPL for the treatment of MGD.[2,5–7] Although IPL treatment had already been used to treat MGD patients in some regions, the specific mechanisms by which IPL affects MGD are yet to be elucidated. Many proposed hypotheses are based on the effects of IPL when treating facial sebaceous abnormalities[2,4–7], though there is no strong evidence to support the idea that the mechanism is the same when treating MGD. Therefore, in order to clarify the specific effects of IPL on MG, examination of the changes in the MG after exposure to IPL was conducted, and these changes were compared to changes in the MG after treatment with eyelid hygiene. Since there were no significant differences in population characteristics, MGD stages, or in most pretreatment indexes between the two groups, the posttreatment differences between the IPL and control groups in the current study appear to be the result of IPL.

Results of this study support those found by Toyos and several doctors.[2,4–7] In addition, the current study confirmed improvements in the symptom score of patients (OSDI), ocular surface injury in patients (conjunctival staining), TBUT, and MG function (meibum quality and MG expressibility) after 3 months of IPL treatment. Except for conjunctival staining, these improvements were also seen in patients undergoing eyelid hygiene treatment. For safety reasons, patients with acute inflammation at the beginning of the study were excluded, since it was improper for those patients to accept eyelid hygiene or IPL treatment immediately. Therefore, the corneal staining in two groups and the conjunctiva staining in

the control group was mild. This is the likely reason why these indexes were not statistically different posttreatment.

What interested us most were the differences in MG morphological change before and after treatment between the two groups. As for the MG macrostructure, the patients in both groups had remarkable MG dropout before treatment (IPL group, 45.72 ± 12.93%; control group 40.28 ± 13.15%). This level of dropout is much higher than that in healthy individuals of a similar age (14.7 ± 5.7%).[15] After treatment, MG dropout decreased by 4–5% in both groups with statistical significances, which is in accordance with the decreasing degree of MG dropout reported in previous studies.[12,13]

When it comes to the microstructure change, differences emerged. Both the IPL and the control groups had significant enlarged MGALDs (IPL group, 101.89 ± 21.44 μm; control group, 98.00 ± 29.01 μm), which were much higher than the cutoff value of 65 μm.[10] Nevertheless, only the IPL group showed improvement in MGALD after 3 months of treatment (Figure 3). MGAUD in IPL group also increased accordingly. Considering the positive relationship between the change of OSDI and the change of MDAUD, it is suggested that IPL treated MGD condition through improving MG microstructure, and we further speculated that the particular improvement in MG microstructure was induced by the photomodulation effect of IPL. Photomodulation was the photobiostimulatory effect originally developed for NASA plant growth experiments 300 in space, and was later discovered efficacy of promoting cell activity like wound healing and photorejuvenation.[16,17] NASA found that the optimal light wavelengths (proven in prior studies of laser and LED light) for photobiostimulation included 680, 730, and 880 nm[16], which are all included in the IPL wavelength spectrum used for treatment. We presumed that the photomodulation stimulates acinar cell activity, thus improving MG microstructure. And this is also the likely reason that one procedure of IPL treatment can last between 6 and 12 months.[2] Furthermore, the positive rate of IC around glandular structures decreased after treatment in only the IPL group. The anti-inflammation effect of IPL has been broadly reported in dermatology studies.[18] Although strong evidence is still lacking, previous ophthalmological studies also considered decreasing inflammation as a possible mechanism of IPL treating MGD.[2,4,7] This study provided primary evidence supporting this hypothesis.

According to the results, IPL not only improved the MG macrostructure, but also improved the MG microstructure, in particular, and decreased the MG inflammation. Consequently, we presumed that photomodualtion and anti-inflammatory effect are two working mechanisms of IPL treating MGD. It is likely that the photothermal effect also plays a role in the mechanism; however, it is beyond the discussion of this study. One limitation of this study is that only primary evidence was provided and the possible mechanisms were only verified on a histological level. Further cytological and molecular studies are required to fully elucidate the mechanisms involved in IPL treating MGD.

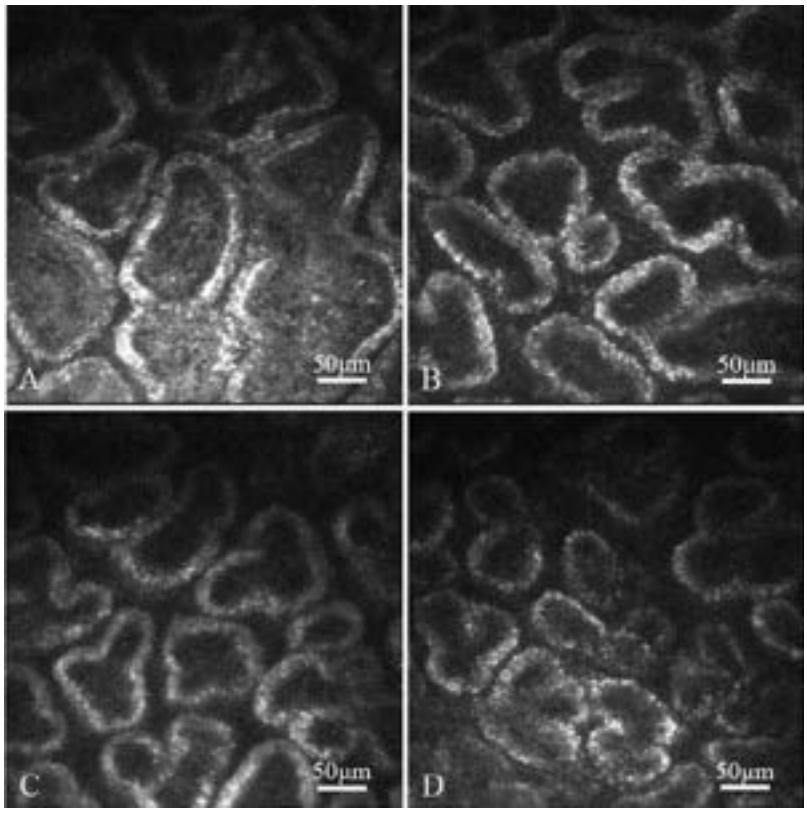

Figure 3. The MG figure under confocal microscopy from a 66-year-old female MGD patient before and after three simple IPL treatments. Enlarged acinar diameter was decreased and AUD was increased after treatment. A, B: before treatment. C, D: after three simple IPL treatments.

In conclusion, IPL treatment improves MG function, MG macrostructure as well as eyelid hygiene, and IPL treatment particularly improves MG microstructure and decreases MG inflammation in MGD patients.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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OPEN

Multicenter Study of Intense Pulsed Light Therapy for Patients With Refractory Meibomian Gland Dysfunction

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Purpose: To evaluate the efficacy of intense pulsed light (IPL) therapy combined with meibomian gland expression (MGX) for refractory meibomian gland dysfunction (MGD) in a prospective study conducted at 3 sites in Japan.

Methods: Patients with refractory obstructive MGD were enrolled and underwent 4 to 8 IPL-MGX treatment sessions at 3-week intervals. Clinical assessment included the Standard Patient Evaluation of Eye Dryness questionnaire; noninvasive breakup time of the tear film and interferometric fringe pattern as determined by tear interferometry; lid margin abnormalities, fluorescein breakup time of the tear film, corneal and conjunctival fluorescein staining (CFS), and meibum grade as evaluated with a slit-lamp microscope; meibomian gland morphology (meiboscore); and tear production as measured by the Schirmer test without anesthesia.

Results: Sixty-two eyes of 31 patients (17 women, 14 men; mean age ± SD, 47.6 ± 16.8 years) were enrolled. The Standard Patient Evaluation of Eye Dryness score ($P < 0.001$), noninvasive breakup time ($P < 0.001$), and interferometric fringe pattern ($P < 0.001$) were significantly improved after therapy, with 74% of eyes showing a change in the interferometric fringe pattern from 1 characteristic of lipid deficiency to the normal condition. Meibum grade, lid margin abnormality scores, fluorescein breakup time, and CFS were also significantly improved ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively) after treatment, whereas the meiboscore and Schirmer test value remained unchanged.

Conclusions: IPL-MGX ameliorated symptoms and improved the condition of the tear film in patients with refractory MGD and is therefore a promising treatment option for this disorder.

Key Words: meibomian gland dysfunction, meibomian gland, intense pulsed light

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Meibomian gland dysfunction (MGD) is a chronic abnormality of meibomian glands characterized by terminal duct obstruction or qualitative or quantitative changes in the glandular secretion of meibum.[1] Individuals with MGD thus manifest an imbalance in components of the tear film because of a deficiency of the lipid layer. The goal of MGD therapy is to provide long-term and stable amelioration of the symptoms of this condition by improving the quality of meibum or increasing meibum flow, thereby normalizing the balance between the lipid layer and the aqueous and mucin layers of the tear film and enhancing tear film stability, as well as by reducing inflammation. Common therapies include application of a warm compress; practice of lid hygiene; dietary supplementation with omega-3 fatty acids; forced meibum expression[2]; intraductal probing[3]; automated thermal pulsation[4]; and administration of topical steroids, topical and oral antibiotics including topical cyclosporine and azithromycin, preservative-free artificial tears, lipid-containing eye drops, and topical diquafosol.[5,6] Despite the variety of treatment options available, however, many patients with MGD are refractory to treatment and thus do not experience complete or long-term relief of symptoms.

Intense pulsed light (IPL) therapy is widely adopted cosmetically and therapeutically for removal of hypertrichosis, benign cavernous hemangiomas or venous malformations, telangiectasia, port wine stains, and other pigmented lesions.[7] A systematic review found that IPL is an effective and well-tolerated treatment option for a range of dermatologic conditions, having been shown to result in reduction in the extent of telangiectasia and the severity of facial erythema.[8] The efficacy of IPL therapy for patients with dry eye due to MGD was discovered serendipitously during IPL treatment of facial rosacea.[9] Subsequent studies found that IPL is effective for improvement of subjective symptoms and objective findings in patients with mild to moderate MGD or dry eye.[10–21] Indeed, the combination of IPL and meibomian gland expression (MGX) was found to ameliorate dry eye symptoms and to improve meibomian gland function in

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patients with refractory dry eye, a cohort that included not only individuals with MGD but also those with graft-versus-host disease or Sjögren syndrome.[13] The efficacy of such combination treatment in patients with moderate to advanced MGD was also recently demonstrated in a single-center study.[21]

The purpose of this study was to evaluate the efficacy of IPL combined with MGX for patients with refractory MGD, including those with the most severe stage of the condition, in 3 centers in Japan. Refractory MGD was defined as that which had failed to respond to at least 3 types of conventional therapy prescribed in Japan including topical or systemic anti-inflammatory therapy, topical or systemic antibiotic therapy, topical lubricant eyedrops or ointment, automated thermal pulsation treatment, and intraductal probing over the course of at least 1 year. Given that most patients with MGD have applied a warm compress or practiced lid hygiene at home regardless of disease severity, these home-care remedies were not included as failed therapies in this study.

PATIENTS AND METHODS

The study was approved by the Institutional Review Boards of Itoh Clinic, Mizoguchi Eye Clinic, and Ohshima Eye Hospital, and it adhered to the tenets of the Declaration of Helsinki. The study was performed at each of the 3 participating centers from March to September 2017. Informed consent to study participation was obtained from each patient.

Patients

Individuals with refractory MGD attending Itoh Clinic, Mizoguchi Eye Clinic, or Ohshima Eye Hospital were enrolled in the study. Inclusion criteria included the following: 1) an age of at least 20 years; 2) a diagnosis of obstructive MGD based on the Japanese diagnostic criteria for MGD,[22] which encompass ocular symptoms, plugged gland orifices, vascularity and irregularity of lid margins, and reduced meibum expression (meibum grade of >1, where grade 0 = clear meibum easily expressed, grade 1 = cloudy meibum expressed with mild pressure, grade 2 = cloudy meibum expressed with more than moderate pressure, and grade 3 = meibum could not be expressed even with strong pressure)[23]; 3) failure of at least 3 types of conventional MGD therapy to improve symptoms or objective findings for at least 1 year before study treatment; and 4) a Fitzpatrick[24] skin type of 1 to 4 based on sun sensitivity and appearance. Exclusion criteria included the presence of active skin lesions, skin cancer, or other specific skin pathology or of active ocular infection or ocular inflammatory disease.

Experimental Design

Each patient underwent a series of 4 to 8 treatment sessions at 3-week intervals depending on the meibum grade[23] (4, 6, or 8 sessions for grades 1, 2, and 3, respectively). Each patient was subjected to clinical assessment, as described below both before treatment at each visit and 4 weeks after the final treatment. All patients were asked to continue their current ocular medications. No patient was allowed to initiate therapy with a new topical or systemic agent for dry eye or MGD during the treatment course.

Clinical Assessment

The noninvasive breakup time (NIBUT) and the interferometric fringe pattern of the tear film were determined with a DR-1α tear interferometer (Kowa, Nagoya, Japan), as described previously.[25] Lid margin abnormalities (plugging of meibomian gland orifices and vascularity of lid margins),[26] breakup time [fluorescein breakup time (FBUT)] of the tear film and the corneal and conjunctival *fluorescein* staining score (CFS, 0–9)[27] based on fluorescein staining, and meibum grade (0–3)[23] were evaluated using a slit-lamp microscope. Morphological changes in the meibomian glands were assessed on the basis of the meiboscore (0–6)[28], as determined by noninvasive meibography. Tear fluid production was measured by the Schirmer test, as performed without anesthesia.[29] Symptoms were assessed with the Standard Patient Evaluation of Eye Dryness (SPEED) validated questionnaire (0–28).[30,31]

IPL-MGX Procedure

Before the first treatment, each patient underwent Fitzpatrick[24] skin typing, and the IPL machine (M22; Lumenis, Yokneam, Israel) was adjusted to the appropriate setting (range, 11–14 J/cm^2). At each treatment session, both eyes of the patient were closed and sealed with IPL-Aid disposable eye shields (Honeywell Safety Products, Smithfield, RI). After generous application of ultrasonic gel to the targeted skin area, each patient received ~13 pulses of light (with slightly overlapping applications) from the right preauricular area, across the cheeks and nose, to the left preauricular area, reaching up to the inferior boundary of the eye shields. This procedure was then repeated in a second pass. Immediately after IPL treatment, MGX was performed on both upper and lower eyelids of each eye with an Arita Meibomian Gland Compressor (Katena, Denville, NJ). Pain was minimized during MGX by application of 0.4% oxybuprocaine hydrochloride to each eye.

Statistical Analysis

Data are presented as mean ± SD as indicated. Parameters were compared between before and after treatment with the paired Student *t* test. After testing for homogeneity of variance, we applied the independent *t* test to compare numerical variables and Fisher exact test to compare categorical variables between patients whose eyes showed a change in the SPEED score from baseline (ΔSPEED) of <5 or ≥5. $P < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the study patients are presented in Table 1. Sixty-two eyes of 31 patients with refractory obstructive MGD, including 17 women and 14 men, were

TABLE 1. Characteristics of 31 Study Patients (62 Eyes)

Characteristic	
Age, mean ± SD (range), yr	47.6 ± 16.8 (21–83)
Sex (male/female)	14 (45%)/17 (55%)
Duration of MGD, mean ± SD (range), yr	7.6 ± 5.8 (2–21)
At least 3 meibomian gland dropouts in 1 eyelid	40 eyes of 20 patients (64.5%)
History of contact lens wear	30 eyes of 15 patients (48.4%)
Coincidence of ADDE	26 eyes of 13 patients (41.9%)
Previous ocular surgery, blepharosurgery, or blepharoplasty	20 eyes of 10 patients (32.3%)

ADDE, aqueous-deficient dry eye.

enrolled in the study. The mean age ± SD was 47.6 ± 16.8 years (range of 21–83 years). The mean duration of MGD ± SD was 7.6 ± 5.8 years (range of 2–21 years). Twenty-six eyes of 13 patients (41.9% of eyes) manifested aqueous-deficient dry eye on the basis of a Schirmer test value of <5 mm. More than half (64.5%) of all eyes had at least 3 dropouts of meibomian glands in 1 eyelid as detected by noninvasive meibography. The average number of IPL-MGX treatments received per patient was 6 (range of 4–8). The frequency of other MGD therapies previously administered is shown in Table 2.

The SPEED score was significantly reduced at 4 weeks after the final IPL-MGX treatment session compared with baseline ($P < 0.001$), with 81% of the treated eyes showing amelioration of ocular symptoms (Table 3, Fig. 1). The NIBUT and FBUT were significantly prolonged ($P < 0.001$ for both) at 4 weeks after the final treatment (Table 3), with 70% of treated eyes showing an improvement in the FBUT (Fig. 2) and 84% an improvement in the NIBUT (Fig. 3A). Tear interferometric fringe grading[25] was also significantly improved ($P < 0.001$) at 4 weeks after the final treatment (Fig. 3B), with 74% of treated eyes showing a change in the interferometric fringe pattern from 1 typical of lipid deficiency (crystal-like) to the normal condition (pearl-like). Furthermore, meibum grade, lid margin abnormality scores, and CFS were significantly decreased ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively) at 4 weeks after the final treatment (Table 3). By contrast, the meiboscore and Schirmer test value were not significantly improved after treatment ($P = 0.06$ and $P = 0.29$, respectively) (Table 3).

TABLE 2. Previous Therapies Adopted by 31 Study Patients Without Symptom Improvement

Therapy	No. of Patients	Percentage of Patients
Warm compress	30	97
Topical steroids	20	65
Diquafosol eye drops	18	58
Rebamipide eye drops	15	48
Lid hygiene	13	42
Preservative-free artificial tears	13	42
Omega-3 fatty acid supplementation	10	32
Topical antibiotics	7	23
Hyaluronic acid	7	23
Minocycline or clarithromycin	5	16
Automated thermal pulsation	4	13
Intraductal probing	3	10

TABLE 3. Comparison of Ocular Assessment Between Before Treatment (Baseline) and 4 Weeks After the Final of a Series of IPL-MGX Treatment Sessions

Characteristic	Potential Range	Mean ± SD		*P*
		Baseline	After Treatment	
SPEED score	0–28	13.8 ± 4.5	6.7 ± 5.1	<0.001
NIBUT, s		3.3 ± 2.4	7.8 ± 4.3	<0.001
Lid margin abnormalities				
Plugging	0–3	1.8 ± 1.1	0.5 ± 0.7	<0.001
Vascularity	0–3	1.5 ± 0.8	0.4 ± 0.6	<0.001
CFS	0–9	0.9 ± 1.4	0.4 ± 0.8	0.002
FBUT, s		3.7 ± 2.9	5.8 ± 2.8	<0.001
Schirmer test value, mm		8.6 ± 7.5	11.5 ± 10.8	0.29
Meiboscore	0–6	4.1 ± 1.6	4.0 ± 1.5	0.06
Meibum grade	0–3	2.3 ± 0.9	1.1 ± 1.1	<0.001

P values were determined with the paired Student *t* test.

The characteristics of patients who showed a change in the SPEED score for each eye from baseline to 4 weeks after the final treatment (ΔSPEED) of <5 or ≥5 are presented in Table 4. Age did not differ significantly between the 2 groups ($P = 0.40$). The duration of MGD was significantly longer for the patients with a ΔSPEED of ≥5 than for those with a ΔSPEED of <5 ($P = 0.041$). Eyes with a ΔSPEED of ≥5 underwent significantly more IPL-MGX treatment sessions

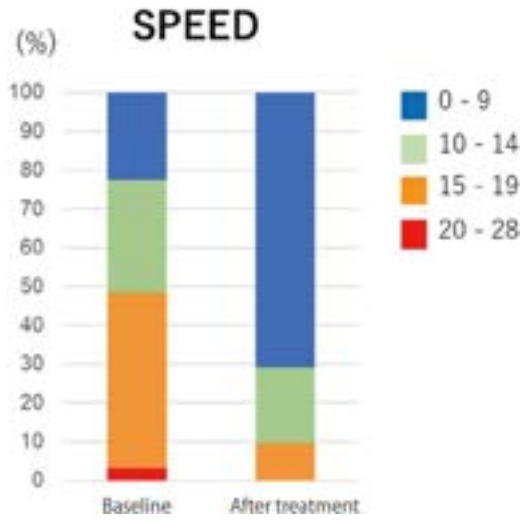

FIGURE 1. Change in the SPEED questionnaire score between baseline and 4 weeks after the final IPL-MGX treatment session.

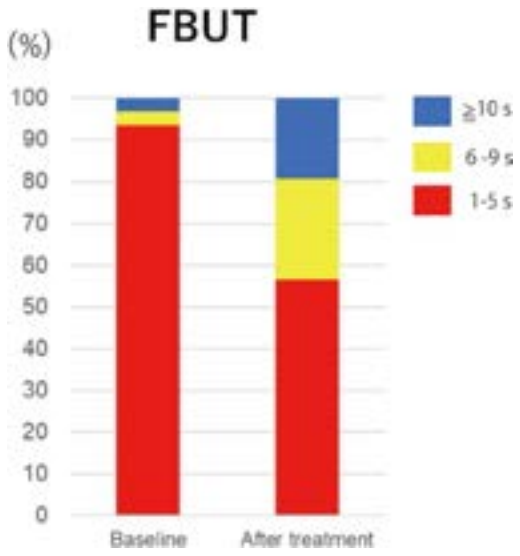

FIGURE 2. Change in the FBUT between baseline and 4 weeks after the final IPL-MGX treatment session.

than did those with a ΔSPEED of <5 ($P < 0.001$). There were no significant differences in sex distribution or the frequencies of at least 3 meibomian gland dropouts in 1 eyelid, history of contact lens wear, coincidence of aqueous-deficient dry eye, or previous ocular surgery between the 2 groups of patients (P = 1.0, 0.45, 1.0, 0.066, and 1.0, respectively).

DISCUSSION

This is the first prospective and multicenter study to show improvement in the subjective symptoms and objective signs of refractory severe MGD after a series of IPL treatments combined with MGX. Tear film stability, lipid layer dynamics, and meibomian gland function all responded positively to treatment, resulting in improvement in the condition of the tear film in the study patients. This study enrolled patients with refractory severe MGD at 3 centers and did not exclude those with a history of contact lens wear, ocular surgery, or any type of MGD management.

We found that IPL-MGX therapy was effective for management of refractory MGD, being associated with improvement in both lipid layer dynamics (tear interferometric fringe pattern) and NIBUT as determined with the DR-1α tear interferometer. IPL was also shown previously to improve the lipid layer grade as determined with the Tearscope Plus interferometer (Keeler, Windsor, United Kingdom) in patients with MGD.[10] This latter study enrolled patients with mild to moderate MGD but not those with refractory MGD, with 82% of the treated eyes showing improvement in the lipid layer grade.[10] In this study, after a course of 4 to 8 IPL-MGX treatments, 74% of eyes with refractory MGD showed a change in the tear interferometric fringe pattern from 1 characteristic of lipid deficiency to the normal condition, indicating that the balance between the lipid and aqueous layers of the tear film had improved. The NIBUT is characteristically reduced in patients with MGD.[32] The previous study of the lipid layer grade also demonstrated a significant improvement in the NIBUT from 5.28 to 14.11 seconds after treatment of the patients with MGD with IPL.[10] In this study, the NIBUT was increased from 3.3 to 7.8 seconds, representing a meaningful clinical improvement, with our previous study having shown that the cutoff value of the NIBUT for dry eye disease as measured by DR-1α is <5 seconds.[25]

Improvement of meibum quality and expressibility is a key factor in treatment of MGD. We found that meibum quality and expressibility were significantly better after IPL-MGX treatment in this study. Similar results were obtained in previous studies.[9,12–15,17,20] IPL application increases skin temperature.[10] Whereas the phase-transition temperature of meibum is 28°C in controls, it is >32°C in patients with MGD.[33] Although eyelid warming at home has been found to be transiently effective for treatment of MGD,[2] the temperature of the eyelid skin was found to increase to 34°C during the application of a warming device but then to decrease rapidly over 10 minutes after device removal.[34] Such eyelid warming at home is thus not sufficient to support long-term melting of meibum.[34] However, IPL has been found to

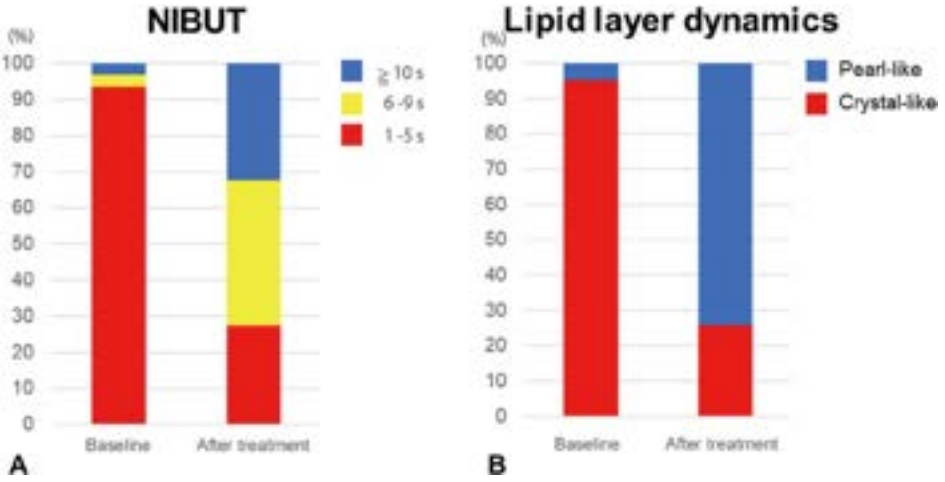

FIGURE 3. Changes in the NIBUT (A) and dynamics of the lipid layer of the tear film, as revealed by a tear interferometric fringe pattern (B) between baseline and 4 weeks after the final IPL-MGX treatment session.

TABLE 4. Characteristics of Patients Who Showed a Change in the SPEED Score of <5 or ≥5 Between Before Treatment (Baseline) and 4 Weeks After the Final of a Series of IPL-MGX Treatment Sessions

Characteristic	Change in the SPEED Score		*P*
	<5 (n = 11)	≥5 (n = 20)	
Age, mean ± SD, yr	44.1 ± 18.5	49.5 ± 16.1	0.40
Sex (male/female)	5 (45.5%)/6 (54.5%)	9 (45.0%)/11 (55.0%)	1.0
Duration of MGD, mean ± SD, yr	5.0 ± 5.3	9.6 ± 5.8	0.041*
At least 3 meibomian gland dropouts in 1 eyelid	6 (54.5%)	14 (70.0%)	0.45
History of contact lens wear	5 (45.5%)	10 (50.0%)	1.0
Coincidence of ADDE	2 (18.2%)	11 (55.0%)	0.066
Previous ocular surgery, blepharosurgery, or blepharoplasty	3 (27.3%)	7 (35.0%)	1.0
Number of IPL-MGX treatments per eye, mean ± SD	4.0 ± 0.0	7.9 ± 0.4	<0.001*

P values were determined with Fisher exact test for categorical variables, and the independent *t* test for continuous variables.

*$P < 0.05$.

ADDE, aqueous-deficient dry eye.

increase the temperature of small vessels (diameter of < 60 μm) in the targeted skin area to between 45 degrees and 70° C,[35] which is likely sufficient to increase the temperature of eyelid skin and the tarsal conjunctiva adjacent to the meibomian glands and thereby to melt meibum.[16]

Two types of lid margin abnormality—plugging of meibomian gland orifices and vascularity of the lid margin—were evaluated in this study and were found to be significantly improved after IPL-MGX treatment, consistent with the results of previous studies.[9,14] IPL therapy is believed to be effective for MGD in part through its heating of the eyelid and consequent melting of meibum.[16] Plugging of meibomian gland orifices would therefore be expected to be ameliorated by such treatment. In addition, hemoglobin absorbs light at a wavelength of 580 nm,[36] with such absorption during IPL therapy resulting in coagulation of blood in abnormal vessels of telangiectasia and eventually in closure of the vessels and reduced vascularization.[9] Such attenuation of abnormal vascularity in patients with MGD seems to reduce both secretion of inflammatory mediators and bacterial growth.[9,21]

Self-reported ocular symptoms covered by the SPEED questionnaire were significantly ameliorated after IPL-MGX treatment in this study, similar to the results of previous studies.[10,13,15,17,18] Twenty-five (81%) and 20 (65%) of the 31 patients in this study thus showed a decrease in the SPPED score of at least 3 or 5 points, respectively. The CFS was also significantly reduced after the treatment sessions, again consistent with previous data.[10,14,15,17,20] The patients enrolled in this study had MGD for 7.6 ± 5.8 years, and conventional therapies had not been effective. Indeed, >60% of enrolled eyes showed at least 3 meibomian gland dropouts in 1 eyelid, indicative of the disease severity. Such severe disease was too difficult to manage even with a combination of several conventional therapies. However, a series of IPL-MGX therapy sessions were able to improve subjective symptoms and objective findings including meibum quality and quantity, lid margin abnormalities, and stability and homeostasis of the tear film.

The potential mechanisms for ameliorating subjective symptoms and objective findings of MGD are considered, as mentioned above, to promote melting of meibum,[9,16] to attenuate local release of inflammatory factors from the abnormal vessels,[18,37,38] and to reduce bacterial load of the eyelid margin.[39]

There are several limitations to our study. First, the study design was single arm and was based on both eyes of a small number of patients. Further studies with a larger number of patients and a control group are necessary. Second, the duration of follow-up was limited to 4 weeks after the final treatment. Longer follow-up periods will be necessary to assess the long-term effectiveness and safety of IPL treatment. Third, all the patients at each site continued their current medications during the study. A more controlled experimental design will be preferable for future studies. Fourth, IPL treatment is not covered by national insurance in Japan. Although the enrolled patients did not pay for IPL treatment in this study, this situation might introduce inherent bias.

In conclusion, our results suggest that IPL-MGX therapy is effective for patients with refractory MGD whose severe disease is difficult to manage with other conventional therapies. IPL-MGX thus has the potential to help many patients with MGD and is a promising modality for refractory MGD in particular.

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Original Research

Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction

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ABSTRACT

Purpose: To evaluate the efficacy and safety of intense pulsed light (IPL) combined with meibomian gland expression (MGX) for treatment of refractory meibomian gland dysfunction (MGD).

Methods: Ninety eyes of 45 patients were randomly assigned to receive either the combination of IPL and MGX or MGX alone (control). Each eye underwent eight treatment sessions at 3-week intervals. Parameters were evaluated before and during treatment as well as at 3–11 weeks after the last treatment session. Measured parameters included the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score, noninvasive breakup time (NIBUT), fluorescein breakup time (BUT), lipid layer grade, lipid layer thickness (LLT), lid margin abnormalities, corneal and conjunctival fluorescein staining (CFS) score, meibum grade, and meiboscore.

Results: A significant improvement in lipid layer grade was apparent in the IPL-MGX group from 6 to 32 weeks after treatment onset (adjusted $P < 0.001$) but was not observed in the control group. The IPL-MGX group also showed significant improvements in LLT, NIBUT, BUT, lid margin abnormalities, and meibum grade compared with the control group at 24 and 32 weeks (adjusted $P < 0.001$) as well as significant improvements in the SPEED score at 32 weeks (adjusted $P = 0.044$) and in CFS score at 24 (adjusted $P = 0.015$) and 32 (adjusted $P = 0.006$) weeks.

Conclusions: The combination of IPL and MGX improved homeostasis of the tear film and ameliorated ocular symptoms in patients with refractory MGD and is thus a promising modality for treatment of this condition.

1. Introduction

Dry eye disease is defined as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms that result in part from tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities [1]. Intense pulsed light (IPL) therapy has been shown to ameliorate ocular symptoms, tear film instability, and ocular surface inflammation and damage in dry eye associated with meibomian gland dysfunction (MGD) [2–14]. We previously showed that the Kowa DR-1α tear interferometer is able to evaluate the balance between the lipid and aqueous layers of the tear film [15]. These two components compensate for each other to maintain homeostasis of the tear film [15,16], but the effect of IPL treatment on the balance between them has been unknown.

MGD is a chronic abnormality of meibomian glands characterized by terminal duct obstruction or qualitative or quantitative changes in glandular secretion [17]. It gives rise to an imbalance in the tear film due to a deficiency of the lipid layer. MGD is the leading cause of evaporative dry eye [17], and it accounts for most cases of dry eye overall [18]. The goal of MGD therapy is to provide a long-term amelioration of symptoms by improving the quality of meibum or increasing meibum flow—and thereby normalizing the balance between the lipid and aqueous layers of the tear film and restoring tear film stability—as well as by reducing inflammation. Common therapies include the application of a warm compress, the practice of lid hygiene, dietary supplementation with omega-3 fatty acids, forced meibum expression [17], intraductal probing [19], automated thermal pulsation [20], and the administration of preservative-free eyedrops, lipid-containing eyedrops, diquafosol eyedrops [21], topical cyclosporine or

Abbreviations/acronyms: IPL, intense pulsed light; MGD, meibomian gland dysfunction; MGX, meibomian gland expression; LLT, lipid layer thickness; NIBUT, noninvasive breakup time; BUT, breakup time; CFS, corneal and conjunctival fluorescein staining; SPEED, Standard Patient Evaluation of Eye Dryness

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azithromycin, and oral doxycycline. Despite the variety of treatment options available, however, patients often do not experience complete or long-term relief of symptoms.

IPL therapy is widely adopted in the cosmetic industry as well as therapeutically for the removal of hypertrichosis, benign cavernous hemangiomas or venous malformations, telangiectasia, port wine stains, and pigmented lesions [22]. A systematic review showed that IPL is an effective and well-tolerated treatment option for a range of dermatologic conditions including telangiectasia and facial erythema [23]. An improvement in ocular surface health was observed serendipitously in individuals undergoing IPL for the dermatologic manifestations of rosacea, leading to interest in IPL as a potential therapy for MGD [24]. IPL alone was thus found to improve subjective symptoms and objective findings [2,6], whereas the combination of IPL and meibomian gland expression (MGX) improved dry eye symptoms and gland function [4,5,7,14], in patients with MGD.

We previously showed that the combination of IPL and MGX ameliorated symptoms and improved the condition of the tear film in a single-arm study with patients with refractory MGD [25]. To evaluate further the efficacy and safety of combined therapy with IPL and MGX in patients with refractory MGD, we have now performed a prospective, controlled study to examine the comprehensive effects of this approach in comparison with MGX alone.

2. Methods

The study was approved by the Institutional Review Board of Itoh Clinic, adhered to the tenets of the Declaration of Helsinki, and was performed at Itoh Clinic from May 2016 to August 2017. Written informed consent was obtained from each patient before enrollment in the study (UMIN000022747).

2.1. Subjects

Patients with refractory MGD attending Itoh Clinic were enrolled. Inclusion criteria were as follows [1]: age of at least 20 years [2]; diagnosis of MGD according to Japanese MGD diagnostic criteria [26] including ocular symptoms, plugged gland orifices, vascularity of lid margins, irregularity of lid margins, and decreased meibum quality and quantity (Shimazaki grading) [3,27] Fitzpatrick skin type of 1–4 according to sun sensitivity and appearance of the skin [28], as well as the absence of active lesions, skin cancer, or specific skin pathology that would exclude treatment with IPL; and [4] refractory MGD as defined by the failure to respond over a period of at least 2 years to at least three types of conventional therapy prescribed in Japan, including topical or systemic anti-inflammatory therapy, topical or systemic antibiotic therapy, lubricant eyedrops or topical ointment, automated thermal pulsation, and intraductal probing. Given that most patients with MGD have applied a warm compress or practiced lid hygiene at home regardless of disease severity, these home-care remedies were not included as failed therapies in the present study.

2.2. Experimental design

Refractory MGD patients were randomly assigned to receive either IPL with MGX (IPL-MGX) or MGX alone as a control. Each patient underwent a series of eight treatment sessions at 3-week intervals. After the eight treatment sessions, each patient underwent three follow-up examinations over the course of 11 weeks (Fig. 1). All patients used a warming compress once a day and diquafosol eyedrops (Diquas; Santen, Osaka, Japan) six times a day during the study including the follow-up period. Clinical assessment was performed as described below.

2.3. Clinical assessment

The safety of IPL-MGX treatment was evaluated by measurement of visual acuity, lens opacity, and intraocular pressure as well as by fundus examination before and 32 weeks after the first treatment session. For evaluation of treatment efficacy, the following parameters were measured before each treatment and at each follow-up visit: lipid layer thickness (LLT) of the tear film as determined with a LipiView instrument (TearScience, Morrisville, NC) [29], noninvasive breakup time (NIBUT) of the tear film and tear interferometric fringe pattern as determined with the DR-1α tear interferometer (Kowa, Aichi, Japan) [15], lid margin abnormalities [30] as observed with a slitlamp microscope, breakup time (BUT) of the tear film as determined by fluorescein staining as well as the corneal and conjunctival staining (CFS) score [31], meibum grade(27) as determined by slitlamp microscopy, morphological changes of meibomian glands as assessed by noninvasive meibography (meiboscore) [32], and tear production as measured by the Schirmer test performed without anesthetic [33]. Symptoms were also assessed with the Standard Patient Evaluation of Eye Dryness (SPEED) [34] validated questionnaire.

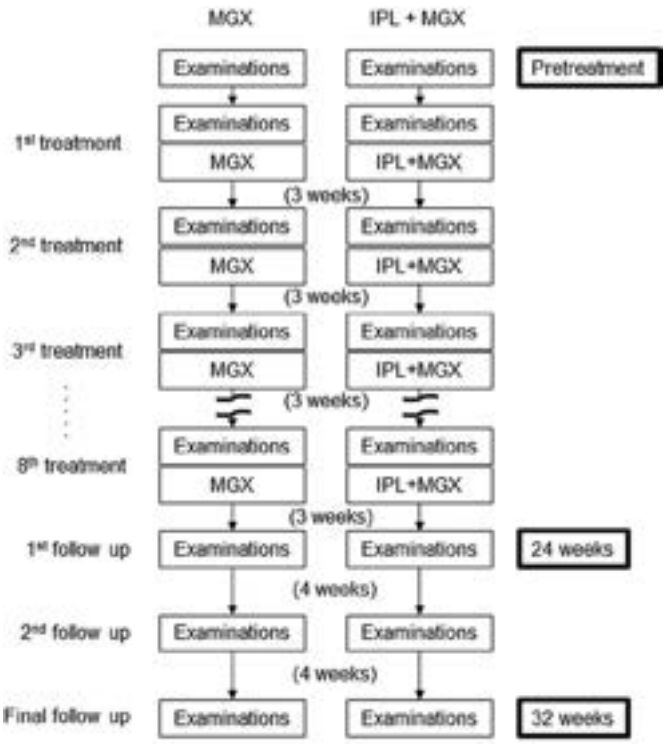

Fig. 1. Treatment and follow-up protocol for the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Each patient underwent a series of eight treatment sessions at 3-week intervals and was subjected to clinical assessment before treatment at each visit as well as 3, 7, and 11 weeks after the final treatment.

2.4. Combined treatment with IPL and MGX

Before the first IPL treatment, each patient underwent Fitzpatrick skin typing [28], and the IPL machine (M22; Lumenis, Yokneam, Israel) was adjusted to the appropriate setting (range of 11–14 J/cm^2). At each treatment session, both eyelids were closed and sealed with IPL-Aid disposable eye shields (Honeywell Safety Products, Smithfield, RI). After generous application of ultrasonic gel to the treatment area, patients received ~13 light pulses (with slightly overlapping areas of application) from the left preauricular area, across the cheeks and nose, to the right preauricular area, with the treated area reaching up to the inferior boundary of the eye shields. The procedure was then repeated in a second pass. Immediately after the IPL treatment, MGX was performed on both upper and lower eyelids of each eye with an Arita Meibomian Gland Compressor (Katena, Denville, NJ). Pain was

minimized during this procedure by topical application of 0.4% oxybuprocaine hydrochloride.

2.5. Control (MGX only) treatment

MGX was performed on both upper and lower eyelids of each eye with an Arita Meibomian Gland Compressor (Katena) every 3 weeks. Eyedrops containing 0.4% oxybuprocaine hydrochloride were administered to minimize pain.

2.6. Statistical analysis

Sample size was calculated on the basis of assumed mean differences in LLT of 27.4 and 29.6 nm between the IPL-MGX group and the control group at 24 and 32 weeks after treatment onset, respectively, with corresponding SD values of 17.9 and 17.2 nm; in NIBUT of 3.9 and 4.8 s between the IPL-MGX and control groups at 24 and 32 weeks after treatment onset, respectively, with corresponding SD values of 0.7 and 0.9 s; and in meibum grade of 1.1 and 1.4 between the two groups at 24 and 32 weeks after treatment onset, respectively, with corresponding SD values of 0.6 and 0.7. These assumed differences were based on the findings of a pilot study with 20 eyes of 10 patients in each group. With these assumptions, a sample size of 24 eyes per group would yield a power of > 90% to show a significant difference with a two-sample *t*-test. We chose an α level of 0.025 to ensure an overall type I error rate of 0.05 according to the Bonferroni procedure. After testing for homogeneity of variance, we used the paired Student's *t*-test to compare variables between before and either 24 or 32 weeks after treatment onset as well as the unpaired *t*-test to compare pretreatment or post-treatment variables between the control and IPL-MGX groups. Comparison of NIBUT, BUT, SPEED score, plugging, and vascularity between before and various times after the onset of treatment was performed with the paired *t*-test, whereas that of tear interferometric fringe pattern between before and after treatment was performed with Fisher's exact test. Bonferroni's correction was applied to correct for multiple comparisons. Adjusted *P* values were obtained by multiplying *P* values by the number of comparisons in the Bonferroni's correction. Statistical analysis was performed with JMP Pro version 11 software (SAS, Cary, NC). All statistical tests were two sided, and a *P* value of < 0.05 was considered statistically significant.

3. Results

Patient demographics are shown in Table 1. Ninety eyes of 45 patients were enrolled in the study. Three patients in the MGX (control) group subsequently withdrew from the study because of pain during the procedure, leaving a total of 20 patients in the MGX group and 22 patients in the IPL-MGX group.

3.1. Safety of IPL-MGX

Visual acuity, intraocular pressure, lens opacity, and fundus condition showed no change between before and 32 weeks after treatment onset in either treatment group (data not shown).

3.2. Efficacy of IPL-MGX

The characteristics of the eyes in the IPL-MGX group and the control group before as well as 24 and 32 weeks after treatment onset are shown in Table 2. No significant differences in parameters were detected between the two groups before treatment. The SPEED score was significantly reduced at both 24 and 32 weeks after treatment onset in both groups. Whereas the SPEED score did not differ significantly between the two groups at 24 weeks, it was significantly smaller in the IPL-MGX group than in the control group at 32 weeks. Significant increases in NIBUT and BUT as well as significant decreases in plugging and meibum grade were also apparent at both time points after treatment initiation in both groups. However, the eyes in the IPL-MGX group showed a significantly better improvement in NIBUT, BUT, plugging, and meibum grade compared with those in the control group. A significant increase in LLT as well as significant decreases in vascularity and CFS score were detected at both time points after treatment only in the IPL-MGX group. Irregularity, meiboscore, and Schirmer test value at 24 and 32 weeks after treatment onset did not differ significantly between the control and IPL-MGX groups. An improvement in SPEED score, NIBUT, BUT, plugging, meibum grade, LLT, vascularity, and CFS score was thus still apparent at 11 weeks after the final treatment session in the IPL-MGX group, with such an improvement in LLT, vascularity, and CFS score not being observed in the control group.

The time courses of the SPEED score, NIBUT, BUT, plugging, and vascularity before, during, and after treatment in the two groups are shown in Figs. 2–6, respectively. Although the SPEED score, NIBUT, and BUT were significantly improved in the control group during and after treatment compared with before treatment, these parameters did not achieve the cutoff values for diagnosis of dry eye. The SPEED score in the IPL-MGX group was decreased significantly from 3 to 32 weeks after treatment onset compared with before treatment, whereas that in the control group was significantly reduced from 15 to 32 weeks (Fig. 2). Significant increases in NIBUT (Fig. 3) and BUT (Fig. 4) were apparent during and after treatment in both groups. The IPL-MGX group also showed a significant decrease in plugging (Fig. 5) and vascularity (Fig. 6) from 3 to 32 weeks after treatment onset, whereas a significant decrease in plugging was not apparent until 6 weeks in the control group.

Finally, the time course of lipid layer grade(15) in the two treatment groups is shown in Fig. 7. The tear interferometric fringe pattern in the control group maintained its crystal-like appearance, indicative of a thin lipid layer, both during and after treatment. A significant improvement in lipid layer dynamics, with a shift in interferometric pattern from crystal-like to pearl-like appearance, indicative of the normal tear film condition, was apparent from 6 to 32 weeks after treatment onset in the IPL-MGX group.

4. Discussion

This is the first prospective and randomized study to show that a

Table 1
Characteristics of the study subjects in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups.

Characteristic	IPL-MGX group (n = 22)	Control (MGX) group (n = 20)
Age (years), mean ± SD (range)	61.0 ± 18.0 (23–81)	61.9 ± 12.2 (39–78)
Sex (male/female)	9 (41%)/13 (59%)	8 (40%)/12 (60%)
Duration of MGD (years), mean ± SD (range)	9.6 ± 5.9 [2–21]	8.7 ± 4.5 [2–15]
At least three meibomian gland dropouts in one eyelid	17 (77.3%)	15 (75%)
History of contact lens wear	12 (54.5%)	12 (60.0%)
Coincidence of ADDE	12 (54.5%)	8 (40%)
Previous ocular surgery, blepharosurgery, or blepharoplasty	6 (27.3%)	8 (40%)

MGD, meibomian gland dysfunction; ADDE, aqueous-deficient dry eye.

Table 2
Characteristics of intense pulsed light (IPL)-meibomian gland expression (MGX) and MGX (control) groups before as well as 24 and 32 weeks after treatment onset.

Characteristic	Group	Pretreatment		24 weeks after treatment onset				32 weeks after treatment onset			
		Mean ± SD	Adjusted P value for IPL-MGX vs. control	Mean ± SD	Mean change ± SE	Adjusted P value vs. Pretreatment	Adjusted P value for IPL-MGX vs. control	Mean ± SD	Mean change ± SE	Adjusted P value vs. Pretreatment	Adjusted P value for IPL-MGX vs. control
SPEED score (0–28)	IPL-MGX	14.7 ± 3.4	0.39	5.9 ± 6.0	−8.3 ± 0.9	< 0.001**	0.24	5.5 ± 5.4	−9.2 ± 0.9	< 0.001**	0.044*
	Control	12.7 ± 4.8		9.1 ± 3.8	−3.7 ± 0.6	< 0.001**		9.2 ± 3.9	−3.6 ± 0.6	< 0.001**	
LLT (nm)	IPL-MGX	46.0 ± 10.0	1.00	67.3 ± 17.7	21.3 ± 2.6	< 0.001**	< 0.001**	66.1 ± 18.0	20.1 ± 2.7	< 0.001**	< 0.001**
	Control	48.8 ± 17.3		50.5 ± 16.9	1.8 ± 1.9	0.7		49.5 ± 16.4	0.8 ± 1.7	1.00	
Plugging (0–3)	IPL-MGX	1.9 ± 0.8	0.57	0.2 ± 0.4	−1.7 ± 0.1	< 0.001**	< 0.001**	0.1 ± 0.3	−1.8 ± 0.1	< 0.001**	< 0.001**
	Control	2.2 ± 0.8		1.7 ± 0.7	−0.5 ± 0.1	< 0.001**		1.7 ± 0.7	−0.5 ± 0.1	< 0.001**	
Vascularity (0–3)	IPL-MGX	1.5 ± 0.8	1.00	0.2 ± 0.4	−1.3 ± 0.1	< 0.001**	< 0.001**	0.2 ± 0.4	−1.3 ± 0.1	< 0.001**	< 0.001**
	Control	1.4 ± 0.9		1.4 ± 0.9	0.0 ± 0.0			1.4 ± 0.9	0.0 ± 0.0		
Irregularity (0–2)	IPL-MGX	0.9 ± 0.9	1.00	0.8 ± 0.8	−0.1 ± 0.0	0.17	0.84	0.8 ± 0.8	−0.1 ± 0.1	0.047*	0.5
	Control	1.1 ± 0.8		1.0 ± 0.8	0.0 ± 0.0	0.65		1.0 ± 0.8	0.0 ± 0.0	0.65	
Meiboscore (0–6)	IPL-MGX	4.5 ± 1.3	0.82	4.2 ± 1.2	−0.3 ± 0.1	0.003*	1	4.2 ± 1.2	−0.3 ± 0.1	< 0.001**	1
	Control	4.2 ± 1.1		4.2 ± 1.1	0.0 ± 0.0	0.65		4.2 ± 1.1	0.0 ± 0.0	0.65	
Meibum grade (0–3)	IPL-MGX	2.2 ± 0.8	0.83	0.3 ± 0.6	−1.9 ± 0.1	< 0.001**	< 0.001**	0.3 ± 0.6	−1.8 ± 0.1	< 0.001**	< 0.001**
	Control	2.0 ± 0.5		1.4 ± 0.7	−0.6 ± 0.1	< 0.001**		1.8 ± 0.7	−0.3 ± 0.1	0.002*	
NIBUT (s)	IPL-MGX	2.5 ± 1.2	1.00	6.6 ± 2.4	4.1 ± 0.3	< 0.001**	< 0.001**	7.0 ± 2.7	4.5 ± 0.4	< 0.001**	< 0.001**
	Control	2.4 ± 1.2		3.3 ± 0.7	0.9 ± 0.2	< 0.001**		3.0 ± 0.9	0.6 ± 0.2	< 0.001**	
BUT (s)	IPL-MGX	2.9 ± 0.9	1.00	6.2 ± 2.4	3.3 ± 0.4	< 0.001**	< 0.001**	6.6 ± 2.4	3.7 ± 0.4	< 0.001**	< 0.001**
	Control	2.8 ± 1.1		3.7 ± 0.9	0.9 ± 0.2	< 0.001**		3.1 ± 1.0	0.4 ± 0.1	0.005*	
CFS score (0–9)	IPL-MGX	1.1 ± 1.4	0.68	0.2 ± 0.4	−1.0 ± 0.2	< 0.001**	0.015*	0.1 ± 0.3	−1.0 ± 0.2	< 0.001**	0.006*
	Control	0.8 ± 1.1		0.8 ± 1.2	0.0 ± 0.1	1		0.8 ± 1.2	0.0 ± 0.1	1.0	
Schirmer value (mm)	IPL-MGX	8.5 ± 7.7	1.00	8.8 ± 7.0	0.3 ± 0.8	1	0.69	8.4 ± 5.9	−0.1 ± 0.6	1.00	0.5
	Control	9.6 ± 9.5		11.0 ± 9.2	1.4 ± 0.5	0.003*		10.9 ± 9.5	1.3 ± 0.5	0.026*	

SPEED, Standard Patent Evaluation of Eye Dryness; LLT, lipid layer thickness; NIBUT, noninvasive breakup time; BUT, breakup time; CFS, corneal-conjunctival staining.

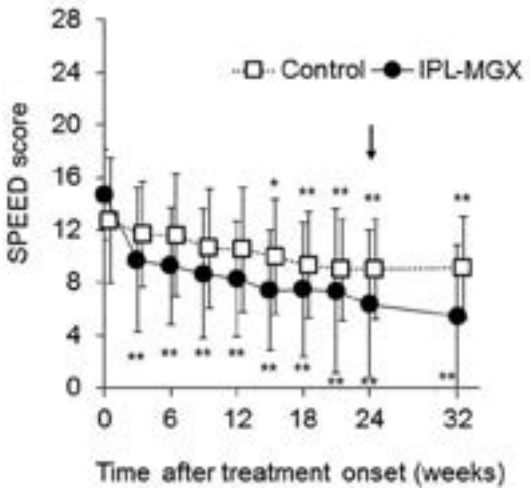

Fig. 2. Time course of the Standard Patient Evaluation of Eye Dryness (SPEED) score before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data are means ± SD (n = 22 and 20, respectively). *Adjusted $P < 0.05$, **adjusted $P < 0.001$ versus corresponding pretreatment (time 0) value (paired *t*-test with Bonferroni's correction for nine comparisons). Arrow indicates first examination of the follow-up period.

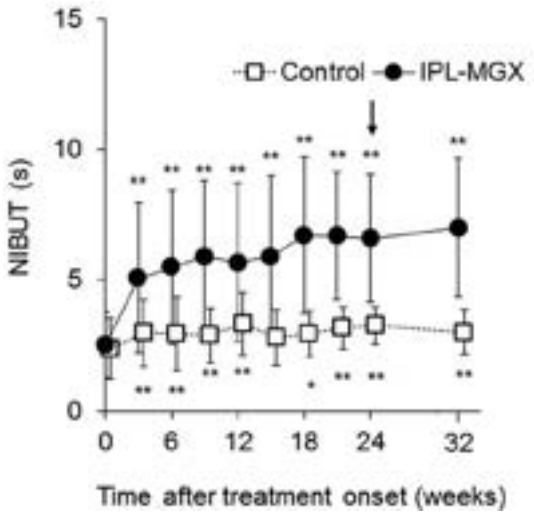

Fig. 3. Time course of tear film noninvasive breakup time (NIBUT) before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data are means ± SD (n = 44 and 40, respectively). *Adjusted $P < 0.05$, **adjusted $P < 0.001$ versus corresponding pretreatment (time 0) value (paired *t*-test with Bonferroni's correction for nine comparisons). Arrow indicates first examination of the follow-up period.

series of IPL-MGX treatment sessions significantly improved subjective symptoms and objective signs compared with MGX alone in patients with refractory MGD. We evaluated a total of 12 parameters including those related to meibomian glands and the lipid layer of the tear film both before treatment as well as at each of the eight treatment sessions and for up to 11 weeks after the final treatment. Our Results thus indicate that IPL-MGX is a promising therapeutic approach for patients with refractory MGD.

Both IPL-MGX and MGX alone resulted in a significant improvement in various measured parameters compared with pretreatment values. IPL-MGX thus significantly improved the SPEED score and CFS score, tear film–related parameters such as NIBUT, LLT, and BUT, eyelid conditions such as vascularity and plugging, as well as both the

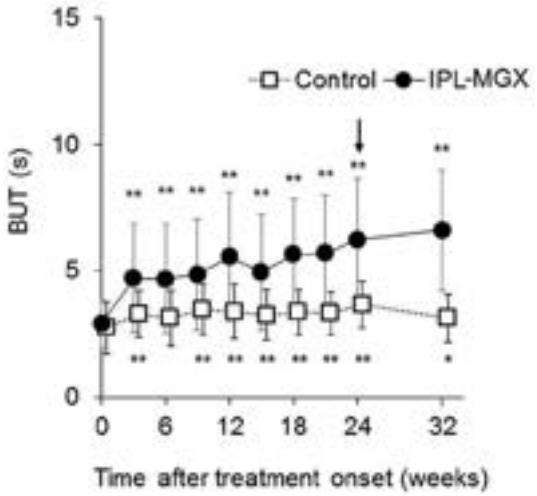

Fig. 4. Time course of tear film breakup time (BUT) measured by fluorescein staining before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data are means ± SD (n = 44 and 40, respectively). *Adjusted $P < 0.05$, **adjusted $P < 0.001$ versus corresponding pretreatment (time 0) value (paired *t*-test with Bonferroni's correction for nine comparisons). Arrow indicates first examination of the follow-up period.

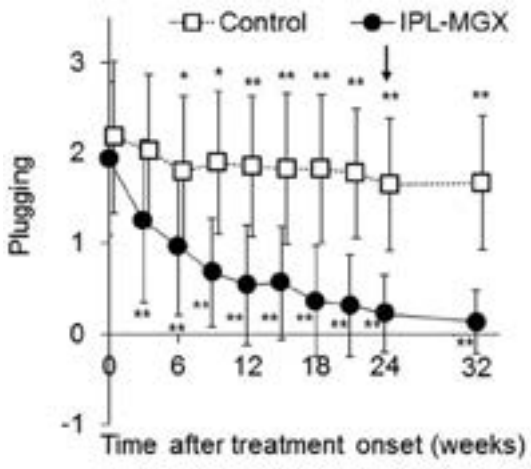

Fig. 5. Time course of plugging before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data are means ± SD (n = 44 and 40, respectively). *Adjusted $P < 0.05$, **adjusted $P < 0.001$ versus corresponding pretreatment (time 0) value (paired *t*-test with Bonferroni's correction for nine comparisons). Arrow indicates first examination of the follow-up period.

meiboscore and meibum grade at 24 weeks after treatment initiation (3 weeks after the final treatment session). These effects remained apparent at 32 weeks after the onset of treatment (11 weeks after the final treatment session). Although MGX alone also improved several tear film and eyelid parameters at both 24 and 32 weeks after treatment onset, the effects of IPL-MGX treatment on NIBUT, LLT, plugging, vascularity, BUT, CFS score, and meibum grade at both 24 and 32 weeks were significantly greater than those of MGX alone. The SPEED score was also reduced to a significantly greater extent at 32 weeks by IPL-MGX compared with MGX alone. Furthermore, LLT, vascularity, CFS score, and the meiboscore were improved significantly only in the IPL-MGX group. Irregularity, which is thought to be the irreversible result of traction after meibomian gland dropout, was ameliorated in the IPL-MGX group at 32 weeks, whereas the Schirmer test value, which reflects tear fluid production, was increased in the control group at both 24 and

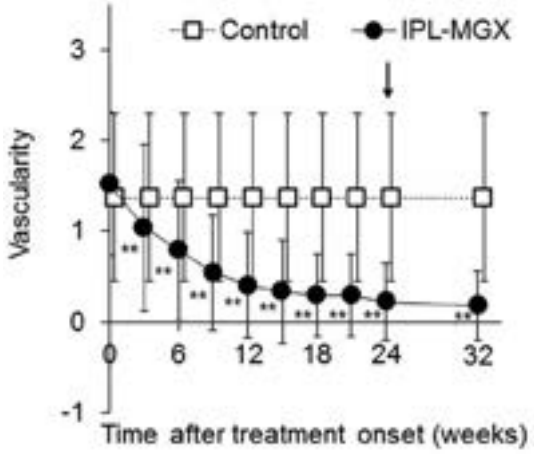

Fig. 6. Time course of vascularity before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data are means ± SD (n = 44 and 40, respectively). **Adjusted $P < 0.001$ versus corresponding pretreatment (time 0) value (paired *t*-test with Bonferroni's correction for nine comparisons). Arrow indicates first examination of the follow-up period.

32 weeks. However, neither irregularity nor the Schirmer test value differed between the two groups at either time point.

The SPEED score was significantly improved from a mean value of 14.7 to 5.9 and from 12.7 to 9.1 between before and 24 weeks after treatment initiation in the IPL-MGX and control groups, respectively. At 32 weeks, the mean values were 5.5 and 9.2 in the IPL-MGX and control groups, respectively. The cutoff value of the SPEED score for evaluation of dry eye disease is 9 [35], with individuals with a score of 9 or higher thus complaining of ocular symptoms of dry eye. Whereas the amelioration of symptoms by MGX alone was statistically significant, it might therefore not have been clinically effective. IPL-MGX treatment improved ocular symptoms to such an extent that the SPEED score was substantially below the cutoff value for dry eye. A similar pattern was observed for NIBUT (cutoff value of 5 s) [15] and BUT (cutoff value of 5 s) [36], with IPL-MGX improving these parameters from the abnormal to normal range whereas MGX alone induced significant but clinically ineffective changes.

MGX was first described in 1921 by Gifford [37] as an effective method for rehabilitation of meibomian glands and amelioration of dye eye symptoms. Korb and Greiner showed that MGX improved both LLT and symptoms in 10 patients with MGD [38]. More recently, Lee et al. demonstrated efficacy of weekly mechanical squeezing of meibomian glands for MGD patients [39]. In the present study, we also found that MGX alone resulted in significant improvements in various parameters. However, MGX causes pain in some patients. Indeed, three patients withdrew from the control arm of the present study because of such pain. Of interest, MGX was acceptable after IPL for all patients enrolled in the IPL-MGX arm, possibly because IPL softens meibum and thereby reduces the pain associated with MGX.

There are several potential mechanisms for the amelioration of ocular surface symptoms and signs by IPL in MGD patients. First, IPL warms meibomian glands through the thin periocular skin and thereby melts meibum [8,24]. Second, the IPL device emits energy that is absorbed by chromophores in hemoglobin and thereby closes abnormal vessels in the eyelid margin and adjacent conjunctiva and prevents the release of inflammatory factors by these vessels [40,41]. The concentrations of inflammatory factors including interleukin-17A, interleukin-6, and prostaglandin E_2 in tear fluid were recently found to be reduced by IPL therapy [10]. Third, IPL may relieve inflammatory or neurogenic pain [42]. And fourth, IPL treatment can result in an immediate reduction in bacterial load of the eyelid margin and surrounding adnexa and in a consequent attenuation of inflammation [43].

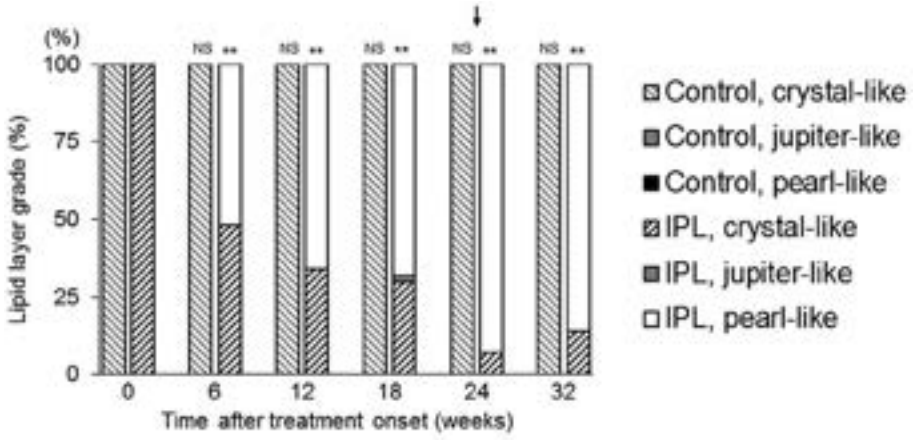

Fig. 7. Time course of lipid layer grade before, during, and after treatment in the intense pulsed light (IPL)–meibomian gland expression (MGX) and MGX (control) groups. Data represent the percentage of eyes (n = 44 and 40, respectively). **Adjusted $P < 0.001$; NS, not significant versus corresponding pretreatment (time 0) value (Fisher's exact test with Bonferroni's correction for five comparisons). Arrow indicates the first examination of the follow-up period.

We found that IPL-MGX improved vascularity, whereas MGX alone did not, with this effect of IPL-MGX possibly being due to the anti-inflammatory effect of IPL.

In the present study, we applied eight sessions of IPL-MGX treatment for patients with refractory MGD. An average of seven sessions of IPL treatment was previously shown to be required for symptomatic improvement in patients with mild dry eye [24]. Given that we enrolled only patients with refractory MGD, we speculated that more than seven sessions of IPL might be necessary. Our Results show that 66% and 93% of subjects had recovered a balance in tear film components, as indicated by the pearl-like appearance of the tear interferometric pattern, after four and eight sessions of IPL-MGX, respectively. This improvement in tear film homeostasis remained apparent 32 weeks after treatment onset. NIBUT is characteristically reduced in patients with MGD [44], and we observed an increase in mean NIBUT from 2.5 to 6.6 s after eight IPL-MGX sessions (24 weeks after treatment onset) and to 7.0 s after 11 weeks of follow-up. These changes represent a meaningful clinical improvement, given that we previously showed the cutoff value of NIBUT as measured with the DR-1α tear interferometer to be 5 s [15]. In contrast, MGX alone did not improve lipid layer dynamics as reflected by the tear interferometric pattern. We did not detect any adverse effects such as a burning sensation in any of the subjects treated with IPL-MGX. Although further studies will be required to confirm and extend our findings, the results of the present study suggest that eight IPL-MGX sessions may be necessary for the effective treatment of refractory MGD.

With regard to limitations of our study, the number of enrolled patients may not be sufficiently large to determine an adequate protocol for the treatment of refractory MGD. Furthermore, given that the skin type of most Japanese individuals is classified as Fitzpatrick type 3, the reactivity of the skin to light or ultraviolet may differ between the study patients and individuals of other ethnicities. Similar studies with patients of other ethnic groups will thus be required. In addition, the mechanism underlying the effectiveness of IPL-MGX treatment was not demonstrated.

In conclusion, we have shown that the combination of IPL and MGX is safe and effective for the treatment of refractory MGD. Although further studies will be necessary to develop and establish this treatment procedure for the clinic, our Results suggest that repeated IPL-MGX sessions improve homeostasis of tear film components in patients with refractory MGD.

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Disclosure

R.A. holds patents on the noncontact meibography technique described in this manuscript (Japanese patent registration no. 5281846; U.S. patent publication no. 2011–0273550A1; European patent publication no. 2189108A1), is a consultant for Kowa Company (Aichi, Japan) and Lumenis Japan (Tokyo, Japan), and has received financial support from TearScience (Morrisville, NC). The other authors declare no potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2018.11.004.

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Original Research

Intense Pulsed Light Applied Directly on Eyelids Combined with Meibomian Gland Expression to Treat Meibomian Gland Dysfunction

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Abstract

Objective: To determine the efficacy and safety of intense pulsed light (IPL) applied directly on the eyelids and meibomian gland expression (MGX) in treating meibomian gland dysfunction (MGD). ***Background:*** IPL application on the periocular skin effectively improves meibomian gland secretion and tear film break-up time (TBUT) in patients with MGD/dry eye. ***Methods:*** This prospective, randomized, double-masked, controlled study involved 44 patients. One eye was randomly selected for IPL treatment; the other served as a control. Study eyes received three IPL treatments at 4-week intervals; IPL was applied directly on the eyelids, and the eye was protected with a Jaeger lid plate. Control eyes received sham IPL treatments. Both eyes received MGX and artificial tears. Meibomian gland yielding secretion score (MGYSS), TBUT, Standard Patient Evaluation of Eye Dryness (SPEED), cornea fluorescein staining (CFS), meibography, best corrected visual acuity (BCVA), intraocular pressure (IOP), and fundus examination were performed. ***Results:*** Compared to the baseline, MGYSS, TBUT, and SPEED and CFS scores improved in the study eyes, while only SPEED and CFS scores improved in the control eyes ($p < 0.001$ for all). Changes in MGYSS and TBUT were higher in the study eyes than in the control eyes ($p < 0.05$), but changes in SPEED and CFS scores were similar ($p > 0.05$). BCVA and IOP improved in both the study and control eyes ($p < 0.05$). Five patients experienced mild pain and burning during IPL treatment. One patient suffered partial eyelash loss. ***Conclusions:*** IPL combined with MGX safely and effectively treated MGD.

Keywords: intense pulsed light, meibomian gland dysfunction, dry eye, meibomian gland secretion function

Introduction

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion.[1] This results in the alteration of the tear film, eye irritation, clinically apparent inflammation of the eyelid margin, and ocular surface diseases.[1,2] The prevalence of MGD varies widely and is much higher in Asia than elsewhere.[3] Among senior citizens, MGD prevalence ranges from 46.2% to 69.3% among Asians,[4–7] while it is only 3.5–21.9% among Caucasians of a similar age.[3,8] Common therapies for MGD include lid hygiene, lid warm compresses or heat application, meibomian gland expression (MGX), artificial tears, topical and systemic antibiotics, and anti-inflammatory agents.[9] However, these treatments provide limited relief and are generally unsatisfactory.[9,10]

Intense pulsed light (IPL) is a widely used dermatological treatment for conditions such as facial telangiectasia, facial rosacea, pigmented lesions, and excessive hair growth.[11,12] In 2003, Toyos observed an improvement in the signs and symptoms of MGD in patients who received IPL treatment for facial rosacea.[13] Over the past decade, he has developed an IPL treatment protocol for MGD/dry eye.[14] In recent years, other ophthalmologists have studied the efficacy and safety of IPL treatment of MGD/dry eye. Several retrospective studies have shown that IPL treatment relieves dry eye symptoms, improves meibomian gland secretion, and lengthens tear film break-up time (TBUT) in patients with MGD/dry eye.[13,15–17] Craig et al.[18] conducted a prospective, randomized, double-masked clinical study of IPL treatment for MGD, and demonstrated its efficacy and safety.

In previous studies positive treatment outcomes were obtained even though IPL was applied on the cheeks adjacent to

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the inferior periocular skin. We hypothesized that IPL application directly on the eyelids, under proper protection, will result in even better outcomes. Moreover, thus far, all published research on the IPL treatment of MGD has been conducted in the Caucasian population. Skin characteristics such as color and thickness differ between Asians and Caucasians, which may affect IPL treatment outcomes among Asian MGD patients. To date, the efficacy and safety of IPL treatment in Asian MGD patients have not been described.

In this study, we determined the efficacy and safety of IPL treatment combined with MGX in Asian patients with MGD. In contrast to previous studies, IPL was applied directly on the upper and lower eyelids under the protection of a Jaeger lid plate.

Materials and Methods

Ethics and consent

This prospective, randomized, double-masked, controlled study was approved by the Ethics Committee of Peking University First Hospital (no.: 2015[1009]). The clinical trial was registered in the Chinese Clinical Trial Registry (registration no.: ChiCRT-INR-16010256). The study was conducted following the tenets of the Declaration of Helsinki. Written consent was obtained from all participants before their inclusion into the trial.

Subjects

We selected consecutive MGD patients who were treated at the Ophthalmology Department of Peking University First Hospital between March and July 2016. The inclusion criteria were as follows: (1) age above 18 years, (2) obstruction of MG orifices observed under slit lamp examination, (3) meibomian gland yielding secretion score (MGYSS)[19] of lower eyelid of no more than 12, (4) Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score[20] of at least 6 in both eyes, and (5) Fitzpatrick skin types 1–4 according to sun sensitivity and appearance of the skin.[21] The exclusion criteria included the following: (1) any intraocular inflammation, ocular surgery, or ocular trauma in the past 6 months, (2) ocular infection or allergy, (3) any eyelid structural abnormality, (4) any systematic diseases that may lead to dry eye disease, (5) tanning in the past 4 weeks, (6) skin cancer or pigmented lesion in the treatment zone, (7) pregnancy or lactation.

General schedule

Screening for the study included the following procedures, in the order given: SPEED questionnaire, Snellen best corrected visual acuity (BCVA) measurement, intraocular pressure (IOP) measurement, silt lamp biomicroscopy, TBUT measurement, cornea fluorescein staining (CFS) assessment, meibomian gland assessment and infrared meibography, and fundus examination. The Schirmer test is not included in the diagnostic criteria for MGD nor was it included as an outcome measure in this study.

Patients who satisfied the selection criteria and signed the informed consent form were enrolled in the study. Before the first treatment session, one of the two eyes was randomly assigned as the study eye according to a computer-generated randomization chart. We chose the first number in the chart as a starting point, and then counted along the row. Odd numbers meant that the right eye was the study eye, while even numbers meant that the left was the study eye. The fellow eye was assigned as the control eye. Each patient underwent three treatment sessions (T1, T2, and T3) performed at 4-week (± 1 day) intervals. To minimize bias, clinicians who performed the screening or follow-up assessments were not involved in the treatment procedures. A camera flash light was used to imitate IPL flashes during both IPL/sham IPL applications. Thus, the patients were masked to which eye was treated. Table 1 summarizes the schedule of examinations and treatments performed for each patient.

Treatment procedure

We used the M22 IPL system with optimal pulse technology (Lumenis Ltd., Yokneam, Israel), which has a xenon lamp that emits IPL at 515–1200 nm and a 560-nm filter. The optimal pulse technology makes IPL pulses more stable and highly repeatable, so treatment with M22 is more effective and safer than treatments with traditional IPL systems.

After removing dirt and extra oil from the face and eyelids with a cosmetic face wash, the upper and lower eyelids were numbed with a topical anesthetic (compound lidocaine cream; Ziguang Pharmaceutical Co. Ltd., Beijing, China). After 30 min, the cream was washed off, and the skin was dried. A drop of 0.4% oxybuprocaine hydrochloride (Benoxil, Santen Pharmaceutical Co. Ltd., Osaka, Japan) was then administered onto the conjunctival sac. This last step was repeated after 5 min.

Immediately before IPL application, a layer of ultrasound gel was applied on the area to be treated. The cornea and sclera were fully occluded by placing a Jaeger lid plate (with 18 mm and 22 mm curved wide blades, Suzhou Mingren Medical Equipment Co. Ltd., Suzhou, China) on the conjunctival sac, next to the palpebral conjunctiva on the opposite side of treatment zones (Fig. 1). The blade moved with IPL pluses during treatment to ensure that cornea and sclera were not exposed directly to IPL fluence. For IPL treatment of the study eye, the fluence was set to 14–16 J/cm^2 (depending on the Fitzpatrick skin type, Table 2). A dermatologist then applied a series of 12 overlapping IPL pulses around the periocular areas on the upper and lower eyelids (Fig. 2). The distance between the IPL pulses and the eyelid

Table 1. Schedule for Each Visit

	Baseline	*Visit 1*	*Visit 2*	*Visit 3*
SPEED	×	×	×	×
BCVA & IOP	×			×
Slit lamp biomicroscopy	×	×	×	×
TBUT	×	×	×	×
CFS	×	×	×	×
MGA	×	×	×	×
Meibography	×			×
Fundus examination	×			×

Visit 1, day 28 after T1; visit 2, day 28 after T2; visit 3, day 28 after T3.

BCVA, best corrected visual acuity; CFS, cornea fluorescein staining; IOP, intraocular pressure; SPEED, standard patient evaluation of eye dryness; TBUT, tear film break-up time; ×, the examination was performed.

FIG. 1. Protection of the cornea and sclera with the Jaeger lid plate placed in the conjunctival sac during IPL treatment. The Jaeger lid plate is 10 cm long with 18-mm and 22-mm curved wide blades. IPL, intense pulsed light.

margin was 2–3 mm. The fluence was then set to 0 J/cm^2, and the same protection method and IPL treatment procedure were repeated for the control eye.

After removal of the ultrasound gel, an ophthalmologist performed MGX with the forceps-shaped Arita meibomian gland compressor (Katena Products, Inc., Denville, NJ). The ophthalmologist applied force on opposite sides of the compressor to empty meibum from the upper and lower eyelids of both eyes. For the entire duration of the study, patients were instructed to use artificial tears (Systane Lubricant Eye Drops; Alcon, Fort Worth, TX) three times a day, in both eyes.

Outcome measures

The primary outcome measure was the MGYSS. This score reflects meibomian gland function and was measured using a meibomian gland evaluator (MGE; Tear Science, Inc., Morrisville, NC) according to the Lane protocol.[19] Fifteen glands each on the upper and lower eyelids were evaluated. For each gland, the secretion was graded as follows: 0, no secretion; 1, inspissated/toothpaste consistency; 2, cloudy liquid secretion; and 3, clear liquid secretion. The MGYSS was the sum of the grades for all 15 glands, and ranged from 0 to 45.[19] The score for the upper eyelid was termed the u-MGYSS, and that for the lower eyelid was termed l-MGYSS.

The secondary outcome measures included SPEED score, TBUT, CFS score, and meibography findings. The SPEED questionnaire[20] was used to evaluate the severity and frequency of dry eye symptoms. TBUT was measured using moist fluorescein sodium strips (Jingming New Technological Development Co. Ltd., Tianjin, China). After the fluorescein was instilled into the conjunctival sac, the patient was asked to blink several times. Then, the tear film was observed using biomicroscopy under a cobalt blue filter. The average TBUT of three repeated measurements was recorded for each eye. Following the TBUT measurements, CFS assessment was performed. The cornea was divided into four quadrants. Each quadrant was graded on a scale of 0–3 as follows[22]: 0, no punctate staining; 1, 1–30 punctate lesions; 2, >30 punctate lesions but no confluent lesions; and 3, confluent lesions or ulcer. The total CFS score of all four quadrants ranged from 0 to 12.

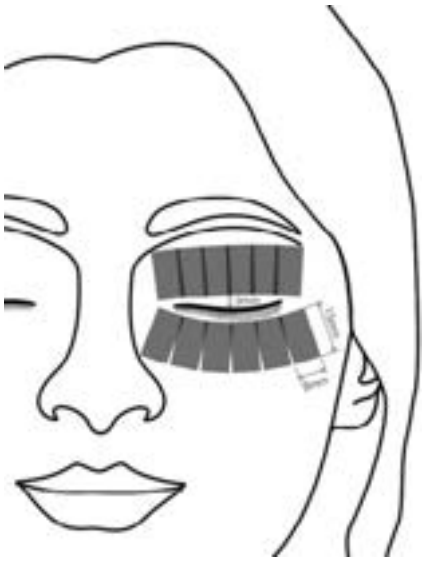

FIG. 2. IPL treatment zone including six overlapping periocular areas (8 × 15 mm each) on each eyelid.

Meibography was performed using the method described by Arita et al.[23] Each eyelid was turned over and observed under a slit lamp equipped with an infrared filter (Topcon Corp., Tokyo, Japan). In each eyelid, the extent of meibomian gland loss was scored as follows (meiboscore): 0, no loss; 1, less than one-third; 2, between one- and two-thirds; and 3, more than two-thirds.

Safety analysis

The Snellen BCVA, IOP, slit lamp biomicroscopy, and fundus examinations were performed to evaluate treatment safety. Adverse events were either reported by the patients or observed by clinicians according to the schedule of

Table 2. Fitzpatrick Skin Types and Fluence Level

Fitzpatrick skin type	*Erythema and tanning reactions to first sun exposure/skin appearance*	*Fluence (J/mm^2)*	*Pulse No.*	*Pulse width (ms)*
I	Always burn, never tan/pale white	No patients	—	—
II	Usually burn, tan less than average (with difficulty)/white	16	Triple	3.5
III	Sometimes mild burn, tan about average/light brown	15	Triple	3.5
IV	Rarely burn, tan more than average (with ease)/medium brown	14	Triple	3.5
V	(Brown-skinned persons)/dark brown	Excluded	—	—
VI	(Black-skinned persons)/very dark brown or black	Excluded	—	—

examinations (Table 1). The type, severity, and relationships of any adverse events to the device or procedure were recorded.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 (IBM Corporation, Armonk, NY). Descriptive statistics are presented as means ± standard deviations. Outcome measures before and after treatment were analyzed using the Friedman two-way analysis of variance, with the pairwise Wilcoxon test for *post hoc* testing. Differences between the treated and control eyes were analyzed with the pairwise Wilcoxon test. Snellen visual acuities were converted to logMAR equivalents.[24] The LogMAR BCVA and IOP were analyzed with two-tailed paired *t*-tests. Statistical significance was set at the $\alpha = 0.05$ level.

Results

General information

A total of 46 patients were enrolled in the study, of whom 44 patients, including 12 men (27%) and 32 women (73%), completed the study. Two patients quit the study due to reasons not related to the study, and were not included in the analysis. The average patient age was 46.3 ± 16.9 years (range, 23–86 years).

Primary outcome measure

The results for the primary outcome measure MGYSS are presented in Fig. 3. The MYGSS of both the lower and upper eyelids gradually increased in the study eyes ($p < 0.001$ for both eyelids, Friedman two-way analysis of variance; Fig. 3)

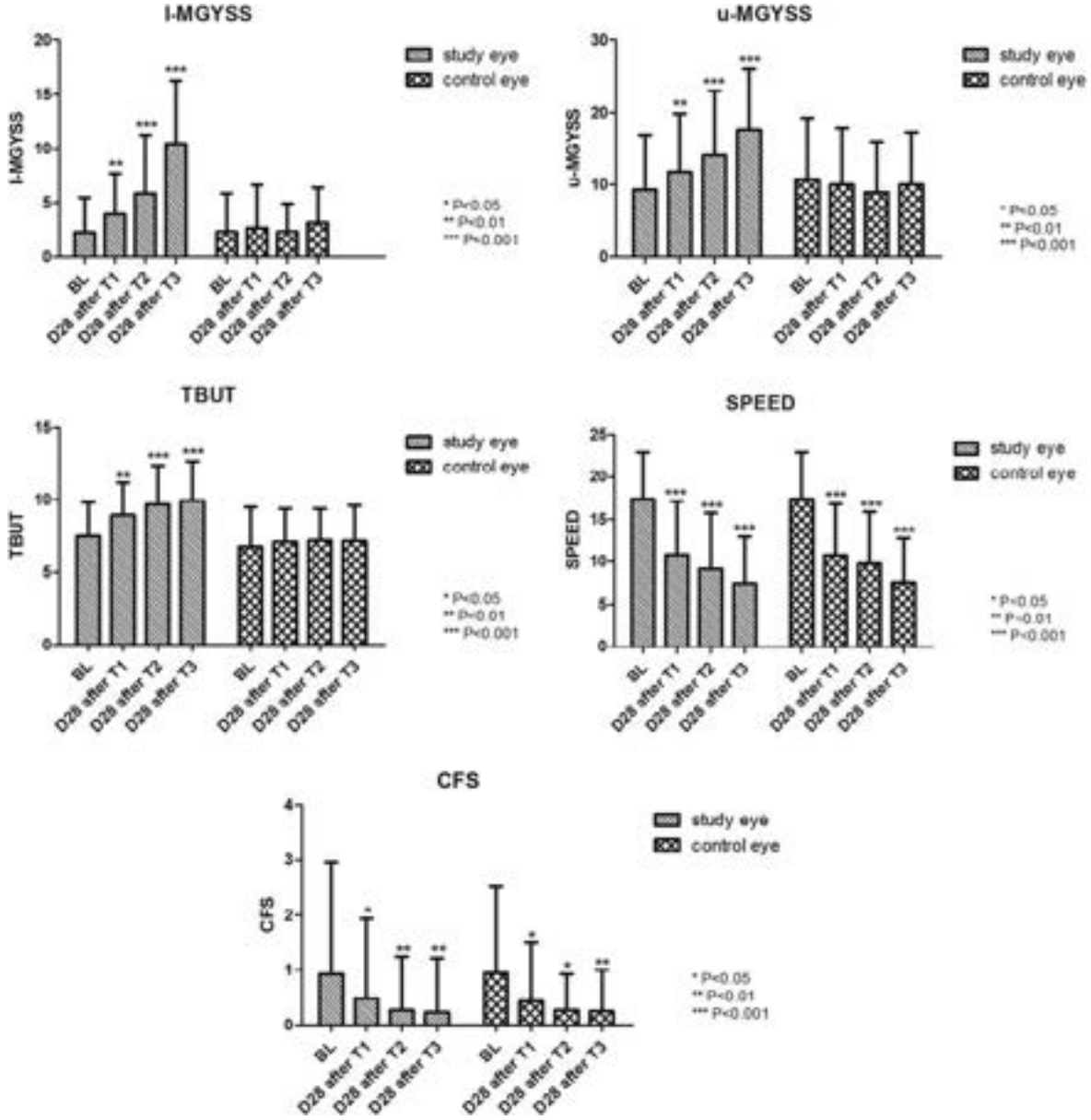

FIG. 3. Longitudinal analysis of MGYSS, TBUT, SPEED scores, and CFS scores in the study and control eyes. (Friedman two-way analysis of variance, pairwise Wilcoxon for *post hoc* testing, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared to the baseline). CFS, cornea fluorescein staining; MGYSS, meibomian gland yielding secretion score; SPEED, standard patient evaluation of eye dryness; TBUT, tear film break-up time.

Table 3. Changes of Treatment Measures in Study and Control Eye at Each Visit

	BL	*D28 after T1 vs. BL*	*D28 after T2 vs. BL*	*D28 after T3 vs. BL*
1-MGYSS				
Study eye	2.3 ± 3.2	1.7 ± 4.1 (73.9%)	3.6 ± 5.6 (156.5%)	8.2 ± 6.2 (356.5%)
Control eye	2.3 ± 3.6	0.4 ± 4.5 (17.4%)	0.00 ± 4.1 (0.0%)	0.9 ± 4.2 (39.1%)
p value		0.06	0.001	<0.001
u-MGYSS				
Study eye	9.3 ± 7.5	2.4 ± 6.1 (25.8%)	4.7 ± 7.3 (50.5%)	8.2 ± 8.0 (88.2%)
Control eye	10.7 ± 8.6	–0.6 ± 5.0 (–5.6%)	–1.7 ± 5.8 (–15.9%)	–0.7 ± 5.2 (–6.5%)
p value		0.011	<0.001	<0.001
TBUT				
Study eye	7.5 ± 2.4	1.5 ± 2.7 (20.0%)	2.2 ± 3.1 (29.3%)	2.5 ± 3.3 (33.0%)
Control eye	6.8 ± 2.7	0.3 ± 2.3 (4.4%)	0.4 ± 2.4 (5.9%)	0.4 ± 2.8 (5.9%)
p value		0.010	0.000	0.000
SPEED				
Study eye	17.4 ± 5.5	–6.8 ± 6.0 (–39.0%)	–8.3 ± 7.9 (–47.7%)	–10.1 ± 6.7 (–58.0%)
Control eye	17.4 ± 5.5	–6.9 ± 528 (–39.7%)	–7.7 ± 7.1 (–44.25%)	–10.0 ± 6.5 (–57.5%)
p value		0.918	0.254	0.510
CFS				
Study eye	0.9 ± 2.0	–0.5 ± 1.3 (–55.6%)	–0.7 ± 2.3 (–77.8%)	–0.7 ± 1.4 (–77.8%)
Control eye	1.0 ± 1.5	–0.5 ± 1.7 (–50.0%)	–0.7 ± 1.7 (–70.0%)	–0.7 ± 1.7 (–70.0%)
p value		0.651	0.707	0.958

BL, baseline; T, treatment; MGYSS, meibomian gland yielding secretion score.

but did not change in the control eyes ($p = 0.231$ and $p = 0.088$ for the lower and upper eyelids, respectively). On day 28 after each treatment session, the changes in MGYSSs of the lower and upper eyelids were significantly higher in the study eyes than in the control eyes, ($p < 0.05$ for all, except lower eyelids at T1, Table 3, pairwise Wilcoxon test, rate of MGYSS changes showed in parentheses).

Secondary outcome measures

The TBUT, SPEED scores, and CFS scores are presented in Fig. 3. The TBUT gradually increased over the course of treatment in the study eyes ($p < 0.001$, Friedman two-way analysis of variance; Fig. 3) but did not significantly change in the control eyes ($p = 0.272$). On day 28 after each treatment session, the change in TBUT was significantly higher in the study eyes than in the control eyes ($p < 0.01$, pairwise Wilcoxon test; Table 3, rate of TBUT changes shown in parentheses). SPEED and CFS scores significantly decreased with treatment in both the study and control eyes ($p < 0.001$, Friedman two-way analysis of variance; Fig. 3), and neither score significantly differed between the study and control eyes (pairwise Wilcoxon test; Table 3, rate of SPEED and CFS changes shown in parentheses).

The meiboscores in the study eyes (1.43 ± 0.59, upper eyelid; 1.48 ± 0.76, lower eyelid) and the control eyes (1.43 ± 0.66, upper eyelid; 1.55 ± 0.76, lower eyelid) remained unchanged at the end of the study compared to the baseline.

Safety evaluation

According to Holladay's method,[24] Snellen visual acuities were converted to logMAR equivalents. At the baseline, the logMAR equivalent BCVA in the study and control eyes was 0.12 ± 0.26 and 0.11 ± 0.15, respectively. By the end of the study (day 28 after the third treatment session), the logMAR equivalent BCVA in both the study eyes (0.07 ± 0.27) and the control eyes (0.07 ± 0.15) significantly improved ($p = 0.003$ and $p = 0.01$, respectively; paired *t*-test). At the baseline, the IOP was 14.95 ± 2.75 mm Hg in the study eyes and 15.27 ± 2.82 mm Hg in the control eyes. On day 28 after the third treatment session, the IOP significantly decreased in both the study eyes (13.86 ± 2.60 mm Hg, $p = 0.001$; paired *t*-test) and the control eyes (14.36 ± 2.60 mm Hg, $p = 0.007$, paired *t*-test).

Of the 44 study patients, 5 complained of mild pain and burning during the IPL treatment, and mild redness of the eyelids was observed in their study eyes immediately after the IPL treatment. However, none of these patients dropped out of the study because of the discomfort. After the application of cold compresses for 5 min, the discomfort was relieved in all five patients. No irreversible eyelid skin injury occurred. Due to the clinician's IPL performance, one patient suffered a partial loss of eyelashes after the IPL treatment and did not fully recover until 3 months after the end of the study (Fig. 4). No intraocular inflammation, iris

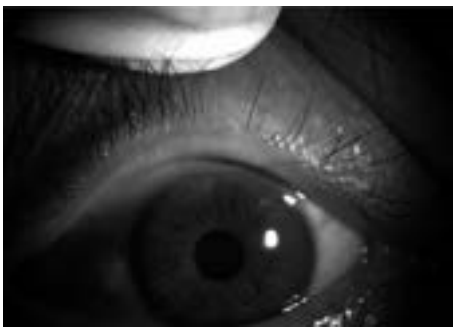

FIG. 4. Case 13, a 53-year-old man. Partial loss of eyelashes due to IPL treatment 3 months after the end of the study.

transillumination defects, or ocular surface or fundus injuries were observed.

Discussion

This article is the first prospective, randomized, double-masked, controlled study of IPL treatment applied directly on the eyelids for MGD. Our results showed that combined IPL treatment and MGX was significantly better than MGX alone in terms of the improvement in meibomian gland secretion function, TBUT, dry eye symptoms, and ocular surface condition. Craig et al.[18] used IPL treatment on the facial skin next to the lower eyelids in MGD patients. By the third treatment (day 45), the lipid layer grade and noninvasive TBUT had significantly improved in the IPL-treated eyes compared to the baseline and control eyes. In our study, the treated eyes showed an improvement in MGYSS and TBUT on the 28th day after the first treatment session, compared to the baseline and control eyes. Moreover, these parameters continued to improve over the course of the treatment until the end of the study.

In the study eyes, we noticed that even though glands loss was similar in the upper and lower eyelids (1.43 ± 0.59 vs. 1.48 ± 0.76), the improvement in gland secretion function was significantly greater in the lower eyelids than in the upper eyelids (356.5% vs. 88.2% at the end of the study). Bron et al.[25,26] proposed the tear gradient theory, according to which tear evaporation leads to a rise in solute concentration, especially the concentration of proinflammatory proteins in the tear meniscus. The resultant protein accumulation damages the meibomian gland orifices, leading to decreased secretion and MGD. We have previously showed decreased inflammatory factors in the tear film after IPL treatment in MGD patients.[27] Due to gravity and eyelid movement, the tear meniscus in the upper eyelid is smaller than that in the lower eyelids, and consequently, contains fewer inflammatory factors. Thus, we hypothesized that IPL treatment may be more effective for the lower eyelids by reducing the accumulation of inflammatory molecules.

SPEED and CFS scores improved in both the treated and control eyes, without any significant differences between the treated and control eyes. This may be attributable to MGX and artificial tears treatment in both eyes. Similar results have been reported by Craig et al.[18] This may imply a complicated relationship between symptoms and signs, which needs to be further researched.[15]

Research on the effect of IPL treatment on the meibomian glands is still limited. Possible mechanisms of action underlying the effects of IPL treatment in MGD include the thermal effect of IPL facilitating meibomian gland secretion by softening meibum, ablation of telangiectasia decreasing inflammatory factors released around the glands, and reduction of bacteria and other microorganisms on the eyelids.[10,13] The meibomian gland is a sebaceous gland. Several studies on IPL treatment of acne vulgaris[28,29] have reported that IPL reduces inflammatory infiltrates around the glands and the surface area of sebaceous glands. Liu et al.[27] found that inflammatory factors were reduced in the tears of MGD patients after IPL treatment. The above results indicate that the anti-inflammatory effect of IPL treatment on sebaceous or meibomian glands may be one of the possible mechanisms of action of this treatment.

In 2003, Toyos observed that IPL treatment could relieve dry eye symptoms in MGD/dry eye patients with facial rosacea.[13] Since then, several studies have shown that IPL treatment is effective and safe for MGD/dry eye,[13,14,18] especially in refractory cases.[15,17] In previous studies, due to safety concerns,[13] the IPL treatment zone was located on the facial skin adjacent to the lower eyelid and not directly on the eyelids.[13–16,18] To ensure treatment safety, we used the Jaeger lid plate as a shield during IPL therapy. No severe adverse events due to the use of the Jaeger lid plate, such as corneal or conjunctival injury, anterior chamber inflammation, or fundus injury, were observed during the study. Only five patients complained of burning and pain during IPL treatment and showed mild skin redness in the treatment zone. This may have been related to the high treatment energy we used in the study.

At the end of the study, BCVA was significantly improved in both the study and control eyes, as compared to the baseline. We believe that this result is attributable to the more stable tear film and the repair of the corneal epithelium. Unstable tear film and epithelial defects introduce irregularities in the corneal surface, which impair vision.[30] Thus, it is possible for IPL treatment to increase visual acuity, since corneal scattering was improved as a result of improvements in epithelial defects and tear film stability. The IOP in both the study and control eyes was significantly decreased by approximately 1 mmHg. Tsubota et al.[31] reported that dry eye patients blink twice as much as normal controls. In our study, intraocular pressure was measured using an air-puff tonometer. The results of air-puff tonometers can be affected by eyelid blinking. After the dry eye syndrome was corrected, patients may have blinked less when they were told to stare at the tonometer probe. This better compliance may have led to decreased bias caused by half-opened eyelids. In future studies, we recommend that the Goldmann applanation tonometer be used to avoid this bias.

There are certain limitations to our study. The majority of our patients were women, which may affect the representativeness of our findings. We chose a relatively fixed treatment energy (14–16 J/cm^2), which might have influenced the treatment outcomes. In subsequent studies, researchers should enlarge the sample size, lengthen the observation period, adjust the IPL parameters/protocol to maximize treatment benefit, and explore the mechanisms underlying the effects of IPL treatment for MGD. OCT images of the iris, angle, and ciliary body should be studied to confirm the safety of IPL on these structures.

In summary, three sessions of IPL treatments applied directly on the eyelids combined with MGX are effective and safe for MGD treatment by improving meibomian gland secretion function and increasing TBUT. Our results may provide a solid foundation for future studies on IPL treatment for MGD/dry eye in the Asian population.

Author Disclosure Statement

No competing financial interests exist.

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Original Research

Long-Term Effects of Intense Pulsed Light Combined with Meibomian Gland Expression in the Treatment of Meibomian Gland Dysfunction

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Abstract

Objective: To evaluate the long-term effects of intense pulsed light (IPL) combined with meibomian gland expression (MGX) in the treatment of meibomian gland dysfunction (MGD).
Background: Although IPL has been proven to be effective in the treatment of MGD, any report regarding its long-term efficacy is unavailable by now.
Methods: The randomly selected study eye received a series of three IPL treatments that were applied directly on eyelids with an interval of 4 weeks (treatment energy, 14–16 J/cm^2). The control eye received three sham IPL treatments (0 J/cm^2). MGX was performed on both eyes. Meibomian gland yielding secretion score (MGYSS) and tear film break-up time (TBUT) were evaluated at baseline and at 1, 3, 6, and 9 months after treatments.
Results: In the study eyes, MGYSS of both the upper and lower eyelids and TBUT improved at 1, 3, 6 months after treatments ($p < 0.01$). MGYSS in lower eyelids continued to improve at 9 months ($p < 0.05$). The changes in MGYSS and TBUT after treatment were larger in the study eyes than in the control eyes at 1, 3, 6 months ($p < 0.01$), but no difference at 9 months ($p > 0.05$). The percentage improvement in the MGYSS of lower eyelids after treatment was higher than that of upper eyelids.
Conclusions: Three consecutive IPL treatments combined with MGX improved MG secretion function and TBUT by 6 months after treatment in MGD patients. The improvement in MG secretion function was greater in the lower eyelid than in the upper eyelid.

Keywords: intense pulsed light, meibomian gland dysfunction, meibomian gland secretion function, long-term, efficacy

Introduction

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion.[1] MGD is the main cause of evaporative dry eye and results in an unstable tear film and symptoms such as eye dryness, eye irritation, foreign body sensation, burning, watering, and eye fatigue.[1,2] The prevalence of MGD varies widely and is especially high in the Asian population.[3] Among senior Asian citizens, the prevalence of MGD ranges from 46.2% to 69.3%.[3] Currently available therapies for MGD include eyelid margin hygiene, hot compresses, meibomian gland expression (MGX), artificial tears, anti-inflammatory drops, and topical or oral antibiotics. These treatments only provide short-term relief and are generally unsatisfactory.[4,5]

Intense pulsed light (IPL) treatment involves the use of a xenon flash lamp emitting light at wavelengths ranging from 500 to 1200 nm, which are selectively absorbed by various chromophores (such as hemoglobin, melanin, and water). Along with light, the lamp also produces heat. IPL is widely used in dermatology and cosmetic fields to treat conditions such as facial telangiectasia, facial rosacea, pigmented lesions, and excessive hair growth through selective photothermolysis to destroy vascular structures, bacteria, pigments, and hair follicles, and inhibition of inflammatory mediators.[6,7] In 2002, Dr Toyos serendipitously observed that the symptoms of MGD and related dry eye were relieved in patients who had undergone IPL treatment for facial rosacea.[8] Since then, other ophthalmologists have studied the efficacy of IPL treatment for MGD/dry eye. Several retrospective studies and a few prospective studies have shown that three to four treatment sessions of IPL

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applied on the cheeks near the inferior periocular area can relieve the symptoms of MGD, improve meibomian gland secretion, and lengthen tear break-up time (TBUT) in MGD/dry eye patients.[8–14] The proposed mechanisms underlying these effects are meibum softening by the thermal effect of IPL,[15] ablation of telangiectasia, which results in a decrease in inflammatory factors, and reduction of bacteria and other microorganisms.[16,17] However, the long-term efficacy of IPL treatment has not yet been studied.

In our previous study, we modified the currently used IPL treatment method and evaluated the short-term effects of our modified treatment protocol.[18] In our method, IPL was applied directly on the upper and lower eyelids, while the cornea and sclera were under protection. MGX was performed after IPL treatment.

In our previous study, the treated eyes showed an improvement in both meibomian gland secretion function and TBUT on the 28th day after the first treatment session, and these parameters continued to improve over the course of the treatment. Further, no serious adverse ocular and dermal effects were detected during the study.

In the present study, we aimed to determine the long-term efficacy of the combined IPL treatment and MGX protocol we devised in our earlier study. We followed up the MGD patients who had undergone a series of three IPL treatments in our previous study for 9 months.

Materials and Methods

Ethics and consent

This prospective, randomized, double-masked, controlled study was approved by the ethics committee of Peking University First Hospital (no. 2015[1009]). The clinical trial was registered in Chinese Clinical Trial Registry (registration no. ChiCRT-INR-16010256). The study was conducted following the tenets of the Declaration of Helsinki. Written consent was obtained from all participants before their inclusion in the clinical trial.

Patients

Patients were recruited from the Department of Ophthalmology of Peking University First Hospital between January 2016 and April 2017. The inclusion criteria were as follows: (1) age above 18 years, (2) Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of at least 6 for both eyes, (3) meibomian gland yielding secretion score (MGYSS) of no more than 12 for the lower eyelid, and (4) Fitzpatrick skin type 1–4.[19] The exclusion criteria included the following: (1) any intraocular inflammation, ocular surgery, or ocular trauma in the past 6 months, (2) ocular infection or allergy, (3) any eyelid structural abnormality, (4) any systematic diseases that may lead to dry eye disease, (5) tanning in the 4 weeks before enrolment, (6) skin cancer or pigmented lesion in the treatment zone, and (7) pregnancy or lactation.

Forty-four MGD patients satisfied the selection criteria and enrolled in this study. All of the participants signed the informed consent form and underwent three treatment sessions of our modified IPL plus Max protocol. Of these, 28 patients completed the entire 9-month follow-up assessment and were included in this study.

Treatment procedure

One eye was randomly selected as the study eye according to a computer-generated randomization program; the fellow eye served as the control eye. The study eye received three IPL treatments at 4-week intervals, while the control eye received a sham IPL treatment. Both eyes were treated with MGX and artificial tears.

After washing face with cosmetic face cleanser, the eyelid skin was numbed with a topical anesthetic (compound lidocaine cream; Ziguang Pharmaceutical Co. Ltd., Beijing, China). After 30 min, the numbing cream was wiped away. A drop of 0.4% oxybuprocaine hydrochloride (Benoxil; Santen Pharmaceutical Co. Ltd, Osaka, Japan) was instilled into the conjunctival sac, and another drop was instilled 5 min later.

A layer of cooled ultrasound gel was applied on the upper and lower eyelid skin. A Jaeger lid plate (Suzhou Mingren Medical Equipment Co. Ltd., Suzhou, China) was placed in the conjunctival sac to fully occlude the cornea and sclera during the treatment. An M22 IPL system with optimal pulse technology (Lumenis Ltd., Tel Aviv, Israel) was used in our study. It has a xenon lamp emitting IPL at 515–1200 nm and a 560-nm filter. The optimal pulse technology makes IPL pulses more stable and highly repeatable. For the study eye, the fluence of the IPL system was set to 14–16 J/cm^2 depending on the Fitzpatrick skin type of the patient. A dermatologist applied a series of 12 overlapping IPL pulses directly on the upper and lower eyelids (Fig. 1). The distance between IPL pulses and the eyelid margin was 2–3 mm. For the control eye, the fluence was set to 0 J/cm^2.

After removal of the ultrasound gel, an ophthalmologist performed MGX on the upper and lower eyelids using the Arita meibomian gland compressor (Katena Products, Inc., Denville, NJ). After the procedure, patients were instructed to use artificial tears (Systane Lubricant Eye Drops; Alcon Laboratories, Inc., Fort Worth, TX) on both eyes whenever they felt it necessary, but no more than three times a day.

The complete therapy included three treatment sessions performed at 4-week intervals. The clinicians who

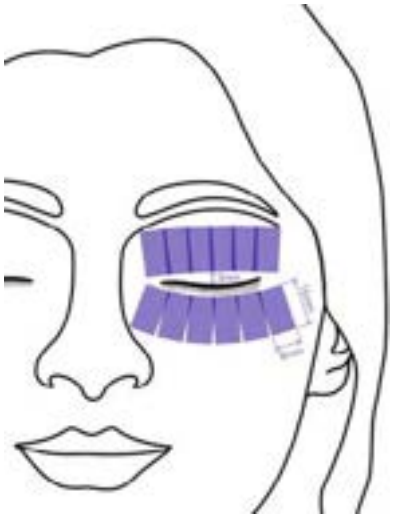

FIG. 1. IPL treatment zone including 12 overlapping periocular areas, each of which measures 8×15 mm. IPL, intense pulsed light.

performed the treatments were not involved in the subsequent examination process to minimize bias. The patients were examined at baseline and at 1, 3, 6, and 9 months after the treatment. The following examinations were performed in the order given: SPEED questionnaire, TBUT, corneal fluorescein staining (CFS), and meibomian gland assessment.

Primary outcome measure

The primary outcome measure was the MGYSS, which reflected the meibomian gland secretion function. The MGYSS was measured using a meibomian gland evaluator (MGE; Tear Science, Inc., Morrisville, NC) according to the Lane protocol.[20] Fifteen glands of temporal, central, and nasal regions in both upper and lower eyelids were evaluated. For each of these glands, the secretion was graded as follows: 0, no secretion; 1, inspissated/toothpaste consistency; 2, cloudy liquid secretion; and 3, clear liquid secretion. The scores were then summed to a single MGYSS, termed u-MGYSS for the upper eyelid and l-MGYSS for the lower eyelid. The MGYSS thus ranged from 0 to 45.

Secondary outcome measures

Tear film break-up time. A fluorescein sodium strip (Jingming New Technological Development Co. Ltd., Tianjin, China) was moistened with sterile saline, and fluorescein was gently instilled into the lower bulbar conjunctiva taking care not to cause any eye irritation. The patient was asked to blink naturally several times and then to stare straight ahead without blinking. The time between the last complete blink and the first appearance of a dry spot or a disruption in the tear film was observed and recorded under a slit lamp microscope with a cobalt blue light filter. The procedure was performed three times, and the average value was acquired for each eye.

SPEED score. The SPEED questionnaire[21] was used to evaluate the severity and frequency of MGD-related dry eye symptoms. The SPEED score ranges between 0 and 28.

CFS score. After TBUT measurement, the CFS score was calculated. The cornea was divided into four quadrants. Each quadrant was graded from 0 to 3 using the criteria[22] issued by the Corneal Disease Group of the Ophthalmological Society in 2013: 0, no punctate staining; 1, 1–30 punctate lesions; 2, >30 punctate lesions but no confluent lesions; and 3, confluent lesions or ulcer. The total CFS score of the four quadrants ranged from 0 to 12.

Statistical analysis

Statistical analysis was performed with SPSS 20.0 (IBM Corporation, Armonk, NY). Descriptive statistics are presented as means ± standard deviations. Outcome measures before and after treatment were analyzed using the Friedman two-way analysis of variance, with the pairwise Wilcoxon test for *post hoc* testing. Differences between study and control eyes were analyzed using the pairwise Wilcoxon test. Statistical significance was set at the $\alpha = 0.05$ level.

Results

General information

A total of 28 patients, including 10 men and 18 women, completed the entire therapy and follow-up assessment protocol and were included in the analysis. The average age of the patients was 42.17 ± 17.62 years (range, 24–78 years). In the study, 8, 18, and 2 participants were of Fitzpatrick type 2, 3, 4 separately. The study eye (15 right eyes and 13 left eyes) received three IPL treatments performed at 4-week intervals, while the control eye (13 right eyes and 15 left eyes) received a sham IPL treatment. Both eyes were treated with MGX and artificial tears.

Primary outcome measure

The results of the MYGSS are presented in Figure 2 and Table 1. The u-MYGSS did not differ between the study eyes (10.21 ± 7.46) and the control eyes (11.18 ± 9.341) at baseline ($p = 0.542$). In the study eyes, the u-MYGSS

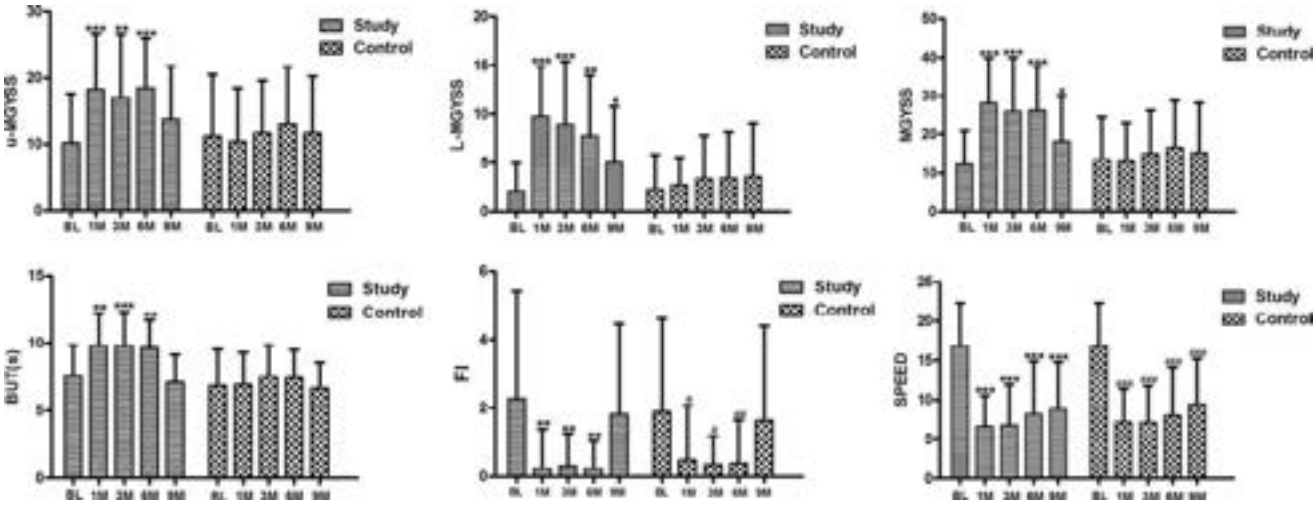

FIG. 2. Longitudinal analysis of MGYSS, TBUT, SPEED scores, and CFS scores in the study and control eyes ($*^{\#}p < 0.05$, $**^{\#\#}p < 0.01$, $***^{\#\#\#}p < 0.001$ compared to the baseline). CFS, corneal fluorescein staining; MGYSS, meibomian gland yielding secretion score; TBUT, tear film break-up time; SPEED, standard patient evaluation of eye dryness.

TABLE 1. CHANGES IN TREATMENT MEASURES IN THE STUDY AND CONTROL EYES AT EACH FOLLOW-UP TIME POINT

		BL	*1 M vs. BL*	*3 M vs. BL*	*6 M vs. BL*	*9 M vs. BL*
l-MGYSS	Study eye	2.04 ± 2.937	7.71 ± 5.227 (377.9%)	6.93 ± 6.716 (339.7%)	5.68 ± 6.794 (278.4%)	3.00 ± 6.689 (147.0%)
	Control eye	2.32 ± 3.497	0.43 ± 3.479 (18.53%)	1.07 ± 4.706 (46.1%)	1.11 ± 4.533 (47.8%)	1.29 ± 5.401 (55.6%)
	p value	0.775	<0.001	<0.001	0.001	0.127
u-MGYSS	Study eye	10.21 ± 7.460	8.11 ± 8.539 (79.4%)	6.86 ± 9.392 (67.2%)	8.29 ± 8.268 (81.2%)	3.61 ± 10.650 (35.4%)
	Control eye	11.18 ± 9.341	−0.79 ± 5.757 (−7.1%)	0.43 ± 5.941 (3.9%)	1.96 ± 7.341 (17.5%)	0.46 ± 10.748 (4.1%)
	p value	0.542	0.001	0.002	0.002	0.042
MGYSS	Study eye	12.32 ± 8.520	15.79 ± 11.080 (128.2%)	13.71 ± 12.907 (111.2%)	13.93 ± 10.920 (113.1%)	5.82 ± 12.821 (47.2%)
	Control eye	13.50 ± 11.054	−0.36 ± 7.077 (−2.7%)	1.5 ± 8.834 (11.1%)	3.07 ± 9.775 (22.7%)	1.75 ± 14.089 (12.96%)
	p value	0.466	<0.001	<0.001	<0.001	0.033
TBUT	Study eye	7.64 ± 2.231	2.18 ± 2.881 (28.5%)	2.18 ± 2.539 (28.5%)	2.04 ± 2.659 (26.7%)	−0.54 ± 2.848 (7.1%)
	Control eye	6.86 ± 2.690	0.07 ± 2.854 (1.0%)	0.68 ± 2.554 (9.9%)	0.57 ± 3.532 (8.3%)	−0.18 ± 2.829 (2.6%)
	p value	0.088	0.001	0.003	0.005	0.759
SPEED	Study eye	16.82 ± 5.478	−10.21 ± 5.418 (−60.7%)	−10.04 ± 6.466 (−59.7%)	−8.64 ± 7.597 (−51.4%)	−8.04 ± 6.269 (−47.8%)
	Control eye	16.82 ± 5.478	−9.64 ± 4.885 (−57.3%)	−9.71 ± 5.715 (−57.7%)	−8.86 ± 7.337 (−52.7%)	−7.36 ± 6.099 (−43.8%)
	p value	1.000	0.234	0.438	0.893	0.029
CFS	Study eye	2.29 ± 3.125	−2.04 ± 2.589 (−89.1%)	−1.96 ± 3.361 (−85.6%)	−2.04 ± 3.305 (−89.1%)	−0.46 ± 3.346 (−24.5%)
	Control eye	1.89 ± 2.726	−1.39 ± 2.872 (−73.5%)	−1.54 ± 3.037 (−81.5%)	−1.50 ± 2.809 (−79.4%)	−0.25 ± 3.807 (−13.2%)
	p value	0.362	0.170	0.376	0.194	0.777

BL, baseline; CFS, corneal fluorescein staining; M, months; MGYSS, meibomian gland yielding secretion score; TBUT, tear film break-up time; SPEED, standard patient evaluation of eye dryness.

significantly increased compared to the baseline at 1, 3, and 6 months after the treatment ($p < 0.01$), but did not further increase at 9 months ($p > 0.05$). In the control eyes, the u-MGYSS did not significantly improve after treatment ($p > 0.05$; Fig. 2). The changes in the u-MYGSS after treatment compared to the baseline were significantly higher in the study eyes than in the control eyes at 1, 3, 6, and 9 months ($p = 0.001$, 0.002, 0.002, 0.042, respectively).

The l-MYGSS also did not differ between the study eyes (2.04 ± 2.937) and the control eyes (2.32 ± 3.497) at baseline ($p = 0.775$). In the study eyes, the l-MYGSS significantly increased at 1, 3, 6, and 9 months after treatment ($p < 0.05$). In the control eyes, the l-MGYSS showed no significant improvement after treatment ($p > 0.05$; Fig. 2). The changes in l-MYGSS after treatment were significantly higher in the study eyes than in the control eyes at 1, 3, and 6 months ($p < 0.001$), but no difference was seen at 9 months ($p = 0.127$; Table 1). The percentage improvement compared to the baseline in l-MGYSS at 1, 3, 6, and 9 months after treatment was 377.9%, 339.7%, 278.4%, and 147.0%, respectively, while that in u-MGYSS was 79.4%, 67.2%, 81.2%, and 35.4%, respectively (Table 1).

Secondary outcome measures

Tear film break-up time. The results of TBUT are presented in Figure 2 and Table 1. At baseline, TBUT did not differ between the study (7.64 ± 2.231 sec) and control eyes (6.86 ± 2.690 sec; $p = 0.088$). In the study eyes, TBUT significantly increased compared to the baseline at 1, 3, and 6 months after the treatment ($p < 0.01$, < 0.001, 0.01, respectively). TBUT values returned to baseline at 9 months ($p > 0.05$). In the control eyes, TBUT showed no significant improvement after treatment ($p > 0.05$; Fig. 2). The changes in TBUT were significantly higher in the study eyes than in the control eyes at 1, 3, and 6 months after treatment ($p = 0.001$, 0.003, 0.005, respectively), but no difference was observed at 9 months ($p = 0.759$; Table 1).

SPEED score. Statistically significant improvements in SPEED scores were observed in both the study and control eyes after treatment at each assessment time point ($p < 0.05$; Fig. 2). There were no significant differences in SPEED scores between the study and control eyes (Table 1).

CFS score. Statistically significant improvements in CFS scores were observed in both the study and control eyes until 6 months after treatment ($p < 0.05$; Fig. 2). Moreover, the CFS scores did not differ between the study and control eyes (Table 1).

Discussion

In this study, IPL treatment applied directly on the eyelids combined with MGX provided sustained relief for at least 6 months to MGD patients by improving meibomian gland secretion function, increasing TBUT, and improving symptoms and the ocular surface.

MGD is a common cause of evaporative dry eye and a highly prevalent ocular surface disease. Current therapeutic approaches for MGD include physical treatments (like eyelid margin hygiene, eyelid hot compresses, MGX), drug therapy (artificial tears, anti-inflammatory drops, topical or oral

antibiotics), and dietary therapy.[4,5] However, the effects of these treatments are transient and unsatisfactory, and thus, new therapeutic methods must be developed.

Since Dr Toyos first noticed an improvement in MGD/dry eye symptoms in a patient who underwent IPL treatment for rosacea, some retrospective and a few prospective studies have confirmed that IPL could safely and effectively relieve the signs and symptoms of MGD and related dry eye.[8–14] Due to safety concerns, IPL was only applied on the cheeks adjacent to the lower eyelid under eye shield protection in these studies.[8–14] Further, these studies only evaluated the immediate and short-term effects of IPL treatment. The long-term efficacy of IPL treatment has not yet been studied.

In our previous study, we modified the IPL treatment method by applying IPL directly on both the upper and lower eyelids with full protection and after MGX. The short-term results showed that IPL on the eyelids combined with MGX was safe and yielded effects more rapidly.[18]

To further evaluate the long-term efficacy of IPL treatment applied directly on the eyelids combined with MGX in MGD patients and to identify evidence for determining the retreatment period, we followed up the patients in our previous study for 9 months after the therapy. We found that both u-MGYSS and l-MGYSS significantly improved in the study eyes at 1, 3, and 6 months after the treatment. At 9 months, the l-MGYSS continued to improve, while the u-MGYSS showed no further improvement after the initial treatment. These results indicated that the treatment effects could last for at least 6 months. It is worth noting that the u-MGYSS was five times higher than the l-MGYSS at baseline. This is consistent with the results of other studies, which have shown that meibomian gland loss is more obvious in the lower eyelids than in the upper eyelids.[23,24] These results may be attributable to gravity leading to meibum stagnation in the glandular ducts and orifices in the lower eyelid.[23,24] Further, in the tear gradient theory proposed by Bron[25] et al., tear evaporation leads to an increase in solute concentration, including pro-inflammatory protein concentration in the tear meniscus. The resultant protein accumulation is related to MGD formation. The tear meniscus in the upper eyelids is smaller than that in the lower eyelids due to gravity and eyelid movement and, consequently, contains fewer inflammatory factors. The results of our previous study showed decreased inflammatory factors in the tear film after IPL treatment in MGD patients.[26] Maybe reducing the accumulation of inflammatory molecules is the reason why IPL treatment is more effective for the lower eyelids.

In our study, the percentage improvement compared to baseline in the l-MGYSS was 377.9%, 339.7%, 278.4%, and 147.0% at 1, 3, 6, and 9 months after the treatment, respectively, while the corresponding improvements in the u-MGYSS were 79.4%, 67.2%, 81.2%, and 35.4%. As the percentage improvement in the l-MGYSS at 9 months was still 147%, we conclude that a series of three IPL treatments combined with MGX produced a greater improvement in meibomian gland secretion function in the lower eyelids than in the upper eyelids.

The TBUT results were similar to the MGYSS results. TBUT was improved in the study eyes at 1, 3, and 6 months and did not improve further at 9 months, indicating that the treatment effects lasted 6 months after treatment. Significant improvement in CFS scores was observed until 6 months after the treatment, but this improvement did not differ between the study and control eyes. This may be because MGX itself is also effective in helping to repair the corneal surface.

Interestingly, we found a statistically significant improvement in SPEED scores until 9 months after treatment, and the improvement did not differ between the study and control eyes. This may be attributable to two reasons: (1) MGX itself is also effective in relieving the symptoms of MGD and related dry eye; and (2) the SPEED questionnaire is a subjective survey, and our study was designed as a double-blind study. We found that the results of a recently published prospective and placebo-controlled study of IPL treatment for MGD conducted by Craig et al.[12] were similar. Although only one eye was treated with IPL, and the other served as a control, SPEED scores improved to similar degrees in both eyes. So there may exist a complicated connection between the signs and symptoms of MGD and related dry eye; psychological effects may also have had an impact. At present though, this finding is difficult to explain, and further investigation is required.

The long-term results of the present study combined with the short-term results of our previous study show that IPL treatment applied directly on the eyelids combined with MGX is safe, effective, and provides rapid and sustained relief (for at least 6 months) to MGD patients by improving meibomian gland secretion function, increasing TBUT, and improving symptoms and the ocular surface. Thus, this treatment is a novel alternative for MGD patients. The exact mechanisms underlying the observed effects of the treatment are unclear. Thermal effect seems to be the least impactful component of IPL treatment, because it could only explain short-term effects but not long-term effects if it works.[27]

This study also provided an initial recommendation for the IPL retreatment period. On average, the therapy may need to be repeated at 6 months after three consecutive IPL treatments applied directly on the eyelids combined with MGX.

There are some limitations in this study. First, some patients were lost to follow-up due to various reasons. Only 28 patients completed the assessments; this might cause potential study bias and affect the representativeness of our sample. The sample size should be enlarged, and the loss to follow-up rate should be reduced in future studies. Second, the number of treatment sessions was fixed, and the treatment energy range (14–16 J/cm^2) was relatively limited, which may have influenced the treatment outcomes. More personalized treatment will require adjustments to the IPL parameters/protocol to maximize the outcomes for different skin types, MGD severity, patient feedback, etc.

Conclusions

Three consecutive IPL treatments applied directly on the eyelids combined with MGX effectively and safely improved meibomian gland secretion function and increased TBUT in MGD patients, and these effects lasted 6 months after the treatments. The improvement in meibomian gland secretion function was greater in the lower eyelid than in the upper eyelid. IPL treatment directly on the eyelids combined with MGX provides a novel alternative for MGD treatment with relatively long-term effectiveness.

Summary

IPL therapy applied directly on the eyelids combined with MGX treated MGD effectively in a relatively long term.

Author Disclosure Statement

The authors have no potential conflicts of interest and financial support to disclose.

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Long-term effects of intense pulsed light treatment on the ocular surface in patients with rosacea-associated meibomian gland dysfunction

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ABSTRACT

Purpose: We aimed to determine the long-term effects of intense pulsed light (IPL) treatment in rosacea-associated meibomian gland dysfunction (MGD).
Methods: We enrolled 17 rosacea subjects with moderate and severe MGD who underwent four IPL sessions at 3-week intervals and were followed up for 12 months. The subjects underwent clinical examinations at baseline (first IPL) and at 3 (second), 6 (third), 9 (fourth), and 12 weeks, as well as 6 and 12 months, after baseline. Ocular surface parameters, including the Ocular Surface Disease Index (OSDI), tear break-up time (TBUT), staining score, and noninvasive Keratograph tear break-up time (NIKBUT), as well as meibomian gland parameters, including the lid margin vascularity and meibum expressibility and quality, were evaluated.
Results: All ocular surface and meibomian gland parameters for all subjects exhibited significant changes from baseline to the final examination (Friedman, $P < 0.050$ for all). In particular, improvements in the lower lid margin vascularity, meibum expressibility and quality, and ocular symptoms persisted up to the final examination (Wilcoxon, $P < 0.050$ for all). However, the improvements of TBUT, staining score, and NIKBUT after IPL were not maintained at 6 and 12 months after baseline.
Conclusions: In rosacea-associated MGD, four IPL treatments at 3-week intervals can improve long-term lid parameters and ocular symptoms without adverse effects.

1. Introduction

Rosacea is a chronic cutaneous disorder characterized by persistent erythema, telangiectasis, papules, and pustules, which primarily occur in the convexities of the central face [1,2]. Approximately 30–50% of patients with rosacea present with a broad spectrum of ocular findings [2]; the most common ocular sign is meibomian gland dysfunction (MGD), observed in several previous studies [3–5]. MGD in ocular rosacea is characterized by telangiectasia and erythema of the lid margin and qualitative and/or quantitative changes in the meibum, including turbid meibum and plugging of the gland orifices [2,4,5].

Ocular rosacea is usually associated with ocular surface inflammation [6–8]. Inflammatory processes can cause ocular surface epithelial damage and low tear secretion in rosacea-associated MGD, compared with normal controls [6–8]. Therefore, control of ocular surface inflammation is important in the treatment of ocular rosacea [2]. Generally, treatments for rosacea-associated MGD include the use of lubricants and maintenance of lid hygiene in the initial stages, similar to treatment for MGD not associated with rosacea. However, rosacea-associated MGD patients have a frequent need for systemic antibiotics or topical anti-inflammatory drugs [2].

Dysregulation of the vasomotor response is suggested as a mechanism for the erythema or telangiectasia in patients with cutaneous rosacea; it causes abnormal vasodilation and inflammatory mediator release [9–11]. Accordingly, some studies have reported that intense pulsed light (IPL) therapy targets these vascular components and decreases facial erythema and telangiectasia in patients with rosacea [1,12–14]. With the use of filters, light of approximately 500 nm can selectively coagulate and close the abnormal blood vessels in the skin, resulting in reduced inflammation [15,16].

Since Toyos reported the effects of IPL on ocular symptoms in facial rosacea patients [17], several studies have included IPL treatment for MGD and demonstrated its therapeutic potential [15,18–24]. These studies showed clinical improvements in tear film abnormality and symptoms due to MGD after IPL treatments. Recently, one study [24] demonstrated a reduction in tear inflammatory markers, as well as corresponding clinical improvements. These findings proved a possible mechanism of IPL effects on MGD.

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To the best of our knowledge, there have been no studies regarding the long-term effects of IPL treatment; previous studies [15,18–24] focused on patients with dry eye disease with MGD, regardless of rosacea. Therefore, we evaluated the long-term effects of four IPL treatments with 3-week intervals, specifically in moderate or severe rosacea-associated MGD patients.

2. Materials and methods

2.1. Subjects

The protocol for this prospective study was written in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Inha University Hospital, Incheon, South Korea (IRB no. 2016-05-010).

From November 2015 to July 2016, study subjects were recruited from among patients visiting the dry eye clinic of Inha University Hospital. Subjects with moderate or severe MGD who fulfilled the diagnostic criteria for rosacea, or who were previously diagnosed with rosacea, were included. The grade of MGD was determined through assessment of meibomian gland parameters: abnormal lid margin vascularity, meibum expressibility, and meibum secretion [25,26]. Moderate or severe MGD was defined as follows: abnormal lid margin vascularity (grade ≥ 2), moderately or severely altered expressibility (grade ≥ 2), and secretion quality (grade ≥ 8) [25,26]. In accordance with the National Rosacea Society guidelines for rosacea [1], eligible subjects had any one of these primary features: transient erythema, persistent erythema, papules/pustules, and telangiectasia. Some subjects also had secondary features, such as phymatous changes. When necessary, we consulted a dermatologist for diagnosis and classification of rosacea. Informed consent was obtained from all eligible subjects after explanation of the purpose and possible consequences of the study.

The exclusion criteria were as follows: age < 20 years; a history of other ocular surgeries or ocular injury within 6 months before the study; presence of ocular diseases, such as infection or allergy; a history of contact lens use or glaucoma medication; contraindication to light therapy; and the presence of tattoos or pigmented lesions in the treatment area.

2.2. Treatment procedure

This prospective case series study was conducted for 12 months in all 17 subjects with rosacea-associated MGD who underwent four IPL treatment sessions at 3-week intervals and were followed up for the entire study period (Fig. 1). IPL treatment was administered on both eyes by using the M22™ Optima™ IPL (Lumenis, Yokneam, Israel), following the technique described by Toyos et al. [18] A 590-nm expert filter and pulse intensity of 11 J/cm^2 were used. Four separate treatment sessions were conducted at 3-week intervals, during which IPL was applied to four periocular areas from the nasal to temporal side below each lower lid, as in a previous report [19]. Following IPL application, the meibomian glands were expressed by using a cotton-tip applicator placed on the inside of the eyelid and the clinician's fingers positioned on the outside of the eyelid; this was performed at multiple sites of the lower lid. All procedures were performed by one of the authors (J.W.J). The subjects were instructed to continue the use of artificial tears and lid hygiene, as they had before participating in this study. They did not use other topical or systemic agents that could affect the ocular surface, from 1 month before the start of the study to the final follow-up.

2.3. Clinical assessments

The subjects were clinically evaluated at baseline (just before the first IPL treatment); 3 (before the second session), 6 (before the third session), 9 (before the 4th session), and 12 weeks after baseline; and 6 and 12 months after baseline. The first four evaluations were conducted just before IPL treatment. Each patient was followed up for a total 12 months from baseline. Data for analysis was obtained from the right eye unless right eye was excluded from the study, in which case (n = 2) data were collected from the left eye.

All measurements were sequentially performed as follows (Fig. 1). The tear film was assessed using the "TF-Scan, noninvasive Keratograph break-up time (NIKBUT)" mode of the Keratograph® 5 M (K5 M; Oculus, Optikgerate, Germany). The subjects were asked to completely blink two times and keep their eyes open for as long as possible. Irregularities in the image indicated instability or break-up of the tear film. At the same time, a video was recorded. The device provided a representation of the tear film break-up over time, and we selected the first break-up time (NIKBUT-first), in accordance with a previously described method [27,28]. Subjective symptoms were graded on a numerical scale from 0 to 4, according to the validated 12-item Ocular Surface Disease Index (OSDI) questionnaire. The total OSDI score was calculated using the following formula: OSDI = (sum of scores for all questions answered × 100)/(total number of answered questions × 4). The total score ranges from 0 to 100 [29]. The fluorescein tear break-up time (TBUT) was measured by applying a single fluorescein strip (Haag-Streit, Koeniz, Switzerland) moistened after instilling a drop of normal saline to the inferior palpebral conjunctiva. The mean time in three attempts was recorded. On the basis of the fluorescein staining pattern noted on slit-lamp biomicroscopy, ocular surface staining was graded from 0 to 3 according to the National Eye Institute (NEI)/Industry Workshop scale of 0–33 [30]. Schirmer's test I was performed only at baseline, without

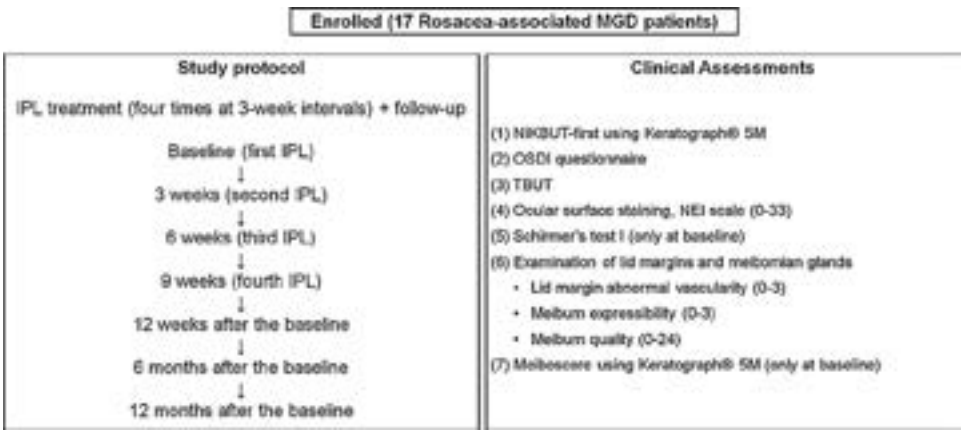

Fig. 1. Study flowchart showing the process and protocols.
MGD, meibomian gland dysfunction; IPL, intense pulsed light; NIKBUT, noninvasive Keratograph® tear break-up time; OSDI, ocular surface disease index.

topical anesthesia. A Schirmer strip was placed in the mid-lateral portion of the lower fornix and the amount of wetting was recorded after 5 min. The subjects were asked to keep their eyes lightly closed during the test.

As previously described, the lid margins and meibomian glands in the lower eyelid were checked for abnormal vascularity and degree of gland expression and meibum quality, respectively [25,26,28,31–34]. According to the degree of lid margin redness and distribution of telangiectasia crossing the orifices, abnormal vascularity in the lower lid margin was assessed on a scale from 0 to 3 [26]. The degree of meibomian gland expressibility was graded after the application of firm digital pressure on five glands in the central third of the lower eyelid: grade 0, five expressible glands; grade 1, three to four expressible glands; grade 2, one to two expressible glands; and grade 3, no expressible gland [25,28,32,34]. The meibum quality for eight lower lid glands was graded as follows: grade 0, clear; grade 1, cloudy; grade 2, cloudy with granular debris; and grade 3, thick and toothpaste-like. Each of the eight glands was graded, and the eight scores were summed to obtain a total score ranging from 0 to 24 [25,28,31,32]. At the baseline examination only, both the upper and lower eyelids were sequentially imaged using the meibography mode of the K5 M [28]. The areas of meibomian gland dropout were assessed using a four-point (0 to 3) grading scale described by Pflugfelder et al. [34]: grade 0, no dropout; grade 1, dropout in less than one-third of the total area; grade 2, dropout in one-third to two-third of the total area; and grade 3, dropout in more than two-third of the total area. The assigned grade was termed the meiboscore [28,34,35].

2.4. Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA). Because the majority of variables were not normally distributed, nonparametric tests were adopted. Categorical data are expressed as frequencies and continuous data are expressed as medians and interquartile ranges (IQRs). Friedman tests were used to compare data across the various time points. Post-hoc test of Wilcoxon signed rank test was performed to compare data between baseline and each post-treatment time point, with Bonferroni correction for multiple comparisons. An adjusted P value (by Bonferroni correction) less than 0.05 was considered statistically significant.

3. Results

Table 1 summarizes the baseline characteristics of the 17 subjects. The median age was 64 years (range, 57–68) years, and seven (41.2%) subjects were women. According to the American National Rosacea Society Expert Committee classification, 12 of the 17 subjects (70.6%) had erythematotelangiectatic rosacea and two (11.8%) had papulopustular rosacea; three subjects (17.6%) also exhibited rhinophyma.

The ocular surface parameters for all subjects, including the OSDI score, Schirmer's test I score, TBUT, ocular surface staining score, and NIKBUT-first, are presented in Table 2, which also shows lid margin and meibomian gland parameters. At baseline, the proportions of subjects with lid margin abnormal vascularity grades 2 and 3 were 5.9% and 94.1%, respectively. Grades 2 and 3 of meibomian gland expressibility were observed in 76.5% and 23.5% of subjects, respectively. The median baseline meiboscore for the upper and lower eyelids was 3 for all subjects.

Table 1
Baseline Characteristics of Subjects with Rosacea-associated MGD.

Variables	Rosacea-associated MGD (n = 17)
Age (y), median (IQR)	64 (57–68)
Sex, n (%)	
Male	10 (58.8%)
Female	7 (41.2%)
Skin rosacea subtype, n (%)	
Subtype 1, Erythematotelangiectatic	12 (70.6%)
Subtype 2, Papulopustular	2 (11.8%)
Subtype 3, Phymatous	3 (17.6%)

IQR = interquartile range; MGD = meibomian gland dysfunction.

Table 2
Baseline Ocular Surface Parameters and Meibomian gland parameters of Subjects with Rosacea-associated MGD.

Variables	Rosacea-associated MGD (n = 17)
Ocular surface parameters, median (IQR)	
Subjective score (OSDI)	50.0 (20.8–66.7)
Schirmer's test I value (mm)	7.0 (1.0–21.0)
TBUT (seconds)	4.0 (3.0–6.0)
Ocular surface staining score (0-33), NEI scale	6.0 (4.0–10.0)
NIKBUT-first (seconds)	3.0 (2.5–5.9)
Lid margin abnormal vascularity (0-3), n (%)	
Grade 0	0
Grade 1	0
Grade 2	1 (5.9%)
Grade 3	16 (94.1%)
Meibomian gland expressibility (0-3), n (%)	
Grade 0	0
Grade 1	0
Grade 2	13 (76.5%)
Grade 3	4 (23.5%)
Meibum quality (0-24), median (IQR)	12 (11–16)
Meiboscore (Total) (0-6), median (IQR)	3.0 (2.0–6.0)

IQR = interquartile range; MGD = meibomian gland dysfunction; OSDI = ocular surface disease index; TBUT = tear break-up time; NEI = national eye institute; NIKBUT = noninvasive Keratograph® break-up time.

Ocular surface parameters, including the OSDI score, TBUT, ocular surface staining score, and NIKBUT-first, and meibomian gland parameters, including the lid margin vascularity and meibum expressibility and quality, exhibited significant changes from baseline to the final examination in all subjects (Friedman, $P < 0.050$ for all, Figs. 2 and 3).

The OSDI score improved after the first IPL treatment and were maintained for 12 months (Friedman, $P < 0.001$; Wilcoxon, $P < 0.050$ for all, Fig. 2). In total, 82.4% (14/17) of subjects reported an improvement in symptoms when individual differences between the baseline and final examinations were considered. Although the remaining three subjects exhibited the same level of symptoms at the final examination, they showed improvements of symptoms during the follow-up period. Their baseline OSDI scores were lower than those of all subjects. At the final examination, 88.2% (15/17) of subjects expressed satisfaction with the IPL treatment and desired additional treatment in the future.

TBUT showed a significant improvement at 6, 9, and 12 weeks after baseline (Wilcoxon, $P = 0.006$, 0.006, and 0.012, respectively). The ocular surface staining score improved after the first IPL treatment and was maintained until 12 weeks (three weeks after treatment completion; Wilcoxon, $P < 0.050$ for all). NIKBUT-first improved at 9 and 12 weeks after baseline (Wilcoxon, both $P = 0.024$). However, improvements of TBUT, staining score, and NIKBUT after IPL were not maintained at 6 and 12 months after baseline.

The meibum quality in the lower lid improved after the first IPL treatment and was maintained for 12 months (Friedman, $P < 0.001$; Wilcoxon, $P < 0.050$ for all; Fig. 2). The proportion of subjects with grade 3 abnormal vascularity decreased from 94.1% at baseline to 35.3% at the final examination (Friedman, $P < 0.001$, Fig. 3A), with an

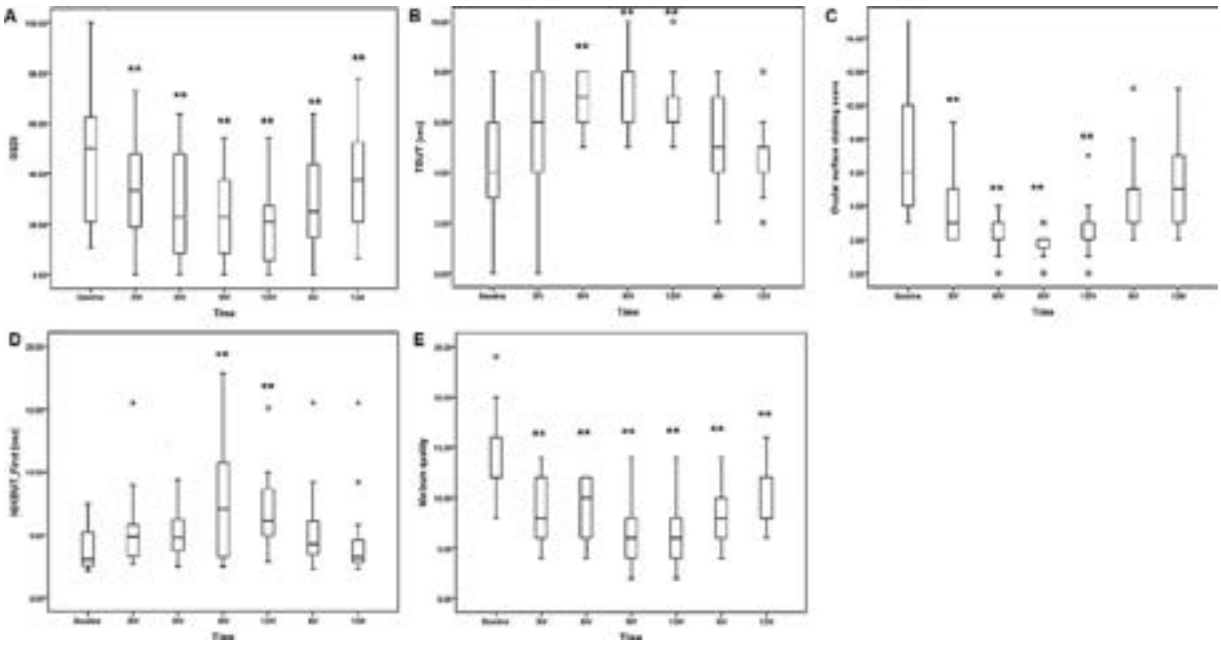

Fig. 2. Box plots showing long-term changes in ocular surface parameters, including the OSDI score (A), TBUT (B), ocular surface staining score (C), NIKBUT-first (D), and meibum quality in the lower lid (E) from baseline to the final examination in patients with rosacea-associated meibomian gland dysfunction (MGD) who underwent intense pulsed light (IPL) treatment.
Horizontal lines in the boxes indicate the median values (second quartile), while the box limits show the third (top) and first quartiles (bottom). Outliers (1.5–3 × interquartile range) are indicated as circles and extremes (> 3 × interquartile range) are indicated as asterisks. Maximum and minimum values are indicated by the top and bottom whisker ends, respectively.
**Significant difference between the baseline value and the value at each follow-up examination (Wilcoxon, $P < 0.050$).
OSDI, Ocular Surface Disease Index; TBUT, tear break-up time; NIKBUT-first, first noninvasive Keratograph® break-up time.

improvement in the median grade between baseline and the other follow-up examinations (Wilcoxon, $P < 0.050$ for all). The proportion of subjects with grade 2 or 3 meibomian gland expressibility decreased from 100% at baseline to 47.1% at the final examination (Friedman, $P < 0.001$; Fig. 3B), with an improvement in the median grade between baseline and the other follow-up examinations (Wilcoxon, $P < 0.050$ for all).

None of the subjects exhibited significant adverse events involving the skin, such as blistering, swelling, and burns, or involving the eye, such as conjunctival swelling or cysts, uveitis, and intraocular damage.

Fig. 4 shows a representative case involving a 51-year-old woman with rosacea-associated MGD who exhibited an improvement in the ocular surface condition from baseline to the final examination.

4. Discussion

In this prospective case series, we evaluated the long-term effects of IPL treatment in subjects with moderate or severe rosacea-associated MGD. Although IPL treatment has demonstrated clinical efficacy in patients with cutaneous rosacea and, recently, patients with MGD with

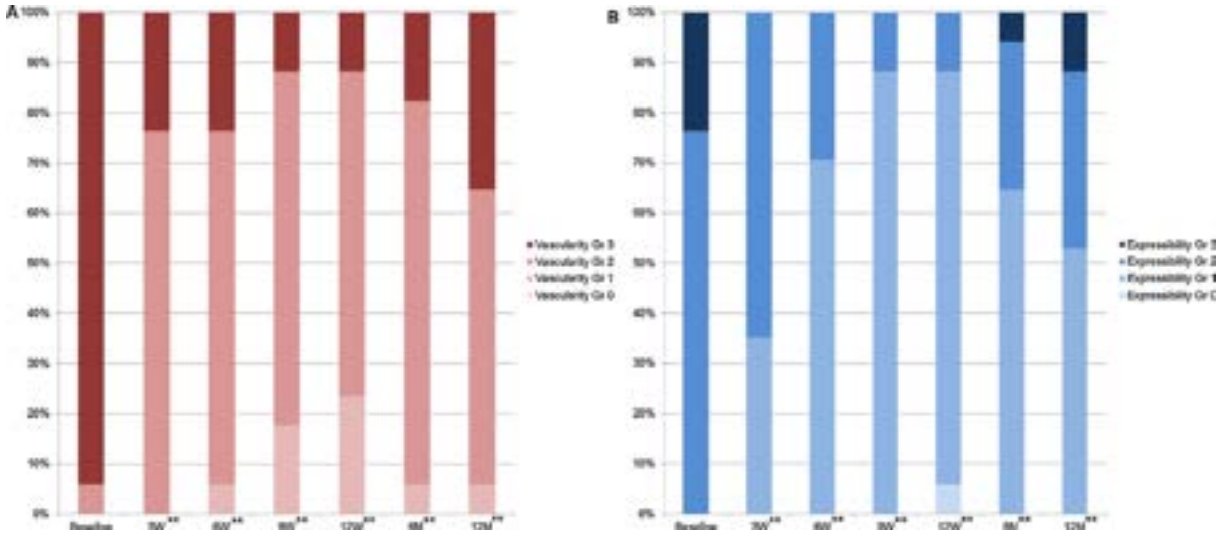

Fig. 3. Long-term changes in the lid margin vascularity and meibomian gland expressibility grade from baseline to the final examination in patients with rosacea-associated meibomian gland dysfunction (MGD) who underwent intense pulsed light (IPL) treatment.
**Significant difference between the baseline value and the value at each follow-up examination (Wilcoxon, $P < 0.050$).

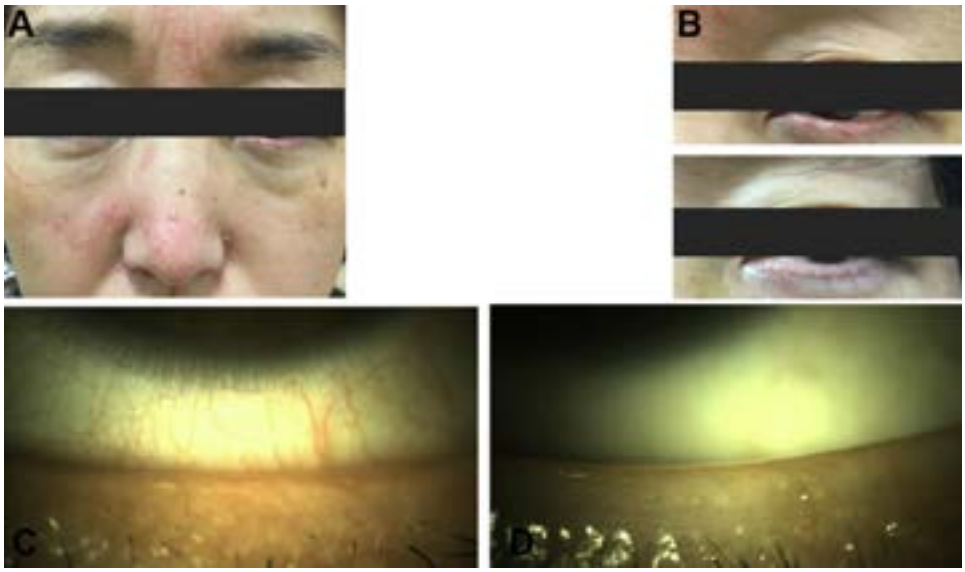

Fig. 4. A representative case of rosacea-associated meibomian gland dysfunction (MGD) exhibiting an improvement in the ocular surface condition from baseline to the final examination after four intense pulsed light (IPL) treatments.
A 51-year-old woman was treated for cutaneous rosacea at the Department of Dermatology 6 years ago. Persistent erythema and telangiectasia were noted in her cheeks, nose, and central forehead, and the redness of the lower lid margin were shown (A). Reduced redness of the lid margin was noted at the baseline and final examination (B). The baseline examination showed redness of the lid margin and bulbar conjunctiva (C), while the final examination revealed reduced redness (D). Ocular surface disease index score improved from 72.92 at baseline to 47.91 at the final examination.

or without rosacea [15,18–24], we attempted to evaluate its effects on the ocular surface in patients with rosacea-associated MGD only.

Our results revealed significant improvements in ocular symptoms from 3 weeks after the first IPL treatment up to the final examination at 12 months. Tear film instability and ocular surface epithelial damage resolved during the treatment period and for 3 weeks after the completion of treatment. The lid margin vascularity, meibum expressibility, and quality also exhibited significant improvements up to the final follow-up examination. Our results are in agreement with those of several previous studies [15,18–24] showing the effects of IPL treatment for MGD.

Following the accidental observation of improvements in ocular discomfort after IPL treatments for patients with rosacea and acne [17], IPL treatment has been tried for patients with MGD with or without cutaneous rosacea [15,17–24]. Although the mechanisms underlying the effects of IPL treatment for MGD remain unclear, previous studies have suggested that the most important mechanism is coagulation and ablation of blood vessels through light absorption by oxyhemoglobin [15]. In particular, vasodilation and the subsequent release of inflammatory mediators play an important part of the pathophysiology in patients with rosacea-associated MGD [9–11]. Therefore, our finding of a decrease in the lid margin vascularity after treatment indicated this mechanism for the treatment effects. Some studies actually showed a decrease in the cutaneous blood flow and presumed a decrease in the extravasation of inflammatory mediators after IPL treatment [15,36]. A recent randomized, double-masked, controlled study [24] showed a decrease in tear inflammatory cytokines such as interleukin (IL)-17 A and IL-6 after IPL treatment for patients with dry eye disease resulting from MGD. They reported that the change in tear prostaglandin E2 correlated with changes in corneal staining scores [24]. Thus, our findings regarding improvement of ocular surface epithelial damage could be explained by a decrease in ocular surface inflammation after IPL.

In addition, the warming effects of IPL treatment and immediate meibum expression could play a role in the improvement of meibomian gland expressibility. Because of increased meibum secretion and a change in the viscosity and quality of meibum, the tear film could become more stable, resulting in an improvement in dry eye symptoms [15]. In rosacea-associated MGD, lid bacteria can alter meibum secretion through the production of lipase, and demodex may correlate with the pathophysiology of rosacea [2]. Therefore, another potential mechanism of action for IPL treatment involves a decrease in infectious pathogens in the eyelid [15].

Although IPL has been proven effective for MGD in previous studies, the subject characteristics, protocols, and outcome measurements differed among those studies; therefore, direct comparison of those results is difficult. However, they commonly showed an improvement in ocular symptoms and the MGD severity using slightly different indicators. One prospective paired-eye study by Craig et al. [19] showed the efficacy of IPL in an MGD patient sample that mostly included relatively young women (20/28) with mild to moderate MGD. On day 45 after only two IPL treatments (on day 1 and 15), they found a benefit of IPL through the assessment of parameters such as the lipid layer grade, noninvasive TBUT, and self-reported visual analog scale scores. Our prospective study also showed a significant improvement in ocular surface parameters after one or two IPL treatment sessions for subjects with rosacea-associated MGD. Craig et al. [19] did not express the meibomian glands after IPL; we believe the positive effects observed in our study were also a result of post-treatment expression. Thus, we cannot conclude that the effects seen in our subjects were solely the result of IPL treatment. In recent trials [17,20,21,23] and clinical practice, IPL treatment followed by meibomian gland expression has been preferred for maximum effects attributed to the expression of warmed and liquefied meibum. Because our subjects had more severe MGD, we believed that meibomian gland expression was necessary.

The follow-up duration in our study was longer than that in previous studies [15,17,19–24]. Improvements in the lower lid margin vascularity, meibum expressibility and quality, and ocular symptoms persisted up to the final examination. Therefore, IPL may be an effective treatment with long-lasting effects for lid parameters and ocular discomfort in subjects with rosacea. However, at 6 and 12 months after baseline, other parameters, including TBUT, ocular surface staining score, and NIKBUT-first, were not different from baseline. Tear film abnormalities in rosacea-associated MGD may be the results of a mixed mechanism involving evaporative dry eye and aqueous tear-deficient dry eye [4,6,8]. These findings suggest that repeated IPL treatment may be required, depending on the ocular surface status in patients with rosacea-associated MGD.

Our study limited the subjects to patients with moderate to severe rosacea-associated MGD, unlike previous studies. The evidence of IPL is also limited in the field of dermatology; however, a sustained decrease in facial erythema and telangiectasia was reported for at least 6 months after four IPL treatments at 3-week intervals [16]. Although there are several treatment options for rosacea, the various signs and symptoms of the condition are nevertheless characterized by remissions and exacerbations [37]. Because ocular discomfort is an important part of

quality of life in these patients, our results showed the possibility of IPL as a safe and an effective treatment option for the ocular surface as well as the skin. However, our study is limited by the small sample size and non-randomized, non-controlled study design. Therefore, our results could be attributed to placebo effects. Hence, further randomized controlled studies are required to clarify our findings.

In conclusion, the findings of the present study suggest that four IPL treatments at 3-week intervals can improve long-term lid parameters and ocular symptoms without adverse effects, in patients with rosacea-associated MGD.

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Conflicts of interest

The authors have no financial conflicts of interest.

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Latent Demodex infection contributes to intense pulsed light aggravated rosacea: cases serial

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Latent Demodex infection contributes to intense pulsed light aggravated rosacea: cases serial

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ABSTRACT

Intense pulsed light (IPL) is a good option for erythema and telangiectasia of rosacea. Demodex, which is light and heat sensitive, is an important risk of Rosacea. Sometimes, IPL can induce rosacea aggravation. Here, we show two cases of erythema rosacea aggravated as pustule in several hours after IPL. Both cases show high density of Demodex after IPL. Neither of them had photosensitivity, systemic disease, or any other contraindication for IPL. One of the patients received IPL again after Demodex infection relieved and this time there was no inflammation induction. We need to attract more attention to IPL-induced rosacea aggravation and latent Demodex infection may act as a cofactor.

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KEYWORDS
Rosacea; Demodex; intense pulsed light

What is already known about this topic?

(1) IPL (Intense Pulsed light) can treat the redness and telangiectasia of rosacea.
(2) Rosacea is associated with Demodex infection.
(3) Demodex is photophobia and light sensitive.

What does this study add?

(1) Demodex infection may contribute to the rosacea aggravation after IPL in a few hours.

Introduction

Erythema and telangiectasia of rosacea treated by intense pulsed light (IPL) can achieve good response(1,2). Sometimes, IPL may induce rosacea aggravation, while the exact mechanism is still unclear. Demodex infection is an important risk for Rosacea(3, 4). Demodex is light and heat sensitive. IPL-generated light and heat may react with Demodex, then induce acute inflammatory and get worse rosacea. Here, we show two similar cases of IPL-aggravated rosacea in several hours. Photosensitivity, systemic disease, or any other contraindication are all excluded before IPL treatment. After aggravation, both cases were detected with high density of Demodex (15–22 cm^2 skin). After Demodex infection is relieved, one of the cases received IPL again without inflammation induction. IPL-induced rosacea aggravation and latent Demodex infection may act as a cofactor. Now we share our two cases as following.

Case 1

A 25-year-old woman presented with consistent erythema on her face. She was diagnosed as Rosacea for 2 years. Before this admission, she was treated with topical 0.03% tacrolimus for 2 months. She denied photosensitivity, allergies, and other systemic diseases. Skin examination showed multiple erythema, scattered papules, and telangiectasia on nasal and cheeks (Figure 1a). The laboratory examination showed that ANA, dsDNA, ENA, and other autoantibodies were negative. As the patient concerns the erythema and telangiectasia, IPL (lumenis, M22, pulse width 5.0 ms, dual pulse, pulse delay 30 ms, 15 J/cm^2) was applied. Cooling device come with the IPL machine and cold air spray were applied during our IPL treatment. Ice cold wet mask was applied with cold air spray immediately after IPL for half an hour. She followed doctor's advice to avoid hot air and sunshine. Sustained itch appeared 6 h later and cannot be alleviated by cold wet spray. About 16 h later, multiple small pustules were developed on nasal and cheeks (Figure 1b). About 24 h post IPL, we checked Demodex folliculorum by standardized skin surface biopsy (6) and found numerous Demodex (23 cm^2 skin) on forehead, cheek, and nasal dorsum. Then, the patient was treated with oral doxycycline 100 mg bid for 4 days and the pustules relieved. But because of stomach discomfort caused by doxycycline, she switched to oral minocycline 100 mg bid for 2 weeks. Meanwhile, she applied cream and cold spray twice a day. At the revisit 4 months later, there was no pustule or obvious erythema on her face (Figure 1c). Demodex detection showed normal range (only 1–2 cm^2 skin).

Case 2

A 50-year-old woman accompanied by repeated facial blush, papules, and pustules for 3 years sought for laser therapy. Previously, she was treated by intermittent oral minocycline 50 mg bid, oral herb medicine, topical clindamycin gel, and

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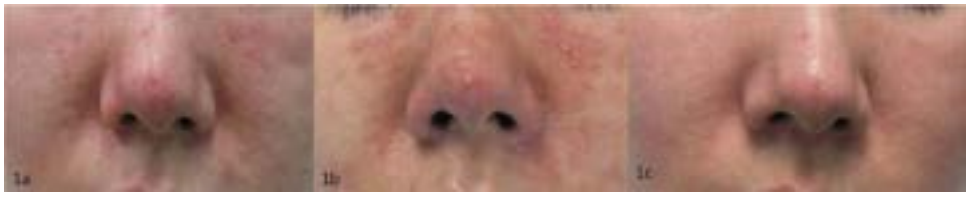

Figure 1. (a) Before 1st IPL; (b) irratation after 1st IPL; (c) after minomycin + topical treatment.

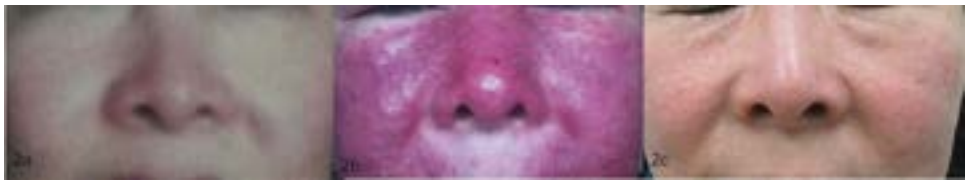

Figure 2. (a) Before 1st IPL; (b) irratation after 1st IPL; (c) after minomycin + topical treatment + IPL again.

topical 0.03% tacrolimus cream. She also had undergone red light (630 nm) treatment four times (twice a week). She denied photosensitivity, allergies, and other systemic diseases. Skin examination showed multiple erythema and scattered telangiectasia on nasal and cheeks. The laboratory examination showed that ANA, dsDNA, ENA, and other autoantibodies were negative. Then, she received IPL treatment (lumenis, M22, pulse width 5.0 ms, dual pulse, pulse delay 30 ms, 15 J/cm^2). She also applied cooling treatment as in Case 1. The next day she developed pustules and papules with significant itching on her face (Figure2b). From the skin sample acquired from her face using adhesive dehydration, there were numerous Demodex (15 cm^2 skin). Then she was treated with oral minocycline 100 mg bid for 1 month. Pustules and papules subsided and there is still diffuse erythema. Demodex detection showed normal range (only 1–2 cm^2 skin). In order to treat the diffuse erythema, IPL was applied again. Meanwhile, 0.03% topical tacrolimus was applied. This time, there was no side effect and the erythema partially relieved after IPL. So she received IPL once a month for eight times and the erythema was almost gone (Figure2c).

Discussion

For the treatment of rosacea, IPL, laser, red, and blue light played an important part. Especially, IPL and pulsed dye laser on telangiectasia and persistent erythema treatment achieved good results(1,2,5,6). Some scholars suggested that IPL should be applied after inflammatory lesions relieved. For acne vulagris treatment, IPL can improve inflammatory papules of acne (7,8). IPL can invoke rosacea which has been buzzed through patients and doctors. These two cases presented rosacea exacerbation in 6–24 h. Both cases detected many Demodex. One of the possibilities is Demodex infection. Intense light irritation may make large amount of *Demodex folliculorum* sensitive, temporary active, or death in one time, thus stimulating the acute inflammatory response. The Demodex infection symptoms had not been found before IPL, which may be due to suppressed inflammation caused by topical tacrolimus. These two patients were also treated with topical tacrolimus for more than 2 weeks. One of the patients treated with IPL after Demodex infection got relieved and did not show rosacea exacerbation, which confirm our hypothesis. Heat may also aggravate rosacea. During and after treatment, cooling treatment was applied and the patients did not feel heat or burn. And the patient treated with IPL again did not show rosacea worse.

The limitation of our report is that only two retrospective cases were analyzed. Here, we just remind doctors to observe and record similar cases and to analyze the causes. In addition, before IPL treatment for rosacea, *Demodex folliculorum* detection may be necessary. If it is high density, be alert and prepared to the aggravation. In the future, more studies should be addressed on the exact mechanism.

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Therapeutic Effect of Intense Pulsed Light on Ocular Demodicosis

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Keywords: *Demodex*, Intense Pulsed Light, Ocular surface, Ocular demodicosis

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ABSTRACT

Purpose: To evaluate the clinical efficacy of Lumenis® M22™ intense pulse light (IPL) in reduction of ocular *Demodex* infestation in eyelashes in a prospective study.

Methods: Forty patients with ocular demodicosis were recruited. Then half were randomly picked to receive the IPL treatment, while the other half got 5% tea tree oil (as the control group). *Demodex* counts, the ocular surface disease index (OSDI) score, lid margin abnormalities, conjunctival congestion, tear break up time (TBUT), corneal staining with fluorescein, meibomian gland (MG) expressibility, meibum quality, modified Schirmer I test with anaesthetic (SIT), were assessed on the day before treatment and after treatment of 30 days and 90 days. Changes in the parameters were compared between the IPL group and the control group on the days after treatment of 30 days and 90 days.

Results: No differences were observed in *Demodex* counts, lid margin abnormalities, conjunctival congestion, corneal staining with fluorescein, MG expressibility, SIT in the two groups on the days after treatment of 30 days and 90 days ($P > 0.05$), whereas there was a statistically significant difference in the OSDI score, TBUT, meibum quality ($P < 0.05$). The *Demodex* eradication rate was more thorough in the IPL group (100%) than in the control group (75%).

Conclusions: Intense pulsed light shows the preferably therapeutic potential for ocular Demodicosis.

Keywords: *Demodex*, Intense Pulsed Light, Ocular surface, Ocular demodicosis

Trial registration: ChiCTR-OON-16010205. Registered 21 December 2016.

INTRODUCTION

Blepharitis and blepharoconjunctivitis are characterized by inflammation of the outer eyelids and the conjunctiva that results in redness, swelling, prickle and stabbing pain, and also can lead to scarring of the eyelid and loss of proper eyelid function over time. Both they are closely associated with *Demodex* infestation. [1-3] *Demodex* is a microscopic, elongated mite which is the common permanent ectoparasite of humans. [4] The prevalence of *Demodex* infestation increases with age, reaching 84% of the population at age 60 years and 100% of those older than 70 years. [5] Ocular manifestations of *Demodex* infestation include unexplained keratitis, superficial corneal vascularization, marginal infiltration, phlyctenule-like lesions, nodular corneal scarring, etc. [6,7] It was proven that ocular demodicosis can be essentially diagnosed by the modified eyelash sampling and counting method and *in-vivo* confocal microscopy (IVCM). [8-9] However, there are only a few effective treatments at present.

Tea tree oil (TTO) has been effectively used to eradicate ocular *Demodex* infestation. [10] Daily lid scrub with 50% TTO for 4 weeks or 5% TTO for 12 weeks is effective in resolving ocular symptoms and inflammation in the lid margin, conjunctiva, and significantly stabilizing the lipid tear film and improving the visual acuity. [10–12] However, the application of TTO is not convenient for self-administration and can cause irritation in some patients. [12] The most

active ingredient in Cliradex, terpinen-4-ol (T40) has also been identified to be as effective as TTO in reducing infestation of *Demodex* mites and ocular inflammation with minimal side-effects. [13,14] This method is widely used, although the strong odor and long treatment cycle may not be well-tolerated by the most patients. Other methods include: 1) iodized solution for topical cleaning, followed by application of the acaricide Permethrin 1%;[15] 2) ether application complemented by application of yellow mercuric oxide 1% or 2% with Vaseline/lanolin to the eyelashes and lid rim;[16] 3) pilocarpine gel 4%;[12] 4) metronidazole 2% cream;[17] 5) pimecrolimus 1% cream (a calcineurin antagonist)[18] and daily lid scrubbing with baby shampoo. As these methods have to be used continuously for one to three months, it is also difficult for patients to maintain compliance. That role, however, is different from what many people expect and probably wish. So we need a new method to eradicate ocular *Demodex* quickly and completely.

The first report of IPL for treating facial dermatological conditions dates from 1996. [19] In 2002, Prieto et al. were pleasantly surprised to find that *Demodex* organisms appeared coagulated one week after IPL treatment for cutaneous disease. [20] They considered that these IPL settings induced coagulation necrosis of *Demodex* organisms while preserving the surrounding hair follicles. It is possible that *Demodex* contains a chromophore that renders the parasite more sensitive to the energy delivered by IPL. Additionally, it is likely that approximately spherical structures such as *Demodex* may not be able to transfer as much energy as the open-ended cylindrical hair follicles. The ocular demodicosis and facial demodicosis belong to the same origin. Until now, there has a few reports of eradicating ocular demodicosis using IPL. [21]

The purpose of this study was to evaluate the therapeutic effect of intense pulsed light on ocular demodicosis in 20 patients with a history of recurrent blepharitis compared with the 20 patients with a history of recurrent blepharitis with 5% tea tree oil treatment.

METHODS

Subjects

This study was conducted in compliance with the Declaration of Helsinki for research involving human participants and was approved by the Ethics Committee of the Eye, Ear, Nose, and Throat (EENT) Hospital of Fudan University. Written informed consent was obtained from all participants before the examination.

This is a simple blind, random controlled clinical trial and the examiner was masked to the treatment groups. Forty patients were recruited from the EENT Hospital of Fudan University, Shanghai, China. All patients with blepharitis experienced ocular demodicosis [17]. Forty patients were randomly divided into two groups. Twenty participants underwent IPL treatment (12 males and 8 females, aged 39.15±10.98 years). Twenty participants underwent 5% tea tree oil treatment (14 males and 6 females, aged 38.25±12.34 years). Subjects who had acute episodes of ocular surface or facial skin diseases, history of sun exposure or allergic disease within one month, any topical or systemic diseases that could affect results (facial skin cancer, recurrent herpes simplex, graft-versus-host disease, systemic lupus erythaematosus, etc.), eye surgery and medical treatment or any other treatment that could affect intense pulsed light treatment and results were excluded.

On the day before treatment and after treatment of 30 days and 90 days, all enrolled subjects

were tested in the following sequence: ocular surface disease index (OSDI), slit lamp biomicroscopic examination, conjunctival congestion, fluorescein tear film break-up time (F-BUT), corneal fluorescein staining (CFS), modified Schirmer I test with anaesthetic (SIT), meibomian gland assessment including MG expressibility, meibum quality. Measurements in all patients were conducted by a single operator. Also, only the right eye of each patient was analysed.

Ocular demodicosis confirmation

Ocular demodicosis was confirmed by light microscopic examination (LME) of epilated lashes as previously reported. [13, 22] Briefly, four lashes with cylindrical dandruff (CD)were epilated from each eyelid under slit lamp from one eye and mounted on glass slides. One drop of saline or fluorescein solution was applied to dissolve the CD and to allow embedded *Demodex* to migrate out. The total *Demodex* counts were determined under a light microscope. *Demodex* counts greater than or equal to 1 were *Demodex-positive.* We defined "successful eradication" as a reduction of the count to 0 during examination one month or three months after treatment. [17]

Lid margin abnormalities

Lid margin abnormalities were scored from 0 to 4 based on the presence of 4 criteria: [23] irregular lid margins, vascular engorgement, plugging of meibomian gland orifices and shift of the mucocutaneous junction.

Conjunctival congestion assessment

According to Institute for Eye Research (IER), [24] conjunctival congestion was graded as 0 (no congestion), 1 (congestion confined to the fornix with bright red blood vessels), 2 (obvious congestion that reached the palpebral fissure with crimson and fuzzy blood vessels), or 3 (diffuse congestion, fuchsia-coloured blood vessels and unclear meibomian gland texture).

Dry eye symptom assessment

The OSDI questionnaire was used to assess subjective DE symptoms. The questionnaire consisted of 3 subscales including bothersome symptoms, visual function and environmental triggers. Each answer was scored on a 5-point scale from 0 (indicating least severe) to 4 (indicating the most severe). Total scores ranged from 0 to 100, with higher scores indicating more severe symptoms.

Schirmer I test

Modified Schirmer I test with anaesthetic (SIT) was used to assess tear production by inserting a sterile dry strip (Jingming, Tianjing, China) into the lateral canthus of the lower eyelid away from the cornea for 5 minutes. The length of the strip that was wetted by absorbed tears was then measured to evaluate tear secretion function. Potential scores of the Schirmer I test ranged from 0 to 30 mm.

Tear film stability

Tear film stability was evaluated by TBUT. TBUT was measured by instilling fluorescein into the lower conjunctival sac with a fluorescein strip (Jingming, Tianjing, China) moistened with preservative-free saline solution. The patient was then required to blink several times to ensure adequate coating of the dye on the cornea. Using a cobalt blue filter and slit lamp biomicroscopy, the interval between the last complete blink and appearance of the first black spot in the stained tear film was recorded as the TBUT. The test was repeated 3 times and the average TBUT was calculated.

Corneal staining with fluorescein

The CFS was measured using the same fluorescein-impregnated strip used for TBUT. The grading system recommended by NEI divides the cornea into 5 zones (central, superior, temporal,

nasal and inferior). For each zone, the CFS severity was graded on a scale from 0 to 3. Therefore, the maximum score was 15. [25]

MG expressibility

Assessment of MG expressibility was conducted by applying digital pressure on the upper tarsus, after which the degree of expressibility was assessed on a scale of 0 to 3 for 5 glands in the middle part, according to the number of glands expressible: 0, all glands; 1, 3 to 4 glands; 2, 1 to 2 glands; and 3, no glands. [26]

Meibum quality

To evaluate meibum quality, eight glands of the central part of the upper lid were assessed on a scale of 0-3 for each gland: 0, clear; 1, cloudy; 2 cloudy with debris (granular); and 3, thick, like toothpaste (total score range, 0-24). [26]

5%TTO treatment

Each patient had 90 days treatment, TTO purchased from Essential Oil Company (Portland, OR) was mixed with petroleum jelly to 5% (vol/vol) TTO in a sterile hoo, lid massage with 5% TTO 15 minutes a day. [14]

IPL treatment

Each patient had three treatments. The following section describes the treatment methodology for administering IPL using the Lumenis® M22™ IPL system in this study: M22 system (Figure 1) is 510(k) cleared in the United States by the U.S. FDA for aesthetic applications (K142860). The M22 system is a multi-application, multi-technology system which comprises a system console, an operator control panel, an LCD monitor with touch-screen technology, and several treatment heads and handpieces. A thin (1-2 mm) coat of coupling gel was applied to the entire area to be treated, from ear to ear, including the nose, before administering IPL. The system is

continuously monitored and controlled by its internal computer. The treatments were performed using the proprietary "dry eye mode" setting, and energy parameters were determined based on skin type (skin type settings 1-4 and mode A-F) and patient tolerance and/or comfort. Skin type was determined using the Fitzpatrick scale; only patients with skin type 4 or lower were treated with IPL. IPL treatments were administered three times. Disposable safety eye wear was provided to all study participants, the safety eyewear was used for the treating physician and other medical personnel present in the room.

Statistical analyses

For the randomized study, the sample size calculation for patients was done according to the previous study by Hong and colleagues. [27] Our hypothesis was that there would be a 25% relative difference in between the IPL group and the control group, which meant that a sample size of 20 patients in each group was needed to get a power of 80% for a significance level of 5% with a two-tailed test. All analyses were performed by independent experts who were unaware of the treatment-group assignments. Numerical data were presented as mean ± standard deviation. The normal distribution test was conducted in the variables, and all the variables were normally distributed. The paired t-test was used to compare *Demodex* counts, lid margin abnormalities, conjunctival congestion, corneal fluorescence staining, meibomian gland (MG) expressibility, meibum quality, MSR and OSDI before and after treatment. Two-tailed Student's t-test was used to determine significant differences between data sets. Analyses were performed using SPSS V. 19.0 software (SPSS Inc.; Chicago, IL). *P* values less than 0.05 were considered statistically significant.

RESULTS

Forty patients were recruited from the EENT Hospital of Fudan University, Shanghai, China. All patients with blepharitis experienced ocular demodicosis. Twenty participants underwent IPL treatment (12 males and 8 females, aged 39.15 ± 10.98 years). Twenty participants underwent 5% tea tree oil treatment (14 males and 6 females, aged 38.25 ± 12.34 years), There were no significant differences in baseline datum of demographic data (Table 1), *D*emodex counts, OSDI, lid margin abnormality, meibum quality, MG expressibility, conjunctival congestion, SIT, TBUT, corneal staining with fluorescein between the IPL group and the control ($P > 0.05$) (Table 2). Compared with the control group, the IPL group took a faster effect. The mean mite count/8 lashes were decreased significantly after IPL treatment of 1 month using light microscopy (from 13.05 ± 8.49 to 2.35 ± 3.18; $P < 0.01$). The overall *Demodex* eradication rate was 55% (11/20). Compared with baseline, the OSDI scores, lid margin abnormalities, conjunctival congestion, meibum quality, MG expressibility were significantly decreased after treatment ($P < 0.05$ for each comparison). No significant difference was noted in Schirmer test values, TBUT and corneal staining with fluorescein between before and after treatment ($P > 0.05$ for each comparison). The parameters of *Demodex* counts, OSDI, lid margin abnormality, meibum quality, MG expressibility, conjunctival congestion, SIT, TBUT, corneal fluorescence staining between IPL group and the control group were compared. No differences were observed among groups with regard to the mean *Demodex* counts, lid margin abnormality, MG expressibility, conjunctival congestion, SIT, corneal staining with fluorescein, meibum quality and TBUT from baseline to the first month and the third month ($P > 0.05$), whereas there was a statistically significant difference in the mean OSDI in 1month treatment (-8.90±19.30 versus -19.44±24.44,

P=0.042, Table 3). Together, the results suggest that the IPL treatment is quicker and better in improving the objective visual quality.

The mean mite count/8 lashes decreased significantly after IPL treatment of 3 months using light microscopy (from 13.05 ± 8.49 to 0.00 ± 0.00; $P < 0.01$). The overall *Demodex* eradication rate was 100% (20/20). Compared with baseline, the OSDI scores, lid margin abnormalities, conjunctival congestion, meibum quality, TBUT, MG expressibility and corneal staining with fluorescein were significantly decreased after treatment ($P < 0.05$ for each comparison). No significant difference was noted in Schirmer test values between before and after treatment ($P > 0.05$ for each comparison). Compares the parameters of *Demodex* counts, OSDI, lid margin abnormality, meibum quality, MG expressibility, conjunctival congestion, SIT, TBUT, corneal staining with fluorescein between IPL group and the control group. No differences were observed among groups with regard to the mean *Demodex* counts, Lid margin abnormality, MG expressibility, conjunctival congestion, SIT, corneal staining with fluorescein in 1 month or 3 months treatment ($P > 0.05$), whereas there was a statistically significant difference in the mean OSDI (-15.57±27.77 versus -25.64±30.96, $P< 0.01$), meibum quality(-1.10±2.67 versus -4.20± 3.72, $P< 0.01$) and TBUT (-0.50±1.64 versus 2.45±2.44, $P< 0.01$) between the two groups in 3 months treatment. (Table 3) The eradication rate was more and reliable in the IPL group (100% VS 75%). (Table 3) Taken together, these results suggest that the IPL treatment has a better efficacy in eradicating *Demodex* and improving the function of meibomian glands in three months later (Figure 2).

DISCUSSION

This study found that application of IPL near the eyelids can effectively eradicate ocular Demodicosis with improved symptoms and ocular surface signs. However, the mechanism of killing *Demodex* using IPL treatment has not yet been recognized. A possible mechanism follows: M22 intense pulsed light (IPL) is a multi-application, multi-technology system with high-intensity light sources. Emitted polychromatic light extends from visible (515 nm) to the infrared spectrum (1200 nm). The light is directed to the skin tissue and absorbed by the targeted structure, resulting in the production of heat. *In vitro* experiments have shown that *Demodex* organisms live for a long time in 8 ~ 30 °C, with a suitable temperature for growth between 20 ~ 30 °C and an optimum growth temperature of between 25 ~ 26 °C. Temperatures under 0 °C or above 37 °C were not beneficial to growth and development of *Demodex*, 54 °C was the lethal temperature and 58 °C was the temperature required to eliminate mites effectively. [28] We speculated that the heat generated by IPL reached the temperature required to eliminate mites effectively. Additionally, as Prieto et al. found, *Demodex* organisms appeared to be coagulated one week after IPL treatment for cutaneous disease. [20] They considered that these IPL settings induced coagulation necrosis of *Demodex* organisms while preserving the surrounding hair follicles. *Demodex* organisms contain chromophores that render the parasite more sensitive to the energy delivered by IPL. Furthermore, the shape of the target structure is important in determining the response to the energy delivered. [29] It is likely that approximately spherical structures such as *Demodex* may not be able to transfer as much energy as open-ended cylindrical hair follicles. In addition, our results suggest that the overall eradication rate was 55% (11/20) in one month after IPL treatment, and by three months it has reached 100%，and the life cycle of mites is about 15 days. We speculated that IPL can regulate its germ cells, affecting its ability to reproduce.

The related researches suggest a clear improvement in symptoms and signs following treatment of posterior blepharitis using the Lumenis® M22™ IPL system. Recent work evaluated the effect of IPL for treatment of MGD in a prospective, randomized, placebo- controlled, double-masked and paired-eye study. [30, 31] Lipid layer grade, meibum composition or structure and subjective symptom scores all improved significantly from baseline to post-treatment in the treated eye, but not the control eye. [30] The results showed that IPL directly killed eyelid margin demodicosis in agreement with these previous reports. Preeya et al. hypothesized that the primary mechanisms for the treatment effect of IPL included reduction of chronic inflammation and improvement of meibum outflow by reducing eyelid margin telangiectasias. [32] The flash lamp used in IPL treatments emits a broad- spectrum light. There are 2 main chromophores in the skin: melanin and hemoglobin. The oxyhemoglobin absorption curve has multiple peaks that can be targeted for therapeutic use. The absorption peak at 578 nm allows the use of yellow light to induce selective photothermolysis in blood vessels. Once the yellow light travels through the superficial skin, the majority of absorption occurs in oxyhemoglobin, where it is then converted to heat. This in turn leads to vasculature destruction and thus reduction of inflammatory markers presenting at the eyelids. [32]

The study also showed that lid margin abnormalities and conjunctival congestion were significantly decreased one month and three months after IPL treatment. Some other explanations include facilitating expression by softening the meibum as a result of heat transfer to the eyelids and meibomian glands. [33] It also demonstrated that meibum quality and MG expressibility decreased significantly one month and three months after IPL treatment. The study confirms the above hypotheses. From our point of view, the primary mechanisms for the treatment effect of IPL for eyelid disease include not only reduction of chronic inflammation,

improvement of meibum outflow by reduction of eyelid margin telangiectasias and softening of meibum as a result of heat but also direct killing of *Demodex* from eyelid lashes by the production of heat. *Demodex* folliculorum mites live in hair follicles and sebaceous glands and often coexist with the bacillus oleronius bacterium. These organisms are known to cause an inflammatory response and have been linked to blepharitis and blepharokeratoconjunctivitis. Eradicating *Demodex* mites would have the indirect effect of decreasing the bacterial load on the eyelids, reducing the immune response and relieving symptoms associated with the eyelid margin and ocular surface. [34]

Additionally, compared with the traditional classical method of 5% TTO treatment for 3 months in a row, we found that though there were no differences among groups with regard to the mean *Demodex* counts, but the successful eradication rate was higher in IPL groups than in control groups. There was a statistically significant difference in the mean OSDI in 1 and 3 month treatment, meibum quality and TBUT between control and IPL groups ($P < 0.05$). The IPL treatment could take effect more quickly and could be more easily accepted by patients. Treatment with 5% TTO may stimulate the *Demodex* to exit the lash follicle. This unique action might be crucial in eradicating *Demodex*, [21] whereas IPL may take advantage of high temperature to kill the mites directly, affect its ability to reproduce and ease meibomian gland dysfunction to damage the environment where mites live. The principle of the two methods is different，but patients need only three times treatments by IPL, so it is a simple and effective method.

There are some limitations in this study: A large sample size and extended research are needed to optimize the parameters and the frequency for IPL treatment. Another limitation in this study is

the use of fluorescein tear break-up time instead of a non-invasive procedure, the volume of fluorescein delivered to the tear film affected the TBUT values and that larger amounts of fluorescein instilled tended to lengthen its duration. In addition, the use of topical anaesthesia to assess tear volume tended to lower than without, because the rate of reflex tearing is known to decrease following instillation of a topical anaesthesic. Topical anaesthesic decreased corneal sensitivity, so they may lead to a low OSDI score. The eyelid margin *Demodex* include two types: one is from eyelid lashes and another from meibomian glands. This study epilated the eyelashes to evaluate *Demodex* counts and ignored the meibomian gland. IPL could have a different effect on *Demodex* infestation in meibomian glands. If an in-vivo confocal microscopy was performed and its added advantage of assessing and reporting changes in *Demodex* infested in meibomian glands, the detection rate of the *Demodex* would be higher and the results would be more accurate.

In summary, our findings suggest that the IPL treatment shows therapeutic potential for ocular demodicosis.

Abbreviations:

intense pulsed light	**IPL**
tear break up time	**TBUT**
meibomian gland	**MG**
ocular surface disease index	**OSDI**
in vivo confocal microscopy	**IVCM**
tea tree oil	**TTO**
Eye, Ear, Nose, and Throat	**EENT**

corneal fluorescein staining	**CFS**
Schirmer I test	**SIT**
cylindrical dandruff	**CD**
light microscopic examination	**LME**
Institute for Eye Research	**IER**

Declarations:

This study was conducted in compliance with the Declaration of Helsinki for research involving human participants and was approved by the Ethics Committee of the Eye, Ear, Nose, and Throat (EENT) Hospital of Fudan University. Written informed consent was obtained from all participants before the examination.

Consent for publication:

Written informed consent to publish was obtained from all participants before the examination.

Availability of data and material:

The main data of our study presented in the tables of the main paper

Competing interests:

The authors declare that they have no competing interests

Authors' contributions:

The manuscript was written through contributions of all authors. All authors read and approved the final version of the manuscript

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Figure 1: Lumenis® M22™ IPL system. Multifunctional M22 platform and IPL handpiece.

Figure 2: The palpebral margin of before and after treatment(90 days) in two groups of patients . A. Before the IPL treatment, demodex was strongly positive and meibomian gland dysfunction; B. After the 90 days treatment of IPL, demodex was negative and the meibomian gland improved significantly; C. Before the TTO treatment, demodex was strongly positive and meibomian gland dysfunction; D. After the 90 days treatment of TTO, demodex was negative and the meibomian gland was slightly better

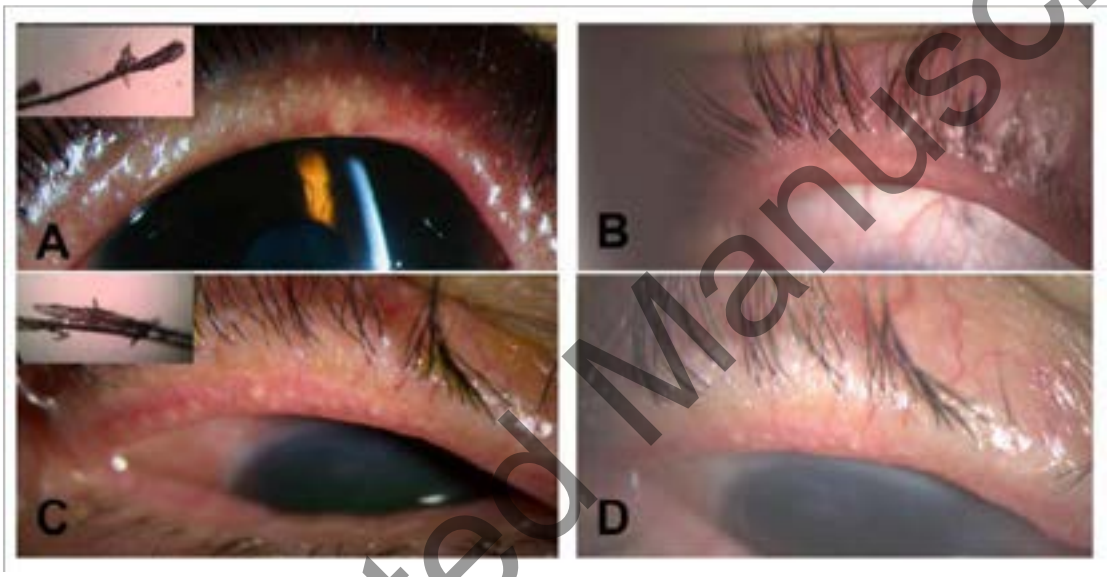

Table 1 Demographic datum in IPL group and the control(Mean±SD)

	Control (n=20)	IPL (n=20)	*P*-value
Age (years)	39.15±10.98	38.25±12.34	0.903
F/M	8/12	6/14	0.523

Table 2 Comparison of baseline data between controls and IPL treatment group (Mean±SD)

	Control (n=20)	IPL (n=20)	*P*-value
Demodex counts	12.85±6.49	13.05±8.49	0.849
OSDI	33.46±29.08	30.47±30.45	0.489
Lid margin abnormality	0.70±0.47	0.75±0.44	0.740
Meibum quality	5.45±3.66	5.55±3.79	0.912
MG expressibility	1.45±0.51	1.50±0.51	0.767
Conjunctival congestion	0.65±0.49	0.70±0.47	0.752
SIT (mm/5 min)	6.7±6.63	6.35±6.42	0.793
TBUT (s)	5.4±1.79	5.6±1.67	0.772
Corneal fluorescence staining	0.45±0.69	0.40±0.75	0.639

Table 3 Changes in the variables from baseline to 1 month and 3 months after treatment (Mean±SD)

	One month			Three months		
	control	IPL	*P*-value	control	IPL	*P*-value
Demodex counts	-9.90±7.21	-10.70±8.47	0.755	-11.05±6.89	-13.05±8.49	0.780
OSDI	-8.90±19.30	-19.44±24.44	0.042*	-15.57±27.77	-25.64±30.96	<0.01**
Lid margin abnormality	-0.20±0.52	-0.50±0.51	0.085	-0.35±0.59	-0.55±0.51	0.294
Meibum quality	-0.95±2.31	-3.10±4.22	0.087	-1.10±2.67	-4.20±3.72	0.006**
MG expressibility	-0.05±0.22	-0.35±0.49	0.050	-0.25±0.64	-0.35±0.67	0.559
Conjunctival congestion	-0.20±0.52	-0.50±0.51	0.085	-0.35±0.59	-0.55±0.51	0.294
SIT (mm/5 min)	0.00±1.52	0.00±0.86	0.947	-0.10±1.74	0.15±1.93	0.603
TBUT (s)	0.00±1.52	0.20±0.83	0.700	-0.50±1.64	2.45±2.44	<0.01**
Corneal fluorescence staining	-0.05±0.22	0.20±0.52	0.299	-0.30±0.57	-0.25±0.44	0.942

* $P < 0.05$; ** $P < 0.01$.

SCIENTIFIC REPORTS

OPEN

Meibum Expressibility Improvement as a Therapeutic Target of Intense Pulsed Light Treatment in Meibomian Gland Dysfunction and Its Association with Tear Inflammatory Cytokines

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Many recent studies have demonstrated the efficacy of intense pulsed light (IPL) for the treatment of meibomian gland dysfunction (MGD); however, its effective treatment targets have not yet been elucidated. This study aimed to investigate the baseline characteristics associated with an improvement in symptoms after IPL treatment; to examine the course of change in inflammatory tear cytokines, meibomian gland function, and tear stability; and to investigate the correlation between cytokines and ocular surface parameters. Thirty participants underwent three sessions of IPL treatment. During each examination, tear film lipid layer interferometry, meibography, tear meniscus height measurement, tear sampling, and slit-lamp examination were performed, and the Ocular Surface Disease Index (OSDI) questionnaire was administered. Meibum quality, meibum expressibility, lid margin abnormality, tear film break-up time (TBUT), ocular surface staining, and the OSDI significantly improved after treatment. Poor meibum expressibility and short TBUT were associated with greater recovery in the OSDI after IPL. Tear levels of IL-4, IL-6, IL-10, IL-17A, and TNF-α decreased after IPL, and IL-6, and TNF-α were correlated with the improvement in meibum expressibility. Therefore, IPL treatment improved meibomian gland function, stabilized the tear film, and decreased ocular surface inflammation. Patients with obstructive MGD and tear instability were more likely to experience an improvement in ocular discomfort after IPL treatment.

Meibomian gland dysfunction (MGD) is a prevalent cause of evaporative dry eye, affecting more than 50% of the Asian population[1]. However, many patients do not benefit from currently available treatments such as lid hygiene, meibum expression, and anti-inflammatory therapy[2].

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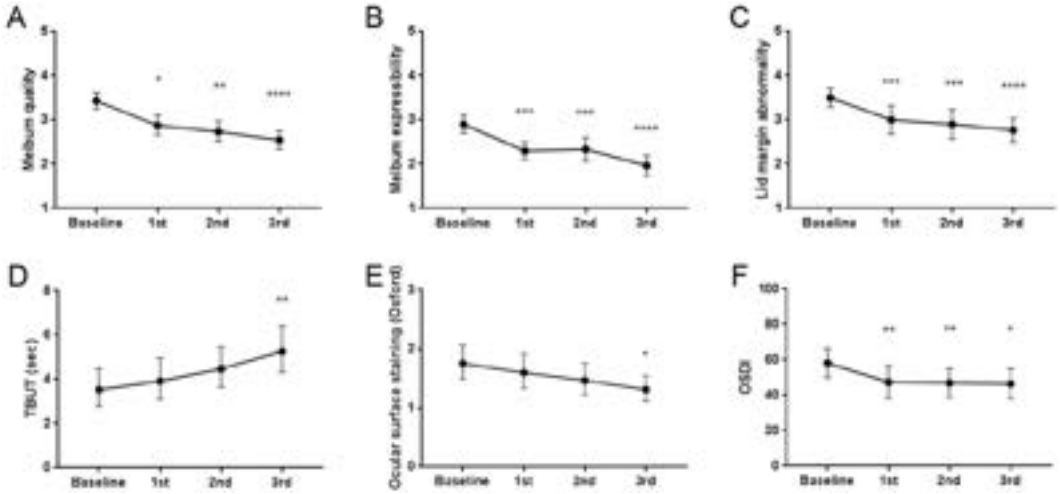

Figure 1. Change in clinical parameters following each intense pulsed light treatment session in patients with meibomian gland dysfunction. (**A**) Meibum quality, (**B**) meibum expressibility, (**C**) lid margin abnormality, (**D**) tear film break-up time (TBUT), (**E**) ocular surface staining score using the Oxford scheme, and (**F**) Ocular Surface Disease Index (OSDI). $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$; Friedman test or repeated-measure analysis of variance (ANOVA) with post-hoc multiple comparison analysis, comparing the value after each session to that of the baseline. Individual points and error bars represent the mean (**B**,**C**,**F**) or the geometric mean (**A**,**D**,**E**) and 95% confidence interval.

Concurrent improvement of ocular surface conditions observed in patients treated for rosacea of their face, led to the potential implementation of intense pulsed light (IPL) for the treatment of MGD[3]. IPL has been widely used in dermatology to treat various conditions such as rosacea, benign vascular lesions, and pigmented lesions[4]. It utilizes a noncoherent, polychromatic light source to yield selective photothermolysis, wherein a specific wavelength of light is absorbed by a chromophore and converted into heat to destroy the target tissue[4,5]. Previous studies have reported favorable outcomes given the therapeutic effect of IPL in patients with MGD[6–14]. The potential mechanisms of action of IPL in MGD include the coagulation of telangiectasia, which may lead to a decrease in inflammation[15], and the liquefaction of the viscous meibum and dilation of the clogged meibomian gland ducts caused by the heat energy[11].

Tear cytokines have been reported to be elevated in dry eye and MGD, and to be correlated with symptoms and clinical parameters[16,17]. Therefore, a serial evaluation of the changes in tear cytokine levels and clinical assessment throughout the sequential treatment period would help explain the anti-inflammatory effect of IPL, as well as in determining the correlation between inflammation and the clinical outcome. A recent study showed that IPL treatment can reduce the levels of tear inflammatory markers IL-17A and IL-6 in patients with MGD[18]. In addition, the altered levels of IL-6 in tears correlated with the changes in the number of meibomian glands producing a clear secretion from the lower lid after IPL treatment[18]. Although IL-17A and IL-6 are well known to play a role in the pathogenesis of dry eye, MGD is a multifactorial disorder accompanied by ocular surface inflammation, but its etiology and pathogenesis remain unknown. TNF-α is another pleiotropic proinflammatory cytokine that has been associated with dry eye disease (DED)[19]. Moreover, DED has been considered a Th1-dominant disease; however, reports have suggested that autoantibodies may be involved in the pathogenic mechanism[20]. Therefore, it would be useful to also investigate cytokines associated with the Th2 response.

In the current study, the proposed anti-inflammatory effect of IPL was further investigated by analyzing additional tear inflammatory cytokines other than those previously evaluated. In addition, the clinical signs that changed in correlation with the inflammatory cytokine levels were investigated. The clinical characteristics of patients who experienced the greatest alleviation of ocular discomfort after IPL treatment were also explored. Hence, we sought to identify the important clinical factors and inflammatory cytokines associated with the treatment effect of IPL in patients with MGD.

Results

Clinical parameter changes and IPL. The mean scores (range) of meibum expressibility, lid margin abnormality, OSDI, and meibomian gland dropout were 2.9 (2–4), 3.5 (3–4), 58.2 (4.2–92.0), and 3.2 (2–5), respectively. The geometric means (range) of meibum quality score, ocular surface staining score, and TBUT were 3.4 (3–4), 1.8 (1–4), and 3.5 (0.5–9.0), respectively. Therefore, the subjects had moderate to severe MGD according to the clinical signs of MGD (meibum expressibility, lid margin abnormality, and meibomian gland dropout) and accompanying severe DED in terms of a short TBUT and high OSDI score.

The changes in clinical parameters over the time period of the three IPL sessions are outlined in Fig. 1. Meibum quality, meibum expressibility, and lid margin abnormality improved after IPL treatment, as shown by the decrease in their scores. TBUT increased and the ocular surface staining score decreased serially with

Variable (Baseline value)	Unstandardized coefficient (B)	Standardized coefficient (β)	*P* value
Meibum expressibility	−18.2	−0.396	0.003
TBUT	4.5	0.453	0.007
Sex (female)	−19.1	−0.396	0.019

Table 1. Multiple linear regression analysis of the association of the change in OSDI score with baseline clinical conditions. The change in the OSDI score is defined as the OSDI after the 3rd treatment session – the OSDI at baseline. Age ($P = 0.950$), meibum quality ($P = 0.980$), lid margin abnormality ($P = 0.928$), and ocular surface staining ($P = 0.767$) were excluded from the model by using the stepwise method. *P* value for the overall model is 0.002 and adjusted R^2 is 0.368. OSDI = Ocular Surface Disease Index; TBUT = tear film break-up time.

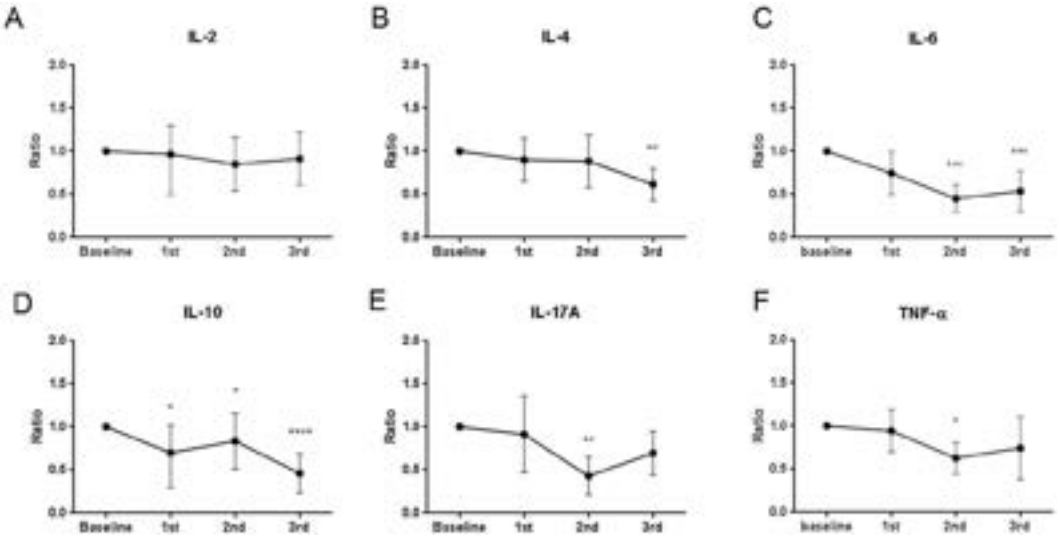

Figure 2. Change in cytokine profiles following each intense pulsed light (IPL) treatment session as a ratio compared to the baseline. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$; analysis of variance (ANOVA) (**C**,**F**) or Kruskal-Wallis test (**A**,**B**,**D**,**E**) with post-hoc analysis, comparing the value after each session to that of the baseline. Individual points and error bars represent the mean (**C**,**F**) or the median (**A**,**B**,**D**,**E**) and 95% confidence interval.

treatment. The OSDI scores also decreased with IPL treatment. LLT, meibomian gland dropout, and tear meniscus area did not show any significant changes.

Clinical parameters associated with the improvement in symptoms. We constructed a multiple regression model to identify the individual clinical parameters associated with the improvement in the discomfort score, OSDI, after IPL treatment (Table 1). The OSDI score after three treatment sessions decreased from the baseline score by 18.2 for each additional meibum expressibility score at baseline and increased from the baseline by 4.5 for each additional second of TBUT at baseline (Table 1). Thus, the worse baseline meibum expressibility scores and shorter baseline TBUT were associated with a greater reduction in the OSDI score after three treatment sessions. In addition, the OSDI score tended to decrease more in women than in men (Table 1).

Tear inflammatory cytokines and IPL. The tear cytokine levels were sequentially monitored to assess the anti-inflammatory effect of IPL. IL-4, IL-6, IL-10, IL-17A, and TNF-α levels showed a significant decrease over the time course (Fig. 2). However, the change in IL-2 level was not significant ($P = 0.117$, Kruskal-Wallis test). Although a slight increasing trend in IL-6, IL-17A, and TNF-α levels was observed after the third IPL session, the difference was not statistically significant (IL-6, $P = 0.904$; IL-17A, $P = 0.394$; TNF-α, $P = 0.875$).

Correlation between meibomian gland function and tear inflammatory cytokines. To investigate whether the change in tear cytokine levels was related to the change in meibomian gland function, a correlation analysis was performed between the tear cytokine levels, IL-4, IL-6, IL-10, IL-17A and TNF-α, which decreased significantly after IPL treatment, and meibum quality and meibum expressibility. A positive correlation was observed between the changes in meibum expressibility and changes in IL-6 ($r = 0.598$, $p = 0.02$) and TNF-α ($r = 0.755$, $p = 0.01$) levels (Fig. 3). The correlation between the improvement in meibum expressibility and the decrease in IL-10 was significant in the correlation analysis ($r = 0.533$, $p = 0.009$), however became insignificant after the bonferroni correction ($p = 0.09$). Potential complications and adverse events, including uveitis and iris damage, did not occur in any of the patients.

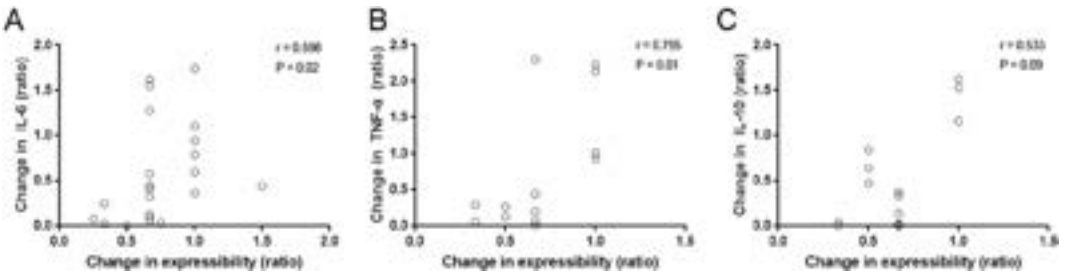

Figure 3. Scatter plot showing the correlations between the change in meibum expressibility and the change in the levels of tear cytokines IL-6 (**A**), TNF-α (**B**), and IL-10 (**C**). r = Spearman's correlation coefficient.

Discussion

IPL treatment was applied to patients with moderate to severe MGD and severe DED. Among the clinical parameters that responded to IPL treatment (Fig. 1), meibum expressibility showed the strongest relationship with the improvement in the OSDI score when other parameters were statistically controlled (Table 1). Additionally, meibum expressibility correlated with multiple inflammatory tear cytokines, IL-6 and TNF-α, whose levels were shown to decrease with IPL treatment (Figs 2 and 3).

IPL treatment improved the clinical parameters associated with meibomian gland function, including meibum quality, expressibility, and the lid margin abnormality score. A possible mechanism of action of IPL has been suggested as the local warming effect, which liquefies the inspissated meibum and encourages more regular outflow[11]. Previous studies have also reported improved meibum viscosity and oil flow score[10] and a significant increase in meibomian gland expression[8,12,14]. The forced expression of meibomian glands after IPL treatment may also have contributed to the improvement in clinical parameters; however, previous studies have reported improved lipid layer grade[7], improved meibomian gland secretion quality and expressibility[9], increased TBUT[7,9], and improvement in symptom scores[7,9] after IPL treatment alone.

Improvement in the parameters related to meibomian gland function could improve the quality of the tear lipid layer and reinforce tear film integrity. In fact, TBUT and ocular surface staining improved after IPL treatment, and this result was well correlated with the results of previous studies[7,9,12–14]. However, the stabilization of the ocular surface was not accompanied by an increase either in the tear meniscus area or in LLT of the tear film. A previous study also found no change in tear meniscus height after IPL treatment[7], and another study reported no change in LLT after IPL treatment[13]. Therefore, improved meibum quality and expressibility possibly strengthened the tear film and prevented tear evaporation, without affecting the tear volume itself.

Increased LLT was associated with increased age and female sex, as well as hypersecretory MGD and lid margin inflammation in a previous report[21]. Thus, the quantified LLT is affected by demographic factors and other confounders, and may not directly reflect meibomian gland function. A previous report that showed lipid layer improvement after IPL treatment examined the pattern of the tear film by using a different interferometry device[7], while the interferometry in our study automatically calculated the LLT of the lower part of the cornea. Thus, the automatically quantified LLT may not be able to accurately portray the lipid layer status throughout the ocular surface, and the lipid quality of the tear film, instead of the thickness itself, may be more important in ocular surface stabilization. Qualitative lipid change is known to occur in MGD, and the change in lipid composition interferes with the adherence of the outermost lipid layer to the intermediate aqueous component, thus contributing to tear film instability and vulnerability to evaporation[22].

The improvement in clinical parameters was accompanied by a reduction in patient-reported symptoms, the OSDI, and this was in concordance with the findings of previous studies[6–8,12,14]. The OSDI has been proven a reliable and valid tool in discriminating the severity of DED[23]. Women and those with a greater number of unexpressible meibomian glands and shorter TBUT showed a significant degree of reduction in the posttreatment OSDI score (Table 1). This was consistent with the findings of a previous study, which reported that patients with initially worse meibomian gland expressibility showed greater improvement on the OSDI after IPL treatment[12]. Therefore, those with obstructive MGD with decreased meibum expressibility and tear film instability are most likely to experience an improvement in ocular discomfort after IPL treatment.

Tear cytokine assays provide evidence for the ocular surface inflammation. IL-6 and IL-17A were reported to decrease in tears of MGD patients after IPL treatment[18]. In the current study, IL-4, IL-6, IL-10, IL-17A and TNF-α, which are cytokines known to be associated with DED[24,25], decreased significantly following IPL treatment in MGD patients. The decrease in multiple tear cytokine concentration after IPL treatment may indicate that IPL was able to reduce inflammation which is one of the pathogenic mechanisms of MGD.

IL-6 and TNF-α are pleiotropic proinflammatory cytokines, which have been described as the key molecules in DED[19,24]. A previous report showed that IL-6 level was significantly increased in the tears of patients with DED, and it correlated with various ocular surface parameters, including TBUT, Schirmer test, and the keratoepitheliolasty score[26]. IL-17, whose level was also shown to be significantly increased in patients with MGD and DED[25], is primarily produced by Th-17 cells and is known to increase the production of other inflammatory cytokines such as IL-6, TNF-α, IL-1, and IL-8, as well as the recruitment of leukocytes.

Although DED has been considered a Th1-dominant disease, evidence that autoantibodies may also be engaged in the pathogenic mechanism[20] may explain our finding that the levels of IL-4 and IL-10, cytokines involved in the Th2 response, decreased after IPL treatment. IL-4 and IL-10 have previously been detected on the

ocular surface of patients with DED[24]. IL-10 is predominantly an inhibitory cytokine that has multiple effects on immunoregulation, inflammation, and antibody production[27]. It is secreted not only by macrophages and Th2 cells, but also by regulatory T cells (Treg). Treg cells have been shown to suppress ocular surface inflammation associated with DED[28], and studies have demonstrated that a Th17 cell subset, previously mentioned as a primary effector cell in DED, counteracts the Treg-mediated suppression in DED[29].

The improvement in meibum expressibility positively correlated with the reduction in the levels of multiple tear inflammatory cytokines, such as IL-6 and TNF-α (Fig. 3). This finding was consistent with that of a previous report, which showed that the change in IL-6 level after IPL treatment correlated with the change in meibomian gland secretion in the lower lid[18].

The probable mechanism behind the relationship between meibum expressibility and tear inflammatory cytokines could be explained by the following pathogenesis of MGD. Increased meibum viscosity and reduced expression may arise from the changes in meibum composition[30]. The stasis of the meibum can promote bacterial growth, which may then lead to the increased release of esterases and lipid-degrading lipases. The increased enzyme activity not only increases meibum melting temperature, but also generates free fatty acids that can lead to hyperkeratinization and inflammation[31]. These changes in lipid composition lead to further meibomian gland obstruction, ocular surface instability, and increased tear evaporation, contributing to the development of DED and patient discomfort. Therefore, ocular surface inflammation and meibomian gland expressibility are interactively involved in the cascade of the pathophysiologic mechanism of MGD, and our results suggest that the improvement in inflammation and meibum expressibility after IPL treatment is mutually inclusive, and that they might be important therapeutic targets of IPL treatment in patients with MGD.

The limitations of this study include a small sample size, lack of a control group, and a risk of the placebo effect and investigator bias. However, a previous paired-eye study showed that IPL treatment greatly improved tear film quality and reduced dry eye symptoms than did a placebo treatment[7]. The follow-up period after treatment termination was short. Hence, further investigation is needed to assess the long-term effectiveness and safety of IPL treatment. Future studies with larger sample sizes will be helpful in replicating and extending our findings. Additionally, it would have been helpful if the extent of lid margin vascularity was graded and its association with tear cytokines was evaluated, since one of the main mechanisms of action of IPL is coagulation of the superficial vessels. Furthermore, the clinical examinations were performed by one investigator, however we used the standardized grading scales reported by the International Workshop on Meibomian Gland Dysfunction[32]. Therefore, the measurement quality of the acquired data is less likely to be compromised.

Conclusions

Patients with low meibum expressibility and tear film instability experienced greater improvement in symptoms after IPL treatment. The improvement in meibum expressibility was also associated with a decrease in tear inflammatory cytokine levels. Therefore, meibum expressibility improvement might be a good therapeutic target of IPL treatment in patients with MGD and DED, and could be an indicator of ocular surface inflammation during IPL treatment.

Methods

Patient selection. This prospective study adhered to the tenets of the Declaration of Helsinki and was approved by the Severance Hospital Institutional Review Board, Seoul, South Korea (1-2016-0010). All participants agreed and signed the written informed consent prior to enrollment. The study was registered at the Clinical Research Information Service (CRIS) under the registration number KCT0003051 (06/07/2018).

Participants over 19 years of age and diagnosed with moderate or severe MGD at Severance Hospital, Seoul, Korea, were screened for eligibility. MGD was staged according to the severity of symptoms, including ocular discomfort, and clinical signs, including lid margin features, meibum secretion, meibum expressibility, and ocular surface staining[2]. Participants were enrolled if they satisfied the following criteria for MGD staging. Moderate MGD was defined by moderate symptoms and MGD clinical signs (plugging and vascularity of the lid margins, meibum quality grade 2–3, and expressibility grade 3), and mild to moderate ocular surface staining (grade $\geq$ 1). Severe MGD was diagnosed on the basis of pronounced symptoms with limitation of daily activities, severe MGD signs (dropout, displacement of the lid margins, meibum quality grade $\geq$ 3, and expressibility grade 4), increased ocular surface staining (grade $\geq$ 1), and inflammatory signs (conjunctival hyperemia and phlyctenules). Patients with (1) Fitzpatrick skin type V or VI; (2) active allergy, infection, or ocular surface inflammatory disease unrelated to dry eye or MGD; (3) systemic diseases or medication use in which light therapy is contraindicated; (4) uncontrolled systemic disease; (5) ocular surgery history within 6 months before study initiation; (6) contact lens use; (7) tattoos, semipermanent makeup, and pigmented lesions in the treatment area; and (8) clinical skin treatments within 2 months were excluded, as were (9) pregnant patients and nursing mothers.

The eye with a higher stage of MGD was chosen for the study. If the MGD stage was equivalent in both the eyes, the right eye was enrolled. Thirty eyes of 30 patients who completed three sessions of IPL and four clinical examinations and tear sample collection were included in the analysis. The mean age of the patients was 51 ± 18 years, and 76.7% of them were women.

Treatment technique. Patients received three sessions of IPL treatment at 3 week intervals. All treatment adhered to the Toyos protocol[6]. IPL-Aid Disposable Eye Shields (Honeywell Safety Products, Smithfield, RI, USA) were placed to protect the participants' eyes. A cooling gel was generously applied to the treatment area, and homogenously sculpted light pulses of 590-nm wavelength and intensity ranging from 12 to 14 J/cm^2 were delivered to the periocular skin inferior and lateral to the eye by using the M22 IPL machine (Lumenis Ltd., Israel). A 590-nm filter was selected to allow for selective photothermolysis of hemoglobin within the blood vessels, which had an optimal absorption range of 577–600 nm[33]. The fluence was initially set at 13 J/cm^2, a previously reported

setting for the treatment of rosacea and telangiectasia[34], and was adjusted individually according to the patients' tolerance and comfort. Approximately 15 overlapping pulses were applied from the preauricular area, across the cheeks and nose to the contralateral side, and bordering close to the inferior boundary of the eye shields to ensure the light pulses were delivered as close as possible to the lower eyelids. After the initial pass was completed, more ultrasound gel was applied, and the treatment was repeated for a second pass. After IPL treatment, manual expression of the meibomian glands of both the upper and lower eyelids was performed using meibum expressor forceps. The patients were instructed to maintain lid scrub and to use artificial tears during the treatment period.

Clinical assessments. The clinical assessments were executed at baseline, at each separate treatment session, and at 3 weeks after the last session. All evaluations were performed before the IPL treatment at every visit. The order of the examinations was such that the influence of a preceding test on the subsequent test was minimized. All patients underwent tear film lipid layer interferometry, followed by tear meniscus area measurement by using anterior segment optical coherence tomography. Thereafter, tear sampling was performed, followed by slit-lamp examinations, including a fluorescein tear break-up time (TBUT), measurement of ocular surface staining, and examination of the lid margin and meibomian glands. All clinical examinations were undertaken by a single masked investigator (M.C.), and the IPL treatment was performed by another investigator (K.Y.S.).

Lipid layer thickness (LLT) measurement and meibography were performed using an interferometer (LipiView®, TearScience Inc, Morrisville, NC, USA) as previously described[35]. LLT is derived from the reflected tear film image, and is calculated as interferometric color units (ICUs), where 1 ICU represents approximately 1 nm. The maximum LLT that can be measured is 100 nm. The lower eyelids were everted to obtain infrared images of the meibomian glands. Meibomian gland dropout was scored on a 1 to 5 meiboscale, graded according to the area of gland loss (1, 0%; 2, $<25\%$; 3, 25–50%; 4, 51–75%; and 5, $>75\%$)[36].

A 3-mm vertical image at the middle of the lower eyelids was scanned using Fourier-domain optical coherence tomography (RTVue; Optovue, Inc., Fremont, CA, USA) to measure the area for the lower tear meniscus[37]. It was defined as the area enclosed by the boundaries of the tear meniscus, cornea, and lower palpebral conjunctiva.

TBUT was measured by applying a fluorescein-impregnated strip (Haag-Streit, Koeniz, Switzerland) to the inferior palpebral conjunctiva. The mean time of three attempts was calculated. Thereafter, the Oxford scheme was used to grade corneal and conjunctival staining from 1 to 6[38].

Firm digital pressure was applied to the five central glands of the lower lid to evaluate meibum expressibility and quality. Meibum expressibility was scored as 1, all 5 glands; 2, 3–4 glands; 3, 1–2 glands; and 4, 0 glands[39], and meibum quality was scored as 1, clear; 2, cloudy; 3, cloudy and particulate; and 4, inspissated, and was recorded as the highest grade expressed by the examined glands[40]. The lid margin abnormality score was calculated as the sum of the following four parameters: vascular engorgement, meibomian gland orifice plugging, irregularity of the lid margin, and mucocutaneous junction displacement (each parameter was given 1 point if present)[41]. Subjective symptoms were assessed using the Ocular Surface Disease Index (OSDI)[23].

Tear sample collection and cytokine analysis. Tear samples were collected from all patients at every visit. We instilled 30 µL of phosphate-buffered saline into the inferior conjunctival fornix, and then collected 20 µL of the unstimulated tear fluid and buffer by using a micropipette. The samples were individually collected, each allocated into separate 0.5-mL Eppendorf tubes (Eppendorf, Fremont, CA, USA), and were preserved at a very low temperature of −70 °C until further analysis.

The levels of tear cytokines were analyzed using a multiplex bead-based immunoassay (BD™ Cytometric Bead Array Human Soluble Protein Flex Set; BD Biosciences, San Jose, CA, USA). The cytokines IL-2, IL-4, IL-6, IL-10, IL-17A, and TNF-α were investigated. The tear samples were incubated with antibody-coated capture beads and the detector antibody-phycoerythrin agent at room temperature for 3 hours. The samples were washed to remove the unbound antibodies. Flow cytometry was performed, and FCAP Array™ v3.0 (BD Cytometric Bead Array software; BD Biosciences) was used to interpolate the sample concentrations by comparison to a standard curve and to analyze the data.

Statistical analysis. Prospective power calculations for sample size requirements were conducted before study initiation. A minimum of 25 participants was required to detect an effect size of 0.6 to achieve a power of 80% and a two-sided statistical significance level of 5%. To assess the time course changes in the clinical parameters over the three treatment sessions, repeated-measure analysis of variance (ANOVA) or Friedman test was applied depending on the normality of data. Those with normal distribution were analyzed using a parametric test, and the arithmetic mean was calculated. If the data were not normally distributed, logarithmic transformation of the dataset was performed, and the geometric mean was calculated. If significant differences were observed, the Bonferroni post-hoc test or Dunn's test for multiple comparisons was performed to compare the baseline and posttreatment data at individual time points. Multiple regression models were constructed to identify baseline clinical parameters associated with the changes in the OSDI scores after treatment. The tear cytokine data were transformed into ratios by using the baseline value as the reference. The outliers were identified using robust regression followed by the outlier identification method and were excluded. Thereafter, ANOVA or the Kruskal-Wallis test was used to compare multiple variables, including the baseline and sequential measurements at each visit after the corresponding treatment session. If significant differences were observed, Dunnett's or Dunn's post-hoc test was performed to compare the baseline and posttreatment values after each session. Spearman's rank-order correlation was used to investigate the association between the change in tear cytokine levels and the improvement in meibomian gland function, and Bonferroni correction was conducted. The data were transformed into ratios of the results after the final session to the baseline value, and these ratios were used in the analysis. Statistical analyses were conducted using IBM SPSS Statistics for Windows/Macintosh, Version 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 7.0 (GraphPad Software Inc., La Jolla, CA, USA).

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions
M.C., S.M.N. and K.Y.S. conceived and designed the study. M.C., S.J.H., Y.W.J., Y.J.C., I.J. and M.H.A acquired the data. M.C., B.Y.K., E.K.K., T.K., S.M.N. and K.Y.S. contributed to data analysis and interpretation. M.C., S.M.N. and K.Y.S. prepared the manuscript. All authors reviewed and approved the final manuscript.

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• Clinical Research •

Comparison of anti-inflammatory effects of intense pulsed light with tobramycin/dexamethasone plus warm compress on dry eye associated meibomian gland dysfunction

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Abstract

• AIM: To compare the anti-inflammatory effects of intense pulsed light (IPL) with tobramycin/dexamethasone plus warm compress through clinical signs and cytokines in tears.

• METHODS: Eighty-two patients with dry eye disease (DED) associated meibomian gland dysfunction (MGD) were divided into two groups. Group A was treated with IPL, and Group B was treated with tobramycin/dexamethasone plus warm compress. Ocular Surface Disease Index (OSDI), tear film breakup time (TBUT), corneal fluorescein staining (CFS), meibomian gland expressibility (MGE), meibum quality, gland dropout and tear cytokine levels were evaluated before treatment, 1wk and 1mo after treatment.

• RESULTS: TBUT in Group A was higher (*P*=0.035), and MGE score was lower than Group B at 1mo (*P*=0.001). The changes of interleukin (IL)-17A and IL-1β levels in tears were lower in Group A compared with that in Group B at 1wk after treatment (*P*=0.05, *P*=0.005).

• CONCLUSION: Treatment with IPL can improve TBUT and MGE and downregulate levels of IL-17A and IL-1β in tears of patients with DED associated MGD better than treatment with tobramycin/dexamethasone plus warm compress in one-month treatment period.

• KEYWORDS: intense pulsed light; meibomian gland dysfunction; dry eye disease; interleukin-17A; interleukin-1β
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INTRODUCTION

Meibomian gland dysfunction (MGD) is mainly characterized by terminal duct obstruction and abnormality in meibum secretion[1], which alters the tear film and decreases its functional integrity[2]. MGD may occur as an isolated disorder, but it may also be accompanied by dry eye disease (DED)[3]. DED is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms[4]. DED has been divided into evaporative and aqueous deficiency subtypes, and MGD is the most common cause of evaporative dry eye[3-5]. According to some studies, the overall prevalence of MGD varies widely from 3.5% to 70% and the prevalence of DED ranges from 5% to 50%, both of which is related to age, race and district[6-7]. It's reported by the Dry Eye Workshop II (DEWS II) that 32.9% of dry eye patients associates with MGD[7].

Tear instability and tear hyperosmolarity associated with MGD, could activate stress signaling pathways in the ocular surface epithelium and resident immune cells, therefore trigger production of inflammatory cytokines. It's regarded as a self-perpetuating "dry eye inflammatory vicious cycle"[8]. Several studies have reported the levels of interleukin (IL)-6, IL-17A and IL-1β in tears of dry eye patients were higher than that in normal subjects[9-13]. Moreover, IL-6 levels in tears have become one of the evaluation indexes for DED[14]. Assessment based on inflammation will improve the selection of treatment. Treatments recommended for DED associated MGD includes warm compress, lid massage, antibiotic and anti-inflammatory ointments, and artificial tears[15]. Unfortunately, warm compress is hard to standardize and its troublesome procedure reduces patients' compliance[16-17]. Some anti-inflammatory ointments can't be used consecutively because of their side effects, which may decrease the treatment efficiency. To avoid the drawback of conventional treatment, a new therapy named intense pulsed light (IPL) was proposed by some

researchers[18-23]. IPL devices could direct light extended from 515 nm to 1200 nm to the skin near the eye lid. The probable mechanisms of IPL treating DED associated MGD include heat transfer, antibiotic effect and preventing inflammatory mediators from the meibomian glands[24]. Although the clinical effects of IPL on DED associated MGD has already been proved by several studies[19,21-23], no one has compared the anti-inflammatory effects of IPL with tobramycin/dexamethasone plus warm compress. This study aimed at comparing IPL with tobramycin/dexamethasone plus warm compress on DED associated MGD from perspective of anti-inflammatory effects.

SUBJECTS AND METHODS

Ethical Approval The study continued for one year from November 2016 to November 2017. Patients who had been diagnosed as DED associated MGD were recruited. Informed consents were obtained from all patients before the study. The study was approved by the biomedical ethics committee of Peking University Third Hospital and adhered to the tenets of the Declaration of Helsinki. The study was registered at clinicaltrials.gov (NCT 02958514).

Patients were diagnosed as MGD on the basis of the criteria provided by the Tear Film and Ocular Surface Society (TFOS)[25-26]: 1) ocular symptoms; 2) abnormal morphologic lid features; 3) alterations of meibomian gland secretion. Patients with either 1) + 2) or 1) + 3) could be diagnosed as MGD. Meanwhile, patients were also diagnosed as DED based on criteria provided by the Dry Eye Workshop (DEWS)[27]: 1) the Ocular Surface Disease Index (OSDI) >13; 2) tear film breakup time (TBUT) ≤5s or 5s<TBUT≤10s with positive corneal fluorescein staining (CFS).

Patients were excluded from the study if they met each criteria as follow: 1) under the age of 18y; 2) ocular infection and allergy; 3) allergic to hormonal drugs; 4) abnormalities of anatomy or movements of eyeballs; 5) ocular surgical history or trauma within 3mo; 6) Fitzpatrick Skin Types IV, V and VI[28]; 7) with tattoos, pigmented lesions or skin cancer in the treatment area; 8) radiotherapy or chemotherapy history within 1y; 9) pregnancy or lactation; 10) autoimmune disease.

Intervention Procedure Patients were divided into two groups randomly according to a computer-generated randomization program. Patients received bilateral treatment, but only the severer eye was enrolled in the study. Patients in Group A were treated with IPL once per month, and sodium hyaluronate eye drops (Hycosan, EUSAN GmbH, Germany) four times a day. Patients in Group B were given tobramycin/dexamethasone ointment (Tobradex, Alcon, Belgium) plus warm compress once every night and sodium hyaluronate eye drops four times a day.

The IPL device (M22, Lumenis, USA) was used in this study. Pulse intensity ranged from 12 to 14 J/cm². Pulse width was 6ms. IPL treatment was performed by a same doctor and was given as follow: 1) Clean the treatment area on both upper and lower eyelids with cotton swabs; 2) Apply compound lidocaine cream (Beijing Unisplendour Pharmaceutical Co., Ltd.) for anesthesia for 30min; 3) Protective shield was placed over the cornea and sclera, and the other eye was protected by an eyeshade; 4) IPL was administered to the periocular area on both upper and lower eyelids (8 mm×15 mm each); 5) Give the treatment area a 10-minute cold compress with a cold wash cloth.

As for Group B, patients received tobramycin/dexamethasone ointment and a 10-minute warm compress (45℃-50℃) once every night at home for one month. Data were obtained from patients in Group A and Group B before treatment (referred to as baseline), 1wk and 1mo after treatment.

Clinical Evaluation To compare the clinical effects of the two groups, tests were conducted in the same order that minimized the extent to which one test influenced the tests that followed. 1) Subjective symptoms of patients were evaluated by the OSDI questionnaire. 2) Measurement of TBUT was facilitated by viewing with a blue exciter filter after instilling sodium fluorescein onto the bulbar conjunctiva with a fluorescein sodium ophthalmic strip (Liaoning Meizilin Pharmaceutical Co., Ltd., China). TBUT was measured three times for each patient and made an average[5]. 3) CFS score was quantified according to the system provided by National Eye Institute[29]. 4) The central glands of eyelid were pressed to enumerate meibomian gland expressibility (MGE) score. It was scored according to the number of the five glands from which a meibum secretion could be expressed (0=5 glands expressing, 1=3 to 4 glands expressing, 2=1 to 2 glands expressing and 3= none gland expressing)[30]. MGE of the upper and lower eyelids should be scored respectively and then the two scores were added. 5) Meibums quality from the upper and lower eyelids were scored respectively (0= clear and fluid-like, 1= cloudy and fluid-like, 2= cloudy and granular, and 3= whitish, toothpaste-like)[31], and then the two scores were added as a meibum quality score. 6) The severity of gland dropout was scored by observing the morphology of meibomian glands with infrared meibography system (Topcon, Japan). Magnification was set at 10× and image resolution at 640×480. The upper and lower eyelids were scored respectively (0= normal, 1= dropout <1/3, 2= dropout between 1/3-2/3, and 3= dropout >2/3)[30], and then the two scores were added.

Tear Sample Collection and Analysis Tear collection was performed before any other test at baseline, 1wk and 1mo after treatment. Tear samples were collected non-traumatically from the inferior tear meniscus. Glass capillary micropipettes (Drummond Scientific, Broomall, PA, USA) were used to collect 5 μL of tears. Tear samples were fully eluted into a sterile collection tube (Sigma-Aldrich, St. Louis, MO, USA) at once. Tubes with tear samples were kept cold (4℃) during

Table 1 Clinical outcomes in Group A and Group B at baseline, 1wk and 1mo

Parameters	Group	Baseline	1wk	1mo
OSDI	A	38.92±2.59	29.98±3.31[a]	25.72±4.52[b]
	B	38.14±2.39	31.07±2.44[b]	21.48±4.79[b]
TBUT(s)	A	4.17±0.31	5.34±0.37[b]	5.87±0.44[b,d]
	B	3.80±0.28	4.71±0.33[a]	4.63±0.31[a]
CFS	A	2.24±0.42	1.39±0.34[a]	1.18±0.35[a]
	B	2.85±0.49	1.68±0.41[b]	1.24±0.38[a]
MGE	A	3.71±0.20	2.63±0.19[c]	1.61±0.15[b,e]
	B	3.80±0.21	3.12±0.22[b]	2.61±0.23[b]
Meibum quality	A	2.22±0.22	2.00±0.20	2.53±0.32
	B	2.54±0.22	2.15±0.20	2.94±0.33
Gland dropout	A	3.80±0.17	3.80±0.13	4.18±0.21
	B	3.87±0.13	3.70±0.11	4.12±0.19

OSDI: Ocular surface disease index; TBUT: Tear film breakup time; CFS: Corneal fluorescein staining; MGE: Meibomian gland expressibility. [a]P<0.05, [b]P<0.01, [c]P<0.001, comparing with baseline. [d]P<0.05, [e]P<0.01, comparing Group A with Group B.

collection, and then stored at -80°C until activity assays were performed. The concentrations of IL-17A, IL-1β and IL-6 in tears were analyzed using a Milliplex Map Kit (HSTCMAG-28SK, EMD Millipore Corporation, USA). Data acquisition and analysis were integrated seamlessly with the Bio-Plex Luminex 200 XYP instrument (Bio-Rad Laboratories). The threshold sensitivities of IL-17A, IL-1β and IL-6 were >3.3 pg/mL, >1.4 pg/mL and >1.1 pg/mL, respectively.

Statistical Analysis SPSS 23 was used to analyze the data. Data were expressed as mean±standard error of the mean (SEM). As the concentrations of IL-17A, IL-1β and IL-6 in tears vary greatly among individuals, changes of cytokines were compared between Group A and Group B. Analysis between baseline and 1wk or 1mo in the same group was performed by Wilcoxon signed rank test. Analysis between Group A and Group B was performed by Mann Whitney U test. Outcomes were considered significant if P<0.05.

RESULTS

Patients and Clinical Outcomes Eighty-two patients were included in this study. Forty-one patients were analyzed in Group A (10 males and 31 females), with a mean age of 54.44±16.19 (range 22-80)y. Forty-one patients were analyzed in Group B (11 males and 30 females), with a mean age of 55.22±16.71 (range 23-86)y. The visual acuity and intraocular pressure of patients were stable during treatment in both groups. Compared Group A with Group B, there was no difference in OSDI, TBUT, CFS, MGE, meibum quality, gland dropout and levels of IL-6, IL-17A, IL-1β in tears at pre-treatment baseline (P>0.05).

OSDI, CFS, TBUT and MGE scores were improved in both Group A and Group B at 1wk and 1mo after treatment compared with baseline, which were of statistically differences (all P<0.05). However, there was no significant difference in meibum quality scores and gland dropout scores between each time point and baseline in both groups (all P>0.05; Table 1).

Compared Group A with Group B, there was no difference in TBUT and MGE score at 1wk (P>0.05). Compared with Group B, TBUT in Group A was higher than that in Group B at 1mo (P=0.035), and MGE score in Group A was lower than that in Group B at 1mo (P=0.001). However, there was no significant differences between Group A and Group B on OSDI, CFS, meibum quality scores and gland dropout scores at 1wk or 1mo (all P>0.05).

Changes of Tear Cytokine Levels The concentrations of IL-6, IL-17A and IL-1β in tears at baseline, 1wk and 1mo were shown in Table 2. Changes of IL-6, IL-17A and IL-1β were defined as the concentrations of IL-6, IL-17A and IL-1β at 1wk or 1mo minus the concentrations of IL-6, IL-17A and IL-1β at baseline, respectively.

The changes of IL-6 in Group A were -83.94±36.55 pg/mL at 1wk and -61.74±35.94 pg/mL at 1mo. The changes of IL-6 in Group B were -72.68±23.39 pg/mL at 1wk and -84.16±23.87 pg/mL at 1mo. In Group A, change of IL-6 at 1wk was lower than that at 1mo, though there was no statistical difference (P=0.249). In Group B, change of IL-6 was lower at 1mo compared with that at 1wk (P=0.015). Compared Group A with Group B, change of IL-6 did not differ significantly at either 1wk or 1mo (P=0.556, P=0.104; Figure 1).

The changes of IL-17A in Group A were -1.96±1.52 pg/mL at 1wk and 0.18±1.77 pg/mL at 1mo. The changes of IL-17A in Group B were 2.30±1.68 pg/mL at 1wk and -1.07±1.35 pg/mL at 1mo. In either Group A or Group B, change of IL-17A at 1wk did not differ significantly from that at 1mo (both P>0.05). Compared with Group B at 1wk, the change of IL-17A in Group A was lower, which was statistically different (P=0.05). Compared with Group B at 1mo, the change of IL-17A in Group A did not differ significantly (P=0.534; Figure 2).

The changes of IL-1β in Group A were -0.61±0.26 pg/mL at 1wk and -0.07±0.33 pg/mL at 1mo. The changes of IL-1β in Group B were 0.35±0.26 pg/mL at 1wk and 0.39±0.44 pg/mL

Table 2 Concentrations of tear cytokines in Group A and Group B at baseline, 1wk and 1mo pg/mL

Parameters	Group	Baseline	1wk	Change	1mo	Change
IL-6	A	126.90±39.68	42.96±7.99	-83.94±36.55	65.16±18.71	-61.74±35.94
	B	129.21±27.21	56.52±12.8	-72.68±23.39	32.40±7.14	-84.16±23.87
IL-17A	A	17.31±2.09	15.35±1.98	-1.96±1.52	17.49±2.17	0.18±1.77
	B	15.81±1.89	18.11±2.28	2.30±1.68	14.74±1.87	-1.07±1.35
IL-1β	A	3.62±0.34	3.01±0.39	-0.61±0.26	3.55±0.35	-0.07±0.33
	B	3.18±0.33	3.53±0.34	0.35±0.26	3.57±0.56	0.39±0.44

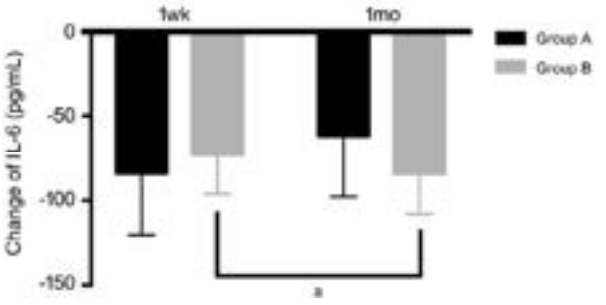

Figure 1 Changes of IL-6 at 1wk and 1mo in Group A and Group B IL: Interleukin. Change of IL-6: The concentration of IL-6 at 1wk or 1mo minus the concentration of IL-6 at baseline. [a]P<0.05 comparing 1wk with 1mo in Group B.

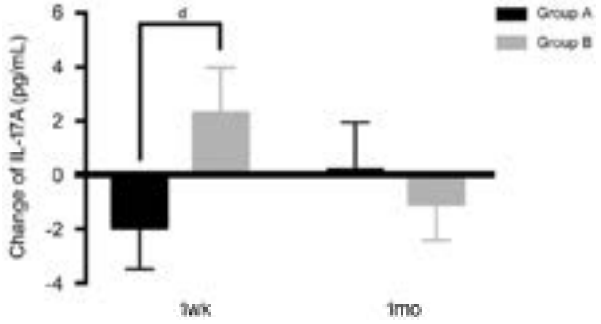

Figure 2 Changes of IL-17A at 1wk and 1mo in Group A and Group B Change of IL-17A: The concentration of IL-17A at 1wk or 1mo minus the concentration of IL-17A at baseline. [d]P<0.05 comparing Group A with Group B at 1wk.

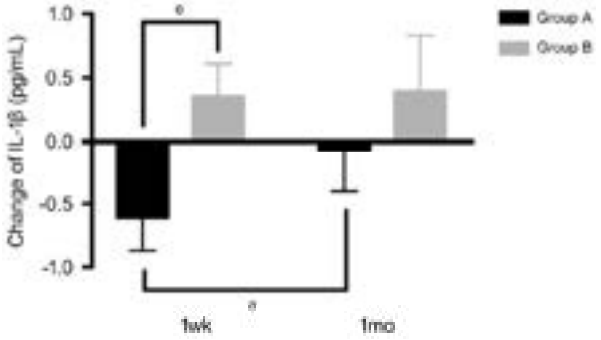

Figure 3 Changes of IL-1β at 1wk and 1mo in Group A and Group B Change of IL-1β: The concentration of IL-1β at 1wk or 1mo minus the concentration of IL-1β at baseline. [a]P<0.05 comparing 1wk with 1mo in Group A. [e]P<0.01 comparing Group A with Group B at 1wk.

at 1mo. In Group A, change of IL-1β was lower at 1wk than that at 1mo (P=0.027). In Group B, there was no significant difference compared change of IL-1β at 1wk with that at 1mo (P=0.224). Compared with Group B at 1wk, the change of IL-1β in Group A was lower, which differed significantly (P=0.005). Compared with Group B at 1mo, the change of IL-1β in Group A did not differ statistically (P=0.626; Figure 3).

DISCUSSION

IPL is a new treatment for patients with DED associated MGD. However, the mechanisms of IPL to treat DED associated MGD still remain uncertain currently. The probable mechanisms included heat transfer, antibiotic effect and anti-inflammatory effect. The light emitted from IPL device was selectively absorbed by chromophores in hemoglobin, subsequently releasing thermal energy, which heated and destructed the abnormal vasculature in the eyelid margin and adjacent conjunctiva, thus preventing inflammatory mediators from the meibomian glands[24]. The probable mechanisms of IPL covered almost all the principles to treat DED associated MGD in classical therapy. Tobramycin/dexamethasone is widely used as an antibacterial and anti-inflammatory combination by ophthalmologist. Dexamethasone is a pure glucocorticoid agonist. It's already known that therapeutic doses of dexamethasone have been shown to inhibit influx of macrophage and neutrophil, accompanied by a substantial downregulation of inflammatory cytokine production such as IL-6[32-33]. Several studies have reported the improvements of symptoms and signs of DED associated MGD after IPL[19-20]. Some studies indicated that IPL treatment could downregulate levels of IL-6 and IL-17A in tears of patients with DED associated MGD, comparing with placebo group[21]. However, the anti-inflammatory effects of IPL still remained unknown when comparing to tobramycin/dexamethasone plus warm compress. The clinical symptoms and signs for DED associated MGD after IPL were compared with tobramycin/dexamethasone plus warm compress in our study. OSDI, TBUT, CFS and MGE scores were all improved after treatment in both Group A and Group B, manifesting the clinical effects of both IPL and tobramycin/dexamethasone plus warm compress. These results coincided with previous reports[19,22,34]. Our study manifested that IPL improved TBUT and MGE more than tobramycin/dexamethasone plus warm compress at 1mo after treatment.

The changes of tear cytokine levels after IPL were compared with tobramycin/dexamethasone plus warm compress in order to evaluate their anti-inflammatory effects. As proved in many studies, hyperosmolar stress could activate mitogen-activated protein kinases (MAPKs) on the ocular surface epithelium and stimulate secretions of IL-1β and IL-6[8]. IL-6 and IL-1β are pro-inflammatory cytokines. IL-1β stimulates the production of other inflammatory cytokines, and then lyse the tight junctions in the superficial corneal epithelium[35]. IL-6 drive the production of IL-17A produced by T-helper cells, and IL-17A could causes corneal barrier disruption[36-38]. These inflammatory mediators could upregulate each other, thus amplifying the inflammatory cascade[39]. We speculated that the batter clinical effects of IPL were due to IPL downregulating more cytokines.

In this study, the effects of IPL and tobramycin/dexamethasone plus warm compress on the changes of IL-6, IL-17A and IL-1β levels in tears were different. The reduction of IL-6 level in tears at 1wk was more than that at 1mo in Group A, but in Group B, the reduction of IL-6 level at 1wk was less than that at 1mo, though there were no statistical difference. It could be speculated that both IPL and tobramycin/dexamethasone plus warm compress could downregulate the level of IL-6 in tears, but the effect of IPL on IL-6 reduced as time went by. As for IL-17A and IL-1β in tears, IPL downregulated the levels of IL-17A and IL-1β at 1wk, while tobramycin/dexamethasone plus warm compress did not. But when time went to 1mo, IL-17A and IL-1β levels in Group A went back to the same level as pre-treatment. It's manifested that IPL downregulated levels of IL-17A and IL-1β in tears more than tobramycin/dexamethasone plus warm compress at 1wk, but the effect could not last for 1mo.

Interestingly, changes of IL-6, IL-17A and IL-1β levels was lowest at about 1wk after IPL, which was earlier than the appearance of clinical outcome peaks at 1mo. It's speculated from this result that changes of tear cytokine levels may be more sensitive indexes than clinical signs to show effects of IPL. Changes of tear cytokine levels had the potential to be predictive indexes of clinical effects duration. When changes of tear cytokine levels were negative, it manifested the effect of IPL was on-going. However, when changes of tear cytokine levels went up to positive, it manifested the effect of IPL was over. This means the need of another time of IPL treatment. The result helped explain why prior researchers gave patients several times of IPL treatment at 4-week intervals.

The study also had some limitations. For the safety, tobramycin/dexamethasone ointment cannot be used consecutively because of its potential side effects such as ocular hypertension and cataract. Thus, Group B in this study was treated with tobramycin and dexamethasone ointment for only one month. It could not be deduced from this study whether further benefit would be realized if tobramycin/dexamethasone was used in Group B for a longer time.

In conclusion, our study suggested that treatment with IPL could improve TBUT and MGE and downregulate levels of IL-17A and IL-1β in tears of patients with DED associated MGD better than treatment with tobramycin/dexamethasone plus warm compress in one-month treatment period.

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RESEARCH ARTICLE Open Access

Clinical results of Intraductal Meibomian gland probing combined with intense pulsed light in treating patients with refractory obstructive Meibomian gland dysfunction: a randomized controlled trial

Xiaodan Huang†, Qiyu Qin†, Linping Wang, Jiao Zheng, Lin Lin and Xiuming Jin*

Abstract

Background: This study aims to optimize the therapeutic regimen for refractory obstructive meibomian gland dysfunction (o-MGD) patients by combining intraductal meibomian gland probing (MGP) and intense pulsed light (IPL) to enhance their positive effects and reduce their limitations.

Methods: This randomized, assessor blind study includes 45 patients (90 eyes) with refractory o-MGD who were divided into 3 groups via allocation concealment: IPL (group I, received an IPL treatment course: 3 times at 3-week intervals), MGP (group II, received MGP one time), and combined MGP-IPL (group III, MGP first followed by an IPL treatment course). Standard Patient Evaluation of Eye Dryness score (SPEED), tear break-up time (TBUT), corneal fluorescein staining (CFS), meibum grade, and lid margin finding results were assessed at baseline, 3 weeks after final treatment for groups I and III, 3 and 12 weeks after MGP for group II. Six months after final treatment, the SPEED and willingness to receive any treatment again were also collected for all groups. Paired Wilcoxon, Mann-Whitney U with Bonferroni correction, and Kruskal-Wallis tests were used for data analysis.

Results: For all 3 groups, all previously mentioned indexes improved significantly following treatment ($P<0.01$). MGP-IPL was better than IPL and MGP in terms of post-treatment SPEED, TBUT, meibum grade, and lid telangiectasia ($P<0.05/3$). Furthermore, the MGP-IPL was better than IPL in terms of lid tenderness and better than MGP in terms of orifice abnormality ($P< 0.05/3$). Six months later, the SPEED for the MGP-IPL was also significantly lower than other groups ($P<0.05/3$). Moreover, no patients in the MGP-IPL group expressed the need to be treated again compared to 35.7% or 20% of patients in the IPL or MGP groups, respectively.

Conclusions: Compared with IPL or MGP alone, the combination MGP-IPL produced best results in relieving all signs and symptoms and helping patients attain long-lasting symptom relief.

Trial registration: http://clinicaltrials.gov, ChiCTR1900021273 (retrospectively registered February 9, 2019).

Keywords: Intraductal meibomian gland probing, Intense pulsed light, Meibum, Tear film, Obstructive meibomian gland dysfunction

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Background

Dry eye has always being considered as a significant health concern that threatens individuals' life quality as well as their personal and economic well-being [1, 2]. Among various types of dry eye diseases, obstructive meibomian gland dysfunction (o-MGD) causing evaporative dry eye has attracted the attention of clinicians and scientists for its chronic course, recurrent potential, and high incidence rate [3, 4]. Moreover, the obstruction of the terminal tract of the meibomian gland (MG) leads to hyposecretion and quality change of meibum from the orifices [5]. These changes of meibum in ocular surfaces can result in instability of the tear film as well as irritation symptoms such as dryness and foreign body sensation [3]. Additionally, unusually elevated intraglandular pressure and aggravated local inflammation caused by meibum stasis further exacerbate the disease course, creating a vicious cycle.

Traditional treatments for o-MGD include warm compress, massage, artificial tears, etc. However, studies have showed that these treatments are not sufficient for symptom relief [6, 7]. And it is difficult for patients to comply with continuous medical therapies. Chinese o-MGD patients, in particular, always meet serious initial symptoms with MG orifices obstruction and no meibum secretion, making the treatment processes even more difficult [8, 9]. In recent years, great strides have been made in terms of new treatment options for refractory o-MGD patients, one of which is intense pulsed light (IPL). IPL, which has long been used in medical cosmetology, can also be effective for dry eye treatment mainly due to its inhibition of telangiectasias along the eyelid that block the way of inflammatory cytokine and its heating effects [10, 11]. Another relatively new method is intraductal meibomian gland probing (MGP), which was first described by Maskin in 2010. MGP uses a special meibomian cannula to probe the plugged meibomian gland, releasing abnormal elevated intraductal pressure and reestablishing a healthy microenvironment favoring the growth of MG tissues [12].

Although the safety and effectiveness of IPL and MGP have been proven in previous studies [8, 10, 11, 13, 14], their deficiencies can also be observed through day-to-day clinical observation. Specifically, the effect of IPL in alleviating stubborn intraductal congestion or intraductal scarring is comparatively limited. And for patients with severe intraductal inflammation or apparent blepharitis, the use of MGP alone is insufficient for decreasing excessive inflammation. Besides, probing is an invasive method for patients. Sik Sarman et al. reported that 20% of patients require repeated probing after an average of 4.6 months [13]. Repeated Probing may bring psychological burden to patients and would possibly cause scar proliferation. It is thus an urgent matter to identify an optimal therapeutic regimen that can reduce the number of invasive treatments, open the MG obstruction, promote the discharge of meibum, and at the same time, control inflammation.

Here, a new treatment method that combined the MGP and IPL courses was devised and then compared with MGP, IPL alone, with the aim of identifying a way in which to strengthen the advantages of MGP and IPL, and at the same time, offset their side-effects. All participating patients had serious refractory o-MGD and more than half of their evaluated meibomian gland orifices obstructed with no lipid secretion. Additionally, their Meibo-Scans showed no extensively atrophied areas.

Methods

This randomized controlled, assessor blind study was conducted between July 1, 2018 and December 30, 2018.

Patient selection and study design

45 patients clinically diagnosed with refractory o-MGD enrolled in this study. The inclusion criteria included: (1) older than 18 years, (2) Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire≥6, (3) more than half of the 15 evaluated meibomian gland orifices in each eyelid were obstructed and had no lipid secretion with extrusion, (4) meibum grade ≤ 24, (5) breakup time of tear film (TBUT) ≤ 5 s, (6) Schirmer test>5 s, (7) Meibo-Scan (OCULUS) revealed less than 1/3 atrophy area of the meibomian gland in both the upper and lower eyelids, (8) refractory was defined as lack of symptom relief with conservative treatment (eyelid warming, massage, and artificial tears) for at least 1 year prior to study treatment. All patients were informed of possible treatment-related complications and the possibility of being assigned to an invasive treatment group. All agreed to receive the possible therapeutic regimen and signed an informed consent form. Patients with a history of corneal contact lens, mite blepharitis, acute eye inflammation, or infection and apparent eyelid margin scarring as well as patients using a lacrimal plug or receiving LASIK (Laser Assisted In-situ Keratomi) were excluded from the study.

The multiple rate comparison method performed with PASS version 15 was used to estimate sample size. The pilot study, which involved 5 patients per group, showed that 20, 20, and 80% of patients in IPL, MGP and MGP-IPL groups experienced effective symptom improvement following treatment (with a decrease in SPEED score before treatment and half a year after final treatment>5). Power calculations with a type I error of 0.05 and type II error of 0.9 were executed. The results showed a sample size of 38 achieves 90% power in detecting an effect size (W) of 0.5774 using a 2 degrees of freedom Chi-Square

Test with a significance level (alpha) of 0.05. So, each group needed at least 13 patients.

Participants were randomly divided into 3 groups (15 patients per group) via block randomization, and allocation concealment was implemented using a closed envelop method. Patients in group I received an IPL treatment course (treated with IPL 3 times at 3-week intervals). Patients in group II received an MGP treatment course (treated with MGP one time). In group III, 3 weeks after initial MGP treatment, patients also received IPL 3 times at 3-week intervals. The clinical effects were assessed at baseline, 3 and 12 weeks following MGP treatment for group II and 3 weeks after final treatment for groups I and III. Furthermore, 6 months following final treatment for all 3 groups, all patients completed SPEED and answered a question in terms of requiring to receive any treatment once more. Patient enrollment, random allocation sequence generation, and intervention assignment were performed by the first author (HXD).

Treatment procedure

Intraductal meibomian canal probing

With the help of SuZhou LiuLiu Medical Equipment co. LTD, we designed a private probe based on the original Maskin probe and a rinse hollow tube (Fig. 1). The probe was 4.5 mm in length with a blunt end 0.12 mm in diameter. The hollow tube was 2.0 mm in length and 0.16 mm in diameter. The process of intraductal MGP proceeded as follows: (1) to ease the pain of probing, 4% lidocaine was injected into the upper and lower eyelids parallel to the palpebral margin, resulting in a local bulgy of the skin. (2) the eyelids were flipped outward with a cotton swab and an operating microscope was positioned over the target eyelid to more clearly show the orifices. Then, the operator inserted the probe into the glands vertically to the orifices. Impact force was required when resistance from the orifices or intraductal was encountered. After probing, chalazion forceps were used to squeeze out remnant meibum. Self-limited hemorrhage was the most common complication, for which a blood point and blood trickle could be observed and no particular treatment was needed. (3) then, a hollow tube was used to swash the meibomian gland by injecting 0.1% Dexamethasone (Guangzhou Baiyun Mountain Pharmaceutical co. LTD, China) and 0.25% Amikacin (Qilu Pharmaceutical co. LTD, China) repeatedly (Fig. 1). (4) eventually, Tobradex eye ointment (Alcon, Belgium) was applied to the conjunctival sac. All MGP procedures were performed by the first author (HXD).

Intense pulsed light

A M22 Multi-pulse therapeutic apparatus was used for treatment. Prior to treatment, 1–2 mm thick ultrasound gel was applied to participants' faces, covering the area from tragus to tragus beneath the eyelid margin, temple, and forehead. Then, the Pre-set Toyos parameters were administered to 1 or 2 treatment area test points to test patient tolerance and comfort. The intensity of the IPL treatment was adjusted to 14 J/cm^2-15 J/cm^2, which was determined via Fitzpatrick Skin Type Grading. Placement of an IPL eye shield over the eyes was necessary to protect eyes from the stimulus of bright light. After this, one back-and-forth flash emitted by an IPL hand piece was placed on each skin area without pressure. Finally, chalazion forceps were used to squeeze MG tissues. Care should be taken to ensure that the treatment areas were identical for each participant and all procedures were conducted by the same doctor (LL).

All participants were required to use artificial tears (Hailu, German) four times a day during the entire follow-up period.

Clinical evaluation

The eye examiners (Jiao Zheng and Linping Wang) were blind in regard to the groups participants were assigned to.

SPEED, CFS and TBUT

A Standard Patient Evaluation of Eye Dryness (SPEED) validated questionnaire (0–28) was used to assess the symptoms, as previously described [15]. Corneal

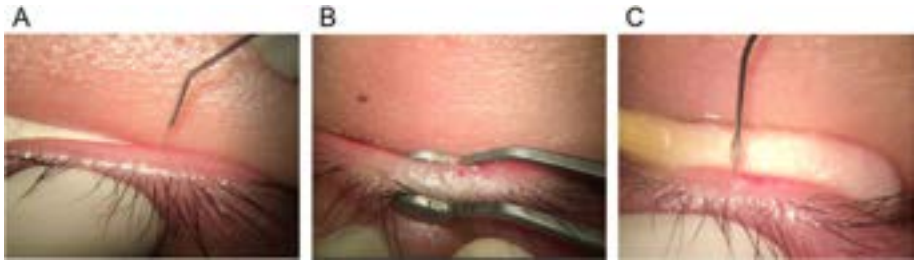

Fig. 1 The treatment procedure and structure of our private probe and rinse hollow tube. **a** the operator inserted the probe into the glands vertically to the orifices. **b** After probing, chalazion forceps were used to squeeze out remnant meibum. **c** Then, a hollow tube was used to swash the meibomian gland by injecting

fluorescein staining (CFS) was evaluated by dividing the cornea into four equal quadrants, and the staining of each section was recorded on a 0–3 scale: 0 = no punctate staining; 1 = less than half staining; 2 = more than half staining; 3 = whole staining; and a composite score for each quadrant (0–12 score) [16]. Tear break-up time (TBUT) was evaluated 3 times and an average value was recorded [17].

Meibum grade

The lower and upper eyelids were divided into 3 parts– nasal, bitamporal, and middle– with a total of 15 glands in each eyelid. The characteristics of each glandular expressate were graded on a scale of 0 to 3: 0 = no secretion; 1 = inspissated-filamentary secretion; 2 = cloudy liquid secretion; and 3 = clear liquid secretion. The scores of each expressed orifice in the 3 different eyelid sections were added together to provide the final meibum grade scores (0–90 score) for the right and left eyes [18].

Lid margin finding results

Lid margin finding results we evaluated included the abnormality of meibomian gland orifices, lid tenderness and telangiectasia, and were noted on a 0–4 scale, with 0 being absent and 4 being the most severe [8, 19].

Statistical analysis

Statistical significance was set at $p < 0.05$, and data analysis was performed using SPSS version 23. Continuous data was presented as means ± SD. A paired Wilcoxon test was employed to compare the parameters prior to and following treatment. Then, comparison was made between the different groups via non-parametric Mann-Whitney U tests with Bonferroni correction, Kruskal-Wallis tests.

Results

A total of 45 patients were at first enrolled in the study, with one patient in the IPL group ending the treatment course due to accidental pregnancy and one patient in the MGP-IPL group for home accidents. The ages of 43 enrolled patients (86 eyes) ranged from 24 to 56 years (mean age 37.56 ± 9.82), with a female to male ratio of 1.39. And there were no observed differences based on gender ($P = 0.409$) and age ($P = 0.376$) among the 3 groups.

During the follow-up period, several MGP-treated patients experienced subcutaneous ecchymosis of the eyelid skin caused by the injection of anesthetics, a symptom that can improve after the administration of a cold compress. And one patient in the IPL group suspended the treatment course due to occurred blepharokeratoconjunctivtis (BKC) after twice IPL treatments, with the final IPL not being performed until BKC was relieved via two-week administration of Tobradex.

The evaluation time for the MGP group was 3 and 12 weeks following MGP treatment, but no difference in all indexes was found to exist between 3 and 12 weeks after MGP treatment (SPEED: 11.87 ± 3.44 vs. 11.93 ± 3.26, $P = 0.933$; TBUT: 4.74 ± 1.28 vs. 4.81 ± 2.03, $P = 0.539$; CFS: 0.73 ± 1.34 vs. 0.80 ± 1.35, $P = 0.801$; meibum grade: 24.73 ± 10.66 vs. 26.57 ± 11.63, $P = 0.534$; lid telangiectasia: 1.73 ± 0.58 vs. 1.73 ± 0.64, $P = 0.946$; orifice abnormality: 2.00 ± 0.74 vs. 1.80 ± 0.85, $P = 0.299$; lid tenderness: 0.60 ± 0.67 vs. 0.57 ± 0.63, $P = 0.901$). In order to increase the comparability of the MGP and MGP-IPL groups (both assessed at 12 weeks after initial MGP treatment), the 12-week-data for the MGP-treated group II was selected as posttreatment data for analysis.

Prior to initial treatment, there were no observed differences among all parameters of the 3 groups (SPEED: $P = 0.339$; TBUT: $P = 0.083$; CFS: $P = 0.517$; meibum grade: $P = 0.139$; lid telangiectasia: $P = 0.105$; orifice abnormality: $P = 0.180$; lid tenderness: $P = 0.175$). After completion of the entire treatment course, all subjective symptoms and objective signs, including SPEED, TBUT, CFS, meibum grade, lid telangiectasia, orifice abnormality, and lid tenderness, were significantly improved for all groups (Table.1).

The improvement of ocular symptoms (SPEED) and TBUT was more apparent in the MGP-IPL group than the IPL and MGP groups ($P = 0.003$ or $P = 0.012$; Fig. 2). However, there were no observed differences in posttreatment CFS among 3 groups (group IPL vs. group MGP, $P = 0.866$; group IPL vs. group MGP-IPL, $P = 0.084$; group MGP vs. group MGP-IPL, $P = 0.123$; Fig. 2). Between group IPL and group MGP, no differences existed in SPEED, TBUT, CFS after treatment (SPEED: $P = 0.339$; TBUT: $P = 0.083$; CFS: $P = 0.517$; Fig. 2).

As for lid margin related indexes, the posttreatment meibum grade and lid telangiectasia improved more for group MGP-IPL than group IPL or group MGP ($P = 0.002$ or $P<0.001$, respectively; Table.1, Fig. 3). Orifice abnormality after treatment was also significantly more improved for the MGP-IPL group than the MGP group ($P = 0.016$; Table.1, Fig. 3). In terms of lid tenderness, group MGP-IPL showed more significant improvement than group IPL ($P<0.001$; Table.1, Fig. 3). No differences in meibum grade, lid telangiectasia, and orifice abnormality were observed among group IPL and group MGP (meibum grade: $P = 0.040$; lid telangiectasia: $P = 0.068$; orifices abnormality: $P = 0.315$; Fig. 3) except for lid tenderness, in which better results were seen in group MGP ($P<0.001$; Table.1, Fig. 3).

As shown in Fig. 4, no patient from any group displayed a SPEED score ≤ 9 before treatment; while following treatment, 14.29, 26.67, and 64.29% of patients in

Table 1 Clinical parameters before and after treatment in refractory O-MGD patients

	Group I (IPL)		P	Group II (MGP)		P	Group III (MGP-IPL)		P
Scores	before	after		before	after		before	after	
SPEED	16.14 ± 3.53	12.43 ± 3.84	<0.001	17.13 ± 3.23	11.93 ± 3.26	<0.001	18.00 ± 3.51	9.00 ± 1.80	<0.001
TBUT	2.66 ± 0.88	4.35 ± 0.88	<0.001	3.21 ± 0.98	4.81 ± 2.03	<0.001	2.78 ± 1.00	6.61 ± 1.57	<0.001
CFS	2.29 ± 2.71	0.96 ± 2.10	<0.001	2.13 ± 2.34	0.80 ± 1.35	<0.001	2.79 ± 2.51	0.29 ± 0.71	<0.001
Meibum grade	7.11 ± 4.57	20.82 ± 11.83	0.003	8.23 ± 3.15	26.57 ± 11.63	<0.001	6.64 ± 3.41	41.11 ± 10.26	<0.001
Lid telangiectasia	2.36 ± 0.49	1.43 ± 0.50	0.006	2.27 ± 0.45	1.73 ± 0.64	0.001	2.54 ± 0.51	1.07 ± 0.26	0.001
Orifice abnormality	2.14 ± 0.52	1.54 ± 0.51	<0.001	2.30 ± 0.60	1.80 ± 0.85	<0.001	2.00 ± 0.67	1.29 ± 0.46	<0.001
Lid tenderness	1.79 ± 0.79	1.36 ± 0.49	0.003	2.13 ± 0.57	0.57 ± 0.63	0.001	1.93 ± 0.81	0.36 ± 0.49	<0.001

P values were determined with a paired Wilcoxon test
"AFTER" was determined as 3 weeks after final treatment for groups I and III and 12 weeks after final treatment for group II

groups I, II, and III, respectively, obtained a score of 0–9 ($P = 0.020$, P was determined by the Fisher exact test). Moreover, it can be seen that all eyes in 3 groups showed a TBUT≤5 s before treatment, but 17.86, 36.67, and 92.9% of eyes in group I, II, and III, respectively, showed a TBUT more than 5 s after treatment ($P = 0.009$, $\chi2 = 7.335$, P was determined by $\chi2$ test; Fig. 5).

Six months after final treatment, the SPEED was still significantly lower in patients receiving MGP-IPL than MGP or IPL alone (11.36 ± 2.10 vs. 14.50 ± 3.76 vs. 14.60 ± 3.11, $P = 0.01$ or $P = 0.004$). Additionally, 35.7% or 20% of patients treated with IPL or MGP alone reported requiring treatment again to rectify recurrent dry eye related symptoms; meanwhile, of the patients who received the combined MGP-IPL course, zero reported a need to be treated again.

Discussion

Previous research has proven that both intraductal meibomian gland probing and intense pulsed light are significantly efficient in helping o-MGD patients achieve relief of symptoms and signs; yet, they also showed that this improvement was only experienced by the majority and symptom recurrence could emerge during the follow-up period [13]. Until now, no research has offered in-depth discussion for these exceptions. It seems researchers all focused on the pleasantly impressive results of these new treatments, but seldom noticed their inadequacies. Although MGP can re-open MG orifices, it is

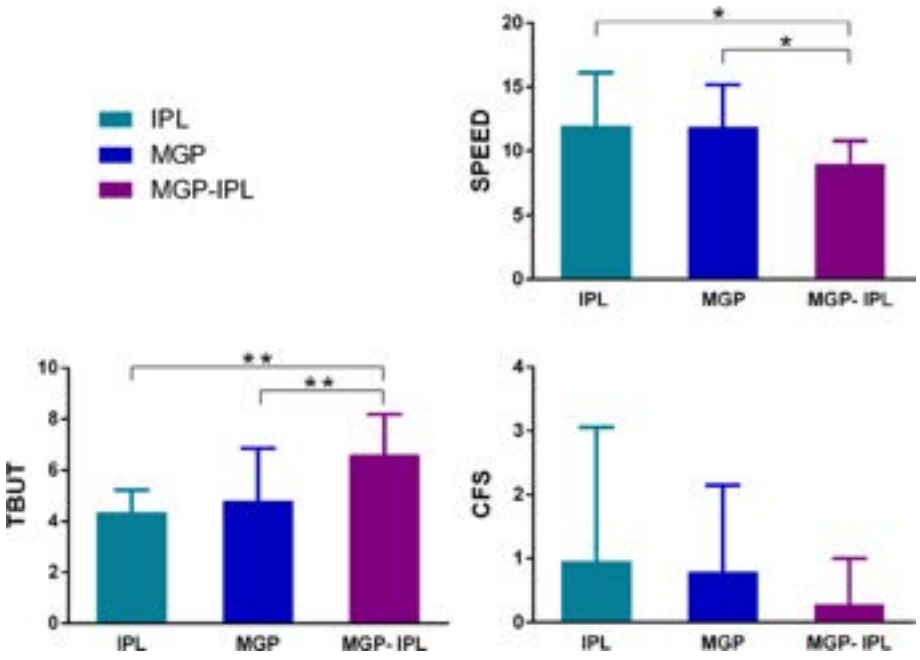

Fig. 2 Comparation of SPEED score, TBUT and CFS after treatment in 3 groups (IPL, MGP, MGP-IPL). Notes: all parameters prior treatment had no statistical differences among 3 groups. *$P \leq 0.05/3$, **$P<0.001$; "AFTER" was determined as 3 weeks after final treatment for groups I and III and 12 weeks after final treatment for group II, the same below

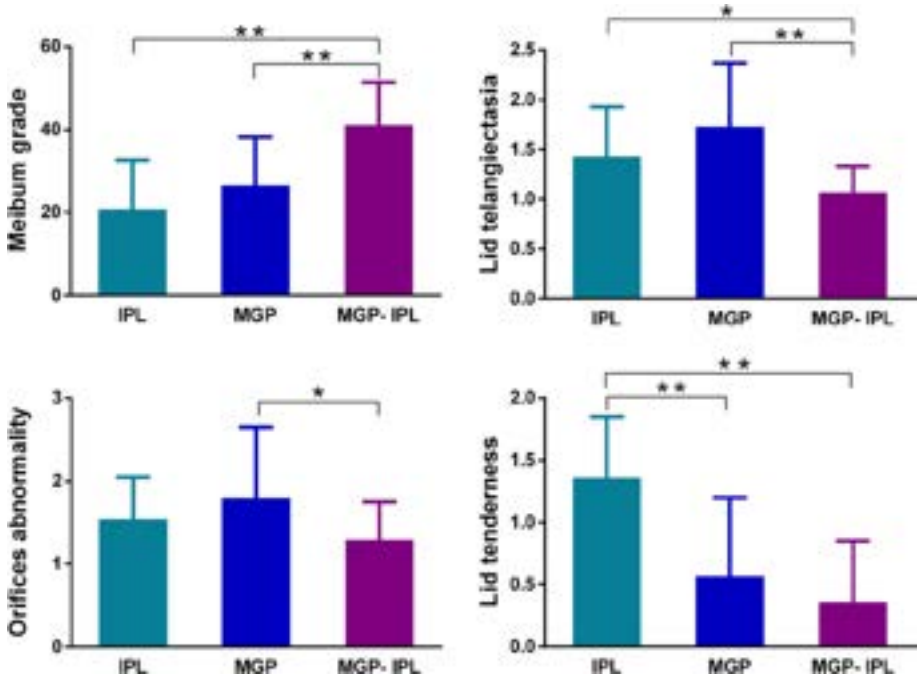

Fig. 3 Comparation of meibum grade and lid margin finding results after treatment in 3 groups. Notes: all parameters prior treatment had no statistical differences among 3 groups. *$P \leq 0.05/3$, **$P<0.001$

limited in terms of controlling inflammation. Moreover, it is an invasive treatment, so the repeated use of MGP should be restricted. IPL treatment is minimally invasive and can promote the discharge of eyelid lipids, reducing the inflammation of the eyelid margin. However, the effect of IPL on MG-obstruction and scarring is limited. Therefore, a new treatment combination that could fully realize the best therapeutic effects of two treatments and reduce the complications of invasive probing is essential.

Reiko Arita et al. recently observed that 81% of IPL-treated refractory o-MGD eyes showed amelioration of ocular symptoms, and 70% showed an improvement in TBUT [20]. Zeba A et al. reported that 91.4% of their patients received MGP described subjective symptomatic improvement during follow-up [21]. Similar results were also obtained in the present study, with 85.7 and 100% of treated eyes in the IPL and MGP groups revealing relief of symptoms, and 96.4 and 93.3% exhibiting increase in TBUT, respectively. However, in the MGP-IPL group, all patients (100%) showed alleviation of dry eye related symptoms as well as the extension of TBUT.

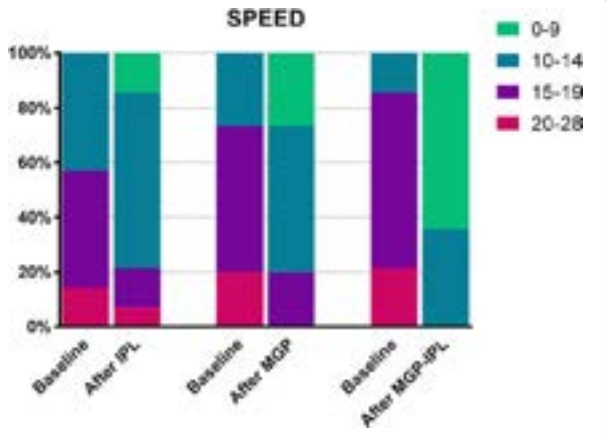

Fig. 4 Change in the SPEED questionnaire score between baseline and after treatment in three groups

As the meibomian gland of an o-MGD patient is usually ill-conditioned, in which abnormal meibum stasis accumulates rather than flows to the ocular surface, increased intraglandular pressure and duct expansion are inevitable [14]. Furthermore, with the recurrent attacks of o-MGD, atrophy of meibomian glands is frequently observed [22]. It was long considered that this atrophy was irreversible until Maskin proposed intraductal meibomian gland probing and proved this treatment can increase MG tissue area and growth of atrophied MGs [12, 22]. Maskin showed that they used transillumination to ensure the gland was longer than the length of the probe before probing. Their most common length of probe was 4 mm. And they showed their probes can probe to the most distal aspects of the duct [12]. Our private probe was 4.5 mm in length, and before probing, we used infrared meibography (IR-M) to know the

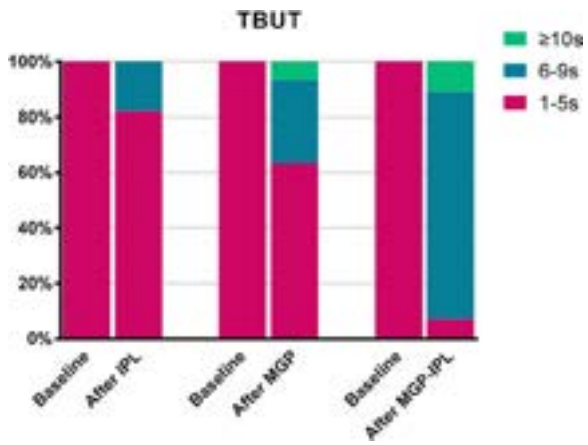

Fig. 5 Change in TBUT between baseline and after treatment in three groups

length of glands, so we believe that our MGP treatment is also enable to affect far distal part of meibomian gland to reopen the blocked sites effectively. Meibomian gland probing mechanically opened the obstructed orifices and ducts. With the pop up of constrained meibum, keratinized epithelium, and debris, the vicious cycle of o-MGD progression was broken, and the majority of patients received immediate symptom relief [10, 21]. However, the quantity of meibum on the ocular surface is not a decisive factor in the retardation of the evaporation of aqueous and the stabilization of the tear film. The meibum lipid quality was found to play an even more important role in maintaining ocular surface equilibrium [14, 23]. Nakayama et al. showed all cases exhibited improvements in meibum viscosity (grades 3–0, 3–1, and 3–2) after MGP treatment, as the abnormal meibum was rapidly released with the sudden orifice opening and then gradually eliminated through blinking [14]. However, there was only one case returning to normal level. Furthermore, a growing amount of evidence has suggested the inflammation reaction played an essential role in the formation of abnormal meibum. The enzymes produced by bacterial flora could result in altered lipid composition with an increased melting point and viscosity [3, 24]. Thus, it was assumed that the single mechanical function of MGP in improving meibum lipid quality is limited. Xiao Ma et al. recommended the use of 0.1% fluorometholone after MGP treatment to diminish inflammation, since MGP predisposes the lid margin to a topical corticosteroid effect [10]. However, it is believed that although MGP increased the responsiveness of the gland to anti-inflammatory drugs, the traditional application of eyedrops or eye ointment following MGP can hardly deliver drugs to the deepest gland lumens. Since the inflammation of o-MGD has been proven to not only exist in the eyelid margin and ocular surface but also within the glands [25], the unthorough evacuation of inflammation after MGP treatment may be essential for the re-obstruction, possibly explaining why not all patients experienced improvement after MGP treatment and why a considerable number of patients needed to receive repeated probing.

The surprising efficacy of IPL in easing the symptoms of MGD patients can be mainly attributed to its effect of vasculature destruction and meibum melting [26, 27]. Lid telangiectasia is a common characteristic of o-MGD, and these tiny vessels along the eyelid margin also increase the accessibility of inflammatory mediators, resulting in aggravated chronic inflammation above the palpebral edge or within the glands [28–30]. The 580 nm wavelength released by intense pulsed light can be absorbed by intravascular hemoglobin and then activate selective photothermolysis, leading to the development of blood clotting. Thus, abnormal vessels gradually shut down and bacterial loading reduces [26]. Apart from that, the heat from either photothermolysis or light energy itself can enhance the liquidity of meibum. And compared to traditional eyelid warming, the heat effect delivered by intense pulsed light is far more lasting and permeable [31]. Surprisingly, instead of showing reduction in symptoms, 2 patients (14.8%) in the present study reported even more serious symptoms at the end of the IPL treatment course. It can be speculated that this deterioration may relate to obstruction sites within the glands. Maskin has proposed six types of o-MGD according to the depths of fixed obstruction and the function of MG [22]. In a meibomian gland with a deep-seated intratubal obstruction or partial distal obstruction, IPL may work well as the vast melting meibum ahead the fixed area can easily move out under the extrusion force caused by forceps or daily blinking. While for the gland that was completely fixed in the distal part, it's actually the opposite, as the stagnant meibum was confined between the terminal of glands and the obstruction site, analogous to staying in a blind alley. The heat released by IPL and the pressure caused by the forceps might paradoxically increase the intraductal pressure and exacerbate the inflammatory response; thus, treatment with IPL alone may not alleviate disease symptoms but instead irritate the condition. This effect can also be indirectly observed in the present data in terms of the posttreatment lid tenderness of the IPL group, despite showing symptom alleviation compared with baseline, still being significantly higher than the MGP and MGP-IPL groups.

It appears that neither IPL nor MGP is the absolute perfect method for treating all refractory o-MGD patients; however, their unique advantages can effectively make up for their inherent deficiencies. This assumption was also confirmed by the present research, as patients

receiving MGP-IPL treatment exhibited the best improvement results. With the initial opening of blocked glands via probing, meibum within the glands can flow without restriction. Additionally, the followed 3 times IPL treatments further restrict inflammation and eliminate the abnormal meibum, resulting in an optimal therapeutic effect. Compared with single IPL or MGP treatment, MGP combined IPL proved to be significantly superior in improving SPEED, TBUT, meibum grade, and lid telangiectasia.

One time MGP did not provide all patients continued symptom relief in the present 6-month observation. Specifically, 20% of patients still required repeated invasive probing, yet such treatment would increase patients' sense of misery. In contrast, the combination of MGP with noninvasive IPL in the present study helped 100% of patients attain enduring symptom relief. This combination treatment may achieve the maximum therapeutic effect of MGP and IPL, reducing the possibility of trauma and scarring caused by repeated probing.

Despite positive outcomes, there are still certain limitations of the present research: First, the participants in the study were comparatively small and the follow-up duration was rather short. Further investigation is thus suggested to evaluate the long-term results of these treatments with a larger number of cases. Second, MGP is an invasive method that is more suitable for patients with severe gland obstruction or gland scarring, while IPL treatment is better for relieving intraductal inflammation. This study found the combination of these two treatments could attain the best results, but it cannot be denied that this treatment mode would bring patients more financial, time and psychological burdens at the same time. Based on these results, it is recommended that patients have at least half of their orifices obstructed in each eyelid but with no apparent meibomian gland atrophy, and at the same time, have higher inflammatory index like lid telangiectasia scores receive combined MGP-IPL therapy to exert the best curative effect of probing and anti-inflammation simultaneously.

Conclusions

IPL, MGP, and combined MGP-IPL are all effective methods for refractory o-MGD patients; however, the combination MGP-IPL method could maximize the therapeutic benefits, which is especially helpful for patients who have severe meibomian gland obstruction and obvious intraductal or eyelid margin inflammation, who want to gain the greatest amelioration in all clinical signs and subjective symptoms or still remain frustrated to either MGP or IPL treatment.

Abbreviations

BKC: Blepharon- keratoconjunctivtis; CFS: Corneal fluorescein staining; IPL: Intense pulsed light; IR-M: infrared meibography; LASIK: Laser Assisted In-situ Keratomi; MG: Meibomian gland; MGP: Intraductal meibomian gland probing; o-MGD: Obstructive meibomian gland dysfunction; SPEED: Standard Patient Evaluation of Eye Dryness score; TBUT: Tear break-up time

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Not applicable.

Additional statement

Our randomized controlled trial study adheres to the CONSORT guidelines.

Authors' contributions

XH: research design, manuscript preparation, and treatment operation; QQ: data analysis and manuscript preparation; LW: data acquisition; JZ: data acquisition; LL: treatment operation; XJ: research design, manuscript preparation. All authors read and approved the final version of this manuscript.

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Availability of data and materials

The datasets obtained and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee at the Affiliated Second Hospital, School of Medicine, Zhejiang University in Hangzhou, China. All the procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Intense Pulsed Light Treatment for Meibomian Gland Dysfunction in Skin Types III/IV

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Abstract

Background and objective: Several cases of meibomian gland dysfunction (MGD), particularly the moderate to severe ones, are considered intractable by traditional therapy. Intense pulsed light (IPL) therapy has emerged as a new choice for management of MGD in recent years, given that use of lasers and optical treatments is typically challenging in patients with darker skin types.
Methods: IPL treatment for MGD is administered in the periorbital area with the thinnest skin in our body, which has an inherent risk of skin side effects. We evaluated the effects and safety of this therapy in Chinese patients with Fitzpatrick skin types III–IV. Forty MGD patients were randomly administered IPL treatment with two types of parameters in the left and the right eye.
Results: Results revealed that both parameter settings of IPL treatment could gradually and effectively raise the tear breakup time (BUT) and ocular surface disease index (OSDI) score. However, younger patients showed better improvement in BUT ($F = 19.54$, $p < 0.01$) and OSDI ($F = 9.93$, $p < 0.01$) compared with older patients.
Conclusions: Overall, results showed that IPL treatment is safe and effective in MGD patients with skin types III–IV.

Keywords: intense pulsed light, IPL, dry eye disease, meibomian gland dysfunction, MGD, skin types III–IV

Introduction

Dry eye disease (DED) is a common disease that causes varying degrees of discomfort and disability of the eye, particularly in patients aged >40 years.[1,2] Evaporative DED is one of the most common types and is primarily caused by meibomian gland dysfunction (MGD).[3] Over 60% of DED patients in Asia suffer from MGD.[4] Asian patients exhibit a higher degree of meibomian gland dropout and incomplete blinking compared with their Caucasian counterparts.[5] Patients with this disease produce abnormal meibum with more free fatty acids that is foamy and affects the stability of the tear film, decreases wax esters, and increases cholesteryl esters, thereby causing obstruction of the meibomian gland and creating an environment for bacteria to settle and proliferate.[6,7] Hence, such patients can develop severe inflammation associated with bacterial overgrowth, which exacerbates the condition.[8,9] Traditional therapies, including supportive care with artificial tears, softening the meibum with warm compresses, clearing abnormal meibum with meibomian gland extrusion, and anti-inflammatory medications, such as topical cyclosporine, azithromycin, and oral doxycycline, provide some relief.[10,11] MGD is a chronic inflammatory DED that has ceaseless development for years. The normal range of breakup time (BUT) is 10–45 sec, which offers a wide span for compensation.[12] Thus, patients with MGD in the early stages usually have subtle dry eye symptoms that seldom appear. Patients with mild symptoms, particularly younger patients, can usually be cured by aforementioned traditional therapies, but management of MGD becomes more challenging with progressing age and medical history.[4]

Intense pulsed light (IPL) devices are nonlaser, high-intensity light sources that use high-output flash lamps to produce a broad wavelength output of noncoherent light, usually ranging from 500 to 1200 nm.[13] IPL functions by selective photothermolysis: when polychromatic light is delivered, the three main chromophores in our skin

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hemoglobin, melanin, and water can be simultaneously targeted, leading to thermotropy and resultant destruction of target tissues such as pigment and vascular lesions. In addition, IPL has been used in dermatology for several years for treatment of rosacea as its abnormal angiotelectasis can be closed by photothermy.[14,15] Rosacea is one of the primary risk factors for MGD as angiotelectasis often exists in both the nose and eyelid margins.[16] In 2002, Toyos et al. discovered positive ophthalmic effects of IPL in patients who underwent treatment for facial rosacea. Along with decreased facial erythema, these patients showed improvement in signs and symptoms of MGD and dry eyes. Based on these observations, the Toyos Clinic continued to develop and refine this treatment.[17] In 2015, Toyos et al. conducted a retrospective, noncomparative, interventional case series with 91 patients who presented with severe DED.[18] Treatment included IPL therapy and gland extrusion over a 30-month study period. A majority of patients reported significant relief after receiving IPL treatment. During the same year, Craig et al. also evaluated the effects of IPL application to the periocular area for treatment of MGD and achieved favorable results.[19] Normal meibum has good antimicrobial properties that keep the lid margin clear from overgrowth. In MGD, abnormal blood vessel growth from chronic inflammation surrounds the meibomian glands and secretes inflammatory mediators that cause malfunction of the glands; this dysfunction leads to formation of abnormal meibum.[20] Thus, possible mechanisms of IPL in treating MGD include the following: photothermy from IPL melts abnormal meibum more directly and efficiently compared with warm compresses as the heating method ensures that heat is transmitted both inside and out.[21] Selective photothermolysis can close the abnormal telangiectasia at the eyelid margin, which restrains the release of inflammatory factors and promotes recovery of the meibomian gland by reducing bacterial invasion.[18]

Applications of lasers and optical treatments are usually challenging in patients with darker skin types[22] because the increased melanin in their skin can absorb more photons and produce photothermal effects, which increases the risk of skin damage.[23,24] The most concerning complication observed in people with darker skin who receive IPL is hyperpigmentation. IPL treatment for MGD is administered in the periorbital area, which comprises the thinnest skin in our body and is the predilection site for pigmented lesions, thus increasing the risk of dermatological side effects. A previous study on side effects from IPL showed that skin pigmentation and IPL fluence are major determinants of side effects after IPL exposure.[25] Another study wherein IPL was administered in certain patients with skin types V–VI suggested that IPL can be effective and safe in patients with very dark skin types but with appropriate parameter selection.[26] However, to date, only few studies have been conducted regarding the use of this therapy in people with darker skin types, resulting in a limited data pool for reference. Most Asian people, including the Chinese, belong to Fitzpatrick skin types III–IV.[27] We aimed to evaluate the effects and safety of MGD lesions treated by IPL in Chinese people and expected to determine the appropriate reference values for optimal parameters. Perhaps this study could serve as a reference for similar research in people with skin types ≥V who receive IPL treatments.

Methods

This study protocol adhered to the tenets of Declaration of Helsinki, and was approved by the institutional review board of the Joint Shantou International Eye Center of Shantou University and Chinese University of Hong Kong. This study was passed and registered in the Chinese Clinical Trial Registry in March 2017 (registration number: ChiCTR-ONC-17010867). Informed consent was obtained from all participants. Datasets generated during this study are available from the corresponding author on reasonable request.

Grouping criteria and assessment index

In total, 40 patients with skin types III–IV (type III: 12.5%, type IV: 87.5%) diagnosed with moderate to severe DED caused by MGD who visited our hospital during April–June 2017 were enrolled into the study. Diagnostic criteria included any one subjective symptom of DED, a BUT of ≤5 sec, positive corneal fluorescein staining, and abnormity of meibomian gland structure and function (according to consensus regarding diagnosis and treatment enacted by clinical experts of DED from the Chinese Medical Association). The aforementioned indices were examined using a slit lamp under a cobalt blue light after fluorescein staining of the corneal epithelia. BUT values were measured three times by using RT-7000 (Tomey Corporation, Nagoya, Japan), and the average value was considered. Ocular surface disease index (OSDI) questionnaires were completed by patients themselves. All enrolled patients had received three IPL treatments by Lumenis One (Lumenis, Inc., Santa Clara, CA). All treatments used a big spot size (15 × 35 mm) and the same pulse parameters (two pulses with 3.0 ms of pulse duration and 30 ms pulse delay), but with different filters and fluence (560 nm and 16 mJ/cm^2, 590 nm and 14 mJ/cm^2) in the left or right eye randomly by a coin toss. Assessment indices, including BUT, OSDI, patient satisfaction, and adverse events, were recorded once before each IPL treatment was administered, while the last assessment was completed 1 month after the last treatment was administered.

Therapeutic procedure

The therapeutic procedure used has been previously published.[18,19]

1. Eyes were protected using a disposable blinder that was white and opaque.
2. A dedicated gel, which was chilled in advance, was applied on the skin area between the ears and under the eyes, including the nose.
3. Regular IPL treatment was administered twice in the area with cold gel application.
4. Meibomian gland massage was performed immediately after IPL treatment.
5. All enrolled patients received three IPL treatments at an interval of 2 weeks between the first and second treatments, and at an interval of 1 month between the second and third treatments. Hyaluronic acid sodium eye drops (Hycosan, EUSAN GmbH, Germany) were used during the treatment interval.

Statistical methods

Data were statistically analyzed using the statistical package for the social sciences (SPSS) software (2010, version 22.0; IBM Corp., Armonk, NY). Data with abnormal distribution were described using mean and standard deviation (SD). Median values were used to describe partially distributed data, and frequency (percentage) was used for categorical data. The group *t*-test was used to compare differences between age groups, and the chi-square test was used for gender comparisons. Differences in data measured during each assessment between the two groups were analyzed using repeated measure. Differences in patient satisfaction were described using generalized estimating equations. A p value (two-tailed) ≤0.05 indicated a statistically significant difference.

Results

Data analysis of age groups: group A (≤40 years); group B (>40 years)

All 40 patients were divided into two age groups: group A ($n=16$, 11 men and 5 women) included individuals aged ≤40 years, and group B ($n=24$, 11 men and 13 women) included individuals aged >40 years. No significant gender differences were noted between the two groups ($\chi^2=2.037$, $p=0.154$). On the contrary, significant differences in BUT were observed for both the right eye (OD) and the left eye (OS) in both groups by every measure (OD: $F=4.50$, $p=0.02$; OS: $F=6.20$, $p=0.04$). In addition, significant differences were noted in the BUT values of both eyes between the two age groups ($F=19.54$, $p<0.01$). In contrast, no significant differences were noted in OSDI scores between both groups by every measure ($F=0.85$, $p=0.41$); however, OSDI of each subject differed significantly by every measure ($F=214.37$, $p<0.01$), and significant differences were noted between the two age groups as well ($F=9.93$, $p<0.01$; Table 1). Assessment of patient satisfaction revealed no significant differences between the two groups by every measure (*Wald* $\chi^2=0.06$, $p=0.99$) or between both groups (*Wald* $\chi^2=1.04$, $p=0.31$), but within each group significant differences were noted by every measure (*Wald* $\chi^2=17.55$, $p<0.01$). Side effects in both groups were compared using the chi-square test, which showed no significant differences (Table 2).

Results indicated that IPL treatment gradually raised BUT values of most patients in the two age groups, reduced their dry eye symptoms, and improved their quality of life. Younger patients from group A showed better improvement in BUT compared with older patients from group B, but patients from both groups were equally satisfied with improvement in their symptoms.

Data analysis of parameter groups

Group C (filter: 560 nm, fluence: 16 mJ/cm^{2}in right; filter: 590 nm, fluence: 14 mJ/cm^{2}in left), group D (filter: 560 nm, fluence: 16 mJ/cm^2 in left; filter: 590 nm, fluence: 14 mJ/cm^2 in right).

All 40 subjects were divided into two groups according to the two types of treatment parameters that were randomly used in the left or right eye: group C ($n=22$, 12 men and 10 women; mean age 49.82 ± 14.50 years) and group D ($n=18$, 10 men and 8 women; mean age 44.17 ± 13.96 years). No significant differences were noted in terms of gender (t/$\chi^2=0.01$, $p=0.95$) and age (t/$\chi^2=1.25$, $p=0.22$) between the two groups.

Of note, significant differences were observed in BUT values of both eyes in both groups by every measure (OD: $F=143.96$, $p<0.01$; OS: $F=126.42$, $p<0.01$). On the contrary, no statistical differences were noted in BUT values for both OD and OS between the two parameter groups (OD: $F=1.05$, $p<0.01$; OS: $F=1.95$, $p=0.17$). Significant differences were noted in OSDI for each patient by every measure ($F=214.46$, $p<0.01$), but no significant between-group difference was noted ($F=0.28$, $p=0.60$; Table 3). Assessment of patient satisfaction revealed differences for each patient by every measure (*Wald* $\chi^2=19.82$, $p<0.01$) but showed no significant between-group differences (*Wald*

Table 1. Comparison of the Four Measurements of Breakup Time and Ocular Surface Disease Index by Age Group

	Group A (n = *16*)			*Group B* (n = *24*)		
Index	*Minimum*	*Mean ± SD*	*Maximum*	*Minimum*	*Mean ± SD*	*Maximum*
BUT						
OD						
1	1.00	3.28 ± 1.38	6.00	0.50	2.27 ± 1.22	6.00
2	3.00	5.22 ± 1.28	8.00	0.50	4.00 ± 1.35	6.00
3	6.00	8.66 ± 1.68	12.00	1.00	6.15 ± 1.94	11.00
4	7.00	11.53 ± 2.81	15.00	1.00	8.35 ± 2.74	14.00
OS						
1	0.50	2.78 ± 1.65	7.00	1.00	2.27 ± 1.06	5.50
2	3.50	5.47 ± 1.52	9.00	1.50	4.27 ± 1.44	7.00
3	6.00	9.47 ± 2.33	15.00	2.00	6.67 ± 2.23	13.00
4	6.00	11.59 ± 2.51	15.00	1.00	9.60 ± 3.02	15.00
OSDI						
1	19.00	24.88 ± 3.14	31.00	21.00	26.92 ± 3.36	32.00
2	15.00	18.81 ± 3.08	25.00	18.00	22.33 ± 2.68	28.00
3	8.00	12.81 ± 4.86	28.00	10.00	15.33 ± 3.58	26.00
4	5.00	9.31 ± 5.06	25.00	8.00	13.13 ± 4.37	29.00

Average BUT values (including both eyes) increased, and OSDI scores decreased with treatment in both age groups.
BUT, breakup time; OD, right eye; OS, left eye; OSDI, ocular surface disease index; SD, standard deviation.

Table 2. Comparison of Side Effects by Age Group

	A (n = *16*)		*B* (n = *24*)			
Index side effects	*No (%)*	*Yes (%)*	*No (%)*	*Yes (%)*	χ^2	P
Erythema						
OD	11 (68.8)	4 (25.0)	13 (54.2)	11 (45.8)	2.95	0.23
OS	8 (50.0)	8 (50.0)	12 (50.0)	12 (50.0)	0.00	1.00
Edema						
OD	14 (87.5)	2 (12.5)	21 (87.5)	3 (12.5)	0.00	1.00
OS	16 (100.0)	0 (0.0)	22 (91.7)	2 (8.3)	Fisher's	0.51
Blister; purpura						
OD	16 (100.0)	0 (0.0)	23 (95.8)	1 (4.2)	Fisher's	1.00
OS	16 (100.0)	0 (0.0)	24 (100.0)	0 (0.0)	—	—
Hyperpigmentation						
OD	16 (100.0)	0 (0.0)	21 (87.5)	3 (12.5)	0.74	0.39
OS	16 (100.0)	0 (0.0)	23 (95.8)	1 (4.2)	Fisher's	1.00
Total	7 (43.8)	9 (56.3)	7 (29.2)	17 (70.8)	0.90	0.34

Side effects in both age groups were compared using the chi-square test, which revealed no significant differences.

$\chi^2 = 1.41$, $p = 0.24$). Side effects in the two groups were compared using the chi-square test. Incidence of erythema in the right eye was higher in group C than in group D, whereas incidence of erythema in the left eye was lower in group C than in group D (right: $\chi^2 = 5.52$, $p = 0.02$; left: $\chi^2 = 10.10$, $p < 0.01$). No significant differences were noted between the groups in terms of other side effects (Table 4). These results suggest that IPL treatment with both types of parameters can effectively improve BUT in patients with MGD as well as dry eye symptoms. No significant differences were noted between the groups in terms of BUT, OSDI, and patient satisfaction.

Discussion

Treatment by laser or light sources usually carries greater risks for people with darker skin types, particularly in the periorbital area, which possesses the thinnest skin in our body.[28] In this study, we aimed to determine optimal parameter settings for MGD patients with skin types III/IV, which would ensure efficacy and safety at the same time. Thus, we compared two types of parameter settings with the same pulse setting (2 pulses, 3.0 ms of pulse duration, and 30 ms pulse delay) but with different light filters and energy densities (group C: 560 nm, 16 mJ/cm^2 vs. group D: 590 nm, 14 mJ/cm^2). According to the mechanism described by Toyos et al., MGD patients usually have abnormal blood vessel growth in their meibomian glands, which results from chronic inflammation. Use of IPL, with the light hot function, on the eyelid can close abnormal angiotelectasis owing to the ability of hemoglobin (Hb) to absorb a large amount of heat, which makes abnormal blood vessels seal, solidify, and shrink.[18] One of the absorption peaks of Hb is 555 nm, and oxyhemoglobin (HbO_2) also has an absorption peak of 577 nm,

Table 3. Comparison of the Four Measurements of Breakup Time and Ocular Surface Disease Index by Parameter Groups

	Group C (n = *22*)			*Group D* (n = *18*)		
Index	*Minimum*	*Mean ± SD*	*Maximum*	*Minimum*	*Mean ± SD*	*Maximum*
BUT						
OD						
1	0.50	2.43 ± 1.03	4.00	1.00	2.97 ± 1.67	6.00
2	2.50	4.25 ± 1.08	6.50	0.50	4.78 ± 1.78	8.00
3	3.50	7.02 ± 1.93	12.00	1.00	7.31 ± 2.55	12.00
4	6.00	9.25 ± 2.45	15.00	1.00	10.08 ± 3.88	15.00
OS						
1	0.50	2.21 ± 0.91	4.00	1.00	2.81 ± 1.69	7.00
2	3.00	4.43 ± 1.20	7.00	1.50	5.14 ± 1.90	9.00
3	4.00	7.34 ± 2.09	12.00	2.00	8.33 ± 3.16	15.00
4	6.50	9.32 ± 2.33	15.00	1.00	9.94 ± 3.74	14.00
OSDI						
1	20.00	26.23 ± 3.53	32.00	119.00	25.94 ± 3.30	32.00
2	15.00	20.82 ± 3.94	26.00	15.00	21.06 ± 3.80	28.00
3	9.00	13.95 ± 2.77	19.00	8.00	14.78 ± 5.65	28.00
4	5.00	10.95 ± 3.26	17.00	5.00	12.93 ± 6.50	29.00

Average BUT values (including both eyes) increased, and OSDI scores decreased with treatment in both parameter groups.

Table 4. Comparison of Side Effects by Parameter Groups

	C (n = *16*)		*D* (n = *24*)			
Index side effects	*No (%)*	*Yes (%)*	*No (%)*	*Yes (%)*	χ^2	P
Erythema						
OD	10 (45.5)	12 (54.5)	14 (82.4)	3 (17.6)	5.52	0.02
OS	16 (72.7)	6 (27.3)	4 (22.2)	14 (77.8)	10.10	<0.01
Edema						
OD	18 (81.8)	4 (18.2)	17 (94.4)	1 (5.6)	0.52	0.47
OS	21 (95.5)	1 (4.5)	17 (94.4)	1 (5.6)	Fisher's	0.70
Blister; purpura						
OD	21 (95.5)	1 (4.5)	18 (100.0)	0 (0.0)	Fisher's	0.55
OS	22 (100.0)	0 (0.0)	18 (100.0)	0 (0.0)	—	—
Hyperpigmentation						
OD	19 (86.4)	3 (13.6)	18 (100)	0 (0.0)	1.05	0.31
OS	21 (95.5)	1 (4.5)	18 (100.0)	0 (0.0)	Fisher's	0.55
Total	10 (45.5)	12 (54.5)	4 (22.2)	14 (77.8)	2.35	0.13

Side effects in the two parameter groups were compared using chi-square test. Incidence of erythema was higher in the right eye in group C than in group D. Incidence of erythema was lower in the left eye of group C than in group D, with statistical significance (Right: $\chi^2 = 5.52$, $p = 0.02$; Left: $\chi^2 = 10.10$, $p < 0.01$). No significant differences were noted in other side effects between both groups.

which is close to 560 nm.[13] Thus, the 560-nm wavelength would have a higher absorption rate by skin blood vessels compared with the 590-nm one. The higher energy density in group A than in group B would allow greater energy absorption by skin surfaces of the same size. In addition, photothermal radiation of IPL therapy would be similar to warm compression therapy but better for treatment because of the different heating methods used, with IPL heating the skin from inside to outside, which increases blood circulation and improves local skin metabolism through residual heat effects. Warm compression therapy primarily heats the epidermis only for a short duration and hardly achieves sufficiently high temperature in the subcutaneous tissue that is adequate for treatment.[29]

Side effects such as erythema, edema, blistering, purpura, and hyperpigmentation were recorded in our study. Erythema was the most common immediate reaction after IPL treatment, usually accompanied by tingling and burning sensations. Although no significant difference was noted in the incidence of erythema between both age groups, the incidence was higher in the higher energy-treated group (group C, 560 nm, 16 mJ/cm^2). Although the patients expressed some concerns and complaints regarding such skin changes and discomfort, these effects usually subsided within 3 days, and most of these subsided on the same day. No significant difference was noted in patient satisfaction between the groups treated with different parameters. Other side effects such as edema, blistering, and hyperpigmentation were rare and disappeared within a few weeks. Few patients from the older age group suffered hyperpigmentation, and one of them developed a blister after IPL treatment (Fig. 1); the blister recovered in 1 week, while cases of hyperpigmentation were either still obvious or gradually subsided during the follow-up period. No similar concerns were reported in patients from the

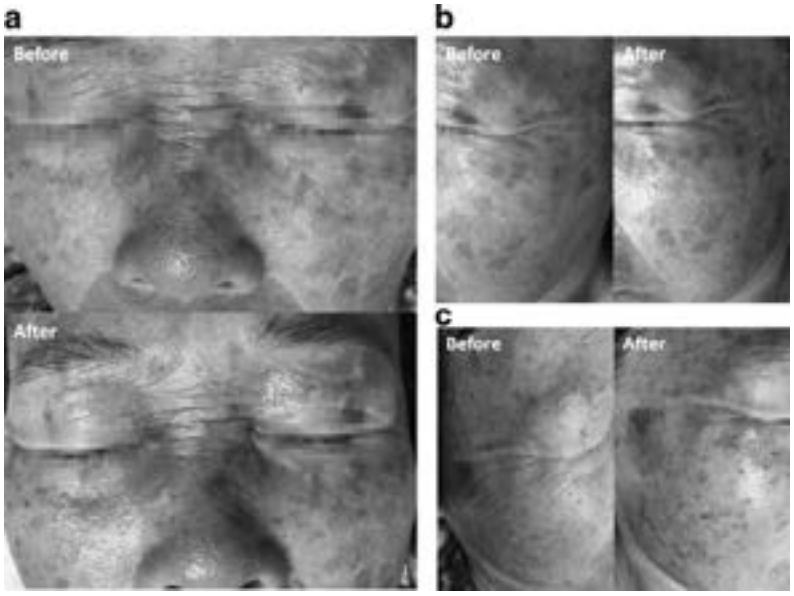

FIG. 1. Hyperpigmentation in a patient from the older group after IPL treatment. The patient suffered from erythema and hyperpigmentation after IPL treatment. The erythema subsided on the second day, but the hyperpigmentation did not subside completely. Photographs were taken in each group **(a–c)** before the first IPL treatment and immediately after the last treatment. **(a)** Comparison of the front view before and after IPL treatment showed no remarkable change. **(b)** Comparison of the left cheek treated by IPL with parameter setting (filter 590 nm, fluence 14 mJ/cm^2) beside the eye showed no obvious change. **(c)** Comparison of the right cheek treated by IPL with parameter setting (filter 560 nm, fluence 16 mJ/cm^2) beside the eye showed obvious, enlarged pigment lesions. IPL, intense pulsed light.

younger group. Moreover, all patients with hyperpigmentation had multiple age spots, sun spots, and discoloration. Aging skin tends to be thinner and has more pigment lesions, which increases the risk of hyperpigmentation.[30,31] Therefore, IPL treatment for aging skin, particularly that with pigment lesions, must be well regulated, although such lesions eventually subside in the long term. Indeed, results from our study showed no significant difference between the two parameter groups in terms of therapeutic efficacy, including BUT, OSDI, and patient satisfaction. The shorter wavelength and higher energy in group C (560 nm, 16 mJ/cm^2) did not achieve better therapeutic effects but induced additional discomfort compared with the lower energy-treated group D. In fact, our results indicate that the parameter settings for group D (590 nm, 14 mJ/cm^2) are a better choice for patients with skin type III/IV as it was equally effective and provided a better ''comfort level'' to patients along with and a decreased risk of skin side effects.

Further, we attempted to characterize age-dependent therapeutic effects after division of patients into two age groups (group A $\leq$40 years; group B $>$ 40 years). The younger group showed greater sensitivity to IPL treatment, with improvement being better and faster compared with the older group even though initial conditions were of similar severity. One possible explanation for this difference could be the greater complexity of the ocular surface structure in older group patients, which could limit the increase of BUT. Thus, MGD is associated with higher morbidity in elderly patients.[32] Another possible explanation could be that metabolism and immune functions might be better in younger group patients.

Comparison of OSDI between the two groups showed no significant difference, although BUT values were better in the younger group. Similarly, no significant differences were noted in assessment of patient satisfaction between both groups. Such subjective assessment may be influenced by lowered expectations regarding therapeutic effects among older patients (than among younger patients) owing to their longer, and possibly complex, medical history. Moreover, this type of subjective assessment, similar to OSDI, may have regional differences that can be affected by age, race, country, social environment, economic capability, and level of education.

Our results showed that BUT values of most patients reached 10 sec after three treatments, which is the standard for clinical cure. In the study by Toyo et al., the average number of IPL treatments and maintenance treatments administered was 7 and 4, respectively.[9] In this study, patients with skin type III/IV appeared to heal faster than Caucasian patients as the average frequency of treatment administration was less. However, our study had some limitations. Majorly, the sample size was small, and there was lack of long-term observation. In addition, we only observed short-term therapeutic efficacy, and factors such as patient relapse after IPL treatment were not taken into account in our study.

Of note, in our field research, we encountered several special cases that were refractory and were administered additional treatment. Certain patients with severe facial telangiectasia were given full-face treatment, or the treatment area was enlarged to cover the telangiectasia. Other patients complained that their upper eyelid symptoms (usually foreign body sensation or conglutination caused by increased oily excretions) were still severe, while the discomfort in their lower eyelid was alleviated after two normal IPL treatments; these patients were given additional upper eyelid IPL radiation with a small light spot. In fact, two MGD patients who also suffered from allergic conjunctivitis showed improvement not only in ocular dryness but also in redness and itching at the same time. Can IPL treatment help patients with allergic conjunctivitis as well? Future research should focus on treatment of MGD with IPL and also explore other possible clinical indications of IPL.

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Author Disclosure Statement

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Clinical Study

Intense Pulsed Light Therapy with Optimal Pulse Technology as an Adjunct Therapy for Moderate to Severe Blepharitis-Associated Keratoconjunctivitis

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Purpose. To evaluate the intense pulsed light (IPL) therapy with optimal pulse technology (OPT, M22™, Lumenis, USA) as an adjunct therapy for the prevention of recurrences in moderate to severe blepharokeratoconjunctivitis (BKC). *Methods*. This open-label nonrandomized clinical trial evaluated 33 patients diagnosed with BKC. Twenty-one patients received four bilateral OPT therapy sessions with Meibomian gland expression (MGX) (treatment group), and 11 patients received MGX alone (controls). This trial was initiated after a four-week pharmacotherapy for BKC in both groups and was scheduled at four-week intervals. Efficacy outcome measures included meibum quality, Meibomian gland (MG) secretion function, eyelid margin signs, corneal fluorescein staining (CFS) score, noninvasive keratography breakup time (NIKBUT), ocular surface disease index (OSDI) score, Schirmer I test (SIT), classification of tear film lipid layer (TFLL), and Meibomian gland dropout (MGDR). Safety outcome measures included visual acuity, intraocular pressure, eye structure damage, and facial skin appearance at each visit. *Results*. Quality of meibum, MG expressibility, eyelid margin signs, and OSDI score showed a statistically significant greater improvement in the treatment group after one to three treatment sessions, compared to controls ($p < 0.05$). While these improved in both groups in comparison to baseline, the NIKBUT and upper and lower eyelid MGDRs significantly improved only in the treatment group ($p < 0.05$). No adverse events occurred in both groups. No BKC recurrences were noted in the treatment group. *Conclusions*. IPL is a safe and effective adjuvant treatment for BKC and possibly more effective in reducing eyelid margin inflammation and prevents recurrences than MGX alone. This trial is registered with ChiCTR-ONN-17013864.

1. Introduction

Blepharitis is a common subacute or chronic inflammation affecting bilateral eyelid margins' skin and mucosa, eyelash follicles, and other adnexal glands. When this chronic inflammatory disease of the palpebral margin is complicated with secondary conjunctivitis and keratopathy, it is clinically referred to as blepharokeratoconjunctivitis (BKC) [1]. The clinical manifestation varies, and the disease may be complicated with corneal infiltration, ulceration, and eventually scarring with a consequent loss of vision [2]. The severity of blepharitis-associated keratoconjunctivitis can be classified as mild, moderate, or severe and is thought to correlate to the severity of Meibomitis in these patients [3]. In addition to the conventional prescribed eye drops [4], which often include artificial tears, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and antibiotics, physical therapy, namely, hot compresses, eyelid massage, and eyelid cleaning, is often incorporated into the BKC treatment plan to reduce recurrences. Nevertheless, the effect is limited, and the disease is likely to relapse. Intense pulsed light (IPL, Quantum™, Lumenis, USA), as a technology of physical

therapy, has been widely applied as part of the treatment of hirsutism, as well as chronic skin damage secondary to dermal vascular diseases or facial skin sun exposure [5, 6]. First reports of a relief in patients' acne rosacea symptoms following IPL therapy were published in the early 2000s [5, 7–9]. As physicians noticed a consequent improvement of their patients' dry eye symptoms, they started assessing the theoretical mechanisms of IPL treatment for MGD and concluded that the treatment may cause selective photothermolysis and reduction of bacteria and/or parasitic growth and provide a temporary local warming effect [10, 11]. Nowadays, IPL is an emerging treatment option for patients with evaporative dry eye disease.

Since BKC and MGD share some common pathological mechanisms, including inflammation, occlusion of Meibomian gland, and new blood vessels sprouting at the eyelid margin, we hypothesized that the IPL may also carry an anti-inflammatory effect in BKC patients. Compared with the original IPL technology, the fifth generation of IPL with optimal pulse technology (OPT, M22™, Lumenis, USA) has better safety, efficacy, and reproducibility that can eliminate energy peak at the beginning of the pulse, avoid ineffective decline at the end of the pulse, and provide homogeneous "squared off" energy distribution with continuous contact cooling [12]. We therefore aimed at evaluating the OPT as an adjunct blepharitis treatment for the prevention of recurrences in patients with previous active BKC.

2. Materials and Methods

2.1. Study Design. We conducted an open-label non-randomized controlled clinical trial, which enrolled moderate to severe BKC adult patients from January 2018 to February 2018 in the Ophthalmology department of the Beijing Tongren Hospital, Capital Medical University. This study was approved by the ethics committee of the Beijing Tongren Hospital, Capital Medical University, and all participants had signed informed consents before treatment was initiated. All the examination procedures were done in accordance with the Declaration of Helsinki and ethics standards as well as specifications of the Chinese clinical trial research studies. The study was enlisted in the clinical trial registry (trial registration no.: ChiCTR17013864).

In all recruited patients, the keratoconjunctivitis was first controlled with topical eye drops for one month, and then the OPT combined with Meibomian gland expression (MGX) (treatment group) or MGX therapy alone (controls) were individually suggested. Treatment was initiated by the patient's preference and was repeated at monthly intervals for four consecutive months. The baseline and the four follow-up visits were coded as *V*0, *V*1, *V*2, *V*3, and *V*4. Subjective symptoms and objective signs were examined and recorded by a single cornea specialist (Y.J.) at each visit.

2.2. Enrollment Criteria. The patients in this study met all of the following inclusion criteria: (1) age older than eighteen; (2) bilateral disease; (3) documented signs of blepharitis, including eyelid hyperemia, capillary dilation, scales, scabs, ulcers of the eyelash root, and/or morphological changes of the Meibomian glands; (4) having concomitant conjunctival and corneal lesions, namely, conjunctival congestion, papillary hyperplasia (papillary tarsal conjunctival inflammation) [3], follicular formation or blister conjunctivitis, corneal peripheral punctate epithelial erosions, infiltration or ulceration, and/or corneal opacity with neovascularization.

2.3. Exclusion Criteria. Patients were excluded from the study if their diagnosis was not consistent with blepharitis-associated keratoconjunctivitis or if they had any of the following conditions: (1) acute inflammation or allergic eye or periocular skin disease; (2) underlying diseases that can be triggered by an exposure to wave lengths between 560 nm and 1200 nm, such as recurrent herpes simplex infections, systemic lupus erythematosus, or porphyria; (3) current pregnancy or lactation; (4) history of radiotherapy or chemotherapy treatment within the first year prior to the study or scheduled radiotherapy or chemotherapy within the two months after the planned OPT treatment.

2.4. Treatment

2.4.1. Drug Therapy. Initial treatment was decided upon the degree of corneal and conjunctival pathology. One drop of 0.1% fluorometholone (5 ml : 5 mg, FML, Allergan, USA) was topically administered three or four times a day; one drop of 0.3% gatifloxacin eye gel (5 g, DIYOU, Shenyang Xingqi, China) was topically administered once or twice daily; and one drop of 0.3% sodium hyaluronate artificial tears (5 ml : 15 mg, AILI, Santen, Japan) was administered four times a day. The keratitis was reexamined after two weeks of treatment. The dosage of corticosteroid eye drops was then gradually tapered, and the other eye drops were discontinued in all the patients within one month of the resolution of corneal manifestations. Only sodium hyaluronate eye drops were continued two to three times per day thereafter. For patients with facial seborrheic dermatitis or acne rosacea, a dermatologist was consulted to determine the appropriate systemic drug regimen. Patients with rosacea were treated with minocycline hydrochloride capsules 50 mg (Wyeth Pharmaceuticals, China), twice a day, and with Fusidic cream (5 g : 0.1 g, Aomei Pharmaceutical, China) twice a day. Patients with seborrheic dermatitis were given oral dantone capsules 0.25 g, three times a day (Hili Pharmaceuticals, China), and selenium disulfide lotion (2.5%, Disano, China) was used twice a week. Oral medications were stopped before OPT + MGX or MGX was initiated.

2.4.2. OPT/MGX versus MGX Treatment. After one month of topical drug treatment, keratoconjunctivitis was resolved in all subjects and the treatment of OPT/MGX or MGX alone was initiated in the treatment and control groups, respectively. All treatment sessions were performed by a single physician (Y.J.) using M22 OPT technology of

Lumenis Medical Laser Co., Ltd. The procedure was performed taking the following measures:

(1) Eye Protection. Wet dressings were applied for skin and periocular hair protection. The physician was instructed to wear protective glasses.

(2) Intensity Adjustment. An 8 mm × 15 mm optical crystal cooling head was used, and the treatment parameters were tailored upon the patients' skin types [13]. Based on this previous study, for Fitzpatrick skin type III, the recommended settings were energy density 14 J/cm^2, optical filter 560 nm, pulse quantity 3, pulse time 3.5 ms, and pulse delay 20 ms. For Fitzpatrick skin type IV, the settings were energy density 12 J/cm^2, optical filter 590 nm, pulse quantity 3, pulse time 3.5 ms, and pulse delay 25 ms. Both cheeks were exposed to a test flare, and in the lack of any skin reaction, treatment was initiated 5 minutes later.

(3) OPT. Medical ultrasonic couplant (250 g, Jinnuote, China) was applied to locate the treatment areas. Eleven points were then marked, including eight points at the lower eyelid margin in two lines from medial to lateral, two more points at the outer canthus, and one more point at the nasal alar. The treatment was done symmetrically on both sides. The coupling gel layer covering the treatment area was about 1-2 mm in thickness. The upper eyelid was not treated directly to avoid a possible light damage to the intraocular structures. The optical crystal directly touched the coupling gel in this area and lightly touched the skin, avoiding any pressure exertion. A pulse was emitted every 1-2 seconds. The coupling agent was removed after two repeated therapy sessions in the treatment area (Figure 1).

(4) MGX. A single 0.5% proparacaine hydrochloride eye drop (15 ml/75 mg, Alcaine, Alcon, Belgium) was applied to the conjunctival sac. Then, the Yoshitomi Meibomian Gland Compressor (AE-4521, ASICO, USA) was used to perform the Meibomian gland massage on the upper and lower eyelids. A small amount of tobramycin dexamethasone eye ointment (3.5 g, TobraDex, Alcon, Belgium) was administered to the palpebral margins after the double eyelids' massage.

(5) Treatment regimen. OPT/MGX or MGX therapy alone was initiated one month after pharmacotherapy was first started and was repeated four times at one-month intervals. Four follow-up visits were scheduled at week 4 (*V*1), week 8 (*V*2), week 12 (*V*3), and week 16 (*V*4) after the first therapy session to assess the eyelid margin, cornea, and conjunctiva by the same ophthalmologist.

2.5. Follow-Up. All the patients had their baseline eye exam recorded before their initial treatment with OPT/MGX or MGX alone. The examinations were performed at the following sequence: visual acuity, noncontact IOP (TX20, Canon, Japan), slit-lamp examination, and direct ophthalmoscopy examination were performed first, followed by the BKC-related examinations 30 minutes later. These included

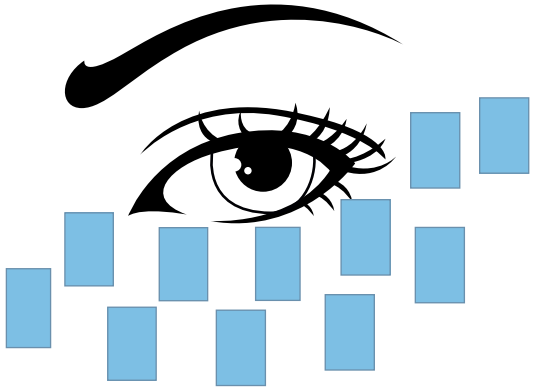

Figure 1: Treatment area by OPT.

CFS score, NIKBUT, OSDI, SIT grading, grading of TFLL, and MGDR. The sequence of examinations was kept identical for each follow-up visit, and they were performed by the same single ophthalmologist (F.R).

Primary outcome measures of treatment's efficacy included quality of meibum, the expressibility of the Meibomian glands, and changes of eyelid margin. Secondary outcome measures of efficacy were assessed by CFS, NIKBUT, OSDI, SIT, grading of TFLL, and MGDR.

Outcome measures were assessed as follows.

2.5.1. Quality of Meibum. Meibomian gland evaluator 1000 (MGE, Tear Science, USA) was located 1-2 mm inferior to the eyelid margin, and the central eight glands of the upper and lower eyelids were gently pressed. The liquid extracted from the Meibomian glands was graded by a classification method described by Bron et al., by which 0 = clear fluid, 1 = cloudy fluid, 2 = cloudy particulate fluid, and 3 = inspissated, toothpaste-like discharge. Each of the central eight glands was separately graded, and a score ranging from 0 to 24 was then given to each eye [14].

2.5.2. Expressibility of the Meibomian Glands. The central five glands of the upper and lower eyelids were pressed. The following grading system based on Pflugfelder et al. study was used, by which 0 = all glands were expressible, 1 = 3-4 glands were expressible, 2 = 1-2 glands were expressible, and 3 = no glands were expressible. Score ranged from 0 to 3 points [15].

2.5.3. Changes of Eyelid Margin. Evaluation of the eyelid margin status was based on the following five signs: blunt rounding shape of the posterior eyelid margin, irregularity or notching of the eyelid margin, and the presence of trichiasis or distichiasis, anterior blepharitis, vascularity, or telangiectasia of the lid margin. One point was assigned to each clinical sign, and the grade ranged from 0 to 5 points [14].

2.5.4. CFS Score. Using the Fluo Imaging corneal dot stain observation program (K5M, Oculus Keratograph 5M, Oculus Optikgerate GmbH, Germany), the cornea was divided into five regions and graded based on dye distribution on the

background of cobalt blue light. Grading ranged from 0 to 15 as follows: 0 = no staining; 1 = 1–5 punctate staining; 2 = 6–15 punctate staining; and 3 = any of the following: ≥16 punctate staining, ≥1 long 1 mm staining sites, any filamentous staining [16].

2.5.5. NIKBUT. Using the K5M tf-scan tear film analysis procedure, the quality and the stability of the tear film were evaluated by a noncontact and fully automatic method. The device automatically recorded the time at first tear breakup point and its location, starting measurements 1.5 seconds after the patient's second blink. Values below 10 seconds were considered pathological.

2.5.6. OSDI Score. The OSDI questionnaire was used to assess the extent of patients' discomfort. The questionnaire included 12 questions [17]. Final grade ranged from 0 to 100 points, and patients with 0–12 points were classified as asymptomatic, patients with 13–32 points were classified as mild to moderate, and patients with 33–100 were classified as severe.

2.5.7. SIT. The Schirmer test I was performed using a filter paper (5 mm × 35 mm Whatmann no. 41) placed inside the lower eyelid. The filtered paper was taken out after five minutes, and the amount of wetting was measured in millimeters. Exam was considered positive if wetting of the paper was 5 mm or less.

2.5.8. Grading of TFLL. Using the K5M, the thickness and stability of the lipid layer were evaluated and the TFLL score ranged from one to five as follows: grade 1: gray, uniform stripes; grade 2: grayish white, but with slight stripes change; grade 3: yellow stripes appear; grade 4: a jumble of colored streaks; and grade 5: black dry spots [18]. A grade >3 was considered abnormal.

2.5.9. MGDR. Using the Meibo-Scan of the K5M, the structure of the Meibomian glands was observed by an infrared light source, and the loss of the glands was then scored from one to three as follows: 1 = the loss of Meibomian glands was less than 1/3 of the total area; grade 2 = the loss of Meibomian glands accounted for 1/3 to 2/3 of the total area; and grade 3 = the loss of Meibomian glands accounted for 2/3 or more of the total area [19].

2.6. Safety. The skin at the treatment site was evaluated for any temporary pigmentary changes, alterations in skin sensation, including tingling, itching, or burning, rashes or blisters, skin edema, signs of an active Herpes Simplex virus infection, or inflammatory hypertension. The ETDRS best-corrected visual acuity and the intraocular pressure were measured before and after treatment. slit-lamp biomicroscopy was performed to rule out any conjunctival, corneal, iridal, or lenticular damage. Any iris depigmentation was documented. The direct ophthalmoscope was then used to perform a dilated fundus exam.

2.7. Statistical Methods. SPSS 19.0 (IBM, USA) was used for statistical analysis. One-way repeated measure analysis of variance enabled comparison of data across the various time points, paired analyses allowed comparison of pre- and posttreatment data at individual time points and multifactor variance analysis permitted comparison between the two groups. Data are reported as mean ± SD. p value ≤ 0.05 was considered statistically significant.

3. Results

Among the 21 adult BKC patients (42 eyes) who consisted the treatment group, there were 13 women (61.9%) and 8 men (38.1%) with a mean age of 42.93 ± 13.25. The 11 adult BKC patients (22 eyes) in the control group consisted of seven women (63.6%) and four men (36.4%) with a mean age of 47.62 ± 14.92.

3.1. Primary Outcome Measures. As shown in Table 1 and Figure 2, the quality of meibum excretion and MG expressibility significantly improved in both the treatment group and the controls with more treatment sessions (OPT/MGX or MGX) applied, and improvement was greater in the treatment group when comparing the Meibum quality of both the upper and lower eyelids ($p = 0.014$ and 0.008, respectively) from the second treatment session and on, while the difference in MG expressibility became evident as early as the first session ($p = 0.002$ and <0.001, respectively). Differences remained significant for the entire follow-up period.

Eyelid margin signs improved in both groups of patients. A statistically significant difference between the groups was evident in the lower eyelids, as soon as the second visit ($p = 0.022$), and kept significant till the last visit, while in the upper eyelids, a statistically significant difference was noted only at the second visit ($p = 0.041$).

3.2. Secondary Outcome Measures. As demonstrated in Table 2 and Figure 3, CFS scores and NIKBUT results were similar between the treatment and control groups ($p > 0.5$). Nevertheless, during the treatment sessions CFS scores significantly differed from baseline in both groups, while the difference in NIKBUT in comparison to baseline was only observed in the treatment group. Subjective symptoms, as reflected by the OSDI, significantly improved after the first therapy session in both groups, and the treatment group showed more subjective improvement as soon as the third follow-up visit and thereafter ($p = 0.029$ at $V3$ and $p = 0.049$ at $V4$). No statistically significant differences were observed among the two groups when comparing the SIT and tear film lipid layer classification, as seen in Table 2. Though the baseline MGDR was significantly lower in the treatment group in both upper and lower eyelids, an improvement throughout the follow-up period occurred solely in this

Table 1: Comparison of primary outcome measures.

Items	Groups	$V0$	$V1$	$V2$	$V3$	$V4$	p^*
Quality of meibum (upper eyelid)	Treatment group	15.83 ± 4.43	12.17 ± 4.59	7.69 ± 3.35	3.79 ± 2.23	2.86 ± 1.44	**<0.001**
	Control group	15.05 ± 3.24	11.50 ± 2.99	9.82 ± 2.84	7.09 ± 2.71	5.77 ± 1.74	**<0.001**
	$p^{\#}$	0.465	0.541	**0.014**	**<0.001**	**<0.001**	
Quality of meibum (lower eyelid)	Treatment group	13.07 ± 4.92	9.00 ± 5.08	6.17 ± 3.89	3.43 ± 2.96	2.55 ± 1.61	**<0.001**
	Control group	13.14 ± 4.97	10.14 ± 4.00	8.82 ± 3.29	6.77 ± 2.78	4.59 ± 1.87	**<0.001**
	$p^{\#}$	0.960	0.366	**0.008**	**<0.001**	**<0.001**	
Expressibility of the Meibomian glands (upper eyelid)	Treatment group	1.62 ± 0.76	1.14 ± 0.65	0.60 ± 0.50	0.05 ± 0.22	0.10 ± 0.30	**<0.001**
	Control group	1.73 ± 0.53	1.68 ± 0.57	1.27 ± 0.45	1.18 ± 0.59	1.18 ± 0.50	**<0.001**
	$p^{\#}$	0.052	**0.002**	**<0.001**	**<0.001**	**<0.001**	
Expressibility of the Meibomian glands (lower eyelid)	Treatment group	1.67 ± 0.57	0.95 ± 0.62	0.55 ± 0.50	0.05 ± 0.22	0.00 ± 0.00	**<0.001**
	Control group	1.91 ± 0.53	1.55 ± 0.51	1.14 ± 0.56	1.00 ± 0.62	0.73 ± 0.70	**<0.001**
	$p^{\#}$	0.102	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Changes of eyelid margin (upper eyelid)	Treatment group	2.67 ± 0.72	2.31 ± 0.71	1.69 ± 0.71	1.21 ± 0.81	0.71 ± 0.71	**<0.001**
	Control group	2.68 ± 0.65	2.36 ± 0.49	2.05 ± 0.49	1.45 ± 0.51	0.91 ± 0.43	**<0.001**
	$p^{\#}$	0.934	0.752	**0.041**	0.212	0.242	
Changes of eyelid margin (lower eyelid)	Treatment group	2.31 ± 0.60	1.90 ± 0.66	1.10 ± 0.76	0.60 ± 0.66	0.31 ± 0.47	**<0.001**
	Control group	2.50 ± 0.67	2.18 ± 0.50	1.55 ± 0.67	1.18 ± 0.59	0.68 ± 0.57	**<0.001**
	$p^{\#}$	0.254	0.088	**0.022**	**0.001**	**0.007**	

$^*p$ value of one-way repeated measure analysis of variance to compare data for each group at different time points; $^{\#}p$ value of multivariate analysis to compare the treatment and control groups at a specific time point.

group ($p = 0.044$ for upper eyelid and $p = 0.016$ for lower eyelid).

Five patients in the treatment group (23.8%) and three patients in the control group (27.3%) had associated dermatologic diseases. After four OPT sessions, the ocular signs and facial skin lesions showed much improvement, indicating high patient satisfaction, while there was no change in dermatosis in the control group.

3.3. Adverse Effects. None of the participants in the treatment group experienced a decrease in best-corrected visual acuity, and intraocular pressures were measured <21 mmHg in all eyes. Only three of the patients (14.3%) reported a burning sensation at the area treated with OPT, but the symptoms resolved after the adjustment of energy parameters without further influencing the treatment. Only 1/21 patients endured hair loss attributable to the proximity of the treatment area to patient's hair line; however, hair regrowth soon pursued on the next visit. No recurrence of BKC was observed in the treatment group, while 2/11 patients (18.2%) in the control group had a documented BKC recurrence at the second or third visit, respectively. No other adverse effects were documented.

4. Discussion

Blepharokeratoconjunctivitis represents a group of recurrent corneal and conjunctival diseases associated with anterior and posterior blepharitis [2]. Posterior blepharitis is thought to play a more significant role in the occurrence of BKC; hence, modification of its name to Meibomitis-related keratoconjunctivitis (MRKC) has been previously suggested [20]. Misdiagnosis of BKC is not uncommon given the subtle nature of the eyelid margin signs and the irreversible tissue damage with a possible consequent vision impairment which may follow [21].

The beneficial effect of IPL as a treatment modality for MGD has been previously reported, with significant improvement in TFLL, BUT, subjective symptom scores, and eyelid margin signs, especially for those with refractory MGD [22–26]. The pivotal mechanism behind IPL with OPT is the induction of selective photothermolysis of oxyhemoglobin of the yellow light, transforming luminous energy into heat energy, enabling coagulation and ablation of abnormal capillaries which also decreases the dissemination of inflammatory factors [6, 27]. This is seen in its effect over various diseases, including rosacea [5]. It is also utilized for the reduction of *Demodex folliculorum* mites and *Bacillus oleronius* bacterium which are potential mediators of blepharitis and MGD [28, 29], and it has a temporary local thermal effect which can melt meibum to facilitate its secretion.

In this study, we show that the IPL of Lumenis M22 with OPT, as an adjunctive therapy to MGX, is a viable therapy for BKC patients and may prevent keratoconjunctivitis recurrence by controlling blepharitis. The IPL treatment in our study patients was initiated immediately after the completion of a one-month topical steroidal treatment, and a clinical assessment that active inflammation has resolved.

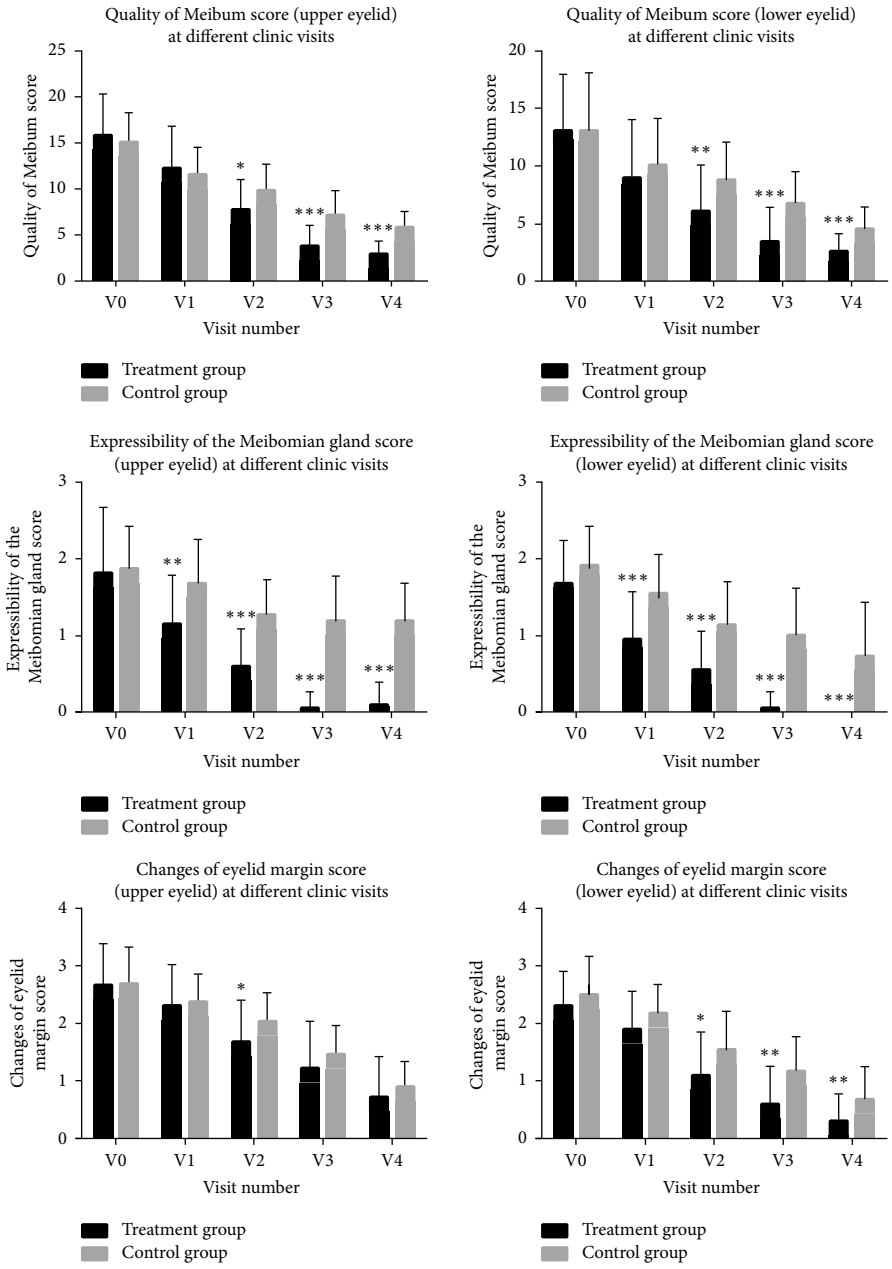

Figure 2: Comparison of quality of meibum secretion, expressibility of the Meibomian glands, and changes of eyelid margin of upper and lower eyelids between the treatment and control groups at different follow-up time points. The baseline and the four follow-up visits were coded as V0, V1, V2, V3, and V4. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

Though the lasting anti-inflammatory effect of the eye drops could have potentially played a role in the late improvement of eyelid signs, both patients and controls have completed the same drop regimen.

Our results show that the OPT can significantly and effectively ameliorate the quality of meibum, improve MG expressibility, and regress eyelid margin signs and subjective symptoms in BKC patients more effectively than the traditional MGX therapy. As previously shown [3], reducing the inflammation of the eyelids by promoting the expression of Meibomian gland secretions and improving the quality of meibum are important steps for the treatment of BKC and for the prevention of its recurrence. Moreover, there is a very good correlation between the Meibomitis and the corneal and conjunctival signs in this group of patients, as previously described by Suzuki et al.

Interestingly, the OPT treatment achieved more improvement of lower eyelid signs from the second visit and thereafter, while the effect of treatment on the upper eyelids signs was more modest. One optional explanation for this discrepancy is the application of IPL at the cheek region, which lies in greater proximity to the inferior palpebral margin. A recent study by Rong et al. [11] reported that in patients receiving IPL treatment on both the upper and

Table 2: Comparison of secondary outcome measures.

Items	Groups	*V*0	*V*1	*V*2	*V*3	*V*4	p^*
CFS score	Treatment group	6.02 ± 3.74	2.86 ± 2.83	2.52 ± 2.38	2.05 ± 2.23	0.67 ± 1.07	**<0.001**
	Control group	6.14 ± 4.44	3.50 ± 2.82	3.82 ± 3.35	2.82 ± 2.92	1.14 ± 1.64	**<0.001**
	$p^{\#}$	0.915	0.391	0.078	0.243	0.173	
NIKBUT	Treatment group	7.38 ± 5.79	7.44 ± 4.14	9.14 ± 4.97	10.71 ± 4.04	12.07 ± 4.14	**<0.001**
	Control group	7.10 ± 5.61	7.17 ± 4.16	8.73 ± 4.95	9.23 ± 4.06	10.53 ± 4.48	0.085
	$p^{\#}$	0.857	0.803	0.759	0.168	0.175	
OSDI score	Treatment group	35.38 ± 15.76	22.08 ± 12.94	16.03 ± 9.54	8.18 ± 8.01	6.89 ± 7.61	**<0.001**
	Control group	44.76 ± 17.06	31.62 ± 15.89	22.32 ± 8.97	14.84 ± 7.32	12.05 ± 4.64	**<0.001**
	$p^{\#}$	0.130	0.077	0.081	**0.029**	**0.049**	
SIT	Treatment group	7.31 ± 5.24	6.81 ± 4.49	7.93 ± 4.19	8.26 ± 3.91	8.93 ± 3.62	0.197
	Control group	8.36 ± 5.17	5.91 ± 2.71	7.77 ± 2.74	7.64 ± 3.05	8.09 ± 3.31	0.168
	$p^{\#}$	0.445	0.393	0.875	0.516	0.370	
Classification of tear film lipid layer	Treatment group	2.67 ± 0.85	2.93 ± 0.87	2.71 ± 0.80	2.64 ± 0.91	2.45 ± 0.83	0.155
	Control group	2.86 ± 0.83	2.91 ± 0.75	2.59 ± 0.80	2.59 ± 0.67	2.45 ± 0.51	0.175
	$p^{\#}$	0.377	0.929	0.561	0.813	0.991	
Meibomian gland dropout (upper eyelid)	Treatment group	2.14 ± 0.84	2.45 ± 0.63	2.60 ± 0.63	2.50 ± 0.63	2.38 ± 0.73	**0.044**
	Control group	2.59 ± 0.67	2.45 ± 0.67	2.55 ± 0.51	2.55 ± 0.60	2.41 ± 0.59	0.857
	$p^{\#}$	**0.035**	0.990	0.750	0.782	0.877	
Meibomian gland dropout (lower eyelid)	Treatment group	2.17 ± 0.82	2.45 ± 0.55	2.64 ± 0.62	2.48 ± 0.71	2.57 ± 0.59	**0.016**
	Control group	2.82 ± 0.39	2.55 ± 0.51	2.73 ± 0.46	2.32 ± 0.72	2.68 ± 0.48	0.062
	$p^{\#}$	**0.001**	0.512	0.574	0.401	0.452	

$^*p$ value of one-way repeated measure analysis of variance to compare data for each group at different time points; $^{\#}p$ value of multivariate analysis to compare the treatment and control groups at a specific time point.

lower eyelids, a significant difference in the quality of meibum of the upper eyelid in comparison with the control group was already noted on day 28 after the first treatment session, while significant differences in our study appeared at the second visit (day 56). We therefore suggest it may be advisable to apply OPT to both the upper and lower eyelids with a proper eyeball protection to gain a better therapeutic effect. Notably, our study was not the first to have demonstrated a beneficial effect over the upper eyelids with IPL treatment limited to the cheek area [30]. While the mechanism for this indirect effect is not entirely clear, we presume that the decrease in secretion of proinflammatory agents from abnormal blood vessels which are affected by the treatment has a local and regional impact on both eyelids. Our results also indicate an early response to the IPL treatment as represented by MG expressibility. This finding can be supported by the previously suggested tear gradient theory, proposed by Bron et al. [31], linking the damage to MG orifices and the subsequent MGD, with the concentration of proinflammatory proteins in the tear meniscus. Since IPL can decrease inflammation in MGD patients, as previously described by Liu et al. [32], it is likely to be represented by an improvement in MG expressibility.

Our study shows that both the treatment and the control groups experienced an improvement in CFS scores, with no significant difference between the groups. This result could be related to the ongoing MGX maintenance treatment that both groups received, which is the traditional therapy for BKC, as previously reported by Rong et al. [11]. Corneal epithelial healing may therefore ensue once the MG function improves and may not be represented as a direct consequence of OPT treatment. The differences in NIKBUT between the treatment and the control groups were not significant in our study, as opposed to Rong et al. [11] and Craig et al. [23] who found significant differences in NIKBUT at days 28 and 45 after the first treatment session, respectively. One possible explanation is the wide spectrum of BKC and MGD severity in different studies. A study by Yin and Gong [33] found that Asian patients with BKC are characterized by a significant decrease in meibum quality and severe MG dropout. Hence, tear film stability may be a harder goal to achieve with treatment, given the challenging baseline gland status. The same could explain the lack of significant difference in classification of TFLL. In general, changes in the function of the glands, as manifested by their impact on the tear film content and stability, as well as cornea staining, may present at a later time point, in comparison to the rather early treatment impact on the Meibomian glands structure. These changes were, therefore, not established in our study, given the relatively short

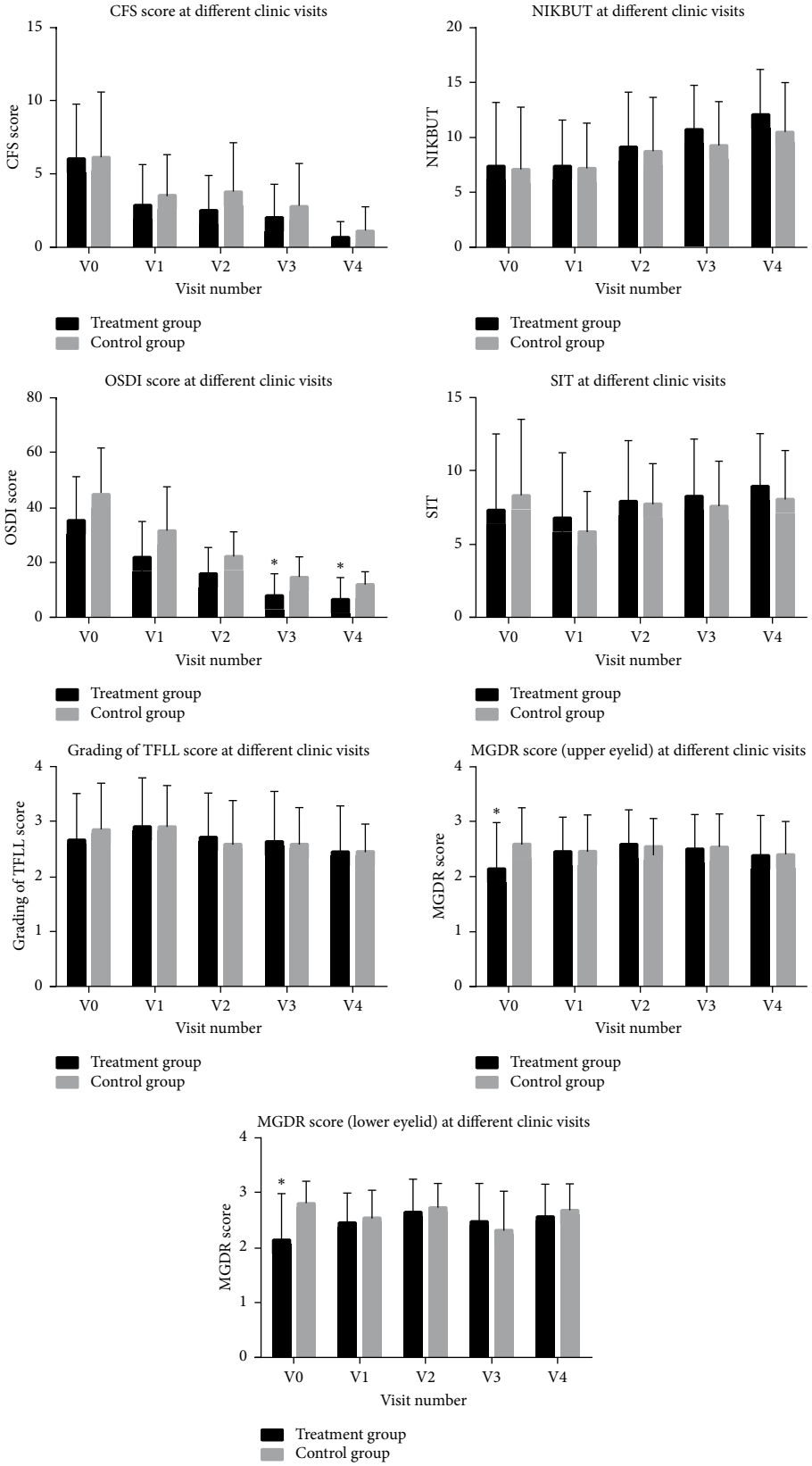

Figure 3: Comparison of CFS scores, NIKBUT, OSDI, SIT, classification of tear film lipid layer, and Meibomian gland dropout of upper and lower eyelid between the treatment and control groups at different follow-up time points. The baseline and the four follow-up visits were coded as $V0$, $V1$, $V2$, $V3$, and $V4$. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

follow-up time. The comparison of MGDR between the groups was somewhat limited given the significant difference between the groups at baseline for both upper and lower eyelids. We could show, however, an improvement of MGDR in the treatment group during the follow-up time, as previously suggested by Yin et al. [34]. The authors suggested that IPL improves MG macrostructure, namely, MGDR, and MG microstructure (i.e., MG acinar longest diameter and MG acinar unit density) and decreases the inflammatory response in the MGs. Therefore, though the severity profile of MGD in BKC patients is usually worse than the average, IPL therapy may still be recommended and may be responsible for stimulating acinar cells and decreasing inflammation. In our study, the patients' subjective satisfaction measures, expressed by the OSDI scores, improved more in the IPL group, in concordance with previous studies [24, 35].

Since OPT-related uveitis and iris photoablation were previously described [36, 37], we enforced eye protection during the entire procedure. No uveitis episodes or adverse effect on vision were documented.

Our study is limited by its small sample size, its open-label nature, a relatively short follow-up, time and strict exclusion criteria of patients with comorbidities. Our preliminary results, however, indicate that IPL with OPT therapy may have an adjunctive effect to the conventional MGX in improving the function of Meibomian glands, controlling ocular surface inflammation, relieving ocular discomfort symptoms, increasing the stability of the tear film, preventing the recurrence of BKC, and avoiding the side effect of long-term drug use. It should therefore be considered an effective adjunct treatment for BKC, specifically in the presence inflammatory skin disorders.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest for the publication of this paper.

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Photobiomodulation and Regenerative Medicine

Evaluation of the Safety and Efficacy of Intense Pulsed Light Treatment with Meibomian Gland Expression of the Upper Eyelids for Dry Eye Disease

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Abstract

Purpose: To investigate the safety of and change from baseline of tear breakup time and visual analog pain scales in dry eye disease subjects with upper lid Meibomian gland dysfunction after intense pulsed light (IPL) treatment assessing global ocular pain severity, ocular pain frequency, and ocular pain in the previous 24 h.
Design: This is a prospective single-site study.
Methods: All patients received active treatment consisting of four treatments spaced no fewer than 2 weeks apart and no longer than 4 weeks apart. The IPL therapy was performed with a Lumenis M22 (Lumenis Ltd., Yokneam, Israel) xenon-based micropulsed IPL utilizing a 590 nm filter with a 6 mm clear SapphireCool cylindrical lightguide for the upper lids with a fluence of 10 J/cm^2 across the upper eyelids, including the tragus for two passes. Patients then received expression of their meibomian glands using two cotton-tipped applicators. Tear breakup data were collected as well as global ocular pain, ocular pain episodes in the past 24 h and frequency of ocular pain episodes.
Results: All of the assessments for the treated eyes improved over the course of treatment. Statistically significant physician increases in measured tear breakup times were measured for each eye independently. Statistically significant decreases in global eye dryness scale, eye dryness in the preceding 24 h, and frequency of ocular pain episodes between treatments were observed. There were no serious or nonserious adverse events in the trial.
Conclusions: This pilot study suggests that a new specialized 6 mm cylindrical handpiece for the M22 Lumenis IPL machine is safe and effective in increasing physician-measured tear breakup time as well as several scales of the symptoms of ocular dryness, including global symptoms, frequency of symptoms, and ocular dryness occurring within the previous 24 h before the study visit.

Keywords: IPL, dry eye, inflammation, Meibomian gland dysfunction

Introduction

Dry eye disease (DED) due to Meibomian gland dysfunction (MGD) is a common and growing health concern with >300 million people worldwide estimated to have some form of dry eye and 5 million in the United States alone. MGD can contribute to evaporative dry eye or occur as a result of chronic inflammation due to an unhealthy ocular surface. MGD is estimated to occur in as much as 70% of some populations, especially in Asia.[1] Meibomian glands are exocrine glands on the inside that secrete sebaceous material onto the surface of the eye. The average adult has 30–50 glands in the upper lid and 20–40 on the lower. Each gland synthesizes and secretes a complex mixture of lipids and proteins to protect and nourish the ocular surface.[2] Meibomian secretions should be clear liquid at body temperature, but may become thick or cloudy or blocked altogether with age or inflammation. Dysfunctional lipids may contribute to bacterial overgrowth, which may in turn contribute to the overall inflammation and worsening of the disease, making them an increasingly important factor in the eye care world.[3]

While many factors are being studied to evaluate exactly what causes MGD, current research points to a combination

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of genetics, environmental factors, and diet. Current treatments for MGD include warm compresses, dietary supplements that include omega-3 fatty acids, meibomian gland probing, meibomian gland expression, topical and systemic nonsteroidal and steroidal preparations, and intense pulsed light (IPL) treatment. Approved topical US Food and Drug Administration (FDA) treatments for dry eye include cyclosporine 0.05%, cyclosporine 0.09%, and lifitegrast 5.0%. Most treatments currently target ocular surface inflammation.[4]

IPL has FDA clearance (K142860) for a variety of dermatological conditions, including facial rosacea, port wine stains, telangiectasias, pigmented lesions, benign venous malformations, benign cavernous hemangiomas, hypertrophic scars, and seborrheic keratosis (Fig. 1). IPL emits light energy in a spectrum from 580 nm to near-infrared 1200 nm.[5] IPL was first noted by Dr. Rolando Toyos to be incidentally helpful for the symptoms of dry eye while patients were receiving treatment for facial rosacea.[6] Other researchers have confirmed these initial findings, and documented improvements in meibum quality, number of functional meibomian glands, and reduction of ocular surface inflammatory markers.[7–9]

IPL seems to improve the signs and symptoms by several discrete mechanisms. First, the heat and infrared portion of the light heats the skin internally up to 50°C to help soften and liquefy abnormal meibum in a way that is not possible with normal warm compresses. Next, the light targets the chromophore in hemoglobin, so that abnormal telangiectasias preferentially absorb more energy to the point of closure for these vessels. Once closed, it is speculated that they are unable to continue secreting inflammatory markers that may perpetuate or even amplify the inflammatory response. IPL also kills bacteria and Demodex species, which may assist in reducing exotoxin and inflammatory loads. IPL has recently been shown to lower interleukins 17 and 6 on the ocular surface after a series of three consecutive treatments spaced 4 weeks apart.[10] Chronic surface inflammation has been shown to inhibit mucin-producing goblet cells and may play a role in suppression of meibomian glands as well.[11] Finally, IPL has been shown to target cytochrome oxidases in mitochondria that may begin the cycle of photobiomodulation, which may lead to generate more energy and begin cellular repair and healing.

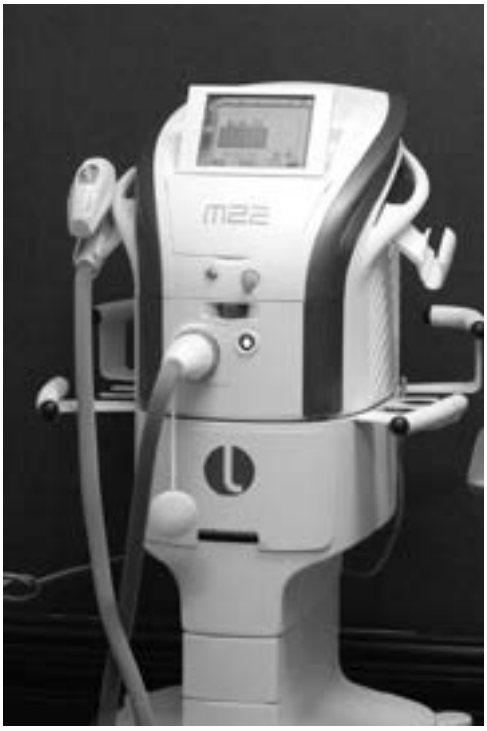

FIG. 1. Lumenis M22.

FIG. 2. Six millimeters cylindrical head.

Prior IPL studies primarily treated lower lids because of the size of the light delivery device (sapphire-cooled light guides of 8×15 or 15×35 mm), the potential for excessive heat accumulation in the brow area, and the potential for hair loss in the eyebrow and upper lash areas. Although the lower lids tend to be the area of greatest pathology, many dry eye patients have significant MGD in the upper lids as well. For these patients, this study evaluated a unique new handpiece with a smaller cylindrical surface area was tested to evaluate both the safety and the efficacy in improvements of signs and symptoms of dry eye due to MGD (Figs. 2 and 3).

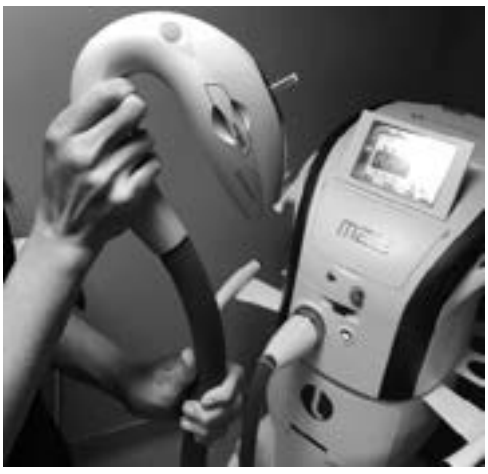

FIG. 3. Six millimeters cylindrical head attached to Lumenis M22.

Table 1. Energy Parameters for Treatment

Wavelength filter	*Fluence J/cm²*	*Treatment duration milliseconds*	*Frequency of treatment*	*Cumulative dose*
590 nm	10	6	Every 2 weeks	40 J/cm²

Methods

Patients were enrolled in this study if they were over the age of 18 and had visible signs of upper lid MGD at the slit lamp examination and persistent dry eye symptoms and ocular pain despite treatment with conservative dry eye therapies. Patients were excluded for the following: eyelid abnormalities, history of IPL treatments in the past year, currently on oral or topical retinoids, history of intraocular surgery in the past year, uncontrolled ocular disease, Fitzpatrick skin type V or VI, neuroparalysis in the planned treatment area, precancerous lesions in the planned treatment area, new topical eye treatments within the past 90 days, legally blind in one eye or some condition in the opinion of the investigator, which might make the patient unsuitable for treatment or follow-up purposes.

Enrolled subjects underwent physician-measured tear breakup time using the standard fluorescein staining method counting the number of seconds that elapse between the last blink of the eye to the appearance of the first dry spot in the tear film. Subjects were then asked to fill out a subjective assessment of their dry eye symptoms, which included an Global Eye Dryness score, an assessment of the patient's perception of their ocular dryness; an Ocular Discomfort Severity score, which measured how severe the patient perceived his or her discomfort over the past 24 h; and an Ocular Discomfort Frequency score, which evaluated how often over the past 24 h the patient had noticed ocular discomfort of any kind. After the initial evaluation was completed, the patient underwent the IPL treatment September 2018 through October 2018. The study protocol was a four-procedure treatment plan, with each procedure spaced no fewer than 2 weeks apart, and no longer than 4 weeks apart. The IPL therapy was performed using a Lumenis M22 IPL machine with the sapphire-cooled 6 mm cylindrical light guide set at a fluence of 10 J/cm^2 (Table 1). Honeywell IPL eye shields (Honeywell Safety Products, Smithfield, RI) were applied to the lower lids covering upper and lower eyelashes, leaving the upper lids exposed for the treatment (Fig. 4). This technique has been previously published with no adverse events.[10] Ultrasound gel was applied from tragus to tragus in a band approximately the height of the nose across the face. The specialized handpiece designed for the upper lids was attached to the machine. Two passes of light at a fluence of 10 J/cm^2 were used across the upper eyelids. Once completed, the shields and ultrasound gel were removed, and patients were moved to a slit lamp.

One drop of Proparacaine was instilled into each eye. Two cotton-tipped applicators were used, one inside the lid, and the other outside the lid, and gentle-to-moderate pressure was applied to push meibum out of the glands along the upper eye lid starting at the lower end of the gland and moving slowly toward the top. After digital expression, one drop of Prolensa (bromfenac 0.07%, Bausch & Lomb, Bridgewater Township, NJ) ophthalmic solution was instilled in each eye, followed by one drop of generic brimonidine (2% ophthalmic solution, Bausch & Lomb, Bridgewater Township, NJ). Patients were dispensed samples of Prolensa to use one drop nightly for four nights after the treatment. For patients who were using artificial tears, Xiidra, omega supplements, or any other type of dry eye treatment at the beginning of the study, they continued use of those treatments throughout the study.

Once the patients had completed four-treatment sessions, they were asked to repeat the same evaluation of Eye Dryness, Ocular Discomfort Severity, and Ocular Discomfort Frequency. Tear breakup time was objectively measured and recorded.

Results

A total of 19 patients had enrolled in the upper lid IPL study. Enrolled patients ranged in age from 23 to 65 with a mean age of 47 years. Women were 67% of enrolled patients. Sixteen of the 19 patients completed the entire four-treatment protocol. Average tear breakup time (TBUT) before the therapy was 1.5 sec. After the treatment, TBUT was increased to 5.2 sec.

As the table immediately below shows, paired *t*-tests showed that statistically significant improvement in tear breakup times was found for both eyes: TBUT right eye (OD) [$t = 6.2$; 95% confidence interval (CI): 2.6–5.3] and TBUT left eye (OS) ($t = 5.4$; CI: 2.6–5.4) (Table 2).

Each of the scores for the dryness survey was ranked on a scale from 0 to 100 and subjectively answered by enrolled patients. Results of the pretreatment survey revealed that

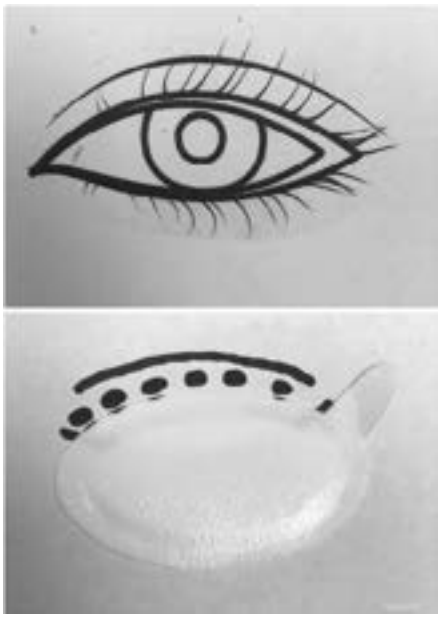

FIG. 4. Ocular image of treatment areas.

Table 2. Statistical Analysis Two-Tailed *t*-Test of Change from Baseline in TBUT OD and OS

Paired samples test									
Paired differences									
					95% Confidence interval of the difference				
		Mean	*Standard deviation*	*Standard error mean*	*Lower*	*Upper*	t	*df*	*Sig (two tailed)*
Pair 1	Change from baseline TBUT OD	3.93	2.37	0.63	2.561	5.29	6.2	13	0.001
Pair 2	Change from baseline TBUT OS	4.02	2.5	0.65	2.639	5.42	6.21	14	0.001

OD, right eye; OS, left eye; TBUT, tear breakup time.

patients in this study rated their Global Eye Dryness score to be an average of 73.74% with 100 being the most severe pain. Ocular Discomfort Severity or pain in the past 24 h scores pretreatment averaged 65.42%, and Ocular Discomfort Frequency of ocular pain episodes pretreatment averaged 76.53%.

Three patients did not complete the study as they were lost to follow-up after 2, 2, and 3 visits, respectively. Their last data values were carried forward. After completing the four-treatment therapy, subjects reported that their Global Eye Dryness score had improved to 27.27%, with an overall average improvement of 51.97%. Ocular Discomfort Severity decreased to 26.93%, with an average improvement of 53.05%. Hundred percent of patients enrolled in the study reported an improvement in the Ocular Discomfort Severity assessment. The improvement in severity ranged from 10% to 98.7%. Ocular Discomfort Frequency decreased to 28.27%, with an improvement of 55.52%. Fourteen of the 15 patients who completed the study reported an improvement in Ocular Discomfort Frequency, ranging from an improvement of −50% to 97% with 1 patient reporting an increase in severity from 8% to 12%.

Overall, patients tolerated the treatment protocol well. There were no serious adverse events. During the IPL therapy administration, 24% of patients reported mild stinging from the light therapy. Sixty-five percent of patients reported moderate discomfort during the digital expression. No patients requested to discontinue the study due to discomfort from IPL or expression. Seventy-one percent of patients reported a subjective improvement in ocular comfort throughout the day. Forty-eight percent of patients reported reduced use of artificial tears throughout the day. Other less commonly occurring (>10%) events patients reported included less redness, less itching, and improved contact lens tolerance. Fifteen of 16 patients were noted to have improved meibum secretion quality (clearer, less viscous) and less intense pressure needed for adequate expression at the conclusion of the study visits.

Discussion

MGD and accompanying DED are prevalent and growing public health conditions. Because inflammation can be self-perpetuating and amplifying, anti-inflammatory treatments are needed to stop the process and reverse the damage caused to the ocular surface.[12] Many patients are intolerant to, not compliant with, or incompletely relieved by current treatment modalities for this disease. IPL therapy has been used extensively in dermatology and has now been used for two decades in ophthalmology for treatment of dry eye with the potential to stop and reverse chronic inflammatory damages in patients with dry eye of variable severity.

Significant progress in illuminating the mechanisms of action has occurred since more and more researchers are contributing to the body of knowledge regarding IPLs effects on the ocular surface, on periocular skin and meibomian glands and their secretions.[13] Normal meibum naturally suppresses bacterial overgrowth, and a return to normalized secretions may in fact be protective of future disease once a subject is sufficiently treated.

Eyelid telangiectasias that occur on the lid margin due to chronic and prolonged exposure to inflammation are particularly responsive to the effects of IPL as the periocular skin is among the thinnest of the body and easily penetrated. The pathophysiology of rosacea, a skin disease that involves the eyes, consists of decade-long slow process of thinning of the skin, loss of connective tissues, passive dilation of blood vessels, and the ingress of new abnormal blood vessels in the affected areas. Closing these abnormal blood vessels should result in reduced amounts of secreted inflammatory mediators and improvements both in skin and on the ocular surface.[14]

The role of photobiomodulation in IPL treatment of eyelids is also now being understood. Photobiomodulation is the term used for light-induced photochemical reactions in biological systems and may be due to laser, LED, broadband and near-infrared light, including IPL with a filtered wavelength of ≥590 nm.[15] It is well known that IPL used in dermatology produces a rejuvenating effect and improvement in skin quality.[16] Photobiomodulation or low-level laser therapy is known to target cytochrome c in mitochondria, which is believed to increase mitochondrial energy production, cell proliferation, and cell migration. This technology has been used to reduce inflammation in various tissues to upregulate antioxidant levels and downregulate genetic material associated with stress-related cell death.[17] This may also be part of the mechanism in which a series of IPL treatments over time result in meibomian glands becoming more functional with the corresponding improvement in the quality of secretions.[18]

Upper lids differ in significant ways from lower lids. On average, there are 25–40 glands in the upper eyelid with the average being 31; the central tarsal gland is ~5.5 mm in length with each gland having the potential to secrete 26 μL

of meibum total in the upper lid. Contrasting that with the lower lid that contains 20–30 glands (average 26), the length of the central tarsal gland is 2 mm with a capacity of 13 μL, making the secretory capacity of the upper lid approximately double that of the lower lid.[19] Gland secretion is typically worse in the lower lids, presumably due to the effect of gravity during the day and the extended contact time of an unhealthy tear film with the lower lids.[20]

The M22 model of IPL is unique in that it uses a cooling sapphire crystal tip to cool the skin, minimizing accumulated thermal damage and reducing both discomfort and side effects associated with treatment. It also allows treatments to be given at shorter intervals, 2 weeks compared with older generation IPL machines that required 4 weeks between treatments for epithelium to recover. Second, the M22 utilizes optimized pulse technology that can deliver more homogeneous pulsed energy to target tissues not found in other IPL models.[21]

The limitations of our pilot study consisted of a small sample size, a lack of sham or placebo control, a single center and nonrandomization of patients. Further study is warranted in this area to explore the reproducibility of data, and to expand the protocol to additional patients and sites.

In this small study, a 6 mm cylindrical cooling sapphire tip applied to the upper eye lids gave patients a significant improvement in tear breakup time as well as in dry eye symptoms. Further study is required to understand which patients would best benefit from upper lid treatment and how to use it in conjunction with lower lid IPL treatments. This study does suggest that the 6 mm cylindrical light guide is a safe and effective addition to the dry eye arsenal in patients suffering from the symptoms of dry eye and visible signs of MGD.

Author Disclosure Statement

No competing financial interests exist.

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Case Reports

Real-Time Video Microscopy of *In Vitro* Demodex Death by Intense Pulsed Light

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Abstract

Objective: To directly observe the *in vitro* real-time effects of intense pulsed light (IPL) on a Demodex mite extracted from an eyelash of a patient with ocular rosacea.
Background: Demodex is a risk factor in the pathogenesis of oculofacial rosacea, meibomian gland dysfunction (MGD), and dry eye disease (DED). Recent studies suggested IPL to control or eradicate Demodex organisms in the periocular area. Despite encouraging reports, the direct effect of IPL on Demodex is not well understood.
Methods: An eyelash infested with Demodex was epilated from a 62-year-old female patient with oculofacial rosacea. Following isolation and adherence of a mite onto a microscope slide, real-time video microscopy was used to capture live images of the organism before, during, and after administration of IPL pulses. IPL pulses were delivered with the M22 IPL (Lumenis), with IPL settings used for treatment of DED due to MGD (the ''Toyos protocol''). A noncontact digital laser infrared thermometer was used to measure the temperature of the slide.
Results: Before the IPL pulses, legs of the Demodex mite spontaneously moved in a repetitive and semicircular motion. During administration of IPL, spontaneous movements of the legs continued. Immediately after administration of five IPL pulses, the temperature of the slide increased from room temperature to 49°C. Immediately afterward, the Demodex mite became completely immobilized. The legs appeared retracted, smoother, less corrugated, bulkier, and less well-defined. Movement of the Demodex mite was not observed at the hourly inspections for 5 h and after 24 h following the application of IPL pulses.
Conclusions: Our video directly demonstrates the effect of IPL on a live Demodex mite extracted from a freshly epilated eyelash. The results suggest that IPL application with settings identical to those used for treatment of DED due to MGD causes a complete destruction of the organism.

Keywords: dry eye, intense pulsed light, demodex, ocular rosacea, meibomian gland disease, blepharitis

Introduction

Demodex folliculorum and *Demodex brevis*, collectively known as Demodex, are a normal part of the ocular and facial microbiome.[1–3] An increase in Demodex mite colonization is a strong risk factor in the pathogenesis of oculofacial rosacea, meibomian gland dysfunction (MGD), and dry eye disease (DED).[4,5] Treatment of DED using intense pulsed light (IPL) has been extremely successful in MGD patients,[6–9] but the mechanisms of action are still not well understood. One of the potential mechanisms is the control or elimination of demodicosis.[9–11]

Prieto et al. took 2-mm punch biopsies from the facial skin of subjects before and after IPL treatment and showed histologic evidence of coagulative death of Demodex organisms.[10] More recently, complete eradication of Demodex mites within eyelashes of MGD patients was observed after treatment with IPL.[11] Another study found that the density of Demodex organisms significantly decreased in treated rosacea patients with pulsed dye laser, another light-based approach.[12] While these studies collectively support the hypothesis that IPL is beneficial for MGD patients by reducing the density of Demodex mites, the immediate and real-time response of these organisms to IPL has not been demonstrated before. In this case study, we present video microscopy of a Demodex organism exposed to a series of IPL pulses, showing real-time evidence of Demodex kill. The IPL settings used in this case study are identical to those developed by the group of Toyos, which was recently reported as effective for treatment of DED due to MGD.[13–16]

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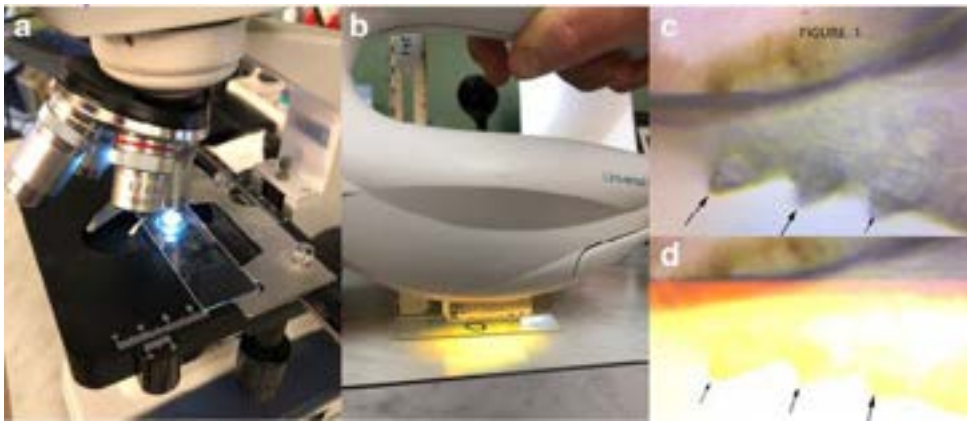

FIG. 1. Experimental setup showing experimental protocol. **(a)** Upright video microscopy showing extracted eyelash mounted on a slide and positioned on microscope stage. **(b)** The rectangular M22 light guide is shown positioned ~5 mm above the eyelash mounted on a glass slide. The slide was briefly removed from the microscope stage to be treated with the IPL light guide. **(c)** A still image from real-time video of Demodex immediately before administration of an IPL pulse using the Toyos settings (Fluence: 11 J/cm^2). **(d)** Same as **c**, during the IPL pulse. The legs of the Demodex mite are indicated with arrows. IPL, intense pulse light.

Case Report

A 62-year-old female with a history of oculofacial rosacea, hordeola, and DED presented to the clinic. An upright light microscope (Fig. 1a) (AmScope 40X-2500X LED Biological Binocular Compound Microscope) was used to confirm the presence of ocular demodicosis at the base of an eyelash epilated from the upper eyelid of the patient. The epilated lash was adhered to the adhesive surface of clear tape and then mounted directly onto a borosilicate glass microscope slide. Video microscopy with a USB Digital Camera Imager attached to the eyepiece of the microscope was then used to image the live Demodex organism.

IPL exposure of the Demodex mite was implemented with the IPL module of an M22 device (Lumenis Ltd., Yokneam, Israel) using treatment parameters shown in Table 1. Just before IPL application, the microscope slide onto which the Demodex mite was mounted was briefly removed from the microscope platform, and the IPL light guide was positioned ~4–5 mm parallel to the surface of the slide (Fig. 1b). Then, five IPL pulses were fired at intervals of 1–2 sec, each pulse with settings identical to those developed by the Toyos' group (Wavelengths: 590 nm to 1200 nm, Pulse structure: triplet of subpulses; Duration per subpulse: 6 msec; fluence per pulse: 12 J/cm^2). The microscope slide was returned to the microscope platform within 25 sec, and video microscopy was resumed. Figure 1c is a snapshot captured just before application of the IPL pulses. The snapshot zooms in on three legs of the Demodex mite protruding from its body (bottom third of the panel). Figure 1d shows a similar snapshot captured during application of an IPL pulse. Due to the strong intensity of the IPL signal, this panel is saturated with yellow light, and details on the Demodex body are lost.

A noncontact digital laser infrared thermometer temperature gun (Nubee NUB8380) was used to measure the temperature of the slide. A temperature of 49°C was measured immediately after the five IPL pulses.

Figure 2 shows individual frames from real-time video of Demodex treated by the IPL pulses. To illustrate the video

Table 1. IPL Treatment Parameters for Demodex Mite

Manufacturer	*Lumenis*
Model identifier	M22 with IPL handpiece
Year produced	2018
Number and type of emitters (laser or LED)	Xenon lamp
Wavelength and bandwidth (nm)	590–1200
Pulse mode (CW or Hz, duty cycle)	Triplet pulse
Beam spot size at target (cm^2)	5.25
Irradiance at target (mW/cm^2)	N/A
If pulsed peak irradiance (mW/cm^2)	N/A
Exposure duration (sec)	N/A
Radiant exposure (J/cm^2 per pulse)	12
Radiant energy (J per pulse)	63
Number of points irradiated	1
Area irradiated (cm^2)	N/A
Application technique	Application of IPL light guide 5 mm perpendicular to a microscopic slide (on which eyelash with specimen was mounted)
Number and frequency of treatment sessions	1
Total radiant energy over entire treatment course (J)	315 (5 pulses × 63 J/pulse)

IPL, intense pulse light; N/A, not available.

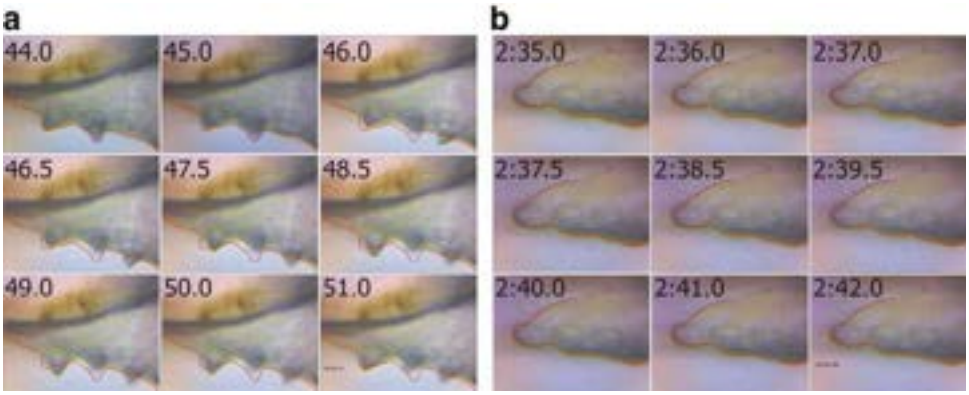

FIG. 2. (a) Individual frames from the movie are sequentially presented (0.5 sec apart) from real-time video of Demodex. In the first frame of the sequence, the Demodex legs are outlined with a red border in the first panel, and this red line was duplicated, unchanged, on all subsequent frames to illustrate the relative movement of the legs in subsequent frames. Images captured before IPL pulses showing the robust activity of the Demodex. **(b)** Individual frames from the movie are sequentially presented (0.5 sec apart) from real-time video of Demodex. In the first frame of the sequence, the Demodex legs are outlined with a red border in the first panel and this red line was duplicated, unchanged, on all subsequent frames to illustrate the relative movement of the legs in subsequent frames. Images captured after five IPL pulses, showing complete and absolute cessation of any movement of the legs of the Demodex. No leg movement was seen at hourly microscopic observation intervals for 5 h and then at 24 h.

movie in a static format, individual frames from the movie are sequentially presented in Fig. 2a (before an IPL pulse) and b (after an IPL pulse). Both figures should be read from left to right within each row and progressing from top to bottom between the rows; adjacent frames are shown in time steps of 1.0 sec, as indicated in the time stamps at the top left corner of each frame. The top left frame shows three legs of the Demodex mite at the beginning of each time sequence. To emphasize the motion of these legs in subsequent frames, a red line was superimposed on the contour of the three legs in the top left frame. This contour line was duplicated, unchanged, on all subsequent frames.

Figure 2a shows a static representation of the video movie captured several seconds before the IPL application. In this sequence of frames, the three legs of the Demodex mite spontaneously move in a repetitive and semicircular motion, with an average irregular rate of about 5 μm/sec. The three legs are not phase locked and appear to move independently from each other.

Figure 2b shows a sequence of frames captured $\sim$25 sec after application of five IPL pulses. The figure shows a complete and absolute cessation of any movement of the legs of the Demodex mite.

Figure 3a and b show a digital magnification of the Demodex mite before and after the IPL application, respectively. Comparison between the two panels shows definite structural changes of the Demodex exoskeleton, following IPL application: the legs appear smoother, less corrugated, and receded. The eyelash (insets) appears to remain intact, although some shrinkage may be evident. No pedal movement was observed hourly for 5 h and after 24 h following the application of IPL pulses (not shown here).

Discussion

IPL is a technique well known for treating facial rosacea and has recently become a recognized nonpharmacologic alternative for ocular rosacea and DED.[6,9,17] Numerous publications have shown the ability of IPL to treat the clinical signs of inflammation associated with DED, and the speculated mechanism includes photocoagulation of abnormal telangiectatic vessels, photobiomodulation of mitochondrial metabolism, and photoimmunomodulatory effects on IL-4, IL-6, IL-10, IL-17A, and TNF-α.[9,14]

However, it is intriguing to consider whether the improvement in the signs and symptoms of DED after IPL treatment could result, in part, from the elimination of Demodex. Indeed, pharmacological eradication of Demodex in patients with ocular rosacea, including tea tree oil, oral Ivermectin, and hypochlorous acid sprays, has been shown to improve symptoms of DED and ocular surface discomfort.[18–20] While Demodex in low numbers is considered part of the normal ocular microbiome, uncontrolled proliferation of Demodex, as occurring in facial rosacea, may represent a dysbiosis in the parasitic infestation, eventually leading to eyelid inflammation and blepharoconjunctivitis.[21,22] Since IPL is effective against demodicosis, as the current study suggests,

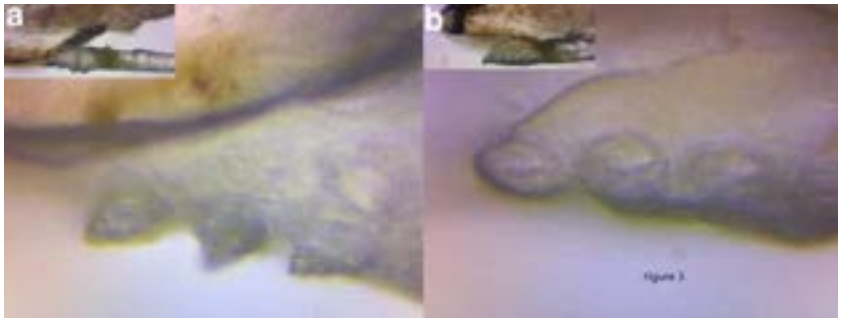

FIG. 3. Digitally magnified images before **(a)** and after **(b)** five IPL pulses with the Toyos settings. The inset shows that a larger perspective of the organism adhered to the eyelash.

at least part of the mechanism by which IPL treatment benefits MGD patients could be attributed to its coagulative effects on Demodex.

Thus far, research studies showing the effect of IPL treatments on Demodex have been limited by indirect evidence using either direct microscopic observation of a few random epilated lashes or skin punch biopsies with histologic analysis. To our knowledge, real-time evidence that IPL is directly microbiocidal has not been shown before. This case report shows real-time video microscopic evidence that IPL pulses (with the same settings as the Toyos protocol, which is used for treatment of DED due to MGD) kill Demodex organism in an *in vitro* environment. While the biochemical mechanism of demodex death and histological confirmation of cellular apoptosis and necrosis remain to be determined, we use the same video microscopic analysis that was established by Tseng and coworkers to support Demodex death or at the very least inactivation.[18]

Several lines of evidence indicate that the death of Demodex induced in our case study is caused by coagulative necrosis. Absorption of IPL energy by chromophores intrinsic to Demodex and the closed cylindrical shape of the Demodex may cause the rapid accumulation of thermal energy and surrounding heating without the possibility of rapid dissipation of heat through its exoskeleton. Our video microscopic observation showing ''smoothed and retracted'' feet (Fig. 3b) is consistent with coagulative necrosis following IPL indicating that the accumulated thermal energy was high enough to be lethal. Demodex thrives between optimal growth temperatures of 16–20°C, but temperatures above 54°C are damaging to Demodex, and temperatures above 58°C are considered lethal.[23] Using the digital laser infrared thermometer, we found that the temperature of the slide after the IPL application was 49°C. While this measurement is a few degrees below the lethal threshold, the temperature of the glass slide during and immediately after the IPL application was probably higher, since there were a few seconds delay between the end of the IPL pulse sequence and the temperature measurement.

Conclusions

In summary, this work shows that standard Toyos dry-eye IPL settings are sufficient to kill the Demodex mite on an epilated lash. Our sequential video images showing complete inactivation are strong evidence that IPL directly and rapidly kills Demodex, presumably by coagulative necrosis, although additional histologic analysis is needed to confirm this mechanism. Because definitive evidence that IPL kills Demodex is still scarce, this case report is relevant for advancing our understanding of the possible role of IPL in eliminating Demodex in rosacea and MGD patients. Further, it brings us closer to understanding the interplay between IPL, Demodex, and the improvement of symptoms in DED.

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Permissions

The patient in this case study has signed a permission allowing the eyelash to be used in this article.

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Evaluation of the efficacy of optimal pulsed technology treatment in patients with cataract and Meibomian gland dysfunction in the perioperative period

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Abstract

Background: The aim of this study was to evaluate the efficacy and safety of M22 Optimal Pulsed Technology (OPT) applied in patients with age-related cataract and Meibomian gland dysfunction (MGD) in perioperative period.

Methods: This prospective observational study was carried out in the Jinan Mingshui Eye Hospital (Zhangqiu, China). We studied 60 patients (30 in the OPT treatment group and 30 in the conventional surgery group) with age-related cataract and MGD who underwent phacoemulsification and evaluated the efficacy of OPT treatment before and 1 month and 3 months after surgery. Ocular Surface Disease Index (OSDI) questionnaire, biomicroscopic examination of lid margins, Meibomian gland yielding secretion score (MGYSS), corneal fluorescein staining scores (CFS), tear film break-up time (TBUT), tear meniscus height (TMH) and the morphology of the MG (meibography) followed by Keratograph 5 M (K5M) were used to assess the patients' conditions.

Results: There were significant differences in the scores of OSDI, MGYSS, TBUT, and CFS between the preoperative and postoperative outcomes ($p < 0.05$). In the OPT treatment group, the postoperative ocular surface condition was obviously better and the patient satisfaction rate was higher than those before surgery. There were significant differences in the scores of OSDI, EMAS, MGYSS and CFS before and 1 month after surgery ($p < 0.05$). In addition, there were also significant differences in the scores of OSDI, EMAS, MGYSS and MGLS before and 3 months after surgery ($p < 0.05$). No complications appeared during OPT treatment.

Conclusions: Cataract surgery can aggravate MGD and is detrimental to ocular surface health. OPT treatment was a safe and effective intervention for patients with MGD and cataract during perioperative period.

Keywords: Age-related cataract, Phacoemulsification, Dry eye, Meibomian gland dysfunction, OPT treatment

Background

Age-related cataract (ARC) is one of the most important causes of visual impairment in the world [1]. With the trend of population ageing, ARC will become the most common eye disease in the world in 2020 [2]. Cataract surgery is one of the most common procedures performed worldwide, and excellent postoperative visual acuity is usually obtained [3]. However, dry eye syndrome (DES) usually occurs after cataract surgery. DES is an ocular surface disease caused by a variety of reasons, characterized by loss of steady state of the tear film and dry eye symptoms, and its pathogenesis includes corneal nerve injury, ocular surface inflammation, goblet cell decrease, and Meibomian gland dysfunction (MGD) [4].

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MGD is a chronic diffuse abnormality of the meibomian glands, usually characterized by terminal duct obstruction and changes in glandular secretion [5]. The prevalence of MGD is as high as 70% in Asians, which has attracted wide attention of clinicians and scientists [6, 7]. MGD can increase tear evaporation and tear osmotic pressure and lead to inflammation of the corneal surface and damage to the corneal epithelium. Therefore, MGD is the major cause of evaporative dry eye and contributes to aqueous-deficient dry eye. Dry eye and tear film dysfunction after cataract surgery, including foreign body sensation, burning sensation, itchy eyes, dryness, poor near sight, redness, decreased contrast sensitivity and irritation, are closely related to MGD [8–14].

There are many clinical treatments for MDG, including artificial tears, warm compression, meibomian gland expression, omega-3 supplementation, cyclosporine, corticosteroids and oral antibiotics. However, those treatment methods have been shown to provide short-term relief of symptoms [15]. In-tense pulsed light (IPL) treatment applies Xenon flash lamp to emitting wavelengths of light ranging from 590 to 1200 nm, which has been used in treatment of rosacea, elangiec-tasia, port-wine stains, and pigmentation of the skin around the eyes. In recent years, IPL has been extended to treat MGD, and has also been introduced into DEWS II [16, 17]. Optimized Pulse Technology (OPT) is adopted in the M22 system (Lumenis Medical Laser Co. Ltd., Yokneam, USA). Its square wave pulse shape is uniform, and the time and energy of intense light emission are more accurate, safe and effective. The three-pulse square wave without energy spikes and attenuation has the advantage of rapidly increasing the temperature of the target tissue under the epidermis to achieve its destruction, while maintaining skin integrity. The sapphire contact cooling technology allows the patient to feel more comfortable and pain free during treatment.

The aim of our study was to evaluate the effect of OPT therapy on patients with age-related cataract combined with mild to moderate MGD. In this study, ocular surface disease index (OSDI) questionnaire, eyelid margin abnormality score (EMAS), Meibomian gland yielding secretion score (MGYSS), corneal fluorescein staining (CFS) scores and Keratograph 5 M (K5M) examination for patients before and after surgery were analyzed to evaluate the effects of OPT therapy on post-operative functional symptomology in patients with MGD combined with age-related cataract.

Methods

Patients

This study was a prospective observational study, and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of Jinan Mingshui Eye Hospital (Jinan, China) (No. 20170802). Written informed consent was obtained from each participant before enrolment. A total of 60 patients with AGC who had mild to moderate MGD in the Mingshui Eye Hospital from October 2017 to December 2017 were included in this study. There were 30 patients with mild MGD and 30 patients with moderate MGD.

Inclusion criteria: (1) patients who were diagnosed as age-related cataract and eligible for cataract surgery; (2) according to the consensus of experts in the diagnosis and treatment of MGD in China in 2017 (Table 1) [8], patients who were diagnosed as mild to moderate MGD; (3) patients who had no history of diabetes, hypertension, and systemic autoimmune diseases such as Sjögren syndrome; (4) Fitzpatrick [18] Skin Classification Type was 1–4; (5) patients who had good education level and normal communication skill, and could communicate with the researchers and express their treatment experience; (6) patients who could understand the different treatment options and volunteer to participate in the study.

Exclusion criteria: (1) patient with infectious blepharitis, seborrheic blepharitis and rouge high-emission MGD; (2) patients had history of ocular trauma or

Table 1 The graduation standard of MGD

Degree	Symptoms	Palpebral margin changes	Secretion character score	Secretion discharge capacity score	Meibomian gland deletion score	Corneal
Mild	Slight, intermittent	Normal or mild hyperemia of palpebral margin and there may be fat cap formation	1	1	1	Normal, no epithelial damage
Moderate	Mild or moderate, persistent	palpebral margin becomes blunt, round and thickened. Meibomian gland mouth was obstruction and protuberance	2	2	2	Mild or moderate epithelial damage, located at the periphery
Severe	Moderate or severe, affecting life or work	The blepharon margin is thickened and the neovascularization is obvious. Fat thrombus formation in meibomian gland mouth	3	3	3	Damage to epithelium and superficial matrix

surgery or long-term medication; (3) patients with severe ocular surface abnormalities; (4) patients had obvious abnormalities in the eyelid margins (> 3 times of positive surgery), reduced meibum expression (grade > 2) or obstructed gland dropout (meibography score > 3).

Evaluation of MGD and DE parameters

The parameters of MGD were assessed by the consensus of the experts on the diagnosis and treatment of meibomian gland dysfunction in 2017 (Table 1) [8]. Each patient underwent routine ophthalmologic examinations, including naked eye and corrected visual acuity, intraocular pressure, slit lamp microscopy (eyelid margin abnormality score, meibomian gland yielding secretion score, and corneal fluorescein staining) and fundus examination. After 30 min of rest, DE questionnaire and DE related examination were performed in the order of OSDI questionnaire, tear meniscus height (TMH), tear break-up time (TBUT) and (MGLS). Examinations of TMH, TBUT, and MG were performed using a K5M ocular surface analyzer. All MGD-related examinations were required to be completed before using eye drops (antibiotic eye drops and topical anesthetics).

Preoperative evaluation of cataract

All patients completed the OSDI questionnaire, which was scored according to previous describes [19]. The 12 items of the OSDI questionnaire were graded on scale 0 to 4, of which 0 indicated no time; 1, sometimes; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score was then calculated on the basis of the following formula: OSDI = [(sum of scores for all questions answered) × 100]/ [(total number of questions answered) × 4]. Thus, the OSDI score was based on a 0 to 100 scale and higher scores indicated more severe symptoms or discomfort.

Microscopic examination. (1) Eyelid margin abnormality score (EMAS) [20]: Eyelid margin abnormalities were scored as 0 (absent) or 1 (present) for the following 4 parameters: vascular engorgement, plugged meibomian gland orifices, anterior or posterior displacement of the mucocutaneous junction, and irregularity of lid margin. The sum was recorded as 0 through 4. (2) Meibomian gland yielding secretion score (MGYSS). The quality degree of the meibum was based on the following: grade 0, clear; grade 1, cloudy; grade 2, cloudy with granular debris; and grade 3, thick like tooth-paste. The upper and lower eyelids of each eye were scored separately, 0 was normal, 1 point and above were abnormal, and the highest score of this item was 6 points. (3) Corneal fluorescein staining (CFS). The cornea was stained with 0.2% sodium fluorescein and positive staining indicated the integrity of the corneal epithelial cells. CFS used the 12-point method [21]: the cornea was divided into four quadrants, each quadrant was scored according to the following criteria: 0, no spot dyeing; 1, 1–30 spots dyeing; 2, > 30 spots dyeing but not fused into tablets; 3, corneal spots dyed point fusion or ulcers.

K5M ocular surface comprehensive analyzer inspection. All selected patients were inspected by the same technician under the operation of the K5M: TMH, TBUT and MGLS.

Cataract surgery

A total of 60 patients were randomly divided into two groups: OPT treatment group and conventional surgery group. Conventional surgery group: patients were routinely prepared according to the clinical path of cataract surgery. OPT treatment group: in addition to routine preoperative preparation according to the clinical path of cataract surgery, the patients in OPT treatment group also received M22 OPT (OPT, Oculus, Wetzlar, K5M Germany) treatment before and 1 and 2 months (± 2 days) after surgery. OPT treatment was performed by the same skin cosmetic surgeon. The operation of OPT treatment was as follows: (1) Washed and dried the face; (2) The patients were asked to wear a special protective eye mask and close eyes; (3) Parameter design: the mode was three-pulse, the pulse time was 6 ms, the pulse interval was 50 ms, and the energy density was (11–16) J/cm^2; (4) Ultrasound gel was applied on the patient's face; (5) using 35 mm × 15 mm light guide crystal; (6) From the inferior temporal margin near the lateral malleolus to the nasal side, 12–16 laser spot were treated. (7) The wavelength of the filter was 590 nm. All cataract surgeries were performed by the same experienced surgeon [22]. The 2.2 mm three-plane tunnel incision on angle scleral was taken over the iliac crest.

No complications occurred during and after surgery. After the treatment, the specialist nurses carried out detailed health education for the patients and their families. Avoid hot water contact (such as sauna, steaming, hot bath, etc.) on the face within 48 h after treatment. Do not rub, scratch or make up. If there was scab in the local area, the scab would be removed within 1–2 weeks and the wound would be healed. Before removing the scab, the infection of the wound should be prevented, the wound should be kept dry, and the pigmentation should be prevented. Avoid direct sunlight exposure after treatment. The treatment area should be well hydrated and repaired. Usually, eye use time should not be too long. After cataract surgery, in addition to routine administration of antibiotics (such as Levofloxacin Eye Drops) and hormone eye drops (such as cortisone eye drops), the patients in OPT treatment group were received OPT treatments at 1 month and 2 months (±2 days) after surgery.

Postoperative follow-up

The follow-up which was performed by the same ophthalmologist was performed for 1 month (the OPT treatment group was performed before the second OPT treatment) and 3 months after the operation in the following order: OSDI questionnaire, slit lamp examination (EMAS, MGYSS, and CFS), and K5M (Oculus, Wetzlar, Germany) examination (TMH, TBUT, and MGLS).

Statistical analyses

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of the data was verified by using the Kolmogorov-Smirnov test. The scores of OSDI, TMH and TBUT were normally distributed values and data were expressed as means ± SD. EMAS, MGYSS, CFS and MGLS were non-normally distributed values and data were expressed as Median (P25, P75). Continuous intergroup variables were analyzed by using an independent t-test, and continuous intragroup variables were tested by a paired t-test. Categorical intergroup variables were analyzed with the nonparametric Kruskal–Wallis test, and categorical variables intragroup were analyzed with the nonparametric Wilcoxon signed-rank test. $P < 0.05$ was considered to be statistically significant.

Results

General clinical symptoms

We studied 30 patients with AGE and MGD for OPT treatment in this study. 8 patients were lost to follow-up and the remaining 22 patients were the subjects of this group. The mean age of the 22 patients was 63.48 ± 8.47 years old (ranged from 56 to 79 years) and 12 patients were female. As for conventional surgery group, we evaluated 30 patients. 5 patients were lost to follow-up and the remaining 25 patients were the subjects of this group. The mean age of the 25 patients was 65.8 ± 8.1 years old (ranged from 54 to 84 years) and 14 patients were female. There were no significant differences in gender and age between the two groups ($p > 0.05$).

Changes in DE syndrome and ocular surface parameters before and after cataract surgery in the conventional operation group

There were significant differences between $OSDI_0$ (pre-OSDI score) and $OSDI_1$ (OSDI score at 1 month postoperatively) (31.19 ± 7.28 vs 33.43 ± 6.32, $p = 0.003$) (Table 1). However, there was no significant difference between $OSDI_0$ and $OSDI_3$ (31.19 ± 7.28 vs 30.51 ± 6.65, $p = 0.256$) (Table 2). It showed that the dry eye symptoms were significantly aggravated 1 month after the operation and recovered to preoperative levels 3 months after the operation.

The pre-MGYSS was 1.00 (1.00, 1.00) (Table 2). One month and 3 months after surgery, the MGYSS was higher than the preoperative MGYSS, respectively (1.00 (1.00, 2.00) vs 1.00 (1.00, 1.00) and 1.00 (1.00, 2.00) vs 1.00 (1.00, 1.00)) (Table 2). There was statistically significant difference between pre-MGYSS and MGYSS 3 months after surgery ($p = 0.002$), indicating that the MGYSS was worse after surgery.

The pre-CFS (CFS_0) was 0.00 (0.00, 1.00) (Table 2). The CFS at 1 month postoperatively (CFS_1) was 1.00 (0.50, 1.00), and the CFS at 3 months postoperatively (CFS_3) was 0.00 (0.00, 1.00) (Table 2). There was significant difference between CFS_0 and CFS_3 ($p = 0.008$), suggesting that the CFS was aggravated after surgery.

The pre-TMH (TMH_0) was 0.18 ± 0.03 mm (Table 2). The TMH was 0.20 + 0.02 mm 1 month after surgery (TMH_1), and the TMH was also 0.20 ± 0.02 mm 3 months after surgery (TMH_3) (Table 2). There were significant differences between TMH_0 and TMH_1 ($p = 0.016$), as well as between TMH_0 and TMH_3 ($p = 0.020$).

Table 2 Comparison of dry eye symptoms and ocular surface parameters in the Conventional surgery group before and after surgery

Parameters	baseline	1 month	3 month	*p* value		
				baseline vs 1 month	baseline vs 3 month	1 month vs 3 month
OSDI[a]	31.19 ± 7.28	33.43 ± 6.32	30.51 ± 6.65	0.003*	0.256	0.001#
EMAS[b]	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.109	0.334	0.763
MGYSS[b]	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.088	0.002*	0.376
CFS[b]	0.00 (0.00, 1.00)	1.00 (0.50, 1.00)	0.00 (0.00, 1.00)	0.074	0.008*	0.564
TMH[a]/mm	0.18 ± 0.03	0.20 ± 0.02	0.20 ± 0.02	0.016*	0.020*	0.635
NITBUT[a]/s	5.52 ± 1.95	5.06 ± 1.54	4.99 ± 1.24	0.002*	0.035*	0.764
MGLS[b]	1.00 (1.00, 2.00)	1.00 (1.00, 1.50)	1.00 (1.00, 2.00)	0.564	0.655	0.157

OSDI Ocular Surface Disease Index, *MGYSS* Meibomian gland yielding secretion score, *CFS* corneal fluorescein staining, *TMH* tear meniscus height, *EMAS* Eyelid margin abnormality score, *MGLS* meibomian gland loss score, *TBUS* tear film break-up time. a: Normal distribution data, the mean is expressed as Mean ± SD, and the paired sample t test is used for comparison between groups. b: Non-normally distributed data, the mean is represented by Median (P25, P75), and the comparison between groups is based on paired sample nonparametric Wilcoxon test. *$p < 0.05$ vs Baseline; #$p < 0.05$ vs 1 month

Those results indicated that the TMH became better after surgery.

The pre-NITBUT ($NITBUT_0$) was 5.52 ± 1.95 s (Table 2). The TBUT was 5.06 ± 1.54 s 1 month after surgery ($NITBUT_1$), and the TBUT was 4.99 ± 1.24 s 3 months after surgery ($NITBUT_3$) (Table 2). There were significant differences between $NITBUT_0$ and $NITBUT_1$ (p = 0.002), as well as between $NITBUT_0$ and $NITBUT_3$ (p = 0.035), which showed that the patient's TBUT was shortened after surgery.

Changes in DE syndrome and ocular surface parameters before and after cataract surgery in the OPT treatment group

The pre-OSDI score ($OSDI_0$) was 31.39 ± 8.57, the OSDI score was 28.10 ± 5.88 months after surgery ($OSDI_1$), and the OSDI score was 21.58 ± 4.97 3 months after surgery ($OSDI_3$) (Table 3). There were significant differences between $OSDI_0$ and $OSDI_1$ (p = 0.027), as well as between $OSDI_0$ and $OSDI_3$ (p = 0.000). Those results showed that after OPT treatment, the symptom of DE after surgery was not only ameliorated, but also superior to preoperative symptom.

The pre-EMAS ($EMAS_0$) was 1.00 (1.00, 2.00), the EMAS was 1.00 (0.00, 1.25) 1 month after surgery ($EMAS_1$), and the EMAS was 1.00 (0.00, 1.00) 3 months after surgery ($EMAS_3$) (Table 3). There were significant differences between $EMAS_0$ and $EMAS_1$ (p = 0.020), as well as between $EMAS_0$ and $EMAS_3$ (p = 0.025), which showed that after OPT treatment, the EMAS was improved.

The Pre-MGYSS was 1.00 (1.00, 1.00) (Table 3). One month and 3 months after surgery, MGYSS were higher than preoperative MGYSS, respectively (1.00 (1.00, 1.00) vs 1.00 (1.00, 1.00) and 1.00 (0.00, 1.00) vs 1.00 (1.00, 1.00)) (Table 3). The difference between preoperative MGYSS and MGYSS 3 months after surgery was statistically significant (p = 0.020), which suggested that after OPT treatment, the MGYSS was improved.

The pre-TBUT ($NITBUT_0$) was 4.98 ± 1.84 s, the TBUT was 5.67 ± 1.80 s 1 month after surgery ($NITBUT_1$), and the TBUT was 5.87 ± 1.17 s 3 months after surgery ($NITBUT_3$) (Table 3). There was significant difference between $NITBUT_0$ and $NITBUT_3$ (p = 0.026), which showed that after OPT treatment, the TBUT was ameliorated.

In the OPT treatment group, the MG structure of some patients was clear, and the loss rate was lower than that before surgery. The difference between the pre-MGLS and MGLS 3 months after surgery was statistically significant (p = 0.002) (Fig. 1).

Changes in ocular surface parameters between OPT treatment group and conventional operation group

One month after surgery, there were notably significant differences in the scores of OSDI, EMAS, MGYSS and CFS between the conventional surgery group and the OPT treatment group ($p < 0.05$). In addition, 3 months after surgery, there were notably significant differences in the scores of OSDI, EMAS, MGYSS and CFS between the conventional surgery group and the OPT treatment group ($p < 0.05$). The postoperative comparison between the OPT treatment group and the conventional surgery group showed that the patients in the OPT treatment group had a better subjective feeling and ocular surface state after surgery (Table 4, Fig. 2).

Discussion

MGD was divided into two major categories based on the secretion of Meibomian glands, namely low delivery and high delivery [23]. The low delivery type, including hypo secretory and obstructive, was the most common type of clinical MGD. Clinically, MGD is often associated with poor outcomes after cataract surgery, refractive surgery, and corneal surgery. Zhang et al. showed that patients with corneal epithelial erosion after cataract surgery combined with MGD may have had MGD

Table 3 Comparison of dry eye symptoms and ocular surface parameters in the OPT treatment group before and after surgery in patients

parameters	baseline	1 month	3 month	*p* value		
				baseline vs 1 month	baseline vs 3 month	1 month vs 3 month
OSDI[a]	31.39 ± 8.57	28.10 ± 5.88	21.58 ± 4.97	0.027*	0.000*	0.000#
EMAS[b]	1.00 (1.00, 2.00)	1.00 (0.00, 1.25)	1.00 (0.00, 1.00)	0.020*	0.025*	0.739
MGYSS[b]	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.00, 1.00)	0.414	0.020*	0.467
CFS[b]	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.577	0.589	1.000
TMHa/mm	0.18 ± 0.31	0.19 ± 0.03	0.19 ± 0.02	0.210	0.147	0.611
NITBUT[a]/s	4.98 ± 1.84	5.67 ± 1.80	5.87 ± 1.17	0.091	0.026*	0.550
MGLS[b]	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 1.00)	0.083	0.002*	0.008#

OSDI Ocular Surface Disease Index, *MGYSS* Meibomian gland yielding secretion score, *CFS* corneal fluorescein staining, *TMH* tear meniscus height, *EMAS* Eyelid margin abnormality score, *MGLS* meibomian gland loss score, *TBUS* tear film break-up time. a: Normal distribution data, the mean is expressed as Mean ± SD, and the paired sample t test is used for comparison between groups. b: Non-normally distributed data, the mean is represented by Median (P25, P75), and the comparison between groups is based on paired sample nonparametric Wilcoxon test. *$p < 0.05$ vs Baseline; #$p < 0.05$ vs 1 month

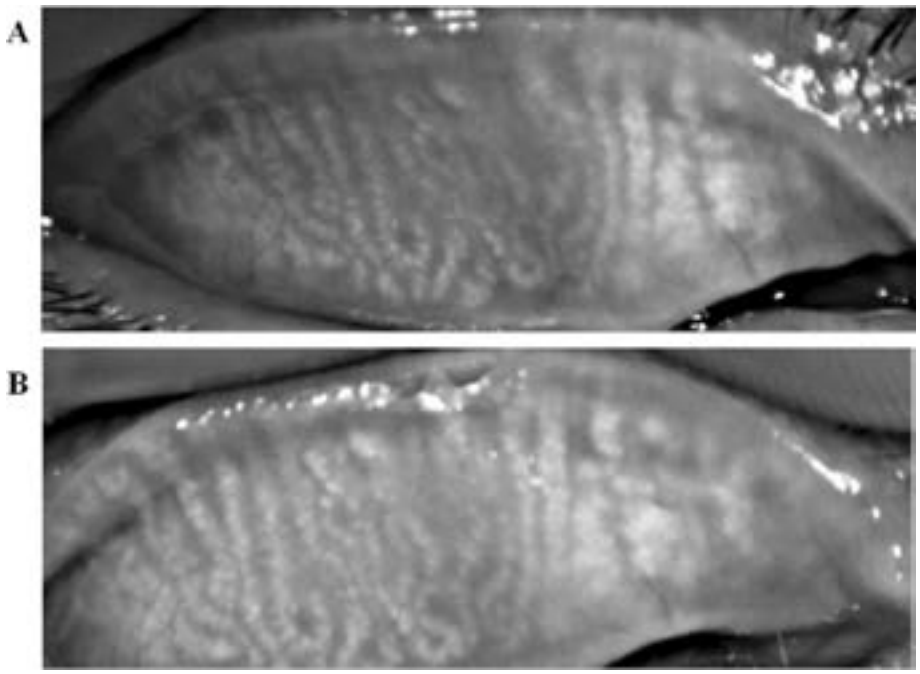

Fig. 1 Meibography images. **a** Meibography image (100 × magnification) before OPT treatment. **b** Meibography image (100 × magnification) after OPT treatment. Compared the image before surgery, the MG structure of some patients was clear, and the loss rate was lower after OPT treatment

before surgery [11]. MGD includes anatomical degeneration and pathophysiological changes, and clinicians and researchers agree that it seriously affects ocular surface health [24]. A large number of studies have shown that cataract surgery can aggravate MGD, resulting in lower satisfaction of patients with the surgical results [9–11, 22, 25]. In this study, there were significant differences in OSDI scores, MGYSS, TBUT, and CFS between the preoperative and postoperative outcomes. The results showed that cataract surgery can accelerate the development of MGD, which can cause dryness or increase the patient's original dryness after surgery. However, there was no significant difference in the morphology and number of Meibomian glands before and after surgery in the conventional surgery group, suggesting that cataract surgery affected the Meibomian gland function of the patients, but did not change the anatomy of the meibomian gland. The purpose of treating MGD is to improve the secretion function of the meibomian glands, to improve the stability of the tear film, and to alleviate the symptoms of DE in patients.

Table 4 Comparison of postoperative ocular surface parameters between OPT treatment group and Conventional operation group

parameters	*p* value		
	baseline	1 month	3 month
Age[a]	0.966		
OSDI[a]	0.931	0.005*	0.000*
EMAS[b]	0.543	0.060	0.033*
MGYSS[b]	0.657	0.004*	0.001*
CFS[b]	0.716	0.006*	0.800
TMH[a]/mm	0.416	0.189	0.110
NITBUT[a]/s	0.295	0.209	0.033*
MGLS[b]	0.544	0.989	0.005*

OSDI Ocular Surface Disease Index, *MGYSS* Meibomian gland yielding secretion score, *CFS* corneal fluorescein staining, *TMH* tear meniscus height, *EMAS* Eyelid margin abnormality score, *MGLS* meibomian gland loss score, *TBUS* tear film break-up time. a: Normal distribution data, the mean is expressed as Mean ± SD, and the paired sample t test is used for comparison between groups. b: Non-normally distributed data, the mean is represented by Median (P25, P75), and the comparison between groups is based on paired sample nonparametric Wilcoxon test. *$p < 0.05$ vs Baseline; #$p < 0.05$: conventional operation group vs OPT treatment group

The current treatment methods for MGD [26] include: (1) physical therapy: eyelid cleaning, hot compress, Meibomian Gland Expression (MGX), acupuncture, Lipi-Flow meibomian gland heat pulsation therapy, OPT treatment, and correcting the patient's blinking habits; (2) drug treatment: artificial tears, non-steroidal anti-inflammatory drugs, antibiotics, hormone eye drops; (3) diet therapy: omega-3 fatty acids. Although there are many ways to treat MGD, there is currently no definitive and effective treatment for MGD. Besides, many treatments cannot be adhered to because of their poor compliance. In-tense pulsed light (IPL) was first reported for

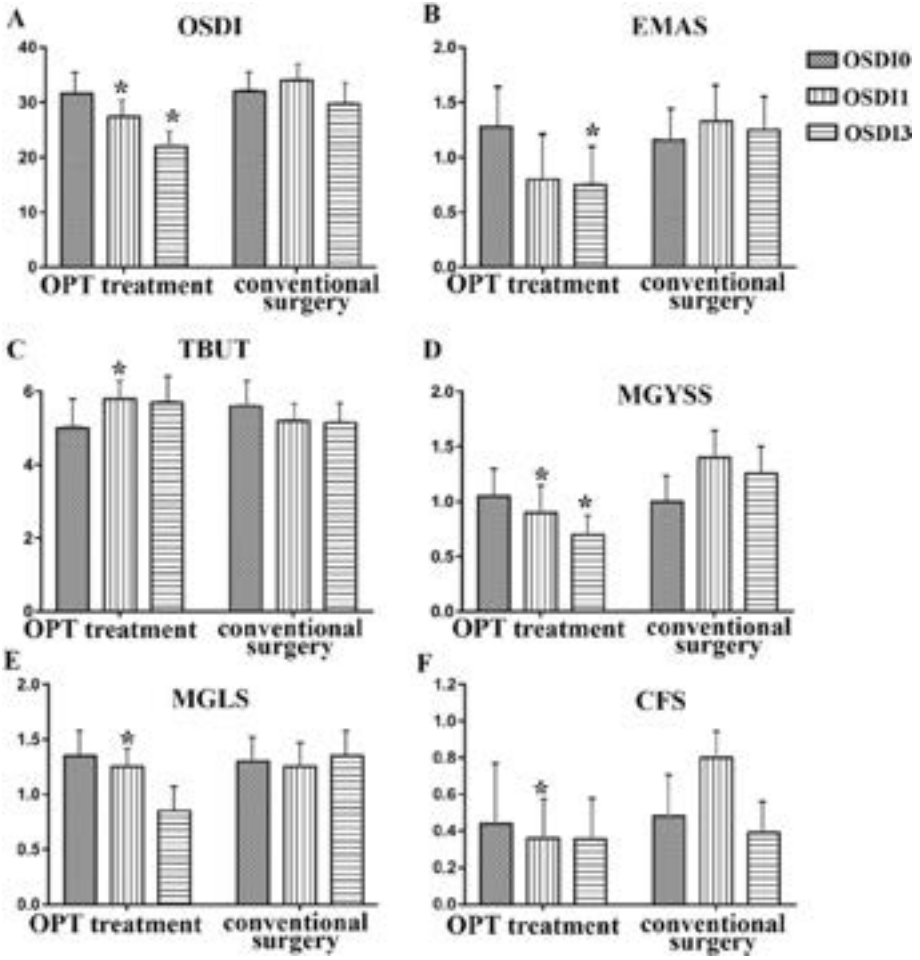

Fig. 2 Changes in DE symptom and ocular surface parameters in the OPT treatment group and the conventional surgery group. **a** OSDI. **b** EMAS. **c** TBUT. **d** MGYSS. **e** MGLS. **f** CFS. *$p < 0.05$ vs the conventional surgery group

the treatment of MGD in 2015 and then there were several studies to report its efficacy in the treatment of MGD. The M22 system uses Optimized Pulsed Technology (OPT), which has a uniform square wave pulse waveform, and the time and energy of intense light emission are more accurate, safe, and effective.

In this study, OPT treatment was better in improving OSDI, TBUT and MG functions. There were significant differences in OSDI, EMAS, MGYSS and CFS 1 month and 3 months after surgery. No complications such as iris depigmentation and dilated pupils appeared during treatment, which indicated the efficacy and safety of OPT treatment. The results of this study are consistent with those of previous studies [27–29].

In previous studies, it was often combined with MGX immediately after OPT treatment, because researchers considered that the thermal effects of OPT may make meibum easy to discharge. However, in this study, patients who underwent OPT treatment did not undergo MGX because there were no high-restorative patients enrolled in this study. The mechanism of OPT treatment for MGD may be the following [30]: (1) thermal effects improved glandular secretion and excretion; (2) inflammatory response and edema of acinar were reduced by blocking dilated capillaries and reducing inflammatory mediators release; (3) the load of bacteria and aphids were decreased. Yin [31] confirmed that OPT not only improved the macrostructure of MG but also changed the microstructure of MG, which suggested that the light simulation mechanism, anti-inflammatory mechanism and photothermic effect were the main mechanisms of OPT treatment for MGD.

Simple eyelid cleaning, hot compress or combined MGX can improve the function of meibomian glands [32, 33]. Sravanthi Vegunta and other researchers have reported that IPL and MGX can significantly improve 89% DE symptoms and 77% meibomian gland function in patients [18]. Dell's study confirmed that the

combination of OPT and MGX was effective in relieving the symptoms and signs of patients with evaporative dry eye secondary to MGD [34].

This study also has some limitations. Firstly, this study was conducted in a relatively small number of subjects. Secondly, the meibomian gland discharge capacity was not scored due to the absence of meibomian gland evaluator. Thirdly, the OPT did not directly act on the upper and lower eyelids. It was reported that direct OPT treatment in upper and lower eyelids would bring more evident effect [30]. In this study, both eyes were treated with OPT at the same time and the range of energy we selected was higher than that reported in previous studies, which may be the reasons for the significant effect of OPT treatment in this study.

Cataract surgery for patients with Age-related cataract is not only for the simple improvement of visual acuity, but also in significantly improving patients' visual quality and even living quality. Therefore, the ophthalmologist is required to carefully evaluate the patient's ocular surface state before surgery, especially for patients with MGD, to improve the satisfaction of patients with MGD in cataract surgery. The ophthalmologist should also educate and intervene the patients before surgery, operate carefully during operation, use drugs rationally after surgery and quest the individualized management mode of patients with different degrees of ocular surface diseases.

Conclusions

In conclusion, our study suggested that phacoemulsification can increase the DE symptoms and MGD. OPT treatment was a safe and effective intervention for patients with cataract and MGD during the perioperative period.

Abbreviations

ARC: Age-related cataract; CFS: Corneal fluorescein staining; DE: Dry eye; EMAS: Eyelid margin abnormality score; IPL: In-tense pulsed light; MGD: Meibomian gland dysfunction; MGX: Meibomian Gland Expression; MGYSS: Meibomian gland yielding secretion score; OPT: Optimal Pulsed Technology; OSDI: Ocular Surface Disease Index; TBUT: Tear film break-up time; TMH: Tear meniscus height

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Authors' contributions

JLG is responsible to the guarantor of integrity of the entire study, study design, definition of intellectual content, literature research, data acquisition & analysis, statistical analysis, manuscript preparation & editing; NL is responsible to the clinical studies, manuscript preparation; XMW, YD, CQW, ZRL and JL are responsible to the clinical studies; LHW is responsible to the guarantor of integrity of the entire study, study concepts, manuscript review. All authors are approved to this manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was a prospective observational study, and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of Jinan Mingshui Eye Hospital (Zhangqiu, China). Written informed consent was obtained from each participant before enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

OptiLight

LUMENIS

Indication for Use:

In EU: Evaporative Dry Eye Disease (DED), also known as dry eye syndrome or lipid tear deficiency, due to Meibomian Gland Dysfunction (MGD). This indication is intended for Fitzpatrick skin types I-V.
In US: Improvement of signs of Dry Eye Disease (DED) due to Meibomian Gland Dysfunction (MGD), also known as evaporative dry eye or lipid deficiency dry eye, in patients 22 years of age and older with moderate to severe signs and symptoms of DED due to MGD and with Fitzpatrick skin types I-IV. IPL is to be applied only to skin on the malar region of the face, from tragus to tragus including the nose (eyes should be fully covered by protective eyewear). IPL is intended to be applied as an adjunct to other modalities, such as meibomian gland expression, artificial tear lubricants and warm compresses. The indications are only relevant where they were approved by the Regulatory Authorities.

Treatment with OptiLight is contraindicated for patients with the following conditions in the treatment area:

Ocular surgery or eyelid surgery or Neuro-paralysis within 6 months prior to the first treatment; Uncontrolled eye disorders affecting the ocular surface; Pre-cancerous lesions, skin cancer or pigmented lesions; Uncontrolled infections or uncontrolled immunosuppressive diseases; Recent Ocular infections; History of cold sores or rashes in the perioral area, including: Herpes simplex 1 & 2, Systemic Lupus erythematosus and porphyria; Use of photosensitive medication and/or herbs that may cause sensitivity within 3 months prior to the first IPL session; Recent radiation therapy to the head or neck or planned radiation therapy; Recent treatment with chemotherapeutic agent or planned chemotherapy; History of migraines, seizures or epilepsy. Patients eyes must be completely occluded during the treatment. Please refer to the operator manual for a complete list of intended use, contraindications and risks.

The following possible side effects can occur following IPL treatments:

Pain/discomfort, damage to natural skin texture, change of pigmentation, scarring, excessive edema, fragile skin, bruising, burns, pruritus and xerosis. Please refer to the user manual or ask your doctor for a complete list of intended use, contraindications and risks.

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