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Intense pulsed light treatment and meibomian gland expression for moderate to advanced meibomian gland dysfunction

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Background: The aim was to evaluate the efficacy of periocular intense pulsed light therapy combined with meibomian gland expression for chronic dry eye due to moderate to advanced meibomian gland dysfunction.
Methods: This single-institution, open-label prospective study involved 26 participants who received bilateral treatments using a proprietary intense pulsed light device (E > Eye, E-Swin, Paris, France) combined with therapeutic meibomian gland expression at baseline, Week 2 and Week 6. Clinical evaluations performed at baseline, Week 4, Week 8 and Week 12 were symptom scores (Ocular Surface Disease Index [OSDI], Ocular Comfort Index [OCI], daily lubricant use, tear break-up time and ocular surface staining). Tear secretion, tear osmolarity, InflammaDry tear immunoassay, corneal sensation, meibomian secretion quality and expressibility, bulbar conjunctival, limbal and lid margin redness and eyelid margin bacterial swab for cultures and colony counts were performed at baseline and Week 8 only.
Results: Significant improvements occurred at Week 8 in meibomian gland expressibility ($p = 0.002$), meibum quality ($p = 0.006$), tear break-up time ($p = 0.002$), corneal staining ($p = 0.001$), lid margin redness ($p = 0.001$), bulbar redness ($p = 0.05$) and limbal redness ($p = 0.001$). Symptom survey outcomes, eyelid margin bacteria colony counts, Schirmer I test, tear osmolarity, corneal sensitivity and daily lubricant use were unchanged. At Week 12, significant improvements in symptoms (OSDI $p = 0.025$; OCI $p = 0.003$), tear break-up time ($p = 0.001$) and corneal staining ($p = 0.001$) occurred. Improvement in OSDI score was correlated to the improvement in ocular surface staining ($R = 0.43$, $p = 0.03$) and associated with baseline meibomian gland expressibility (Kendall tau: the distributions are ordered the same, $p = 0.1$). There were no adverse effects of treatment.
Conclusions: Serial intense pulsed light therapy combined with meibomian gland expression significantly improved dry eye symptoms and clinical signs, including meibomian gland secretion quality and expressibility and ocular surface inflammation. Treatment effects were cumulative and sustained for at least six weeks after the final treatment.

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Key words: dry eye, intense pulsed light therapy, lid margin flora, meibomian gland dysfunction, meibomian gland expression, ocular surface, tear film

Meibomian gland dysfunction (MGD) is characterised by chronic, diffuse abnormalities of the meibomian glands and altered secretion and chemical composition of meibum.[1] MGD leads to increased tear evaporation, increased tear osmolarity and an increased susceptibility to ocular surface inflammation, epithelial damage and discomfort.[2] MGD is the leading cause of dry eye disease and affects between four and 20 per cent of Caucasians and more than 60 per cent of Asians.[3]

Conventional evidenced-based therapy for MGD (warm compresses, eyelid massage and artificial tears, including lipid-containing lubricants) are limited in their efficacy in moderate to advanced disease.[4–6] Prescription medications (topical steroids, topical and oral antibiotics, topical immunomodulatory agents and oral omega 3 essential fatty acids have demonstrated efficacy in reducing symptoms and signs of MGD;[4–6] however side effects and adverse effects,[2,4–6] development of antibiotic resistance,[7] cost, accessibility, off-label use, low level of available evidence and need for ongoing treatment are issues that can limit their long-term use.[2,4–6,8]

Recently, several clinic-based treatments for MGD have been developed, which potentially offer sustained improvement in symptoms. These therapies are particularly attractive to patients and practitioners given adherence to prolonged, time-consuming home-based therapies is traditionally poor.[4,5] Debridement-scaling of the lid margin is a simple procedure that improves dry eye symptoms and meibomian gland function.[9] Intraductal meibomian gland probing, which aims to mechanically open and dilate the natural orifices and ducts of the meibomian glands,[10] is an invasive surgical procedure with long-term efficacy yet to be established.[4,5] Vectored thermal pulsation

(LipiFlow, TearScience, Morrisville, North Carolina, USA), a novel treatment, in which heat and pressure are applied to the eyelid, has demonstrated safety and effectiveness in treating MGD.[4] A single LipiFlow treatment is at least as effective as a three-month, twice-daily lid margin hygiene regimen for treating MGD.[11] Currently, cost issues associated with the LipiFlow device and consumables[12] and lack of efficacy in advanced MGD[13] limit access to treatment.

Intense pulsed light therapy has been applied in the periocular area in dermatology for over a decade in the treatment of excessive periorbital pigmentation[14] and erythematotelangiectatic rosacea.[15] The device and the nature of the light it emits have been reviewed.[16] Following reports that serial periocular intense pulsed light treatments improve signs and symptoms of dry eyes in individuals with acne rosacea and ocular surface disease,[17,18] the clinical application of intense pulsed light devices have been extended to include the treatment of MGD.[13,19–21]

The emerging clinical data regarding the safety and efficacy of intense pulsed light treatment for MGD suggests that a series of two or more intense pulsed light treatments can improve symptoms, tear film characteristics, including tear film break-up time and clinical signs of MGD;[13,17–21] however clinical guidelines regarding candidate selection, the number and frequency of treatments and the efficacy of post-intense pulsed light meibomian gland expression (MGX)[13] are yet to be established. At the time of writing, of the five published studies assessing the efficacy of intense pulsed light as a treatment for MGD, three were retrospective reviews of treatment series involving individuals with moderate to advanced MGD treated with the Quadra Q4 (DermaMed Solutions, LLC, Lenni, Pennsylvania, USA) intense pulsed light system using a proprietary 'dry eye mode' setting. Intense pulsed light was applied both inferior and lateral to both lower eyelids followed by MGX using a fingertip or cotton tip applicator.[13,19,21] A fourth published study was a prospective, double-masked, placebo-controlled, paired-eye study involving the application of the E > Eye (E-Swin, Paris, France), an intense pulsed light device regulatory approved in Australia and New Zealand for treating MGD.[20] Intense pulsed light was applied inferior to the lower eyelid without subsequent MGX in participants with mild to moderate MGD.[20] Using similar methods, the E > Eye device was also used to unilaterally treat Chinese participants with MGD of unspecified severity in an open-label, uncontrolled prospective study.[17]

This study aimed to prospectively evaluate the effect of a series of three bilateral E > Eye intense pulsed light treatments to the inferior and temporal periocular area combined with MGX (intense pulsed light plus MGX), in participants with dry eye due to moderate to advanced MGD and refractory to conventional home-based and clinic-based treatments. Dry eye symptoms and objective tear film and ocular surface parameters were evaluated in a predominantly Caucasian cohort. Our study also aimed to investigate some of the proposed underlying mechanisms responsible for clinical improvements observed with intense pulsed light and MGX.

METHODS

This single-centre, uncontrolled, open-label prospective study was conducted at the Queensland University of Technology Optometry Clinic. The study was performed in accordance with the Declaration of Helsinki of 1975 (revised in Tokyo in 2004) and the requirements of the Queensland University of Technology Human Research Ethics Committee. All participants provided written informed consent.

Participants

Twenty-six symptomatic adult participants (aged 21 to 82 years, 19 female, 21 Caucasian) with a clinical diagnosis of dry eye primarily due to moderate to advanced MGD[1,2,22] that was not controlled with conventional warm compress and eyelid massage and lubricant eye drop therapy[4–6] were recruited (Table 1). Additionally the participants had previously trialled without significant symptomatic or clinical improvement or refused (because of side effects, cost, availability) additional treatments including omega-3 fatty acids (all 26 participants had used this treatment), clinic-based latent moist heat therapy and therapeutic MGX with a stainless steel paddle (all participants), antibacterial honey eye drops (24 participants), topical steroid (20 participants), oral doxycycline (five participants), topical ciclosporin (five participants), topical azithromycin (five participants), LipiFlow (three participants) and intraductal meibomian gland probing (one participant).

Exclusion criteria were: any active infection of the eye or adnexae; a history of herpetic eye disease; active ocular or adnexal allergy, eyelid positional, eyelid closure and/or blinking anomalies: dry eye associated with neurotrophic or cicatricial ocular surface disease; abnormalities of nasolacrimal drainage; ocular surgery; contact lens wear; LipiFlow treatment; meibomian gland probing; oral doxycycline; punctal plug insertion within the previous 12 months; current or recent (within three months) use of any topical eye drops other than preservative free lubricants; planning a pregnancy, pregnant or lactating. Initiation of or alteration to the dose of a systemic medication known to affect tear production within 30 days of the baseline assessment or during the study was also cause for exclusion. Following the manufacturer's treatment protocol, specific additional intense pulsed light exclusions included: the intake of oral steroids; oral retinoids or photosensitising medications; diseases or genetic conditions causing photosensitivity or tending to worsen after light exposure; poorly controlled diabetes; haemophilia, coagulopathies and use of anticoagulants; heart pacemakers; recent cosmetic procedures, implants, skin tattoos or permanent makeup in the treatment area; active suntans and very dark or black African skin (Fitzpatrick Skin Type VI).[15,20,23]

Dry eye associated with MGD was diagnosed based on the following four criteria as recommended by the Diagnosis Subcommittee of the International Workshop on Meibomian Gland Dysfunction:[1] presence of one or more Ocular Comfort Index (OCI) symptoms of ocular surface irritation ('dry', 'gritty', 'stingy', 'tired', 'painful', 'itching')[24] and tear film instability as measured by fluorescein break-up time less than 10 seconds[1] and interpalpebral Oxford ocular surface fluorescein staining (score of one or greater) in either eye[25] and slitlamp biomicroscopic evidence of MGD, namely, diffuse abnormalities of the meibomian glands including terminal duct obstruction, lid margin hyperaemia, thickening, irregularity and telangectasia and/or qualitative and/or quantitative changes in meibomian gland secretion.[1,2]

Following recruitment, all participants commenced a wash-out period of one

Variable	Participants (n = 26)
Age (years)	54.7 ± 15.6
Gender (number male/female)	7/19
Meibomian gland dysfunction severity stage (number 1/2/3/4)	0/0/21/5
Caucasian/Asian	20/6
Fitzpatrick skin type (number 1/2/3/4)	3/17/1/5

Table 1. Participant characteristics at baseline

month. Participants were instructed to continue their current conventional MGD therapy involving twice daily warm compresses (using a warm wet face cloth or heat bag applied to the eyes for five minutes twice daily) followed by lid massage to both eyes. Preservative free lubricant (Systane Ultra, with polyethylene glycol 400 0.4 per cent propylene glycol 0.3 per cent, Alcon, Fort Worth, Texas, USA) was permitted as required in both eyes during washout and throughout the intense pulsed light plus MGX treatment course.

Five additional participants were recruited but did not complete all treatments and follow-up measures due to unrelated issues that prevented their attendance at all treatment and assessment visits (a total of six visits were required). The 16 per cent drop out rate (five of 31) is comparable with that reported for other longitudinal MGD treatment studies.[26,27]

Intense pulsed light and MGX treatment

The E > Eye delivers multiple homogenously sculpted light pulses with a spectral range of 580 to 1,200 nm, according to a proprietary treatment algorithm. Following the manufacturer's treatment protocol for the E > Eye device, four adjacent intense pulsed light flashes were administered to the skin area immediately below the lower eyelid and one intense pulsed light flash on the temple of both eyes. Treatments were performed at baseline (after baseline assessments), Week 2 and Week 6 using a pulse intensity that ranged from 9.8 to 13 J/cm^2. Treatment intensity was set according to the manufacturer's guidelines[20] (based on an individual participant's skin type determined by the Fitzpatrick grading scale[23]) with very lightly pigmented Phototype 1 participants being treated at 13 J/cm^2 and individuals with dark brown complexions being treated at 9.8 J/cm^2.

Treatments were performed on clean skin with participants wearing opaque safety goggles and the intense pulsed light operator wearing protective eye shields. Any moles or pigment spots in the treatment zone were covered with a patch. A 5.0 mm thick layer of conductive gel was applied to the treatment area.

Immediately following intense pulsed light treatment the meibomain glands of both upper and lower eyelid margins were expressed. Manual therapeutic expression was performed at the slitlamp using a stainless steel expression paddle (Mastrota paddle, OCuSOFT, Inc., Rosenberg, Texas, USA) after the instillation of topical anaesthetic (one drop, oxybuprocaine 0.4 per cent minims, Bausch + Lomb, Bridgewater, New Jersey, USA). The Mastrota paddle was placed on the palpebral conjunctiva in the area of the meibomian gland and the investigator placed the index finger on the lid margin skin overlying the meibomain gland being treated. Commencing on the bottom eyelid and moving nasal to temporal along the lid margin, with the participant in upgaze, a firm and consistent digital pressure was applied to the external lid margin, directed at each meibomian gland, moving distal to proximal, over 30 seconds. Expression was repeated for the superior eyelid with the participant in downgaze and again, using the expressor.[19] Therapeutic MGX was an uncomfortable procedure, even when performed with topical anaesthesia.[45] As some degree of temporary lid margin and conjunctival injection was induced following MGX in all participants and as per previous studies involving therapeutic expression,[13,19,21] preservative-free topical anti-inflammatory (two drops, prednisolone sodium phosphate 0.5 per cent, minim form, Bausch + Lomb) was instilled immediately following expression. All treatments were performed on both eyes by one operator. Post-treatment advice prior to discharge was given, namely, continue warm compresses with eyelid massage daily and preservative-free lubricants as required and temporarily avoid heat, direct sunlight exposure and potential chemical or mechanical irritation of the treatment area in the first 24 hours after treatment. Participants were required to keep a daily log of their topical lubricant use.

Ocular surface assessments

The following subjective parameters were assessed: dry eye symptoms on a score of zero to 100 using the OSDI[28] and OCI[24] validated dry eye symptoms surveys. The scores of these questionnaires exhibit a positive correlation with each other with a high validity, reliability, specificity and sensitivity.[29] Daily lubricant use was assessed via participant log books.

Objective parameters were assessed by a single investigator to reduce inter-observer variability and were performed in the order of least to most invasive in an attempt to avoid more invasive tests influencing the outcome of subsequent tests.[30] The test sequence was:

1. Tear osmolarity, a global marker of dry eye, was measured using the TearLab Osmolarity System (TearLab Corporation, San Diego, California, USA) (normal values by this method are below 302.2 ± 8.3 mOsm/l).[31]
2. InflammaDry (Rapid Pathogen Screening, Inc., Sarasota, Florida, USA), a point-of-care immunoassay to detect abnormally elevated matrix metalloproteinase 9 (MMP-9) levels (40 ng/mL or greater). MMP-9 is an inflammatory biomarker that has been shown to be elevated in the tears of patients with dry eyes.[32]
3. Schirmer I test of aqueous tear secretion (without anaesthetic, over five minutes) (values of less than 7.0 mm are considered diagnostic of aqueous tear deficiency).[31]
4. Central corneal sensation was measured with a 0.12 mm nylon monofilament (Cochet-Bonnet aesthesiometer, Luneau Ophthalmlogie, Chartres, France) (normal reference value 5.5 ± 0.8 cm[13]).
5. Conjunctival bulbar and limbal redness (vascular injection) were graded zero

(normal), one (trace), two (mild), three (moderate), four (severe) according to the Efron Grading Scales.[34]

6. Eyelid margin redness (vascularity) was graded zero (normal), one (mild engorgement), two (moderate engorgement), three (severe engorgement), with a score of two or more considered diagnostic of MGD.[35]
7. Ocular surface sodium fluorescein staining enhanced by a yellow written filter was graded using the Oxford Score (zero to 15 for the total exposed inter-palpebral conjunctiva and cornea).[25] One drop of preservative-free fluorescein one per cent was instilled.
8. The fluorescein tear break-up time was assessed immediately after assessment of the staining (average of three readings taken).[1]
9. Meibum quality was assessed in each of eight glands of the central third of the lower lid on a scale of zero to three for each gland: zero (clear), one (cloudy), two (cloudy with debris [granular]) and three (thick, like toothpaste [total score range, zero to 24]).[1] Meibomian gland expressibility was assessed on a scale of zero to three in five glands on the central lower lid, according to the number of glands expressible: zero (all glands), one (three to four glands), two (one to two glands) and three (no glands).[1]
10. A swab of the lower eyelid margin in the more symptomatic eye or if symptoms were equal, the eye with the greatest Oxford staining score was taken for bacterial cultures and colony counts of the most dominant organism/s using previously described methods.[26] An overgrowth of lid margin bacterial isolates occurs in MGD and some clinical therapeutic interventions for MGD reduce lid margin flora.[26,36]

Due to this being an unfunded clinical study, to limit the expenses associated with some consumables (osmolarity cards, InflammaDry) and microbiological assessments (cultures and colony counts) and with the exception of the eyelid margin swab, all assessments were performed on both eyes of each participant at baseline (Week zero) an hour prior to the initial intense pulsed light treatment session and at Week 8 (two weeks after the last intense pulsed light treatment).

Additional assessments of symptoms, lubricant use, tear film stability (film break-up time [FBUT]) and ocular surface corneal staining occurred at Week 4 (two weeks after the second intense pulsed light plus MGX treatment) and 12 weeks (six weeks after the final pulsed light session). These procedures were chosen for more frequent assessment because they are standard clinical measures of dry eye and are integral components of dry eye and MGD clinical trial assessment protocols[2,8] and remain the main criteria used by clinicians and clinical trial experts to assess dry eye disease severity and progression.[37]

Week 8 and Week 12 represent two and six weeks, respectively, after the intense pulsed light plus MGX treatment protocol was completed. These assessment times were chosen to determine the short-term and medium-term effects of serial intense pulsed light plus MGX.

Safety outcomes were assessed via ophthalmic examinations and the recording of any adverse events that occurred throughout the study.

Measurement	Baseline	After IPL Week 8	p
OSDI overall score (0 to 100)	26.3 ± 14.4	22.1 ± 17.8	0.25
OCI value (0 to 100)	37.8 ± 10.8	31.6 ± 12.9	0.09
Meibomian gland expressibility	1.7 ± 1.0	1.1 ± 0.9	*0.002**
Meibum secretion quality	18.5 ± 4.2	14.7 ± 8.7	0.006*
Schirmer I test (mm/5 min)	17.3 ± 11.0	14.9 ± 6.0	0.19
Tear osmolarity (mOsmol/L)	285 ± 9	286 ± 12	0.65
TBUT (seconds)	1.2 ± 1.2	3.1 ± 2.7	0.002*
Corneal sensitivity (mm)	5.4 ± 1.8	5.3 ± 1.7	0.75
Ocular surface staining	4.0 ± 3.1	1.4 ± 1.7	*0.001**
Lid marginal redness	1.0 ± 0.6	0.6 ± 0.5	*0.001**
Bulbar redness	1.8 ± 0.8	1.4 ± 0.7	*0.05**
Limbal redness	1.6 ± 0.7	0.9 ± 0.7	*0.001**
Lid marginal colony count	354 ± 806	190 ± 446	0.28
MMP-9 (≥40 ng/ml)	5	2	*0.08*
Daily lubricant use	3.4 ± 2.2	2.4 ± 1.6	*0.06*

Data are mean ± SD.
*Week 8 data significantly different to baseline at p ≤ 0.05. Italicised p-values represent non-parametric test outcomes.
MMP-9: tear matrix metalloproteinase 9, OCI: Ocular Comfort Index, OSDI: Ocular Surface Disease Index, TBUT: tear break-up time.

Table 2. Comparison of ocular assessment before (baseline) and after a three-treatment series of intense pulsed light (IPL) and meibomian gland expression

Data analysis

The data from each participant's more symptomatic eye at baseline (or if symptoms were equal, the eye with the greatest baseline Oxford staining score) were selected for data analysis. All values are presented as mean and standard deviation, unless indicated otherwise. Statistical Package for the Social Sciences (IBM SPSS, version 18.0, IBM, Armonk, New York, USA) was used for statistical analysis. Repeated measures analysis of variance (ANOVA) (for data collected at four times) and paired t-tests (for data collected at two times) were used for assessment of continuous normally distributed data across time. Non-parametric Friedman χ^2 related sample (Oxford staining score, four times) and the Wilcoxon matched pairs tests (two times) were used for scaled data. The difference between the latest measure (Week 8 or 12) and baseline data was used to quantify the treatment effect.

Associations between different data and baseline measures were analysed using the tailed Pearson correlation analyses for parametric data and the Kendall tau test of association for non-parametric data. A p-value up to 0.05 was considered significant,

Organism	Baseline	After IPL Week 8
Coagulase-negative *Staphylococcus*	15	11
Staphylococcus aureus	1	1
Corynebacterium species	1	1
Moraxella species	1	0
Enterococcus species	1	0
None	7	13

None: no organism species were isolated from the lid margin.

Table 3. Comparison of bacterial species isolated from the lid margin before and after a three-treatment series of intense pulsed light (IPL) and meibomian gland expression

except for Kendall tau, where the variables are related, that is, they have the same order, if $p > 0.05$.

RESULTS

Baseline characteristics

Our participant cohort was classified as having moderate dry eye symptoms at baseline according to the mean baseline OSDI score[29] and moderate to advanced MGD based on the mean baseline Oxford staining score[2] and meibum secretion and expressibility scores[2] (Table 2).

Data to Week 8

Intense pulsed light and MGX produced significant improvement in meibomian gland expressibility (difference in mean [without sign] baseline versus Week 8, 0.54 ± 0.71), meibum quality (3.7 ± 6.4), FBUT (2.0 ± 2.9 seconds), corneal staining (2.6 ± 2.9), lid margin redness (0.4 ± 0.05), bulbar redness (0.5 ± 1.1) and limbal redness (0.7 ± 0.8) at Week 8 (Table 2, rows with starred p-values). Symptom survey outcomes (OSDI and OCI), eyelid margin bacterial colony counts, Schirmer I tear test, tear osmolarity, corneal sensitivity and daily lubricant use were unchanged (Table 2).

The range of organisms cultured from the lid margins of participants is shown in Table 3. The most common cultured organism was the ubiquitous coagulase negative *Staphylococcus*. Fifteen of the 26 participants had cultures that were positive for coagulase negative *Staphylococcus*; however even when only these participants' data were considered, the bacterial colony counts did not significantly change following intense pulsed light and MGX treatment (colony count: baseline, 574 ± 1014; Week 8, 261 ± 538, p = 0.22).

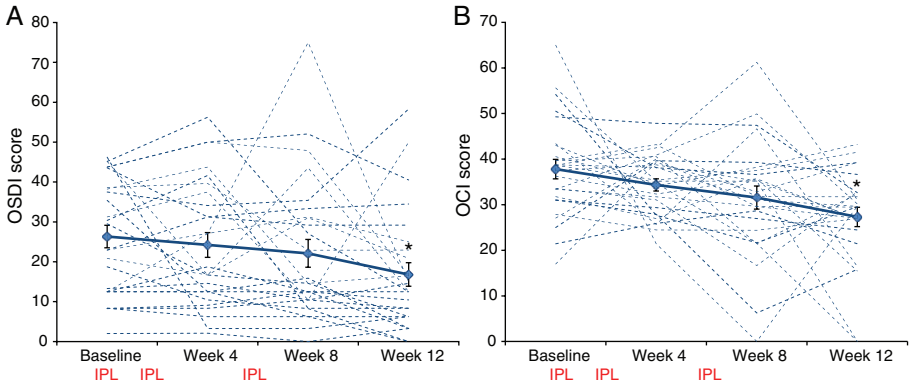

Figure 1. Ocular Surface Disease Index (OSDI) (A) and Ocular Comfort Index (OCI) (B) symptom scores (range: zero to 100) at baseline and Week 4, Week 8 and Week 12 assessments. Intense pulsed light (IPL) therapy was performed immediately following the baseline assessment and at Week 2 and Week 6. Dotted lines represent individual participant data. Solid line represents group data. Data are mean and standard errors of the mean, * indicates significantly different from baseline $p < 0.05$.

Data to Week 12

Ocular Surface Disease Index and OCI surveys and measures of FBUT and ocular surface staining were continued to Week 12. For these four measures 15 of 26 participants had improvements on all four measures, seven of 26 had improvements on three of the four measures and four participants showed no improvement on two or more measures.

Intense pulsed light and MGX produced a significant improvement in symptoms based on both OSDI (reduction 9.5 ± 16.2) and OCI (reduction 10.5 ± 16.2) scores when all the data to Week 12 were included (Figures 1A and 1B; repeated measures ANOVA, OSDI $F_{3,103} = 3.31$, $p = 0.025$; OCI $F_{3,103} = 5.05$, $p = 0.003$) but not when the outcome was assessed only to Week 8 - (Table 2). The data show that symptoms continued to improve from Weeks 8 to 12 even though the last treatment was at Week 6.

The tear film break-up time increased over the measurement period from an average 1.2 ± 1.2 to 3.7 ± 4.1 seconds (Figure 2A, repeated measures ANOVA, $F_{3,103} = 5.85$, $p = 0.001$). The ocular surface staining score reduced over the 12 weeks from 4.0 ± 3.1 to 1.8 ± 2.5 (Figure 2B, Friedman non-parametric $\chi^2 = 17.21$, $p = 0.001$). The improvements in both FBUT and corneal staining were significant by Week 8 (Table 2).

Correlations

The improvement in the OSDI score was correlated to the improvement in the ocular surface staining (Figure 3A, correlation line, R = 0.43, p = 0.03). The reduction in corneal staining was correlated to the baseline lubricant dose (R = 0.50, p = 0.01), baseline corneal staining (R = 0.68, p = 0.0005), baseline bacterial colony count (R = 0.41, p = 0.04) and associated to baseline bulbar redness (Kendall tau: the distributions are ordered the same, p = 0.3).

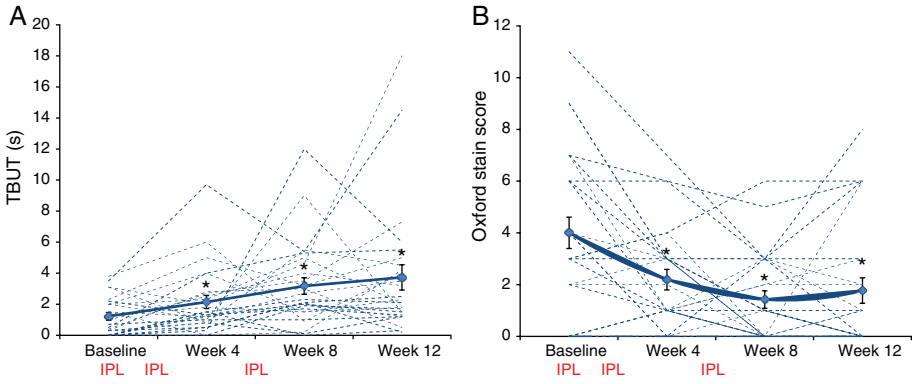

Figure 2. Oxford ocular surface fluorescein staining scores (A) and fluorescein tear break-up time (TBUT) (B) at the baseline and Week 4, Week 8 and Week 12 assessments. Intense pulsed light (IPL) therapy was performed immediately following the baseline assessment and at Week 2 and Week 6. Dotted lines represent individual participant data. Solid line represents group data. Data are mean and standard errors of the mean, * indicates significantly different from baseline $p < 0.05$.

The improvement in the OSDI score was related to the baseline meibomian gland expressibility (Figure 3B, Kendall tau: $p = 0.1$); the poorer the initial meibomian gland expressibility, the greater the improvement on the ODSI. The improvement in the meibum quality was related to baseline lubricant dose (Kendall tau: the distributions are ordered the same, $p = 0.8$); the greater the initial lubricant dose, the greater the improvement in meibum quality. The improvement in limbal redness and lid margin redness were both associated with baseline FBUT (Kendall tau, $p = 1.0$; $p = 0.2$, respectively); the shorter the initial FBUT, the greater the decrease in redness.

Frequency histograms

Frequency histogram plots show that more participants had lower (zero, one improved) and fewer had higher (two, three or worse) meibomian gland expressibility grades (Figure 4A) at Week 8 than at baseline. More participants had lower (one to five, six to 10 improved) and fewer had higher (16 to 20, 21 to 25, poorer) meibum quality (Figure 4B) at Week 8 than at baseline. Both lid marginal redness (Figure 5A) and limbal redness (Figure 5B) frequency plots showed shifts to lower scores (reduced redness) after intense pulsed light.

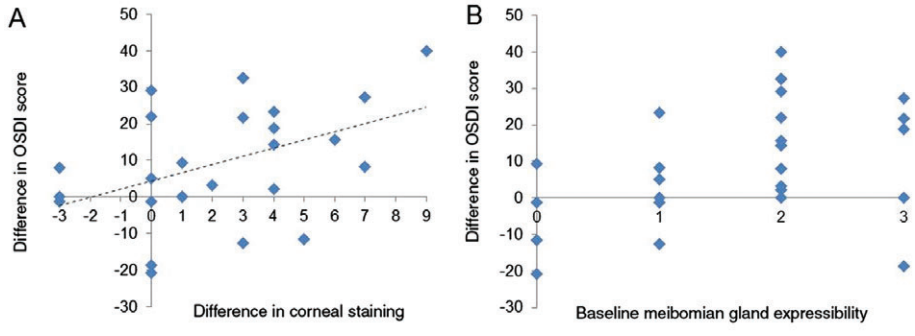

Figure 3. Correlation plot between difference in Ocular Surface Disease Index (OSDI) symptom score and difference in ocular surface staining score at Week 12 (A) and correlation between difference in OSDI score and difference in meibomian gland expressibility at Week 8 (B)

Safety

No adverse effects of treatment were reported other than temporary tolerable discomfort in some individuals associated with therapeutic MGX.

DISCUSSION

Cumulative treatment effect

This is the first prospective study to report the clinical improvements in symptoms and signs of recalcitrant moderate to advanced MGD following a series of intense pulsed light treatments combined with MGX. While clinical signs (tear film instability, ocular surface staining, ocular surface inflammation, meibomian gland expressibility and secretion quality) improved after three treatments at the Week 8 assessment (two weeks after the third and final treatment), a statistically and clinically significant improvement in the symptom scores was not achieved until the Week 12 assessment (six weeks after the final treatment) (Figure 1). The significant effects on dry eye signs at Week 8 (staining score, FBUT) were maintained at Week 12 despite no additional treatments being performed. Figures 1 and 2 illustrate the gradual improvement across the 12 weeks of monitoring. Therefore, our prospective results support previous observations in retrospective chart reviews[13,19,21] of the cumulative and sustained (at least in the short term) effect of intense pulsed light and MGX to treat moderate to advanced MGD.

Symptomatic improvements

Eighty-five per cent (22 of 26) of participants showed an improvement on both subjective and objective measures of ocular surface health following serial intense pulsed light and MGX treatments. The treatment effects were also large enough to be clinically significant. For example, the minimal clinically important difference for the OSDI symptom score after treatment intervention has been determined by Miller and colleagues[29] to be 7.0 to 9.9. In our study a mean OSDI reduction of 9.5 ± 16 from baseline (Figure 1) was achieved at Week 12. Additionally, while not statistically significant, we found a reduction in the need to use artificial tears at Week 8 (Table 2). Vora and Gupta[21] also reported a significant reduction in

OSDI ($p < 0.001$) and a trend toward reduced need for artificial tears in their retrospective review. Vegunta, Patel and Shen[13] obtained a result similar to our study with 89 per cent of cases of severe recalcitrant MGD having improved symptoms on the SPEED2 survey ($p < 0.0001$) at six months after commencing monthly intense pulsed light plus MGX (average of four treatments). Finis and colleagues[38] recently found that SPEED survey results correlated more with clinical parameters of evaporative dry eye and the OSDI results correlated more with parameters of aqueous tear-deficient dry eye. Hence, based on these findings, we would recommend that to compare treatment outcomes across intense pulsed light studies, the SPEED symptom tool is used in future studies.

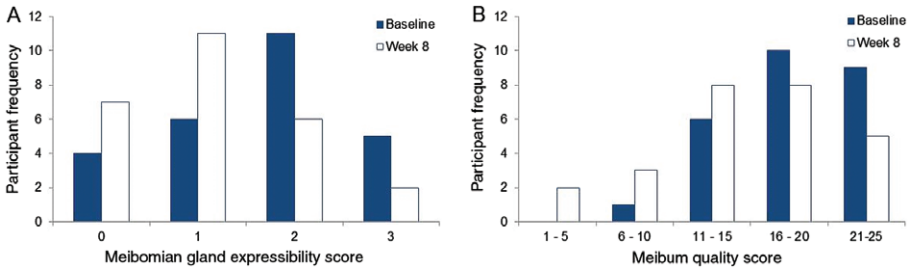

Figure 4. The effect of intense pulsed light (IPL) therapy on meibomian gland expressibility (A) and meibomian gland secretion quality (B). Participant scores before and after (Week 8) IPL treatment.

Effect of intense pulsed light on tear film stability

Tear film stability (FBUT) increased over the measurement period by an average 2.5 seconds (Figure 2A) exceeding that following a three month MGD treatment course of 0.05 per cent Cyclosporine Ophthalmic Emulsion.[27] It also exceeded the reported two second increase in non-invasive tear break-up time at three months post-vectored thermal pulsation (LipiFlow).[11] Other intense pulsed light treatment studies (both prospective and retrospective) report significant improvements in measures of tear film stability with serial intense pulsed light treatment. Craig, Chen and Turnbull[20] reported significant improvement in non-invasive tear break-up time in the treated eye at Day 45, one day after the third treatment (5.28 ± 1.42 seconds to 14.11 ± 9.75 seconds, $p < 0.001$), although MGX did not accompany intense pulsed light in this study. Jiang and colleagues[17] reported a similar magnitude of increase in FBUT compared to our results following four serial intense pulsed light treatments (without MGX). At Day 15 (4.2 ± 1.8 seconds), Day 45 (5.0 ± 1.9 seconds) and Day 75 (4.5 ± 2.5 seconds) FBUT was significantly increased compared to that at the baseline (2.2 ± 1.5 seconds) ($p < 0.01$) in their study.[17]

Vora and Gupta[21] reported significant improvements in tear break-up time (methods not described, outcome data not published, $p < 0.001$) following a series of three or four monthly intense pulsed light and MGX treatments. In a 30-month retrospective review of 91 patient records, Toyos, McGill and Briscoe[19] reported a significant increase in tear break-up time of 4.9 seconds in each eye following a series (median of seven) of monthly intense pulsed light and MGX treatments.

The significant improvement in tear film stability in our study is likely to be due to the observed improvements in meibomian gland expressibility and meibum quality (Figure 4). Other intense pulsed light treatment studies have reported significantly improved measures of meibomian gland function, such as lipid layer quality,[20] meibum quality score,[17,21] meibomian gland expressibility[13,17] and oil flow score.[21]

Correlation of symptomatic improvements with decreased clinical signs

Our intense pulsed light and MGX treatment study is the first to report a correlation between the degree of improvement in symptoms (as measured by the OSDI score) and meibomian gland function. The worse the initial meibomian gland expressibility, the greater the improvement on the OSDI. Similarly, Vegunta, Patel and Shen[13] reported an inverse relationship between change in symptom score (decreased with treatment) and change in meibomian gland expressibility (increased with treatment); however their result was not statistically significant. We acknowledge our result may simply reflect the greater potential for improvement with more advanced disease that is, those with free-flowing meibum and lower symptoms at baseline, cannot be expected to show a similar level of improvement. Nevertheless, these findings are extremely encouraging to sufferers of MGD for which other home-based therapies and clinic-based treatments have been unsuccessful. Both studies involved moderate to advanced recalcitrant MGD cases with the Vegunta, Patel and Shen[13] study having 63 per cent of their intense pulsed light and MGX treated patients having previously received an unsuccessful LipiFlow treatment and a significant number of their cohort having ocular surface co-morbidities such as Sjögren's syndrome, graft versus host disease and post-surgical MGD (cataract, laser *in situ* keratomileusis, blepharoplasty).

Similar to us, Amparo and colleagues[37] found a statistically significant correlation between changes in ocular surface staining and OSDI ($R = 0.35$; $p = 0.005$). The two-grade reduction in interpalpberal ocular surface staining score in our study (4.0 ± 3.1 to 1.8 ± 2.5) at Week 12 compared with baseline (Figure 3) is consistent with a clinically significant reduction in the clinical stage of MGD from Stage 3 to Stage 2.[2] Jiang and colleagues[17] did not achieve significant improvement in staining scores after serial intense pulsed light treatments without MGX; however their study assessed only corneal staining and the mean participant baseline corneal staining score was low (0.15 ± 0.49), limiting the potential to achieve clinically and statistically significant improvements in this parameter.

Lack of effect of intense pulsed light on tear osmolarity

In agreement with our findings, Craig, Chen and Turnbull[20] did not find any change in tear osmolarity or tear evaporation rate with intense pulsed light

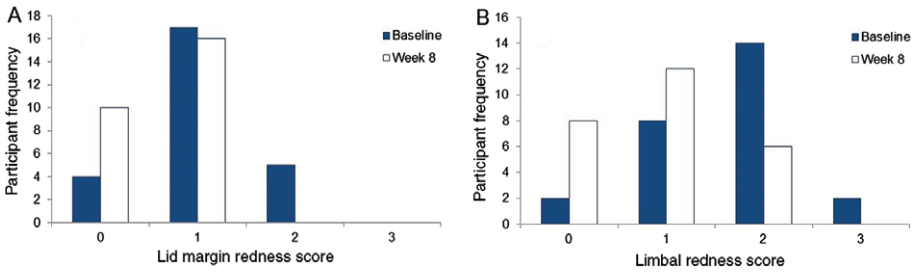

Figure 5. The effect of intense pulsed light (IPL) therapy on lid margin redness (A) and limbal redness (B). Participant scores at before (baseline assessment) and after (Week 8 assessment) IPL treatment (B).

treatment. Toyos[39] reported a mean decrease of 7.8 mOsmol/l ($p = 0.002$) in tear osmolarity one month after intense pulsed light treatment for dry eye in a dry eye participant group characterised by a tear break-up time of less than 10 seconds; however, as was the case in our study, the mean pre-treatment osmolarity for the Toyos' participant cohort fell within the normal range of less than 308 mOsmol/l[40] (303.03 and 301.96 mOsmol/l for right and left eyes, respectively). Hence, it could be argued that the Toyos[39] osmolarity reduction was statistically but not clinically significant.

While tear hyperosmolarity is regarded as the core mechanism causing ocular surface inflammation in dry eye syndrome[41] and has a high diagnostic accuracy for dry eye compared with ocular surface staining, meibomian gland grading, tear film break-up time and Schirmer test,[40] changes in tear osmolarity do not correlate significantly with changes in patient symptoms or corneal fluorescein staining in dry eye disease.[37] Other studies investigating the effects of therapeutic interventions for MGD have involved a participant cohort with moderate to advanced MGD having tear osmolarity in the normal range at baseline and after therapeutic interventions.[11] One possible explanation for this is that MGD without any other ocular tear film and/or ocular surface co-morbidities, such as aqueous tear deficiency, may not be sufficient to overwhelm the homeostatic control in these individuals. Additionally, our participants were already using and continued to use warm compresses and topical lubricants before and during the study, which can lower tear osmolarity.[11,41]

Proposed mechanisms of action

Previously proposed mechanisms for intense pulsed light treatment for MGD include thermal heating of the glands inducing melting of the thickened meibum secretions within the glands and gland dilation facilitating effective clinical expression of the glands.[19] While it is possible that selective absorption of the intense pulsed light could occur at the level of the dermis,[19] the temperature increase of the treated periocular skin after E > Eye intense pulsed light is only one degree Celsius[20] and the use of protective eye goggles prevents the treatment application directly on the gland openings. Other proposed but currently unverified mechanisms include intense pulsed light-induced modification of mitochondrial activity within the meibomian glands to stimulate the glands to function more effectively,[19,20] intense pulsed light decreasing lid marginal bacteria and demodex by photocoagulation, thereby decreasing the pro-inflammatory effects of these organisms on the lid margin[21] and intense pulsed light stimulation of periocular collagen remodelling, which may improve elastosis and connective tissue disorganisation that occurs with MGD and rosacea[21] and may lead to improved meibomian gland function and/or blink function. Additionally, it has been hypothesised that intense pulsed light treatment might also relieve pain associated with inflammation and symptoms of a neurogenic nature and therefore, might at least partially, have been responsible for the symptomatic improvements observed.[17]

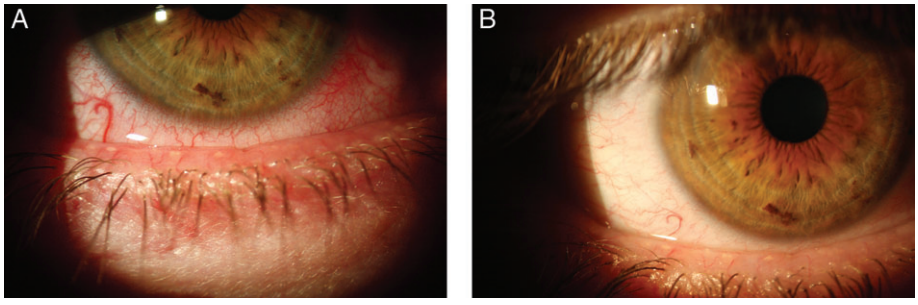

Figure 6. Bulbar and lid margin redness in a participant before (A) and after (Week 12) (B) three sessions of intense pulsed light therapy treatment for meibomian gland dysfunction

Anti-bacterial effects of intense pulsed light

In this study, while there was a possible trend toward reduced lid marginal colony counts, the lack of a significant effect of serial intense pulsed light plus MGX treatments on eyelid margin flora colony counts (Table 2 and Table 3) suggests that changes in lid marginal bacteria may not account for the observed improvements (at least over the short term). In the treatment of acne by light therapy, porphyrins produced within sebaceous follicles by *Proprionibacterium acnes* absorb light between 400 and 700 nm with 415 nm wavelength within the blue light spectrum being most effectively absorbed.[42] Light absorption leads to photo-excitation of porphyrins and subsequent release of singlet oxygen and reactive-free radicals that exert bactericidal effects on *P. acnes*. Longer wavelengths, such as red light delivered by intense pulsed light devices (spectral range of 580 to 1200 nm), activate porphyrins less effectively but penetrate deeper into the skin and may directly target sebaceous glands and exert anti-inflammatory properties by influencing cytokine release from

macrophages.[43] The E > Eye device with a spectral range of 580 to 1,200 nm is unlikely to exhibit significant antibacterial effects on the eyelid marginal bacteria, when the eyelid margins are covered by protective goggles. Additionally, while *P. acnes* is cultured from the lid margins in MGD,[26] lid flora associated with MGD is predominantly *S. aureus* and coagulase-negative *Staphylococcus,*[26] which unlike *P. acnes*, lack endogenous porphyrins and therefore, are not as susceptible to light therapy.[43] Table 3 reflects this lack of significant reduction in *Staphylococcal* species with serial E > Eye intense pulsed light treatment.

Anti-inflammatory effects of intense pulsed light

The significant reduction in lid marginal, conjunctival and limbal injection at Week 8 (Figure 6A and 6B) and the reduction in the number of participants expressing elevated MMP levels in the tears from five of 26 to two of 26 (approaching significance, p = 0.08) provide support for the theory that periocular intense pulsed light treatment acts to decrease inflammation.[13,17,19–21,44] It is proposed that these closed vessels can no longer continue to send pro-inflammatory mediators to the mebomian glands,[44] alter gland function, destabilise the tear film and inflame and damage the ocular surface.

While Craig, Chen and Turnbull[20] did not find a difference in bulbar conjunctival hyperaemia with three E > Eye intense pulsed light treatments, Jiang and colleagues[17] found that conjunctival injection was significantly reduced in treated eyes at Day 15, Day 45 and Day 75 (p = 0.01) involving four serial intense pulsed light treatments. Retrospective chart reviews following a series of three or more intense pulsed light treatments combined with MGX have reported significant reductions in lid margin oedema, facial telangiectasia and lid margin vascularity[21] and 'physician judged' lid margin appearance[19] in more advanced MGD.

Matrix metalloproteinase 9 is a non-specific biomarker for inflammation and is intimately associated with the other mediators of the inflammatory pathway on the ocular surface.[45] MMP-9 levels on the ocular surface have been found to be elevated in MGD;[46] however in a cohort of individuals with dry eye symptoms, less than half tested positive for MMP-9 (using the InflammaDry in-office tear MMP-9 assay) and MMP-9 status was not associated with differences in the clinical dry eye assessment profile.[47] Analysis of tear cytokines and chemokines in individuals with moderate evaporative dry eye due to MGD found that five inflammatory molecules were elevated (Fracktalkine/CX3CL1, IL-1Ra, IL-6, IL-8/CXCL8 and EGF).[47] Incorporation of these inflammatory biomarkers in assessment protocols for future intense pulsed light studies may be of benefit to our understanding of the anti-inflammatory mechanism of intense pulsed light in MGD treatment.

Effect of MGX

Serial therapeutic MGX following intense pulsed light treatment used in this study protocol and other retrospective intense pulsed light treatment chart reviews,[13,19,21] may have had a direct effect on meibomian glands and their function and have been partially or fully responsible for the improvement in symptoms and signs experienced by participants. There are few published reports (only conference abstracts) on the efficacy of therapeutic MGX. An improvement in lipid layer thickness[48] and symptoms[48,49] has been reported; however all of our participants had previously had a clinic-based therapeutic gland expression performed (average two, range one to three) prior to entry to the study without clinical improvement in symptoms and signs. Similarly, Vegunta, Patel and Shen[13] reported significantly improved dry eye symptoms and meibomian gland function following a series of intense pulsed light and MGX in a participant cohort with advanced MGD and non-response to LipiFlow treatment; however Craig, Chen and Turnbull[20] using the same intense pulsed light device and treatment protocol as in our study but without MGX found significant improvements in lipid layer grade, non-invasive tear film break-up time and symptom scores in intense pulsed light treated eyes. Similarly Jiang and colleagues[17] also reported improved symptoms and signs of MGD following serial intense pulsed light treatment without MGX. These results suggest that intense pulsed light treatment is, at least in part, responsible for the observed improvements. Nevertheless, further research is required to prospectively assess intense pulsed light alone versus intense pulsed light with MGX versus without MGX in regard to their contributions to the therapeutic effects observed.

Limitations

A significant source of bias in this study involved a single investigator performing both treatments and assessments. Additionally, this study did not involve randomisation, nor a placebo 'treated' control group. Craig, Chen and Turnbull[20] have discussed the inherent difficulties and limitations associated with conducting 'mock' intense pulsed light treatments. Due to the large number of study visits and treatments required for each participant, we considered it unviable and unethical to have a control group with moderate to advanced disease that attended and underwent a mock intense pulsed light treatment for no potential benefit, as data addressing the efficacy of the same intense pulsed light device and treatment protocol (although without therapeutic MGX and in a participant group with milder disease) has already been published.[20]

Comparison of our results with other studies assessing the efficacy of intense pulsed light in the treatment of MGD are limited by differences in study design, disease severity, MGD diagnostic criteria, tear film and ocular surface parameters assessed, inclusion and exclusion criteria including cohort ethnicity and skin type, spectral range and treatment algorithm of intense pulsed light device used, number and intensity of flashes delivered per treatment, inclusion of therapeutic MGX in the treatment protocol, number of treatments and length of follow-up. As we ceased data collection at Week 12, the duration over which the improvements in symptoms and signs were maintained was not determined, although we can report that at 12 months after initial treatment only one participant had undergone two 'maintenance treatments'[19,21] due to return of dry eye symptoms.

As 17 of 26 participants were Fitzpatrick skin type 2 (Table 1), it was not possible to analyse the effect of intense pulsed light treatment intensity in this study; however our clinical experience and that of others[19,21] indicates that intense pulsed light is most effective clinically for light-skinned individuals (phototype 1 to 3), who can be treated at higher treatment intensities. Yet, Jiang and colleagues[17]

have recently demonstrated efficacy of serial intense pulsed light treatment in Chinese participants with MGD.[17]

The promising results of this study and the others aforementioned provide impetus for multicentre controlled clinical trials to further examine the immediate and longitudinal effects of intense pulsed light in the treatment of recalcitrant MGD and to determine the efficacy of intense pulsed light therapy versus conventional warm compresses and lid massage therapy. Development of evidence-based clinical guidelines for the use of intense pulsed light to treat MGD requires further research into the underlying mechanisms, determination of the characteristics of the ideal intense pulsed light candidate and who would potentially be a non-responder, determination of the most efficacious intense pulsed light treatment device, algorithm and protocol and the indications for and efficacy of 'maintenance' treatments.

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