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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 $\times$ 100)/(total number of answered questions $\times$ 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

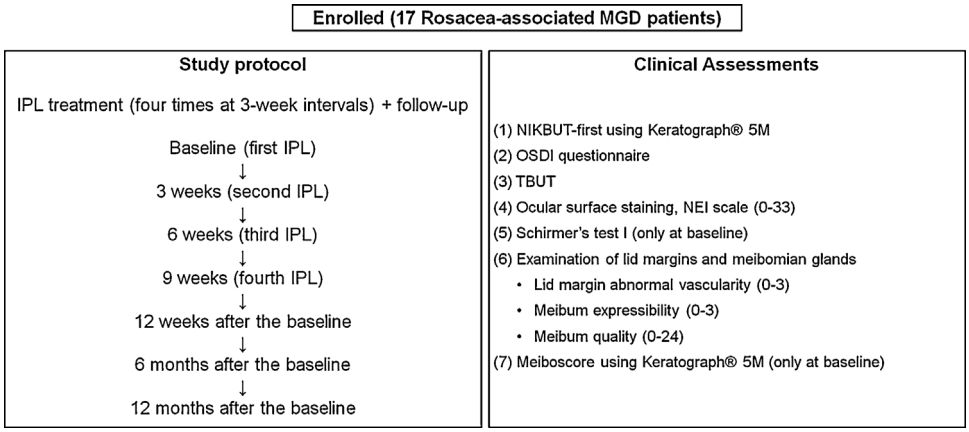

Fig. 1. Study flowchart showing the process and protocols.
MGD, meibomian gland dysfunction; IPL, intense pulsed light; NIKBUT, noninvasive Keratograph® tear break-up time; OSDI, ocular surface disease index.

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

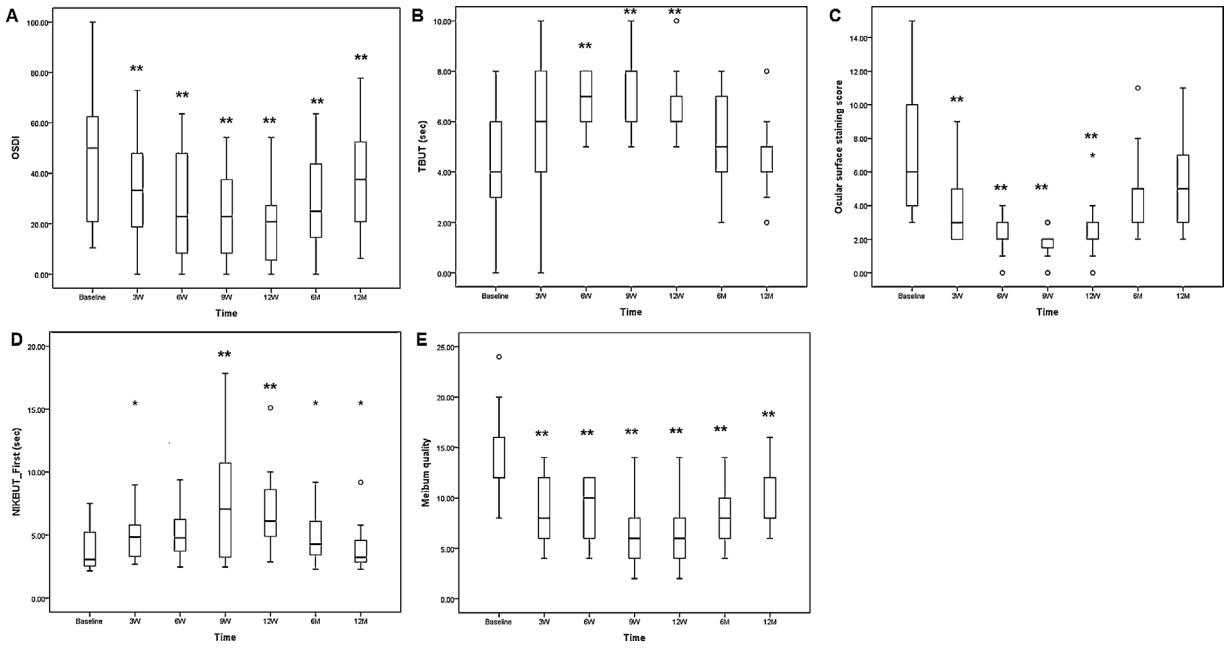

Fig. 2. Box plots showing long-term changes in ocular surface parameters, including the OSDI score (A), TBUT (B), ocular surface staining score (C), NIKBUT-first (D), and meibum quality in the lower lid (E) from baseline to the final examination in patients with rosacea-associated meibomian gland dysfunction (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

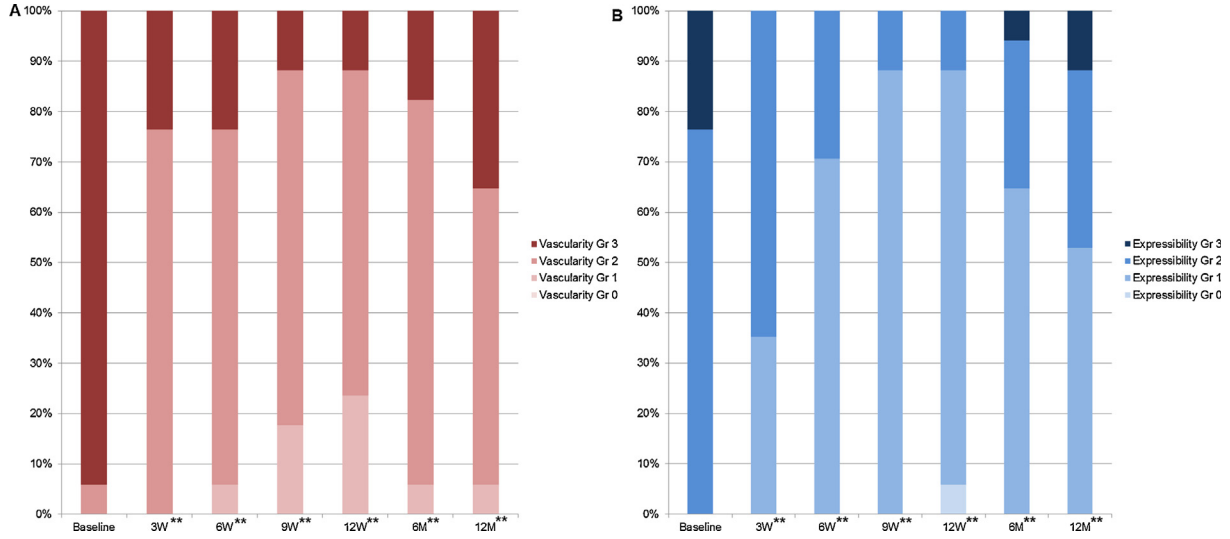

Fig. 3. Long-term changes in the lid margin vascularity and meibomian gland expressibility grade from baseline to the final examination in patients with rosacea-associated meibomian gland dysfunction (MGD) who underwent intense pulsed light (IPL) treatment.
**Significant difference between the baseline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

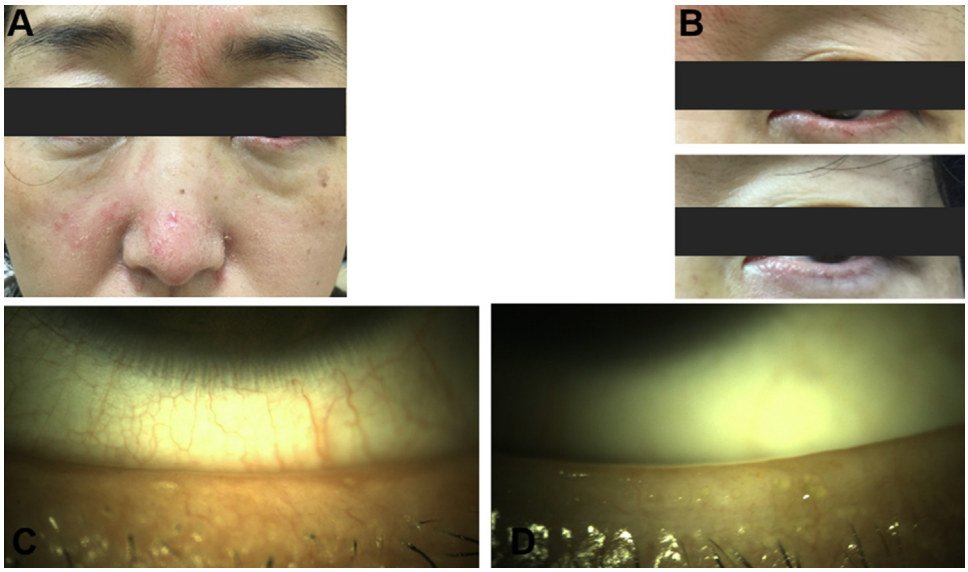

Fig. 4. A representative case of rosacea-associated meibomian gland dysfunction (MGD) exhibiting an improvement in the ocular surface condition from baseline to the final examination after four intense pulsed light (IPL) treatments.
A 51-year-old woman was treated for cutaneous rosacea at the Department 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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