Prospective Trial of Intense Pulsed Light for the Treatment of Meibomian Gland Dysfunction

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Submitted: September 29, 2014
Accepted: February 4, 2015

Citation: Craig JP, Chen Y-H, Turnbull PRK. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2015;56:1965–1970. DOI:10.1167/iovs.14-15764

Purpose. To evaluate the effect of intense pulsed light (IPL) applied to the periocular area for meibomian gland dysfunction (MGD) in a prospective, double-masked, placebo-controlled, paired-eye study.

Methods. Twenty-eight participants underwent IPL treatment, with homogeneously sequenced light pulses delivered to one eye and placebo treatment to the partner control eye at 1, 15, and 45 days following baseline (BL) evaluation. Lipid layer grade (LLG), noninvasive tear break-up time (NIBUT), tear evaporation rate (TER), tear meniscus height (TMH), and subjective symptom score using visual analogue scales (VAS) were compared with BL and control values at each visit.

Results. Lipid layer grade improved significantly from BL to Day (D) 45 in the treated eye ($P < 0.001$), but not the control eye ($P = 0.714$), with 82% of treated eyes improving by at least one LLG. Noninvasive tear break-up time also improved significantly from BL to D45 in the treated ($P < 0.001$) but not in the control eye ($P = 0.056$) and was significantly longer than in the treated eye at D45 (14.1 ± 9.8 seconds versus 8.6 ± 8.2 seconds, $P < 0.001$). The tear evaporation rate was not different in the treated eye compared with the control eye at any visit. Tear meniscus height did not change from BL in either eye ($P > 0.05$). Visual analog scale symptom scores improved from BL in the treated ($P = 0.015$), but not the control eye ($P = 0.245$), with 86% of participants noting reduced symptoms in the treated eye by D45.

Conclusions. Intense pulsed light with multiple sculpted pulses shows therapeutic potential for MGD, improving tear film quality and reducing symptoms of dry eye. (https://www.anzctr.org.au number, ACTRN12614000162617.)

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

Meibomian gland dysfunction (MGD) is a common cause of evaporative dry eye, affecting almost 70% of the population in some parts of the world.[1] It manifests with symptoms of ocular surface burning and irritation, fluctuating visual acuity, and red, often watery, eyes.[2] These symptoms, combined with frequently ineffective treatment options, can severely affect quality of life.[3,4] In MGD, the glands can become narrowed, the acini atrophy and hyperkeratinise,[5] and the meibum increases in viscosity.[6] This reduces meibum outflow, encouraging proliferation of commensal bacteria.[7] These bacteria secrete lipases that can change the composition of lipids in the meibum, increasing the level of esterified cholesterol (and its melting point), which further reduces MG output.[6,8]

Biomicroscopic signs of MGD can be unremarkable in the case of nonobvious obstructive MGD[9] but can include plugged or capped meibomian gland (MG) orifices, along with lid margin thickening, irregularity, telangiectasia, and hyperemia.[10] Comprehensive examination can further reveal MG dropout and solidified toothpaste-like secretions on gland expression in more severe cases.[8,11] Tear break-up time is most often reduced, and the tear film is frequently contaminated by endogenous debris and foam.[11] Ultimately, the meibomian glands fail to secrete a suitable or sufficient oil layer for the tear film, which allows a higher evaporation rate of the underlying aqueous layer, in turn leading to symptoms of dry eye and ocular surface inflammation.[12]

Current management paradigms range from self-administered or practitioner-administered treatments with artificial tears, heat application, and manual gland expression[13,14] (often providing only transient relief) to therapies that aim to restore the natural balance of lipids within the meibum. Such therapies include omega-3 supplementation,[15] topical antibiotics to lessen the local bacterial load, oral tetracyclines to reduce the level of pro-inflammatory cytokines,[16] corticosteroids, or topical cyclosporine.[3] Despite the broad range of therapies available, MGD management is commonly considered unsatisfactory by both clinicians and affected patients, and alternative options for management are continually sought.

Intense pulsed light (IPL) therapy is widely used in the cosmetic industry as well as therapeutically for the removal of hypertrichosis, benign cavernous hemangiomas, benign venous malformations, telangiectasia, port-wine stains, and pigmented lesions.[17] Systematic review demonstrates that IPL is an effective, well-tolerated treatment option for a range of dermatologic conditions, resulting in a reduction in telangiectasia and severity of facial erythema.[18] Concurrent ocular surface health improvements have been observed serendipitously in patients undergoing IPL for the dermatologic manifestations of rosacea, leading to interest in evaluating IPL as a potential therapy for MGD.

Figure 1. IPL treatment was applied to four periocular zones inferior to the eye, while the eyes were protected by opaque goggles. Both eyes received treatment, with a light-blocking filter applied to the tip of the E>Eye in the control eye.

Intense pulsed light devices contain high-intensity light sources, which emit polychromatic light extending from the visible (515 nm) to the infrared spectrum (1200 nm). The light is directed to the skin tissue and is then absorbed by the targeted structure, resulting in the production of heat (>80°C), which destroys the pigmented skin lesions. Appropriate wavelengths can be selected for different targets depending on the absorption behavior and the penetration depth of the light emitted, and specific filters can be chosen to limit the delivery of wavelengths to the treatment area resulting in selective thermal delivery.[17,19]

A third-generation IPL device designed specifically for periocular application with multiple homogenously sculpted light pulses (E>Eye; E-SWIN, Paris, France) has recently become commercially available and is currently the only medically certified IPL device for treating MGD. Delivering multiple homogenously sculpted light pulses with a spectral range of 580 to 1200 nm, according to a proprietary algorithm, the E>Eye has recently become commercially available. This study sought to investigate the potential for IPL applied to the inferior periocular skin, to alter tear film characteristics and symptoms in subjects suffering from MGD. We report the results of what we believe is the first prospective, randomized, double-masked, placebo-controlled clinical trial evaluating IPL as a therapy for MGD.

Methods

Patient Selection

A total of 28 participants (20 female) with mild to moderate clinical signs of MGD,[20] and a mean age of 45 ± 15 years (range, 22–73 years) were enrolled in the prospective study. Prior to enrollment, general health, as well as current and recent medication use, was screened to exclude individuals for whom light therapy was contraindicated. Participants who had received clinical skin treatments within the prior 2 months, or implants beneath the treatment area, were also excluded from the study, as were those with tattoos, semipermanent makeup, or pigmented lesions in the treatment area. Contact lens wearing within 48 hours of commencing the study, or during the study, also resulted in exclusion.

Table. Intense Pulsed Light Treatment Intensity (J/cm²) With E>Eye IPL Device Derived From Fitzpatrick Skin Type Grading

Fitzpatrick Skin Type	Skin Appearance	E>Eye Treatment Level	Fluence, J/cm²
I	Pale white	6	13.0
II	White	5	12.2
III	Light brown	4	11.4
IV	Medium brown	3	10.6
V	Dark brown	2	9.8
VI	Very dark brown/black	Unsuitable for E>Eye IPL	

Experimental Design

The prospective, double-masked, paired-eye, placebo-controlled study was conducted over a period of 45 days, with IPL treatment administered to the skin area immediately below the lower eyelid during three separate treatment sessions on Day (D) 1, D15, and D45 as per manufacturer recommendations. Four pulses were applied as shown in Figure 1 at a pulse intensity that ranged from 9 to 13 J/cm² and was inversely related to the individual skin phototype level as determined by the Fitzpatrick grading scale (Table).[21]

One eye was selected for treatment according to a computer-generated randomization program, with the other eye assigned to serve as a mock-treated control. The researcher collecting the clinical data was masked as to which eye was treated, and participant masking was employed with a white-blocking filter applied over the tip of the IPL probe during application to the nontreated eye only.

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics review committee (UAHPEC 9531). All participants provided written informed consent before participating.

Clinical Assessments

Prior to, and at least 5 minutes following, IPL, a battery of tests was conducted on each eye in the same order, from least to most invasive. Parameters assessed included best spectacle corrected visual acuity (logMAR), bulbar conjunctival injection graded on a visual analog scale (VAS), noninvasive tear break-up time (NIBUT), and fluorescein and lissamine green corneal and conjunctival staining. Further tear film assessment included assignment of the lipid layer grade (LLG) through tear film interferometry[20] (Tearscope Plus; Keeler, Berkshire, UK), tear meniscus height (TMH), tear osmolality (Tearlab Osmolarity System; Tearlab, San Diego, CA, USA), and tear evaporation rate ([TER] VapoMeter; Delfin, Kuopio, Finland). Symptoms were also compared prior to each treatment using the Standard Patient Evaluation of Eye Dryness (SPEED)[22] validated questionnaire, and each subject summarized their perceived severity of dry eye symptoms before and after treatment for each eye, on a VAS anchored at each end with "No symptoms" and "Constant symptoms" as descriptors.

Statistical Testing

Post-IPL scores at D1, D15, and D45 were compared with pre-IPL scores at baseline (BL). Repeated measures analysis enabled comparison of data across the various time points, and paired analyses allowed comparison of pre- and post-IPL data at individual time points. Variables were tested for normality with the Kolmogorov-Smirnoff test. Ordinal variables (e.g., LLG) or those with nonnormal distributions were analyzed with Friedman 2-way analysis of variance (ANOVA), with pairwise

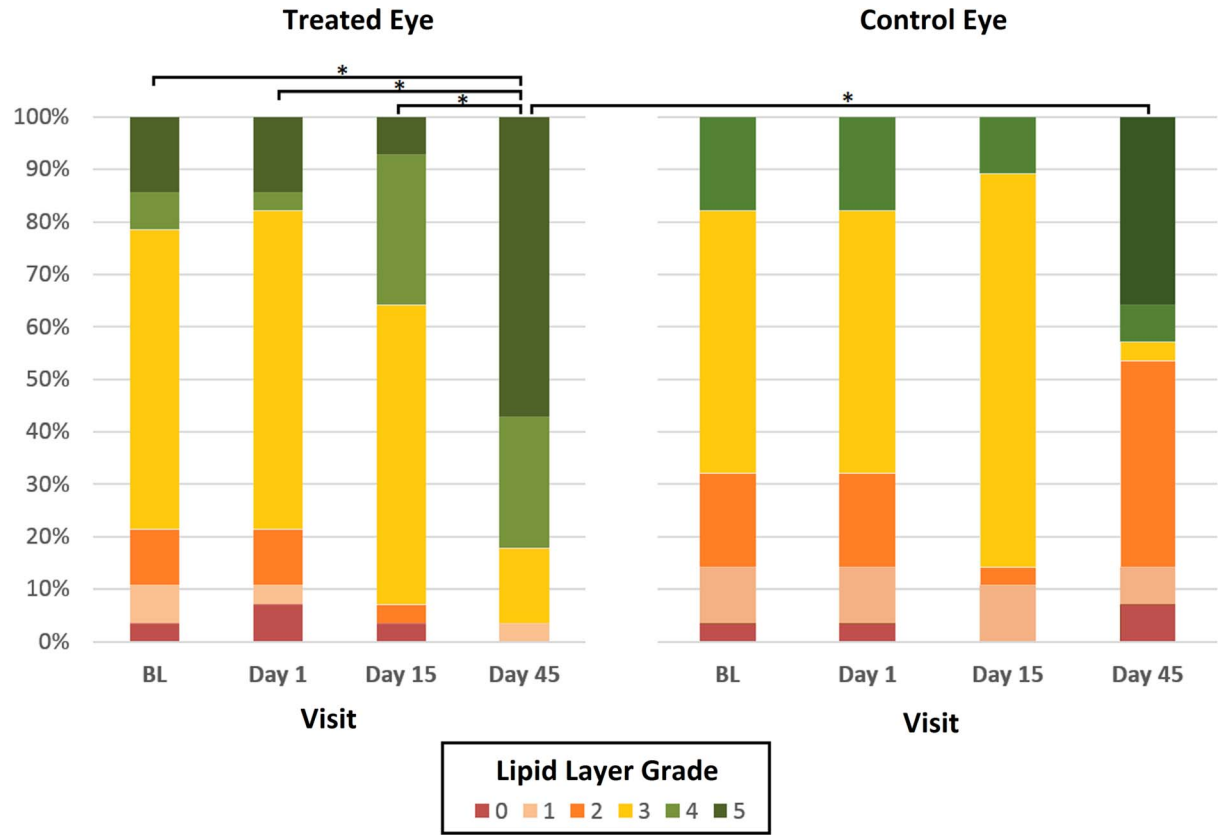

Figure 2. Lipid layer grade (0 = worst) frequencies in the treated (*left*) and control eye (*right*) at BL, D1, D15, and D45. At D45, LLG in the treated eye was higher than at BL ($P < 0.001$), D1 ($P < 0.001$), and D15 ($P = 0.002$). Day 45 LLG was better in the treated eye compared with the control eye ($P = 0.002$). The control eye was not different from BL at any visit ($P = 0.802$). *Significant difference in distribution of LLG at $P < 0.005$.

Wilcoxon (paired) or Mann-Whitney (nonpaired) post hoc testing as required, and are reported as medians with interquartile ranges (IQRs). Normally distributed continuous data are reported as mean ± SD and were assessed with a repeated measures 2-way ANOVA with Tukey honest significant difference (HSD) post hoc testing. Differences between treated and nontreated eye data were compared with the paired samples *t*-test and the Wilcoxon signed rank test for parametric and nonparametric data, respectively. Correlations between parametric and nonparametric data were assessed with Pearson product-moment correlation or Spearman rank order correlation, respectively. Outcomes were considered significant if $P < 0.05$.

Results

The full cohort of 28 enrolled participants completed measurements across all three appointments and were included in the analysis, with all reporting at least some symptoms of MGD and 89% reporting significant symptoms (Ocular Surface Disease Index [OSDI] > 12) (see Supplementary Table S1) prior to treatment. At BL, there was no significant difference between the treated and control eyes in any outcome variable ($P > 0.05$ in all cases).

Clinical Assessment

Lipid layer grade in the treated eye improved from BL (Friedman, $P < 0.001$; Fig. 2), with median improvements between BL and D45 (Wilcoxon, $P < 0.001$), D1 and D45 ($P < 0.001$), and between D15 and D45 ($P = 0.002$). The LLG of the control eye showed no improvement from BL over the three visits (Friedman, $P = 0.802$).

While there was no difference between the treated and control eye lipid grade on D1 (Wilcoxon, $P = 0.932$) or D15 ($P = 0.101$); by D45, lipid grade in the treated eye was better than that of the control eye ($P = 0.002$).

Noninvasive tear break-up time increased from BL to D45 in the treated eye (ANOVA, 5.28 ± 1.42 seconds to 14.11 ± 9.75 seconds; $P < 0.001$; Fig. 3), but not the control eye (5.29 ± 1.42 seconds to 7.31 ± 1.50 seconds; $P = 0.56$). Noninvasive tear break-up time was not different between the treated and control eye at D1 ($P = 0.991$) or D15 ($P = 0.055$) but was higher in the treated eye than the control eye at D45 ($P < 0.001$).

Tear evaporation rate showed high variability between visits, and there were differences in TER between visits in both the treated (Friedman, $P = 0.003$) and control eye ($P = 0.012$); however, there was no overall trend, and the TERs were highly correlated between the eyes at each visit ($P < 0.001$). Further, there was no difference between the control and treated eye at any visit.

Tear osmolarity did not change over the four visits in either the control (ANOVA, $P = 0.741$) or the treated eye ($P = 0.308$). There was also no difference in bulbar conjunctival hyperemia in either the control (Friedman, $P = 0.414$) or the treated eye ($P = 0.348$) nor was there a difference in TMH from BL in either the control (ANOVA, $P = 0.559$) or treated eye ($P = 0.348$).

Questionnaires

Subjective self-reported rating of dry eye symptoms on a single VAS (0–100 mm) showed an improvement over time in

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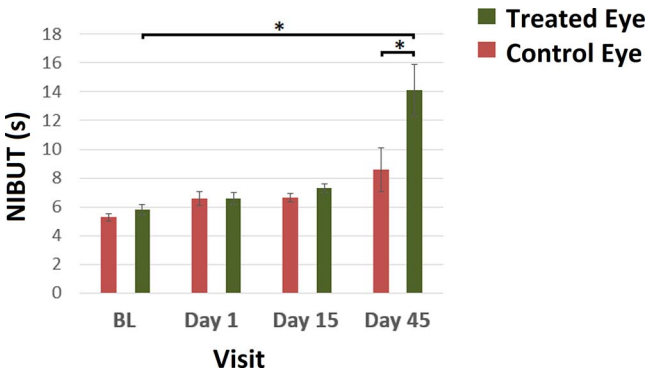

FIGURE 3. Noninvasive tear break-up time of the treated and control eye at each of the four visits. Noninvasive tear break-up time was higher at D45 relative to BL in the treated eye ($P < 0.001$), but not in the control eye ($P = 0.56$). Additionally, NIBUT was significantly higher in the treated eye compared with the control eye at D45 ($P < 0.001$). *Significant difference between groups at $P < 0.005$. *Error bars* denote SEM.

the treated eye (Friedman, $P = 0.015$), but not in the control eye ($P = 0.245$). Post hoc testing showed a decrease in the VAS score in the treated eye at D45 (median, 30.5; IQR, 7.0–60.1) compared with BL (median, 35; IQR, 12.3–64.8; $P = 0.015$).

Median SPEED scores decreased (indicating reduced symptoms) over the time period between D1 and D45 in both the treated eye (Friedman, 14.0–8.5; $P < 0.001$) and control eye (Friedman, 11.0–8.5; $P < 0.001$). The scores between the eyes were highly correlated at each visit (Spearman's r, D1 = 0.922, $P < 0.001$; D15 = 0.874, $P < 0.001$; D45 = 0.871, $P < 0.001$), and there were no significant differences between the treated and control eye SPEED scores at any visit.

DISCUSSION

The management of MGD in clinical practice remains challenging, as patient compliance with physician-recommended self-administered therapies is notoriously poor.[3] Our results suggest therapeutic potential for sculpted pulse IPL therapy with the E>Eye for the management of MGD, on the basis of significant improvements in LLG, tear film stability, and reduced symptoms. The serendipitous discovery of ocular benefits following facial rosacea treatment has led to clinical centers offering IPL as a treatment for MGD on the basis of reports of reduced fluorescein staining and severity of MGD, as well as improvements in visual function and comfort, with some suggesting an apparent cumulative effect.[23–25] However, evidence of the success of this treatment modality to date has been largely anecdotal, arising from retrospective, open-label evaluations, and no randomized controlled, investigator-masked studies are yet available (Vegunta S, et al. *IOVS* 2014;55:ARVO E-Abstract 2018).

This article is the first report of a prospective study of IPL for MGD. The significantly increased lipid quantity on the tear film surface following treatment suggests that outflow of meibum from the glands has been facilitated by the IPL treatment. The benefits, furthermore, appeared to be cumulative, such that after a course of three treatments over 45 days, 82% of treated eyes exhibited significant improvements in their LLG of at least one grade, and 65% exhibited an improvement of at least two lipid grades. Superior LLGs were reflected in the significant increases observed in NIBUT in the treated eyes.[26] Noninvasive tear break-up time is characteristically reduced in MGD,[27] and an increase in mean NIBUT in the treated eye from 5.28 to 14.11 seconds represents a meaningful clinical improvement, as previous research has shown that NIBUT values less than 10 seconds are associated with significantly higher TERs.[27]

The self-reported dry eye symptoms on a VAS improved from BL in the treated eye at D45, but not in the control eye, which suggests at least some of this improvement seen in LLG and NIBUT translates into subjective improvements. However, while SPEED scores were lower at D45 compared with BL in both eyes, this questionnaire did not reveal a difference in symptoms between the eyes. This difference may be a result of the VAS being interpreted more openly, while the SPEED questionnaire specifies exact symptoms over different time periods, which may miss or dilute any changes caused by IPL. Nevertheless, the fact that SPEED symptoms in both eyes improved from BL, with only one eye treated, bodes well for bilateral treatment.

The absence of a significant difference in TER following treatment is perhaps not surprising given the study sample. An increased TER occurs in the presence of a nonvisible or incomplete lipid layer, but where even a thin, continuous lipid layer exists, tear evaporation is inhibited.[27] Thus, unless blinking is actively prohibited during evaporation rate measurement, a finding of increased tear evaporation might not be anticipated owing to the presence of a continuous lipid layer, irrespective of thickness. While blinking was discouraged during evaporation measurement in the current study, it was not prohibited for the sake of patient comfort and potential effect on reflex tearing. The infrequency of noncontinuous lipid layers at BL (only 4% exhibited an LLG of zero) likely contributes to the lack of a significant difference in tear evaporation observed post treatment in the presence of a thickened lipid layer. This finding is further reflected in the tear osmolarity results, which were also observed not to change significantly with treatment. Moreover, while it is possible to demonstrate between-eye differences in LLG and NIBUT parameters, the bilateral nature of the lacrimal gland response would likely diminish any effect in osmolarity observed as a result of changes in a single eye.[28] Nevertheless, the increases observed in LLG and NIBUT support the concept of having created a more robust tear film lipid layer, and the corresponding reduction in SPEED symptoms suggests that the clinical signs possibly translate into a tear film better able to withstand adverse conditions.

Mechanism

The mechanism by which MGD signs and symptoms improved following treatment remains incompletely understood. Proposed mechanisms include heat transfer, which softens the meibum and aids expression.[24] However such a mechanism would be anticipated to induce only short-term effects.[13] A preliminary safety evaluation by the authors using infrared (IR) thermography noted only minimal skin surface temperature changes (<1°) following treatment and removal of the conducting gel. The light-protective goggles worn during treatment provide an additional barrier to direct gland heating as the actual treatment area is located inferior to the lower eyelid and not directly overlying the meibomian glands (Fig. 1).

The observed cumulative effect, which has been noted previously in a retrospective evaluation of IPL (Vegunta S, et al. *IOVS* 2014;55:ARVO E-Abstract 2018), requires an alternative mechanistic explanation. Consistent with the recognized mechanism of action in skin treatment in systemic rosacea,[19] it is possible that thrombosis of the vasculature surrounding the meibomian glands could play a role in diminishing the local release of inflammatory mediators. In addition, the bacterial

load on the lid margin and ocular adnexa could be directly affected by the IPL.[29] There is a further possibility that IPL has the potential to modify the mitochondrial output of reactive oxidative species,[30] which have been implicated in dry eye disease.[31] The wide spectrum light source of E>Eye contains near-IR wavelengths used in low-level laser therapy, a controversial technique,[32] which purportedly acts on mitochondrial cytochrome c.[33]

Limitations

A number of factors suggest that the current study provides a conservative estimate of the potential of IPL to manage MGD. In order for the effects on the tear film to be isolated to the IPL treatment, attempts were made within the study design to limit confounding variables. It may be that more substantial effects would be observed in clinical practice, where a combination of therapeutic approaches, such as pretreatment lid margin debridement or posttreatment gland expression might be employed alongside IPL therapy. An additional limiting factor was the time frame of 45 days, especially as the results appeared to be cumulative. It cannot be deduced from this study whether the results at D45 represent the maximal effect, or whether further benefit would be realized from measurement at a later time point or, indeed, subsequent to further treatments. This time-frame limitation is particularly applicable for the symptomatic evaluation that was carried out before IPL treatment at each visit, meaning that SPEED scores evaluated on D45 actually relate to the symptoms experienced by the participants after having received only 2 treatments (on D1 and D15). A greater effect may have been observed if symptoms had been evaluated beyond D45, as this would account for any perceived improvement in symptoms arising from the third treatment. On the basis of the authors' continued clinical experience with IPL, it is suspected that further treatments are beneficial in many patients, but further controlled trials are required to establish the optimal treatment regime and the potential of IPL therapy.

Placebo control was considered critical in the study design to reduce risk of bias from patient knowledge of which eye had been treated; however, the logistics of conducting a placebo treatment on one eye in each individual presented challenges. Ultimately, mock treatments were performed in an identical fashion to actual treatments but with a white-blocking filter in place. While this had the desired effect with respect to patient masking, a greater relative effect of the therapy might have been observed in the treated eye if the control had been exposed to no treatment at all. The effect of the light escaping from around the blocking filter cannot be accurately quantified, and it is possible that positive differences in lipid layer thickness and stability in the control eye might be partially attributable to an incomplete control. Additionally, the tightly fitting goggles worn during the IPL procedure (Fig. 1) may have contributed to inadvertent MG expression of both eyes during treatment from pressure on the skin overlying the meibomian glands. Despite these factors, which may have served to reduce the apparent effect of treatment, significant differences between the control and treated eyes were seen on D45, suggesting a true and possibly underestimated effect of IPL therapy.

The results presented here show an improvement in both clinical signs and symptoms of MGD following a course of three E>Eye IPL treatments over a 45-day period. Further evaluation of IPL for MGD is required to determine the optimal treatment regime, and to better understand its mechanism of action, which individuals have the greatest potential to benefit, and the duration of the effect of IPL as a therapy for MGD.

Acknowledgments

Supported by a summer studentship grant from the New Zealand Association of Optometrists (YHC) and consumables funding from France Medical.

Disclosure: **J.P. Craig**, France Medical (F); **Y.-H. Chen**, None; **P.R.K. Turnbull**, None

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