Effectiveness and Safety of Intense Pulsed Light in Patients with Meibomian Gland Dysfunction

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ประสิทธิภาพและความปลอดภัยในการรักษาภาวะต่อมไขมันเปลือกตาอุดตันด้วยพลังงานแสงความเข้มสูง

นายยลรวี ปิยะคมน์

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ยลรวี ปิยะคมน์ : ประสิทธิภาพและความปลอดภัยในการรักษาภาวะต่อมไขมันเปลือกตาอุดตันด้วยพลังงานแสงความเข้มสูง. (Effectiveness and Safety of Intense Pulsed Light in Patients with Meibomian Gland Dysfunction) อ.ที่ปรึกษาหลัก : รศ. พญ.งามจิตต์ เกษตรสุวรรณ, อ.ที่ปรึกษาร่วม : พญ.วรรณรัตน์ สาธิตพิฐกุล

การศึกษานี้ เพื่อศึกษาประสิทธิผลในแง่อาการและอาการแสดงของคนไข้ในโรคต่อมไขมันเปลือกตาอุดตัน ตลอดจนศึกษาความปลอดภัยและการเปลี่ยนแปลงของสารอักเสบในน้ำตา ภายหลังจากการรักษาด้วยพลังงานแสงความเข้มข้นสูงจำนวนสามครั้ง การศึกษานี้เป็นการศึกษาทางคลินิคเปรียบเทียบแบบสุ่มและมีกลุ่มควบคุมที่ไม่ได้รับการรักษาที่เป็นประเด็นศึกษา ผู้ป่วยโรคต่อมไขมันเปลือกตาอุดตัน ที่ผ่านเกณฑ์คัดเลือก จะถูกแบ่งกลุ่มแบบสุ่มเป็นสองกลุ่มคือกลุ่มทดลองหรือกลุ่มที่ได้รับการรักษาพลังงานแสงความเข้มข้นสูง และกลุ่มควบคุม หรือกลุ่มที่ได้รับพลังงานแสงหลอก การสุ่มเป็นแบบบล็อกตามความรุนแรงของโรค โดยอาศัยคอมพิวเตอร์ช่วยแบ่ง ผู้ป่วยกลุ่มทดลองจะได้รับการรักษาด้วยพลังงานแสงความเข้มข้นสูง ในวันที่ 0, 15 และ 45 ส่วนกลุ่มควบคุมจะได้รับพลังงานแสงหลอก โดยทั้งสองกลุ่มจะได้รับการรักษาพื้นฐานเช่นเดียวกัน คือ การให้คำแนะนำประคบอุ่น การทำความสะอาดเปลือกตา และการหยอดน้ำตาเทียม ผลลัพธ์หลักที่ศึกษา คือ การตรวจหาเวลาที่น้ำตาสามารถคงสภาพ ผลลัพธ์อื่นๆที่ศึกษา ประกอบด้วย อาการตาแห้ง ความหนาของชั้นน้ำมันของน้ำตา ลักษณะของต่อมไขมันในเปลือกตาด้วยวิธีการถ่ายรูป การตรวจการติดสีของเนื้อเยื่อผิวตา ความสามารถในการขับน้ำมันของต่อมไขมันที่เปลือกตา คุณภาพของน้ำมัน ความเข้มข้นของน้ำตา ปริมาณน้ำตา การตรวจหาสารอักเสบ ได้แก่ อินเตอร์ลิวคิน-1 อาร์เอ และ อินเตอร์ลิวคิน-6 โดยการตรวจต่างๆดังกล่าวมีขึ้นในวันที่ 0, 15, 45, เดือนที่ 3 และ 6 ของการศึกษา มีการศึกษาการวิเคราะห์แยกเป็นรายกลุ่มตามระดับความรุนแรงของโรค และการปฏิบัติตัวของคนไข้ในการรักษาพื้นฐาน ผลการศึกษาพบว่า ผู้ป่วยจำนวนหนึ่งร้อยสิบสี่คนได้รับการแบ่งกลุ่มแบบสุ่ม ออกเป็นกลุ่มทดลองและกลุ่มควบคุม ผลการตรวจหาเวลาที่น้ำตาสามารถคงสภาพในกลุ่มทดลองมีค่ามากกว่ากลุ่มควบคุมในทุกๆวันของการตรวจ ในทุกๆความรุนแรงของโรค และในการปฏิบัติตัวตามคำแนะนำของแพทย์ ทุกรูปแบบอย่างมีนัยสำคัญ ($p<0.001$) ผลการตรวจหาเวลาที่น้ำตาสามารถคงสภาพในกลุ่มทดลองเพิ่มขึ้นในวันที่ 15 ขึ้นสูงสุดในวันที่ 45 ของการรักษา และคงไว้นานตลอดการศึกษา ผลการตรวจคุณภาพของน้ำมันและความสามารถในการขับน้ำมันของต่อมไขมันที่เปลือกตาในกลุ่มทดลองดีขึ้นเมื่อเทียบกับกลุ่มควบคุมอย่างมีนัยสำคัญในทุกๆวันของการตรวจรักษา ($p<0.001$) ผู้ป่วยที่ไม่สามารถประคบอุ่นและเช็ดเปลือกตาได้ ก็สามารถมีคุณภาพของไขมัน และการขับน้ำมันของต่อมไขมันเปลือกตาดีขึ้นได้ด้วยพลังงานแสงความเข้มสูง การติดสีของเนื้อเยื่อผิวตา และลักษณะของต่อมไขมันเปลือกตาในกลุ่มทดลองพบว่าดีขึ้นอย่างมีนัยสำคัญเมื่อเทียบกับกลุ่มควบคุม ในกลุ่มย่อยความรุนแรงระดับ4 ($p<0.05$) อย่างไรก็ตามความเข้มข้นของน้ำตา ปริมาณน้ำตา ปริมาณสารอินเตอร์ลิวคินทั้งสอง ไม่พบความแตกต่างกันระหว่างกลุ่มทดลองและกลุ่มควบคุม ในการศึกษานี้ไม่ปรากฏเหตุการณ์ไม่พึงประสงค์หลังการรักษาด้วยพลังงานแสงความเข้มข้นสูง โดยสรุปการรักษาโรคต่อมไขมันเปลือกตาอุดตันด้วยพลังงานแสงความเข้มข้นสูงมีประสิทธิผลและปลอดภัย โดยเฉพาะอย่างยิ่งในกลุ่มย่อยความรุนแรงระดับ 4

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Effectiveness and Safety of Intense Pulsed Light in Patients with Meibomian Gland Dysfunction. Advisor: Assoc. Prof. Ngamjit Kasetsuwan, M.D. Co-advisor: Vannarut Satitpitakul, M.D.

This study aimed to study the clinical effects and safety in terms of symptoms and signs and to evaluate the change in tear inflammatory cytokines in meibomian gland dysfunction (MGD) after 3 sessions of Intense Pulsed Light (IPL) in a prospective randomized double-masked sham-controlled clinical trial. Patients with MGD who met all criteria were randomly assigned into IPL and sham-IPL group. The stratified blocked randomization was done using the MGD gradeas a stratum by computer-generated assistance. Each patient in IPL group underwent 3 sessions of IPL on day 0, 15 and 45. The other group underwent sham-IPL. Both group received conventional treatment as warm compression, lid scrub and artificial tears. Primary outcome was tear film break-up time. Other clinical parameters included Ocular Surface Disease Index (OSDI), symptoms of dry eyes in visual analog scale score (VAS), tear film lipid layer thickness, meibography grade, ocular surface staining using NEI grading system, meibomian gland expressibility, meibum quality, tear osmoloarity, Schirmer's test and tear cytokines (IL-1Ra and IL-6). The parameters were evaluated on day 0, 15, 45, month 3 and 6. Subgroup analysis according to stage and patient's compliance to conventional treatment were analyzed. One hundred and fourteen patients were randomized and allocated into IPL and sham-IPL group. The tear film break-up time in IPL group was significantly more than that in sham-IPL group in all visits, in any stages and in any kinds of compliance ($p<0.001$). The tear film break-up time increased at day 15, reached its maximum at day 45 and persisted at least six months. The meibum quality score and meibum expressibility in IPL group was significantly better than that in sham-IPL group in all visits ($p<0.001$). Patients who were not strictly complied with the warm compression and lid scrub could have their meibum qualities and expressibilities improved by IPL. Ocular surface staining and meibography grade in IPL group significantly improved more than that in sham-IPL group in stage 4 ($p<0.05$). However, tear osmolarity, Schirmer's test, IL-1Ra and IL-6 levels were not statistically different between two groups. No adverse event occurred in IPL group. In conclusion, our study suggests that IPL is effective and safe to manage patients with meibomian gland dysfunction especially in stage 4 of the disease.

Field of Study:	Clinical Sciences	Student's Signature .....
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		Co-advisor's Signature .....

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Yonrawee Piyacomn

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List of Abbreviations and Acronyms

ATP = Adenosine Triphosphate

BCVA = Best-corrected Visual Acuity

Cox = Cytochrome C Oxidase

D = Day

EGF = Epidermal Growth Factor

IL-1Ra = Interleukins-1 Receptor Agonist

IL-6 = Interleukins-6

IPL = Intense Pulsed Light

IQR = Interquartile Range

LASIK = Laser-assisted in situ Keratomileusis

LOCF = Last Observation Carried Forward

logMAR = Logarithm of the Minimum Angle of Resolution

MAR = Missing At Random

MCAR = Missing Completely At Random

MCD = Mean Clinical Difference

MG = Meibomian Gland

MGD = Meibomian Gland Dysfunction

MGE = Meibomian Gland Evaluator

NEI = National Eye Institiute

nL = Nanolitre

NMAR = Not Missing At Random

OCI = Ocular Comfort Index

OSDI = Ocular Surface Disease Index

PCV = Polypoidal Choroidal Vasculopathy

PRK = Photorefractive Keratectomy

SD = Standard Deviation

SPEED = Standard Patient Evaluation of Eye Dryness Questionnaire

TBUT = Tear Break-up Time

TFLLT = Tear Film Lipid Layer Thickness

UCVA = Uncorrected Visual Acuity

VAS = Visual Analog Scale

VEGF = Vascular Endothelial Growth Factor

Chapter 1 Introduction

Background and rationale

Meibomian gland dysfunction (MGD) is one of the most common causes of dry eye diseases.[1] Over the past decade, several treatment options in MGD have been extensively studied. Mainstay treatment included warm compression, lid massage, ocular lubricants.[1] Other treatments included forceful expression, single vectored thermal pulsation (LipiFlow), intraductal probing, debridement scaling and intense pulsed light (IPL).[1] IPL is a broad spectrum, non-coherent and polychromatic light source with a wavelength spectrum of 500-1200 nm. It can be filtered to allow only a range of wavelengths to be emitted.[2, 3] Different wavelength makes different depth of tissue to absorb a specific light energy.[2, 3] Intense pulsed light (IPL) has been widely used in dermatology as a therapeutic tool for removal of hypertrichosis, benign cavernous hemangioma, benign venous malformations, telangiectasia, port-wine stain and pigmented lesions.[2-4] Concurrent ocular surface improvements have been observed in patients undergone IPL treatment.[3] There were several non-comparative and comparative studies show various clinical results.[2, 3, 5-12] These studies used different IPL machines, different treatment areas and different IPL protocols. Only three prospective clinical trials showed that subjective dry eye symptoms improved and some of the dry eye signs also improved.[2, 10, 12] Nonetheless, there is still inconsistency in the efficacy of IPL among these studies. There were several studies about cytokines change and dry eye disease[13-16]; however, there were only few studies in MGD[10, 16] so the change in ocular surface inflammatory cytokines in patients with MGD after IPL treatment remained unclear.

Since there are limited prospective randomized controlled trials to demonstrate the efficacy and safety and cytokines change, we proposed a prospective randomized

double-masked sham-controlled clinical trial to determine the clinical improvement, safety and the change in inflammatory cytokines after intense pulsed light treatment in patients with meibomian gland dysfunction.

Hypothesis

Primary hypothesis

Intense pulse light (IPL) decreases dry eye symptoms and improves clinical signs of meibomian gland dysfunction

Secondary hypothesis

1. Intense pulsed light (IPL) is safe.
2. Intense pulsed light (IPL) decreases inflammatory cytokines in tears of patients with meibomian gland dysfunction.

Study design

Prospective randomized double-masked sham-controlled clinical trial

Objectives

Primary objective

To study the clinical effects in terms of symptoms and signs of meibomian gland dysfunction (MGD) after 3 sessions of intense pulsed light treatment.

Secondary objectives

1. To study the safety of intense pulsed light treatment in patients with meibomian gland dysfunction
2. To evaluate the change in inflammatory cytokines after intense pulsed light treatment in patients with meibomian gland dysfunction

Key words

Intense pulsed light, meibomian gland dysfunction, dry eye, cytokines

Chapter 2 Literature Review

In 2002, Toyos, the dermatologist, observed that some of the patients diagnosed with skin telangiectasia or rosacea showed clinical improvement in MGD and dry eye

disease after IPL treatment. He conducted a retrospective non-comparative interventional study that ignited the effect of IPL (Diamond Series Q4) on MGD.[3] They performed IPL on the MGD patient's face from tragus to tragus including nose for a total of two passes per session. The patients underwent IPL every 30 days for 4 sessions. This study demonstrated that 93% of the dry eye patients were satisfied with the improvement in dry eye symptoms and 87% also showed the improvement in tear break-up time (TBUT).[3] However, 13% of the patients developed side effects of skin redness and mild swelling.[3] Gupta et al. also performed a retrospective non-comparative study in IPL for MGD treatment.[8] All patients had a minimum of 3 treatments and maximum of 6 treatments, each separated by 3–6 weeks. Approximately 10–15 treatment spots were placed on each side (3 spots to cheek beneath eye, 3 spots to eyelid margin and 5-6 spots to lateral canthus/temple area) and then this was repeated for a total of 2 passes. Gupta et al. found that Dermamed Quadra4 IPL had ability to decrease lid margin edema, lid margin telangiectasia, meibum viscosity, facial telangiectasia and Ocular Surface Disease Index (OSDI) score in a multicenter retrospective cohort study in 2016.[8] Gupta et al. also found significant increase in oil flow score and tear break-up time.[8] No adverse ocular events (such as uveitis, intraocular structure damage, or periocular or facial skin burn) were reported.[8] Vegunta et al. performed a retrospective cohort 6-month study with IPL Dermamed Quadra Q4 followed by meibomian gland expression to both eyes.[11] Patients received 1 to 4 IPL treatments, each spaced 4 to 6 weeks apart. Patients received approximately 30 pulses (with slight overlapping applications) from the right preauricular area, across the cheeks and nose to the left preauricular area, treating up to the inferior boundary of the eye shields. They reported improvement in Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) score in 89% of patients but meibomian gland expression increased in the left eye not in the right eye. No adverse effects were noted in this study.[11] Jiang et al. studied the safety and efficacy of E>Eye (E-SWIN, France) IPL in a prospective open-label non-comparative 75-day study in 2016. IPL treatment was administered to the skin area below the lower eyelid.[9] In each IPL treatment, 4 overlapping ashes were applied to the skin area below the lower eyelid for every eye with

no pressure. All the treatment areas were identical within different subjects. The subjects received four separate treatment sessions on day (D) 1, D15, D45, and D75. Also, Jiang et al. found significant improvement in ocular surface symptom scores and TBUT. However, there was inconsistent improvement in conjunctival injection and meibomian gland expression parameters. Moreover, Jiang et al. found no improvement in ocular surface staining and tear meniscus height. No adverse effect was observed in this study. Among all visits, best spectacle corrected visual acuity was not significantly changed; IOPs of all subjects were lower than 21mmHg. There was no depigmentation, blistering, swelling, redness, and hair loss at the brown and ocular surface. There was no significant eyelash loss during the evaluation, either. No systemic adverse event was observed during the study.[9] Moreover, Albietz and Schmid perfomed a prospective, open-label, non-comparative 3-month study in 2016. 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.[5] Albietz and Schmid found that E>Eye (E-SWIN, Paris) IPL could improve dry eye symptoms in term of Ocular Surface Disease Index (OSDI) score but not in Ocular Confort Index (OCI) .[5] Albietz and Schmid also found no improvement in tear osmolarity, corneal sensitivity, daily lubricants uses, lid margin colony count, MMP-9 and Schirmer I test^2. No adverse events were noted in this study.[5] Caballero et al. reported a prospective non-comparative 45-day study. Five flashes were made in the middle face, starting from medial canthus of the eye and finishing in the temporal area for each side. Treatment was carried out in 4 sessions with a time interval of 15 days between each, a total of 45 days for all patients (day 0/day 15/day 30/day 45).[7] Caballero et al. reported IPL could improve tear break-up time in patients with post cataract surgery, post photorefractive keratectomy (PRK) and patients with no history of ocular surgery but showed no improvement in those after laser-assisted in situ keratomileusis (LASIK). There was no statistically significant change in tear meniscus height and Schirmer II test. Only 2 of the 36 patients experienced an adverse event such as reddening in the face and light sensitivity, which resolved within

a week without requiring treatment. [7] Dell et al. performed a prospective non-comparative 15-week study on IPL treatment by using M22 (Lumenis) IPL. IPL probe was applied on a band of skin that extended from tragus to tragus (coronal axis) and on the cheeks from the maxillary process of the zygomatic bone up to the inferior orbital rim below the lower eyelids (longitudinal axis). Enrolled patients underwent a series of four treatment sessions, 3 weeks apart. By this article, IPL followed by meibomian gland expression could improve SPEED symptoms score, tear break-up time (TBUT), meibomian gland secretion, ocular surface staining, and tear osmolarity. [6] However, Dell et al failed to demonstrate any improvement in tear lipid layer thickness.[6] All articles mentioned above were conducted as either retrospective or prospective non-comparative designs. No adverse events were noted in this study. [6]

There were three prospective comparative studies in IPL treatment in MGD patients. Yin et al. performed a prospective comparative study but without randomization or blinded in 2017. They compared IPL M22 (Lumenis) group (without warm compression and lid scrub) to control group who received warm compression and lid scrub. IPL was performed at periorbital area, not involving the eyelids which were protected underneath the opaque goggles. Three IPL treatments were administered once a month for 3 months. They found that OSDI score, TBUT, meibum quality, meibum expressibility and meibomian gland drop-out improved significantly in both groups but unfortunatedly they did not state statistical difference between these two groups. In addition, there was no change in ocular surface staining and Schirmer's I test in both groups. However, there was improvement in meibomian gland microstructure in IPL group compared with control. No adverse events were noted in this study. [12]

Craig et al. conducted a prospective randomised double-masked paired-eye placebo-controlled study in 2015. IPL (E>Eye (E-SWIN, Paris)) treatment was administered to the skin area immediately below the lower eyelid during three separate treatment sessions on Day (D) 1, D15, and D45 They showed improvements in visual analog scale symptoms but no improvement in SPEED score after 3 sessions of IPL treatments. They also found improvements in lipid layer grade and non-invasive TBUT.

Nevertheless, ocular surface staining, tear meniscus height, tear osmolarity and tear evaporation rate showed no statistical difference between two groups. No adverse events were noted in this study. This study followed the patients for 45 days which was the time point of last IPL treatment.[2] Thus, the true effect magnitude and duration of IPL effect might not be derived.

Liu et al. performed a randomized double-masked controlled clinical trial comparing IPL M22 (Lumenis) followed by meibomian gland expression to sham-IPL at 0,1,2 month. The areas of treatment were both upper and lower eyelids which were different from previous articles. They found decrease in interleukins-6, interleukins-17A and prostaglandins E2. Nevertheless, all three cytokines showed no correlation with symptoms, TBUT and ocular surface staining except that interleukins-6 was correlated with meibomian gland secretion and prostaglandins E2 was correlated with ocular surface staining. This study leads us to be interested in cytokines as one of the mechanisms of IPL efficacy on MGD. No adverse events were noted in this study.[10]

Enríquez-de-Salamanca et al. 8 compared cytokines in evaporative dry eye to control in a prospective non-interventional comparative study in 2010. Among tear lysozyme, interleukins-1β, interleukins-5, interleukins-6, interleukins-8/CXCL-8, interferon-inducible-protein-10, tumor necrotic factor-alpha, vascular endothelial growth factors (VEGF), interfereon-gamma, interleukins-1 receptor agonist (IL-1Ra), fractalkine/CX3CL1, granulocyte-monocyte colony stimulating factor, and epidermal growth factor (EGF), they found that in evaporative dry eye, there was increase in EGF, fractalkine/CX3CL1, interleukins-1 receptor agonist (IL-1Ra), interferon-inducible-protein-10 and VEGF8.[17] Jung et al. 13 reported a prospective observational study in 2016. They compared tear cytokines in mild/no MGD group to stage2-4 MGD group13. Interleukins-6 and tumor necrotic factor alpha significantly increased in stage 2-4 group13.[18]

Chapter 3 Material and Methods

The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Thailand. The IRB number was COA No 553/2018. It also

adhered to the tenets of the Declaration of Helsinki. The study had been registered to clinicaltrials.gov and the registered number was NCT03518398. We enrolled the patients with meibomian gland dysfunction who presented at general eye clinic and Chula Refractive Surgery Center, King Chulalongkorn Memorial Hospital, Bangkok Thailand. Informed consent process included 3 steps. First, trained research assistant explained the research process to the participants without pressure to the participants. Participants could have their information sheets/informed consent forms back home to decide later. Lastly, Participants had to sign their names in written informed consent before joining the research.

The study was funded by the 90 TH Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund) and Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University.

Population

Patients diagnosed with meibomian gland dysfunction

Target Population

Patients diagnosed with meibomian gland dysfunction at out-patient clinic, Department of Ophthalmology, King Chula Memorial Hospital

Control Population

Patients diagnosed with meibomian gland dysfunction at out-patient clinic, Department of Ophthalmology, King Chula Memorial Hospital

Sampling technique

Convenience sampling using consecutive cases

Approach to participants

1. direct recruitment of potential study participants
2. referrals from non-investigator healthcare providers

Operational definitions

1. Meibomian gland dysfunction (MGD) : according to The International Workshop on Meibomian Gland Dysfunction: Report of the Definition and Classification Subcommittee, MGD is *is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.*
2. Severity of Meibomian gland dysfuntion : MGD was staged into four stages as shown in Table 1

Table 1 MGD staging (modified from MGD workshop[9])

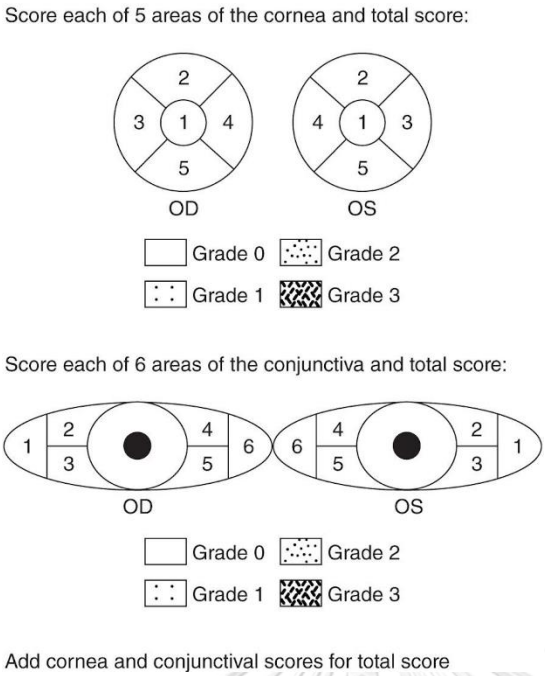
Stage	Symptoms	Clinical signs of MGD	Meibum quality	Meibum expressibility	NEI staining score
1	No discomfort, itching or photophobia	Based on gland expression	≥ 2 to <4	1	No staining
2	Mild symptoms of ocular discomfort, itching or photophobia	Scattered lid margin features	≥4 to <8	1	NEI score 0-7
3	Moderate symptoms of ocular discomfort, itching or photophobia with limitations of activities	Plugging, vascularity	≥8 to <13	2	NEI score 8-23

3. Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning.

4	Marked symptoms of ocular discomfort, itching or photophobia with definite limitations of activities	Dropout, displacement	≥13	3	NEI score 24-33

4. Lipid layer thickness is quantitative values of the tear-film lipid layer depth or thickness by imaging the surface contour of the tear film. We measured this thickness by the LipiView interferometer (TearScience Inc, Morrisville, NC)
5. Meibography is a specialized imaging study developed exclusively for the purpose of directly visualizing the morphology of meibomian glands *in vivo.* We used Keratograph 5M (OCULUS, Wetzlar, Germany) a noncontact, placido ring-based corneal topographer. MG dropout degree was graded : Grade 0 (no loss MGs), Grade 1 (loss of 33% of the whole glands area), Grade 2 (loss of area between 33% and 67%), and Grade 3 (loss of 67% of the whole area)
6. Tear break-up time (TBUT) represents the time elapsed from the last complete eyelid blink until appearance of the first dry spot on the cornea. We used fluorescein tear break-up time in this study. After instillation of a drop of fluorescein paper which was previously dissolved with preservative-free solution in the conjunctival sac, the patients were instructed to blink several times for a few seconds and TBUT was measured 3 times, and then the mean value of measurements was calculated.
7. Ocular surface staining reflects ocular surface inflammation. We used fluorescein dye which was a mildly invasive stain that marks the tear film and defects in the corneal and conjunctival epithelium. We used NEI grading for ocular surface staining score in this study as shown in Figure 1.

Figure 1 NEI staining (modified from MGD workshop[9])



8. Meibum quality is the quality of the meibum content after applying the force onto the eyelids via the same meibomian gland evaluator (MGE). The grading of meibum quality is shown in Table 2

Table 2 Meibum quality (modified from MGD workshop[9])

Evaluate the 8 glands in central third of lower eyelid : total score 0 - 24	
0	Clear
1	Cloudy/Mild Haze
2	Paste (like toothpaste)
3	Obstructed (no secretions)

9. Meibomian gland expressibility is the number of glands expressible after applying force onto the eyelids via the meibomian gland evaluator (MGE), developed by Korb and Blackie (2008) and TearScience (Figure 2), is a handheld instrument used to evaluate meibomian gland (MG) function. The instrument provides a standardized method to apply consistent, gentle pressure at 1.25g/mm^2 to one-third of the lower eyelid. The grading of MG expressibility is demonstrated in Table 3

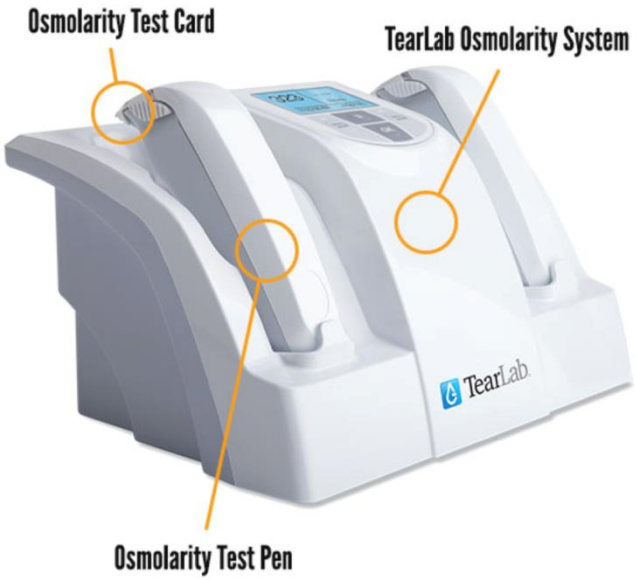
Figure 2 Meibomian gland evaluator

Table 3 Meibum expressibility (modified from MGD workshop[9])

Evaluate the 5 glands in central third of lower eyelid	
Grade	The number of glands expressible
0	All glands
1	3 – 4 glands
2	1 - 2 glands
3	No glands

10. Tear osmolarity is the concentration of the tear. We used TearLab Osmolarity System (San Diego, CA) (Figure 3) which provided a quick and simple method for determining tear osmolarity using nanoliter (nL) volumes of tear fluid collected directly from the eyelid margin. The Test Card was held by the Osmolarity Test Pen, for safe collection.

Figure 3 TearLab Osmolarity System



11. Schirmer's test was used to determine whether the lacrimal glands produced enough tears to keep the eyes adequately moist. Calibrated strips of a non-toxic filter paper were used. One free end was placed within patients' lower eyelids. Both eyes were tested at the same time. Before the test, the patients were given a drop of topical anesthesia to prevent the eyes from tearing due to irritation from the paper. The patients were asked to keep their eyes gently closed for 5 minutes. At the conclusion of the test, the paper strips were removed from each lower eyelid and the amount of wetting of the paper strips was measured.
12. Safety is hereby defined in this study as any harm to participants. Both ocular and non-ocular side effects and complications were reported as a proportion of the number of the affected participants. Participants who were affected by any of these side effects or complications were taken care by our healthcare providers. Participants were able to decide later whether they were willing to continue in the study or leave without necessarily stating the reasons.

Inclusion criteria

1. Able to read, understand and sign an informed consent form
2. 18-80 years of age

3. Fitzpatrick skin type 1-5
4. Able and willing to comply with the treatment/follow-up schedule and requirements
5. Presence of meibomian gland on each lower eyelid's meibography
6. Current diagnosis of stage 1-4 of MGD in both eyes, according to the International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction[9](see table 1,2,3 and figure 1)

Exclusion Criteria

1. To limit confounders or to exclude the factors that might had possible effects on our outcome variables
    a. Contact lens wearer within the past 1 month and throughout the study
    b. Recent ocular surgery or eyelid surgery within the past 6 months
    c. Neuro-paralysis in the planned treatment area within the past 6 months
    d. Subjects who have undergone refractive surgery within the past 6 months
    e. IPL treatment within the past 12 months
    f. Lipiflow treatment, or any equivalent treatments, within the past 12 months
    g. Any anti-glaucomatous eye drop uses within the past 3 months and throughout the study period
2. For safety reasons
    a. Current use of punctal plugs
    b. Pre-cancerous lesions, skin cancer or pigmented lesions in the planned treatment area
    c. Uncontrolled infections or uncontrolled immunosuppressive diseases

d. Diseases in the planned treatment area that could be stimulated by light at 560 nm to 1200 nm (e.g., Herpes simplex 1 and 2, Systemic Lupus Erythematosus, porphyria)
e. Use of photosensitive medications and/or herbs that may cause sensitivity to 560-1200 nm light exposure, such as isotretinoin, tetracycline, or St. John's Wort
f. Pregnancy and lactation
g. Radiation therapy to the head or neck within the past year, or planned radiation therapy throughout study period
h. Treatment with chemotherapeutic agent within the past 8 weeks, or planned chemotherapy throughout study period
i. Declared legally blind in one eye
j. Any condition revealed during the eligibility screening process whereby the physician deems the subject inappropriate for this study

Informed consent process

1. Trained research assitant explained the research process to the participants without pressure to the participants.
2. Participants had their information sheets/informed consent forms back home to decide later.
3. Participants signed their names in written informed consent before joining the research.

Recruitment

The patients who were interested in the research or who were referred from non-investigator healthcare providers discussed with the researchers about the purpose of the IPL, treatment process, the follow-up time, the risk and benefit or the treatment, the randomization of the research and also the important medical history to fulfil the inclusion and exclusion criteria. Those patients who met all the criteria included in the study. The patients had a total power and rights to be out of the study at any time without reporting the reasons.

Treatment allocation (ramdomization technique)

The stratified blocked randomization was done using the MGD grades as a stratum by computer-generated assistance block of 4. There were four strata in this randomization owing to the four stages of MGD (Table 1). The participants were divided into 2 groups. One received IPL. The other received sham-IPL as described later. Furthermore, the tear cytokine analysis was performed in only right eyes of 36 randomized participants.

Allocation concealment

We put the randomization sequence in a opaque sealed opaque envelope.

Intervention and sham

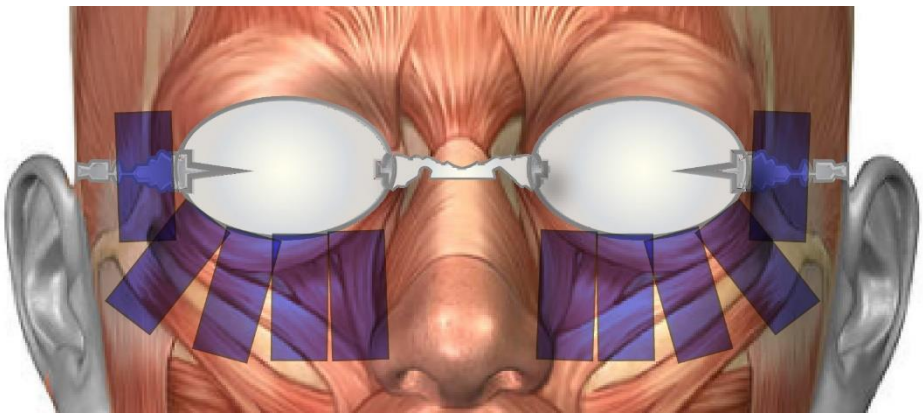
All patients were randomly assigned into 2 groups : treated and sham one. The IPL machine used in this study was E>Eye (E-SWIN, Paris, France) as shown in figure 4. The reason why we used this brand was that at the time we decided to do the study, this brand was the only one commercially available IPL machine (in our country) that had been approved for ocular purpose. In the treated group, IPL treatment was performed by only one well-trained specialist (N.K.) on day 0, day 15 and day 45. The patients did not know whether they were in which groups. The power used in IPL was 9-13 J/cm2 depending upon the Fitzpatrick's skin type (see table 4). After the patients' eyes were protected with the opaque goggles, the cooling gel was spreaded over the treated area. The IPL tip was placed below the inferior lid margin divided into 5 areas from inner canthus toward lateral canthus according to the company's recommendations (Figure 5). Then the IPL began for a total of one pass on each eye. We designed not to perform the treatment flashes on the upper eyelids because of safety concerns. The sham-group patients were placed with the IPL probe onto the same skin area without applied light power. This was administer by the same specialist (N.K.). Again, both the IPL and sham-group the intervention was performed by one well-trained speialist (N.K.)

Figure 4 IPL machine which is E>Eye (E-SWIN, Paris, France)

Table 4 Fitzpatrick's skin type and fluence used

Fitzpatrick skin type	Skin appearance	E > Eye treatment level	Fluence (J/cm2)
I	Pale white	6	13
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	not suitable for IPL	-

Figure 5 Treatment area



Immediatedly after the IPL the patients were asked to grade the pain score using visual analog scale. The patients' skin and eyes were examined again for any complications; for example, skin burn, conjunctival or corneal burn or abrasion.

All participants were advised to use only artificial four times daily back home. The participants were also advised to use commercially available eye compression gel for warm compression for 10 minutes twice daily and lid scrub by ocusoft foam after warm compression as a conventional treatment throughout the study. The participants were also asked not to use other eye drops or other treatment modalities.

Possible complications were skin burn, lid abrasion, conjunctival abrasion, corneal abrasion, iritis and uveitis. The patients who felt pain in the eyes or the eye develops red or blurred, they contacted the primary investigator via the calls.

Outcome measurement

Primary outcome was fluorescein tear break-up time (TBUT) which were measured 3 times, and then the mean value of measurements were calculated.

At baseline, the participants were asked by trained standardized reseach assistant to do the dry eye questionnaire (OSDI) and also to give a dry eye symptoms score in the visual analog scale (VAS). Ocular examintaions included visual acuity both best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, meiboscore using meibography, tear film break-up time using fluorescein technique, NEI staining score, meibum quality and meibomian gland expressibility. After that the patients were asked to wait 10 minutes and

then tear osmolarity measurement using TearLab was done to the right eye of each participant. After that the tear samples of the right eye of the participants who had previously been randomized to be analyzed were collected by instilling 50 microlitres of phosphate-buffer saline into the inferior fornix without topical anesthesia, followed by movement of the eyes to mix the tear fluid content. A total of approximately 10 microlitres of unstimulated tear fluid and buffer were collected from the inferior tear meniscus using a glass capillary micropipette at the lateral canthus. Samples were placed into 200-microlitres Eppendorf tube, then diluted 10-fold using the sample diluent supplied in the cytoline kit and immediately transported in an insulated cooler to a -80 C freezer. After collecting all tear samples, the tear cytokines including IL-1Ra and IL-6 were analyzed using Bio-Plex® 200 system (Bio-Rad, Hercules, CA) as illustrated in figure 6. The positive and negative control were also included in the analysis system. Boundaries of the assay working range are defined by the lower and upper limits of quantification. The lower and upper limits for IL-1Ra were 3.73 and 61,154 pg/ml whereas those for IL-6 were 0.38 and 6,244 pg/ml. Standard curves were generated by using the reference cytokine sample supplied in the kit and were used to calculate the cytokine concentrations in tear samples. Lastly, one drop of topical anesthesia was applied on all of the patients' eyes and five minutes later Schirmer's test was done. The evaluator and ocular examiner was restricted to one well-trained specialist (Y.P.).

Figure 6 Bio-Plex® 200 system (Bio-Rad, Hercules, CA)

All the patients were graded into 4 grades according to severity (see table 1). The stratified randomization was computer-generated with block of 4. Stratum of this randomization in this study was the stage of the disease as mentioned earlier. All patients were randomly assigned into 2 groups : IPL or sham one. The IPL machine used in this study is E>Eye (E-SWIN, Paris, France) as shown in figure 4. In the treated group, IPL was performed by only one researcher (N.K.) on day 0, day 15 and day 45.

Immediatedly after the IPL the patients were asked to grade the pain score using visual analog scale. The patients' skin and eyes were examined again for any complications; for example, skin burn, conjunctival or corneal burn or abrasion.

On day 15, the participants were asked about their side effects of previous session and about the drug adherence. The data about warm compression, lid scrub and the number of artificial tear eye drops per day were asked and recorded. Then the participants were asked by trained standardized reseach assistant to do the dry eye questionnaire (OSDI) and also to give a dry eye symptoms score in the visual analog scale. Ocular examintaions included visual acuity both best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, meiboscore using meibography, tear film break-up time using fluorescein technique, NEI staining score, meibum quality and meibomian gland expressibility

On day 45, the participants were asked about their side effects of previous session and about the drug adherence. The data about warm compression, lid scrub and the number of artificial tear eye drops per day were asked and recorded. Then the participants were asked by trained standardized reseach assistant to do the dry eye questionnaire (OSDI) and also to give a dry eye symptoms score in the visual analog scale (VAS). Ocular examintaions included visual acuity both best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, meiboscore using meibography, tear film break-up time using fluorescein technique, NEI staining score, meibum quality and meibomian gland expressibility. After that the patients were asked to wait 10minutes and then tear osmolarity measurement using TearLab was done to right eye of the each participant.

On month 3, the participants were asked about their side effects of previous session and about the drug adherence. The data about warm compression, lid scrub and the number of artificial tear eye drops per day were asked and recorded. Then the participants were asked by trained standardized reseach assistant to do the dry eye questionnaire (OSDI) and also to give a dry eye symptoms score in the visual analog scale (VAS). Ocular examintaions included visual acuity both best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, meiboscore using meibography, tear film break-up time using fluorescein technique, NEI staining score, meibum quality and meibomian gland expressibility. After that the patients were asked to wait 10 minutes and then tear osmolarity measurement using TearLab was done to the right eye of each participant. After that the tear samples of the right eye of the participants who had previously been randomized to be analyzed will be collected by instilling 50 microlitres of phosphate-buffer saline into the inferior fornix without topical anesthesia, followed by movement of the eyes to mix the tear fluid content. A total of approximately 10 microlitres of unstimulated tear fluid and buffer were collected from the inferior tear meniscus using a glass capillary micropipette at the lateral canthus. Samples were placed into 200-microlitres Eppendorf tube, then diluted 10-fold using the sample diluent supplied in the kit and immediately

transported in an insulated cooler to a -80 C freezer. After collecting all tear samples, the tear cytokines IL-1Ra and IL-6 were analyzed using Bio-Plex® 200 system (Bio-Rad, Hercules, CA). Standard curves were generated by using the reference cytokine sample supplied in the kit and were used to calculate the cytokine concentrations in tear samples. Lastly, one drop of topical anesthesia was applied on all of the patients' eyes and five minutes later Schirmer's test was done. The patients did not receive either IPL or sham-IPL. However, they still received standard treatment (warm compression, lid scrub and artificial tears).

On month 6, the participants were asked about their side effects of previous session and about the drug adherence. The data about warm compression, lid scrub and the number of artificial tear eye drops per day were asked and recorded. Then the participants were asked by trained standardized reseach assistant to do the dry eye questionnaire (OSDI) and also to give a dry eye symptoms score in the visual analog scale (VAS). Ocular examintaions included visual acuity both best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, meiboscore using meibography, tear film break-up time using fluorescein technique, NEI staining score, meibum quality and meibomian gland expressibility. After that the patients were asked to wait 10 minutes and then tear osmolarity measurement using TearLab will be done to the right eye of each participant.

The patients did not receive either IPL or sham-IPL. However, they still received standard treatment (warm compression, lid scrub and artificial tears).

Sample size calculation

Our primary outcome parameter (tear break-up time, seconds) was a continuous data which could only be more than zero in number (positive sign). According to previous studies[2, 3, 5-9, 11, 17], the standard deviation in normal tear at baseline was approximatedly five. We designed our treated group and sham group to be individually independent. Sample size was then calculated using the following formula.

$$N \text{ (patients)} = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \ (1+(t-1)\rho)}{t\ (\Delta MCD / \sigma)^2}$$

where α reflected significant level = 0.05 that made $Z_{0.975} = 1.96$

β reflected power = 90% that made $Z_{0.9} = 1.28$

t was the number of visits which we designed to be 5

ρ is within subject correlation = 0.7 (high)

ΔMCD was mean clinical difference what we thought that this difference meant clinical importance = 3 secs

σ was standard deviation within a group at a particular time (approximately equal to 5)

Accordingly, the number of the participants for each arm of treatment was 45. We expected that there might be some of the missing data due to patients' loss to follow-up so we increased the number of participants by 20%. This made the number of the participants for each arm of treatment is 57. As a result, the total number of participants were 114.

Data collection

Data were recorded in case record form as followed;

Part I : general characteristics : age, sex, occupation, education, stage of MGD severity, underlying diseases, drug allergies, ocular problems/disease, current medications.

Part II : clinical assessment : dry eye questionnaire (OSDI score, VAS), best-corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA), tear film lipid layer thickness using tear film interferometer, Meiboscore using Meibography, tear film break-up time using fluorescein technique, NEI staining score, Meibum quality, Meibomian

gland expressibility, Schirmer's test and for follow period : side effects and comliance were recorded

Part III : Tear samples : tear osmolarity, IL-1Ra, IL-6

Part IV : Side effects and complications

Compliance

The patients were evaluated the number of warm compression and lid scrub by answering the frequency of doing warm compression and lid scrub in times per day and days per weeks. The number of the warm compression in a week was scored as an A. The number of the lid scrub in a week was scored as a B. Then A + B would be summed up as a compliance score (range 0-28). If the score was not more than 9, the patient was classified as a poor compliance. If the score was more than 10 but not more than 18, the patient was classified as a good compliance. If the score was more than 19, then the patient was classified as an excellent compliance.

About the compliance with artificial tear uses, the number of the artificial tear drops uses were asked in every visit and the mean values were calculated. The difference of the number of these drops between IPL and sham group was statistically evaluated.

Blinding

This study was double-blinded. The evaluator (Y.P.) and the participants were blinded to assignment to interventions. The evaluator only examined the patient in the examination room while the intervention was performed by another physician (N.K.) in treatment room. These two rooms were in different areas. The participants did not know which group they were in since there was the opaque goggles covered their eyes and the cooling gel spreaded over the treated area. Both groups the IPL tip was placed below the inferior lid margin divided into 5 areas from inner canthus toward lateral canthus. Then the IPL began for a total of one pass on each eye. The sham-group patients's face was placed with the IPL probe without applied any light power.

Statistical Analysis

Considering continuous parametric data, the mean and standard deviation (SD) of the data were calculated and linear mixed models were used as a statistical test. Regarding ordinal data, the median and interquartile range (IQR) of the data were calculated and ordinal logistic mixed effect model was used as a statistical test. Considering nominal data, the proportion of the data were calculated and nominal logistic mixed effect model was used as a statistical test. Outcomes will be considered significant if p is less than 0.05. Regarding demographic data, Student's t-test was used to analyze the difference of age. Chi-squared test and Fischer's exact test were used to analyze the difference of gender, education, underlying medical problems, current medication used and previous ocular surgery. Mann-Whitney U test was used to was used to analyzed the difference in duration of computer use per day.

Mixed model analysis was used in OSDI score, VAS, UCVA, BCVA, tear film lipid layer thickness, meibography grade, TBUT, ocular surface staining score, meibum quality score, meibum expressibility score, Schirmer's test, tear osmolarity and pain score immediate after IPL. Linear regression analysis was used in cytokines comparison. Dealing with protocol deviation, the researchers will analyze the data by both intention to treat analysis and per protocol analysis. If the results are not in the same direction, the researchers will conclude the results that there is no statistically significant difference. Considering missing data, since we use mixed models for data analysis, both missing completely at random (MCAR) or missing at random (MAR) will be considered already in these statistical tests. However, if not missing at random (NMAR) happens, the researchers will use last observation carried forward (LOCF) to impute the data. Subgroup analysis was analyzed according to stage of the disease and compliance of the patients.

Chapter 4 Results

One hundred and seventy five patients were enrolled in this study. After assessed for eligibility, eleven patients did not meet the inclusion and exclusion criteria, and fifty patients declined to participate the study owing to their inconveniences with the study's

follow-up schedule. One hundred and fourteen patients were randomized and allocated into IPL and sham-IPL group. The period of recruitment started in March, 2018. The recruitment ended in July 2018 when the number of the population had met with the calculated sample size. The period of giving interventions and follow-up started in August, 2018 and ended in March, 2019 when all the participants were followed up for 6 months.

The characteristics of study patients are presented in Table 5. Two hundred and twenty-eight eyes of one hundred and fourteen patients (ninety-nine women and fifteen men) were enrolled in this study. The mean age ± SD was 58.98 ± 12.66 years in IPL group and 59.47 ± 11.43 years in sham-IPL group. The genders in both groups are not statistically significantly different (p=0.166). Female are the more predominant gender in both groups. The mean duration ± SD of computer/tablet using are 3.86 ± 3.12 hours/day in IPL group and 3.72 ± 2.40 hours/day in sham-IPL group (p=0.777). The underlying medical problems including dyslipidemia, hypertension, type2 diabetes, allergic rhinitis, allergic conjunctivitis, migraine, osteoporosis/osteopenia, CA breast, atopic dermatitis, hypothyroidism, depression, kidney diease, gastritis/GERD, ischemic heart disease, viral hepatitis, asthma, benign prostatic hyperplasia, cardiac arrhythmia, vdetigo, hypopituitarism and chronic urticaria are not statistically significantly different in both groups. Systemic mediactions including anti-lipemic drug, diuretics, sulfonylurea DM drug, aspirin, clopidogrel, glucosamine, NSAIDs, calcium, ferrous sulfate, systemic hormones, antidepressant/antipsychotic, antihistamine, propyl thiouracil, antiviral, anti-BPH, sodamint, systemic steroid, pregabalin, senokot, multivitamin, vitamin B1-6-12, vitamin C, vitamin D, lutein, fish oil/omega-3, zinc, biotin, lecithin, niacin, evening primrose, oral contraceptive pills and unidentified herbs are not statistically significantly different in both groups. Ocular drugs including artificial tears and antihistamine/mast cell stabilizer are not statistically significantly different in both groups. The numbers of steroid inhalers and skin users are not statistically significantly different in both groups. The numbers of contact lens wearers are not statistically significantly different in both groups (p=0.768). Nevertheless, those who wore contact lens stopped using the lens more than one month prior to study. The numbers of patients undergone pterygium surgery, cataract

surgery, refractive surgery and botulinum toxin injection at forehead and around the eyes are not statistically significantly different in both groups. Those who underwent these procedures all had the surgery performed more than 6 months prior to study. The numbers of patients who had history of cancer, underwent radiation and chemotherapy are not statistically significantly different in both groups. There are two patients who previously had IPL done (more than 12 months prior to study) in IPL group while there are five patients in sham-IPL groups (p=0.438). There is one patient who had previously LipiFlow done more than 12 months ago in each group (p=1.00). The number of artificial tear use per day were not statistically different between IPL and sham group (p=0.933).

Table 5 Patients' demographics (n=114)

	Mean (Standard deviation)	
	IPL group (n=57)	Sham-IPL group (n=57)
Age (years)	58.96 (12.66)	59.47 (11.43)
Computer use (hr/day)	3.86 (3.12)	3.72 (2.40)
Number of artificial tear use (drops/day)	3.06 (1.41)	3.08 (1.41)
	Number (percentage)	
Sex (patients)	Female 47 (82.46), Male 10 (17.54)	Female 52 (91.23), Male 5 (8.77)
Education (patients)	Elementary 7 (12.28) High School 13 (22.81) Bachelor 24 (42.11) Master/PhD 13 (22.81)	Elementary 3 (5.26) High School 10 (17.54) Bachelor 33 (57.89) Master/PhD 11 (19.30)
Dyslipidemia (patients)	22 (38.6)	22 (38.6)
Allergic rhinitis (patients)	10 (15.79)	10 (15.79)
Hypertension (patients)	20 (35.09)	19 (33.33)

Migraine (patients)	1 (1.75)	2 (3.51)
Mitral valve prolapse (patients)	0 (0)	1 (1.75)
Osteoporosis/osteopenia (patients)	5 (8.77)	8 (14.04)
CA Breast (patients)	0 (0)	2 (3.51)
Type2 Diabetes (patients)	8 (14.04)	5 (8.77)
Allergic conjunctivitis (patients)	6 (10.53)	4 (7.02)
Atopic dermatitis (patients)	5 (8.77)	5 (8.77)
Hypothyroidism (patients)	0 (0)	3 (5.26)
Depression (patients)	2 (3.51)	2 (3.51)
Kidney disease (patients)	1 (1.75)	2 (3.51)
Gastritis/GERD (patients)	3 (5.26)	1 (1.75)
Ischemic heart disease (patients)	1 (1.75)	1 (1.75)
Viral hepatitis B (patients)	1 (1.75)	1 (1.75)
Asthma (patients)	3 (5.26)	1 (1.75)
BPH (patients)	1 (1.75)	0 (0)
Cardiac arrhythmia (patients)	1 (1.75)	0 (0)
Vertigo (patients)	1 (1.75)	0 (0)
Hypopituitarism (patients)	1 (1.75)	0 (0)
Chronic urticarial (patients)	1 (1.75)	0 (0)

Diuretics (patients)	0 (0)	1 (1.75)
Antilipemic drug (patients)	14 (24.56)	18 (31.58)
Sulfonylurea DM drug (patients)	1 (1.75)	1 (1.75)
Calcium (patients)	3 (5.26)	6 (10.53)
Ferrous sulfate (patients)	0 (0)	1 (1.75)
Aspirin (patients)	3 (5.26)	3 (5.26)
Clopidogrel (patients)	0 (0)	1 (1.75)
Glucosamine (patients)	1 (1.75)	2 (3.51)
NSAIDs (patients)	0 (0)	1 (1.75)
Systemic hormones (patients)	1 (1.75)	4 (7.02)
Antidepressant/antipsychotic (patients)	2 (3.51)	2 (3.51)
Antihistamine (patients)	4 (7.02)	2 (3.51)
Propyl thiouracil (PTU) (patients)	0 (0)	1 (1.75)
Antiviral drug (patients)	1 (1.75)	0 (0)
AntiBPH (patients)	1 (1.75)	0 (0)
Sodamint (patients)	1 (1.75)	0 (0)
Systemic steroid (patients)	2 (3.51)	0 (0)
Pregabalin (patients)	2 (3.51)	0 (0)
Senokot (patients)	1 (1.75)	0 (0)

Multivitamin (patients)	14 (24.56)	9 (15.79)
Vitamin D (patients)	3 (5.26)	5 (8.77)
Vitamin B 1-6-12 (patients)	1 (1.75)	6 (10.53)
Vitamin C (patients)	3 (5.26)	4 (7.02)
Lutein (patients)	0 (0)	1 (1.75)
Fish oil / omega-3 (patients)	6 (10.53)	4 (7.02)
Zinc (patients)	2 (3.51)	0 (0)
Biotin (patients)	1 (1.75)	0 (0)
Lecithin (patients)	1 (1.75)	0 (0)
Niacin (patients)	1 (1.75)	0 (0)
Evening primrose (patients)	1 (1.75)	0 (0)
Unidentified herbs (patients)	6 (10.53)	9 (15.79)
Oral contraceptive pills (patients)	1 (1.75)	2 (3.51)
Artificial tear (patients)	35 (62.5)	32 (56.14)
Topical antihistamine/mast cell stabilizer (patients)	4 (7.14)	2 (3.51)
Steroid inhaler (patients)	4 (7.14)	5 (8.77)
Skin steroid (patients)	1 (1.75)	1 (1.75)
Contact lens wearer (quit more than 1 month prior to study) (patients)	7 (12.28)	6 (10.53)

Pterygium surgery (more than 6 months prior to study) (patients)	0 (0)	1 (1.75)
Cataract surgery (more than 6 months prior to study) (patients)	9 (15.79)	9 (15.79)
Lacrimal surgery (patients)	0 (0)	0 (0)
PRK (more than 6 months prior to study) (patients)	0 (0)	0 (0)
LASIK (more than 6 months prior to study) (patients)	1 (1.75)	2 (3.51)
SMILE (more than 6 months prior to study) (patients)	0 (0)	1 (1.75)
Botox injection at forehead or around the eyes (more than 6 months prior to study) (patients)	0 (0)	4 (7.02)
Previous breast cancer (more than 2 years prior to study) (patients)	0 (0)	2 (3.51)
Previous radiation – not involving face area (patients)	2 (3.51)	2 (3.51)
Previous chemotherapy (patients)	1 (1.75)	1 (1.75)

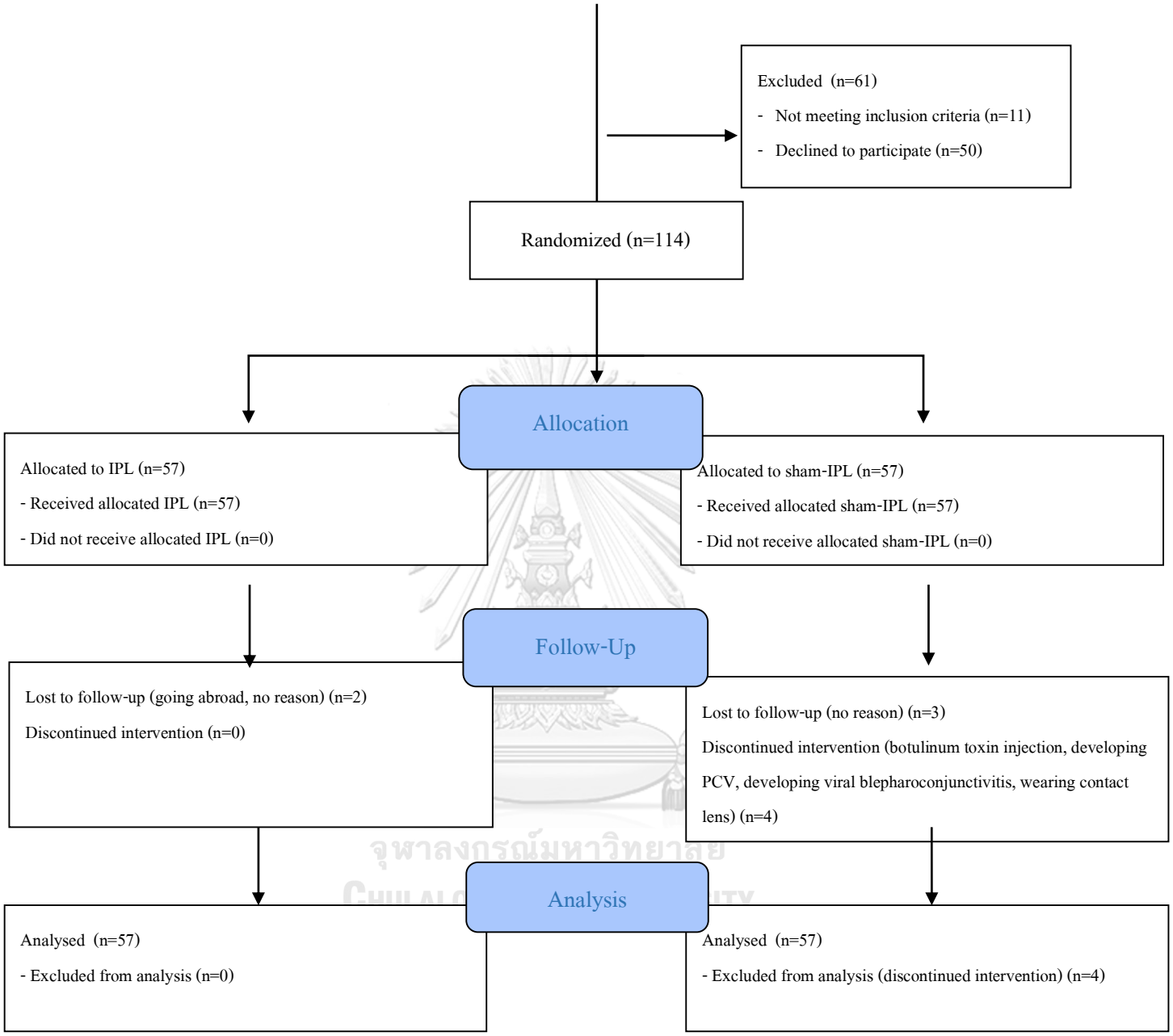
Previous IPL (more than 12 months prior to study) (patients)	2 (3.51)	5 (8.77)
Previous LipiFlow (more than 12 months prior to study) (patients)	1 (1.75)	1 (1.75)

The subgroup analysis was done according to stage of the disease. The number of patients in stage 1, 2, 3 and 4 were fifteen, twenty-three, thirty-four and forty-two respectively.

The Fitzpatrick skin types in our study were type 2 (five patients), 3 (forty-nine patients) and 4 (sixty patients). All patients were Asian.

Two patients in IPL group were lost to follow-up. One patient was lost to follow-up after the first visit and the other was after the fourth visit. Three patients in sham-IPL group were lost to follow-up. One patient was lost to follow-up after the second visit, another was after the third visit, and the other was after the fourth visit. Four patients in sham-IPL group were excluded during the study. One patient had botulinum toxin injection during the study. Another patient developed macular hemorrhage due to Polypoidal choroidal vasculopathy (PCV) in one eye and the visual acuity dropped to counting finger 1 foot. Another patient developed viral blepharoconjunctivitis and refused to continue the intervention. The other patient wore contact lens during the study. There is no protocol deviation in our study. When we considered these reasons of the excluded and loss-to-follow-up patients, those data missing were classified as missing completely at random (MCAR) and missing at random (MAR). These two kinds of data missing were considered already in mixed model analysis. As a result, fifty-seven patients in IPL group and fifty-seven patients were analyzed (Figure 7 : Consort flow diagram). In our study, there was no not missing at random (NMAR).

Figure 7 CONSORT Flow Diagram



Symptoms

Ocular Surface Disease Index (OSDI) score

In IPL group, the mean OSDI score was 38.76 (SD 21.11, range 0-100), 27.90 (SD 20.28, range0-70.83), 25.69 (SD 15.77, range 0-58.33), 25.04 (SD 16.97, range 0-68.75) and 24.29 (SD 16.92, range 66.67) at day 0, day 15, day 45, month 3 and month 6 respectively. On the contrary, in sham-IPL group, the mean OSDI score was 36.02 (SD

21.28, range 0-93.75), 32.23 (SD 21.72, range 2.08-83.33), 29.12 (SD 20.85, range 0-81.25), 29.12 (SD 16.89, range 0-66.67) and 32.71 (20.07, range 4.17-85.42) at day 0, day 15, day 45, month 3 and month 6 respectively. Although at day 15, day 45, month3 and month 6, the mean OSDI in IPL group was lower than that in sham-IPL, only at month 6 the difference was statistically significant (Table6).

Subgroup analysis according to stage of the disease showed that in all stage (1-4), the OSDI score in IPL group was lower than that in sham-IPL group in all visits after the first session of intervention. However, the difference was not statistically significant (Table 7,8,9,10)

Subgroup analysis according to compliance showed that in poor and good compliance group, the OSDI score in IPL group was lower than that in sham-IPL but not statistically significantly in all visits (Table 11.12). In excellent compliance, the OSDI score in IPL group was lower than that in sham-IPL. The difference was statistically different at month 6 (Table 13).

Regarding the comparison of the results over time, OSDI scores in IPL group at day 15, day45, month 3 and month 6 were statistically significantly lower than baseline level at day 0 (Table 14). This showed that the symptoms were better since day 15 and persisted throughout the study. On the contrary, the scores in sham-IPL group at day 15 and month 6 were not statistically difference from baseline (Table 14). The scores in sham-IPL group began to decrease at day 45. Significant improvement of symptoms was faster in IPL group.

Visual Analog Scale (VAS) score

In IPL group the mean VAS score was 4.83 (SD 2.87, range 0-10), 3.79 (SD 2.54, range 0-10), 2.68 (SD 1.63, range 06), 2.94 (SD 1.99, range 0-8) and 2.67 (SD 1.56, range 0-7) at day 0, day 15, day 45, month 3 and month 6 respectively. In contrast, in sham-IPL group, the mean VAS score was 4.16 (SD 2.98, range 0-10), 3.68 (SD 2.92, range 0-9), 3.10 (SD2.42, range 0-8), 3.11 (SD 2.27, range 0-8) and 3.17 (SD 2.47, range 0-9) at day 0, day 15, day 45, month 3 and month 6 respectively. The VAS score, which reflected the

symptoms of dry eye, in IPL group was lower than that in sham-IPL group; however, the difference was not statistically significant (Table6).

Subgroup analysis according to stage of the disease and compliance showed that there was no statistical difference between two groups (Table 7,8,9,10,11,12,13).

Regarding the comparison of the results over time, VAS in IPL group at day 15, day45, month 3 and month 6 were statistically significantly lower than baseline level at day 0 (Table 14). This showed that the symptoms were better since day 15 and persisted throughout the study. On the contrary, the scores in sham-IPL group at day 15 were not statistically difference from baseline (Table 14). The scores in sham-IPL group began to decrease at day 45. Significant improvement of symptoms was faster in IPL group.

Pain score after IPL

About pain score immediate after the IPL session, in IPL group the mean pain score was 0.98 (SD 1.32, range 0-4), 0.65 (SD 1.20, range 0-5) and 0.38 (SD 1.11, range0-6) at day 0, day 15 and day 45. In sham-IPL group, the mean pain score was 0.05 (SD 0.23, range 0-1), 0.05 (SD 0.29, range 0-2) and 0.00 (SD 0.00, range 0-0) at day 0, day 15 and day 45. At all three visits, the pain scores in IPL group were significantly more than those in sham-IPL group (Table6).

Subgroup analysis according to stage of the disease showed that in stage 1 the pain score after IPL in IPL group was statistically higher that that in sham-IPL at day 0 and day 15 (Table7). In stage 2 the pain score after IPL in IPL group was statistically higher that that in sham-IPL only in day 15 (Table8). In stage 3 and 4 the pain score after IPL in IPL group was statistically higher that that in sham-IPL only in day 0 (Table9,10). Apparently, at day 45 (the last session of IPL) we found that in IPL group the pain score was not different from the other group in all stage.

Regarding the comparison of the results over time, the pain score at day 45 were statistically significantly lower than baseline level at day 0 (Table 14). This showed that the patients reported less pain after a few IPL.

Signs

Uncorrected visual acuity (UCVA) in logMAR

In IPL group the mean UCVA was 0.35 (SD 0.39, range 0-1.7), 0.33 (SD 0.41, range 0-1.94), 0.34 (SD 0.37, range 01.82), 0.31 (SD 0.37, range -0.1-1.7) and 0.31 (SD 0.36, range -0.1-1.82) at day 0, day 15, day 45, month 3 and month 6 respectively. Similarly, the mean UCVA in sham-IPL group was 0.41 (SD 0.47, -0.13-2), 0.42 (SD 0.48, range -0.13-2), 0.38 (SD 0.46, range -0.13-2), 0.38 (SD 0.48, range -0.13-2) and 0.39 (SD 0.49, range -0.1-1.86) at day 0, day 15, day 45, month 3 and month 6 respectively (Table6).

Subgroup analysis according to stage of the disease showed that in all stage (1-4) there was no statistically difference between two groups (Table 7,8,9,10).

Subgroup analysis according to compliance showed that in poor and good compliance there was no statistical difference between two groups in all visits (Table 11,12). However, in excellent compliance, the UCVA(logMAR) at day 0 and day 15 in IPL group was statistically lower than that in sham-IPL group (Table 13)

Regarding the comparison of the results over time, UCVA remained unchanged in both IPL and sham-IPL group (Table 14).

Best corrected visual acuity (BCVA) in logMAR

In IPL group the mean BCVA was 0.10 (SD 0.13, range 0-1.3), 0.09 (SD 0.13, range 0-1.3), 0.09 (SD 0.14, range -0.11.3), 0.10 (SD 0.13, range -0.13-1.3) and 0.09 (SD 1.37, range -0.1-1.3) at day 0, day 15, day 45, month 3 and month 6 respectively. Similarly, the mean BCVA in sham-IPL group was 0.12 (SD 0.30, range -0.3-2), 0.09 (SD 0.14, range -0.13-2), 0.06 (SD 0.10, range -0.13-0.4), 0.08 (SD 0.15, range -0.13-0.9) and 0.06 (SD 0.10, range -0.1-0.5) at day 0, day 15, day 45, month 3 and month 6 respectively (Table6).

Subgroup analysis according to stage of the disease showed that in stage 2, only at day 45 and month 6 the BCVA(logMAR) in IPL group was higher than that in sham-IPL group (Table 8). In Stage 1,3,4 the BCVA was not statistically different in day 15, day 45, month 3 and month 6 (Table 7,9,10)

Subgroup analysis according to compliance showed that there was no statistically different between two groups in all visits (Table 11,12,13)

Regarding the comparison of the results over time, BCVA remained unchanged in both IPL and sham-IPL group (Table 14).

Efficacy index

Efficacy index was the ratio of post-IPL UCVA / pre IPL-BCVA. Efficacy index at day 45, month 3 and month 6 was 0.58, 0.61 and 0.61 respectively.

Safety index

Safety index was the ratio of post-IPL BCVA / pre-IPL BCVA). Safety index at day 45, month 3 and month 6 was 1.00, 1.03 and 1.03 respectively.

Tear film lipid layer thickness (TFLLT) in nanometers

In IPL group the mean TFLLT was 61.58 (SD 23.79, range 20-100), 60.54 (SD 22.17, range 21-100), 61.33 (SD 20.07, range 22-100), 67.53 (SD 26.51, range 21-100) and 63.69 (SD 28.76, range 20-100) at day 0, day 15, day 45, month 3 and month 6 respectively. On the contrary, the mean TFLLT in sham-IPL group was 63.99 (SD 25.41, range 20-100), 59.04 (SD 24.39, range 21-100), 60.61 (SD 24.33, range 22-100), 66.40 (SD 26.97, range 21-100) and 62.81 (SD 26.37, range 20-100) at day 0, day 15, day 45, month 3 and month 6 respectively. However, the TFLLT in two groups were not statistically significantly different (Table6).

Subgroup analysis according to stage of the disease showed that in stage 1, 2 and 3 there was no statistical difference between IPL and sham-IPL group (Table 7,8,9) Nevertheless, in stage 4, tear film lipid layer thickness in IPL-group was higher than that in sham-IPL group at all visits including baseline (Table 10).

Subgroup analysis according to compliance showed that in all compliance types there was no statistical difference between IPL and sham-IPL group (Table 11,12,13).

Regarding the comparison of the results over time, TFLLT remained unchanged in both IPL and sham-IPL group (Table 14).

Meibography grade (score 0-3)

In IPL group the mean meibography grade was 1.42 (SD 0.65, range 1-3), 1.38 (SD 0.61, range 1-3), 1.35 (SD 0.61, range 1-3), 1.29 (SD 0.59, range 1-3) and 1.32 (SD 0.62, range 1-3) at day 0, day 15, day 45, month 3 and month 6 respectively. On the contrary, the mean meibography grade in sham-IPL group was 1.50 (SD 0.65, range 1-3), 1.49 (SD 0.62, range 1-3), 1.54 (SD 0.66, range 1-3), 1.34 (SD 0.58, range 1-3) and 1.39 (SD 0.59, range 1-3) at day 0, day 15, day 45, month 3 and month 6 respectively. Nevertheless, the meibography grades in two groups were not statistically significantly different (Table6).

Subgroup analysis according to stage of the disease showed that in stage 1 (the mildest stage) the meibography grade in IPL group was lower than that in sham-IPL group (Table 7) ;however the difference also existed at baseline. In stage 2 and 3, there was no statistical difference between two groups (Table 8,9). In stage 4, the meibography grade in IPL-group was statistically lower than that in sham-IPL group at day 45 and month 6 as shown in the Table 10.

Subgroup analysis according to compliance showed that in all compliance types there was no statistical difference between IPL and sham-IPL group (Table 11,12,13).

Regarding the comparison of the results over time, meibography grades in IPL group at day 45, month 3 and month 6 were statistically significantly lower than baseline level at day 0 (Table 14). On the contrary, in sham-IPL group only at month 3 that the meibography grades were statistically lower than baseline level (Table 14). This means improvement of meibomian gland structure existed and was faster in IPL group.

Tear film break-up time (TBUT) in seconds

In IPL group the mean TBUT was 1.36 (SD 0.82, range 0-3.67), 4.99 (SD 2.83, range 0.67-15), 7.53 (SD 4.03, range 2-18), 6.35 (SD 3.20, range 1-19) and 5.23 (SD 2.91, range 1-17) at day 0, day 15, day 45, month 3 and month 6 respectively. On the other hand, the mean TBUT in sham-IPL group was 1.44 (SD 0.70, range 0.33-3), 1.88 (SD 0.72, range 0.33-3.33), 2.81 (SD 0.92, range 0.67-5), 3.34 (SD 1.48, range 1-10) and 3.11 (SD 0.99,

range 1-5) at day 0, day 15, day 45, month 3 and month 6 respectively. The TBUT in IPL group began to increase significantly after the first session of IPL and reached its maximum (7.53 seconds) at day 45. At month 6 the TBUT in IPL group was 5.23 seconds. In all visits apart from baseline, TBUT in IPL group was statistically significantly higher than that in sham-IPL group ($p<0.001$) (Table6).

Subgroup analysis according to stage of the disease showed that in all stages (1-4) TBUT in IPL group was higher than that in sham-IPL group in day15, day 45 and month 3 (Table 7,8,9,10). In month 6 TBUT in IPL group was higher than that in sham-IPL group in stage 1,3 and 4 (Table 7,9,10)

Subgroup analysis according to compliance showed that in all compliance type the TBUT in IPL group was higher than that in sham-IPL group (Table 11,12,13)

Regarding the comparison of the results over time, TBUT in both IPL and sham-IPL group was lower at day 15, day 45, month 3 and month 6 when compared to baseline level (Table 14).

Ocular surface staining using NEI grading system (score 0-33)

In IPL group the mean staining score was 4.90 (SD 4.46, range 0-20), 3.13 (SD 3.19, range 0-12), 2.03 (SD 2.76, range 2-18), 2.05 (SD 2.09, range 1-19) and 1.92 (SD 2.23, range 1-17) at day 0, day 15, day 45, month 3 and month 6 respectively. Contrastly, the mean staining score in sham-IPL group was 5.21(SD 5.09, range 0-27), 4.15 (SD 5.32, range 0-27), 3.24 (SD 3.87, range 0-20), 2.73 (SD 2.55, range 0-16) and 3.48 (SD 2.93, range 0-18) at day 0, day 15, day 45, month 3 and month 6 respectively. However, the ocular surface staining in two groups were not statistically significantly different (Table6).

Subgroup analysis according to stage of the disease showed that there was no statistical difference between IPL and sham-IPL group in stage 1, 2 and 3 in all visits (Table 7,8,9). However, in stage 4 the ocular surface staining in IPL group was statistically lower than that in sham-IPL group at day 15, day 45 and month 6 (Table 10)

Subgroup analysis according to compliance showed that in poor compliance, the ocular surface staining in IPL group was lower than that in sham-IPL group but not

statistically significantly except at day 15 (Table11). In good and excellent compliance (Table 12,13) the ocular surface staining in two groups were not statistically different.

Regarding the comparison of the results over time, ocular surface staining in both IPL and sham-IPL group was lower at day 15, day 45, month 3 and month 6 when compared to baseline level (Table 14).

Meibum quality score (score 0-24)

In IPL group the mean meibum quality score was 15.82 (SD 5.29, range 3-24), 10.27 (SD 4.74, range 2-21), 7.20 (SD 4.00, range 0-18), 8.60 (SD 5.11, range 0-20) and 8.74 (SD 4.74, range 1-19) at day 0, day 15, day 45, month 3 and month 6 respectively. On the contrary, the mean meibum quality score in sham-IPL group was 15.54 (SD 5.85, range 4-24), 14.81 (SD 5.63, range 3-24), 13.48 (SD 4.81, range 3-22), 13.44 (SD 5.24, range 3-24) and 13.19 (SD 5.01, range 4-24) at day 0, day 15, day 45, month 3 and month 6 respectively. The meibum quality score began to decrease after the first session of IPL and reached its maximal effect after 2-3 sessions. In all visits apart from baseline, meibum quality score in IPL group was statistically significantly lower than that in sham-IPL group ($p<0.001$) (Table6).

Subgroup analysis according to stage of the disease showed that in all stages (1-4) the meibum quality score in IPL group was statistically lower than that in sham-IPL group at day 15, day 45, month 3 and month 6 (Table 7,8,9,10).

Subgroup analysis according to compliance showed that in poor and good compliance, the meibum quality score in IPL group was statistically lower than that in sham-IPL group in all visits (Table 11,12). In excellent compliance, the score was statistically lower than that in sham-IPL group at day 45 (Table 13).

Regarding the comparison of the results over time, meibum quality scores in IPL group at day 15, day 45, month 3 and month 6 were statistically significantly lower than baseline level at day 0 (Table 14). This demonstrated the meibum quality scores were statistically better after the first session of treatment. In contrast, in sham-IPL group, the

scores were not statistically different from baseline level until day 45 (Table 14). This showed that in sham-IPL group required more time to improve.

Meibum expressibility score (score 0-3)

In IPL group the mean meibum expressibility score was 1.44 (SD 0.79, range 0-3), 0.71 (SD 0.61, range 0-2), 0.58 (SD 0.54, range 0-2), 0.59 (SD 0.65, range 0-2) and 0.50 (SD 0.67, range 0-2) at day 0, day 15, day 45, month 3 and month 6 respectively. On the contrary, the mean meibum expressibility score in sham-IPL group was 1.36 (SD 0.88, range 0-3), 1.19 (SD 0.73, range 0-3), 1.03 (SD 0.66, range 0-2), 1.03 (SD 0.83, range 0-3) and 1.12 (SD 0.70, range 0-3) at day 0, day 15, day 45, month 3 and month 6 respectively. The meibum expressibility score began to decreased after the first session of IPL and reached its maximum after 2-3 sessions. In all visits apart from baseline, meibum expressibility score in IPL group was statistically significantly lower than that in sham-IPL group ($p<0.001$) (Table6).

Subgroup analysis according to stage of the disease showed that in stage 1, the score in IPL group was significantly lower than that in sham-IPL group at day 45 and month 6 (Table 7). In stage 2, the score in IPL group was significantly lower than that in sham-IPL group at month 6 (Table 8). In stage 3, the score in IPL group was significantly lower than that in sham-IPL group at day 15 and month 6 (Table 9). In stage 4, the score in IPL group was significantly lower than that in sham-IPL group at day 15, day 45, month 3 and month 6 (Table 10).

Subgroup analysis according to compliance showed that in poor compliance, the meibum expressibility score in IPL group was statistically lower than that in sham–IPL group in all visits (Table 11). However, in good and excellent compliance, the score in IPL group was statistically lower than that in sham-IPL group only at month 6 (Table 12,13) Regarding the comparison of the results over time, meibum expressibility quality scores in IPL group at day 15, day 45, month 3 and month 6 were statistically significantly lower than baseline level at day 0 (Table 14). This demonstrated the meibum expressibility scores were statistically better after the first session of treatment. In contrast, in sham-IPL

group, the scores were only statistically different at day 45 and month 3 when compared to baseline level at day 0 (Table 14). Significant improvement of meibum expressibility was faster in IPL group.

Schirmer's test in millimeters

In IPL group the Schirmer's test was 6.34 (SD 4.03, range 0-24) and 6.92 (SD 4.34, range 1-30) at day 0 and month3 respectively. Similarly, in sham-IPL group the Schirmer's test was 7.20 (SD 5.42, range 0-34) and 8.25 (SD 6.66, range 0-40) at day 0 and month 3 respectively. The difference between two groups was not statistically significant in all visits (Table6).

Subgroup analysis according to stage of the disease showed that in 1, 2 and 4, the Schirmer's test remained unchanged (Table 7,8,10) However, in stage 3, the Schirmer's test score in IPL group was lower than that in sham-IPL group at month 3 (Table 9)

Subgroup analysis according to compliance showed that in poor, good and excellent compliance, there was no statistical difference between IPL and sham-IPL group (Table 11,12,13)

Regarding the comparison of the results over time, Schirmer's test remained unchanged in both IPL and sham-IPL group (Table 14).

Tear osmolarity in mOsm/L

In IPL group the tear osmolarity was 294.02 (SD 16.50, range 275-352), 292.14 (SD 14.81, range 275-344), 190.54 (SD 12.16, range 275-332) and 300.39 (SD 15.01, range 275-346) at day 0, day 45, month 3 and month 6 respectively. Similarly, the tear osmolarity in sham-IPL group was 298.58 (SD 15.14, range 275-344), 292.14 (SD 12.20, range 275-322), 289.25 (SD 10.21, range 275-309) and 302.80 (SD 18.50, range 275-369) at day 0, day 45, month 3 and month 6 respectively. However, the tear osmolarity in two groups were not statistically significantly different (Table6).

Subgroup analysis according to stage of the disease showed that the tear osmolarity in IPL group was not statistically different from that in sham-IPL in all visits in

stage 1, 2 and 4 (Table7,8,10). In stage 3, the tear osmolarity in IPL group was statistically lower than that in sham-IPL group only at month 6, However, in stage 3 the tear osmolarity was not statistically different between two groups in day 15, day 45 and month 3 (Table 9)

Subgroup analysis according to compliance showed that after the first intervention there was no statistical difference between IPL and sham-IPL groups in all poor, good and excellent compliance (Table 11,12,13) Regarding the comparison of the results over time, tear osmolarity remained unchanged in both IPL and sham-IPL group (Table 14).

However, if we only focused on the patients whose baseline tear osmolarity were more than 308 mOsm/L, we found that both in IPL and sham group could significantly decrease the tear osmolarity value at day 15, day 45, month 3 and month 6.

Cytokines

IL-1Ra in pg/ml

In IPL group the tear IL-1Ra was 4215.58 (SD 3418.07, range 236.57-11429.21) and 65.30 (SD 59.11, range 1.412007.12) at baseline and month 3. In sham-IPL group the tear IL-1Ra was 3411.69 (SD 3112.32, range 390.42-10761.31) and 75.47 (SD 127.45, range 0-669.28) at baseline and month 3. There was no statistically different in level between two groups (Table6).

Regarding the comparison of the results over time, tear IL-1Ra levels at month 3 were statistically significantly lower than baseline levels in both IPL and sham-IPL group (Table 14).

IL-6 in pg/ml

In IPL group the tear IL-6 was 39.80 (SD 28.77, range 4.26-81.15) and 10.22 (SD 9.71, range 6.71-41.88) at baseline and month 3. In sham-IPL group the tear IL-6 was 271.73 (SD 464.84, range 4.91-808.48) and 7.58 (SD 1.82, range 3.92-17.71) at baseline and month 3. There was no statistically different in level between two groups (Table6).

Regarding the comparison of the results over time, tear IL-6 levels at month 3 were not statistically significantly different from baseline levels in both IPL and sham-IPL group (Table 14)

Table 6 Outcomes in all visits

Outcome parameters		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.36 (0.82)	4.99 (2.83)	7.53 (4.03)	6.35 (3.20)	5.23 (2.91)
	Sham-IPL	1.44 (0.70)	1.88 (0.72)	2.81 (0.92)	3.34 (1.48)	3.11 (0.99)
	P-value	0.368	<0.001	<0.001	<0.001	<0.001
	Mean difference (95% CI)	-0.08 (-0.36,0.21)	3.10 (2.29,3.91)	4.72 (3.92,5.53)	2.99 (2.16,3.82)	2.16 (1.32,3.00)
OSDI score	IPL	38.76 (21.11)	27.90 (20.28)	25.69 (15.77)	25.04 (16.97)	24.29 (16.92)
	Sham-IPL	36.02 (21.28)	32.23 (21.72)	29.12 (20.85)	29.12 (16.89)	32.71 (20.07)
	P-value	0.492	0.183	0.342	0.286	0.031
	Mean difference (95% CI)	2.74 (-5.13,10.60)	-4.80 (-11.87,2.27)	-3.44 (-10.53,3.65)	-3.91 (-11.11,3.28)	-7.93 (-15.15,-0.72)
VAS	IPL	4.83 (2.87)	3.79 (2.54)	2.68 (1.63)	2.94 (1.99)	2.67 (1.56)
	Sham-IPL	4.16 (2.98)	3.68 (2.92)	3.10 (2.42)	3.11 (2.27)	3.17 (2.47)
	P-value	0.224	0.637	0.635	0.879	0.347
	Mean difference (95% CI)	0.67 (-0.42,1.76)	0.22 (-0.69,1.12)	-0.22 (-1.13,0.69)	-0.07 (-1.01,0.86)	-0.44 (-1.37,0.48)
UCVA (logMAR)	IPL	0.35 (0.39)	0.33 (0.41)	0.34 (0.37)	0.31 (0.37)	0.31 (0.36)
	Sham-IPL	0.41 (0.47)	0.42 (0.48)	0.38 (0.46)	0.38 (0.48)	0.39 (0.49)
	P-value	0.470	0.237	0.583	0.335	0.399
	Mean difference (95% CI)	-0.06 (-0.22,0.10)	-0.09 (-0.25,0.06)	-0.04 (-0.20,0.11)	-0.08 (-0.23,0.08)	-0.07 (-0.22,0.09)
BCVA (logMAR)	IPL	0.10 (0.13)	0.09 (0.13)	0.09 (0.14)	0.10 (0.13)	0.09 (1.37)
	Sham-IPL	0.12 (0.30)	0.09 (0.14)	0.06 (0.10)	0.08 (0.15)	0.06 (0.10)
	P-value	0.607	0.852	0.254	0.652	0.360
	Mean difference (95% CI)	-0.02 (-0.11,0.06)	0.01 (-0.5,0.06)	0.03 (-0.02,0.09)	0.01(-0.04,0.07)	0.03 (-0.03,0.09)
Tear film lipid layer thickness	IPL	61.58 (23.79)	60.54 (22.17)	61.33 (20.07)	67.53 (26.51)	63.69 (28.76)
	Sham-IPL	63.99 (25.41)	59.04 (24.39)	60.61 (24.33)	66.40 (26.97)	62.81 (26.37)
	P-value	0.602	0.778	0.800	0.621	0.669

	Mean difference (95% CI)	-2.41 (-11.55,6.72)	1.30 (-7.78,10.39)	1.19 (-8.02,10.39)	2.33 (-6.91,11.56)	2.02 (-7.25,11.30)
Meibography grade	IPL	1.42 (0.65)	1.38 (0.61)	1.35 (0.61)	1.29 (0.59)	1.32 (0.62)
	Sham-IPL	1.50 (0.65)	1.49 (0.62)	1.54 (0.66)	1.34 (0.58)	1.39 (0.59)
	P-value	0.516	0.291	0.082	0.367	0.281
	Mean difference (95% CI)	-0.08 (-0.32,0.16)	-0.12 (-0.35,0.11)	-0.20 (-0.43,0.03)	-0.11 (-0.34,0.12)	-0.13 (-0.26,0.10)
Staining score (NEI grading system)	IPL	4.90 (4.46)	3.13 (3.19)	2.03 (2.76)	2.06 (2.09)	1.92 (2.23)
	Sham-IPL	5.21 (5.09)	4.15 (5.32)	3.24 (3.87)	2.73 (2.55)	3.48 (2.93)
	P-value	0.625	0.163	0.059	0.114	0.083
	Mean difference (95% CI)	-0.30 (-2.08,1.48)	-1.00 (-2.41,0.41)	-1.36 (-2.78,0.05)	-1.15 (-2.57,0.28)	-1.27 (-2.71,0.17)
Meibum quality	IPL	15.82 (5.29)	10.27 (4.74)	7.20 (4.00)	8.60 (5.11)	8.74 (4.74)
	Sham-IPL	15.54 (5.85)	14.81 (5.63)	13.48 (4.81)	13.44 (5.24)	13.19 (5.01)
	P-value	0.964	<0.001	<0.001	<0.001	<0.001
	Mean difference (95% CI)	0.28 (-1.79,2.35)	-4.55 (-6.39,-2.71)	-6.34 (-8.19,-4.50)	-5.11 (-6.98,-3.24)	-4.76 (-6.65,-2.88)
Meibum expressibility grade	IPL	1.44 (0.79)	0.71 (0.61)	0.58 (0.54)	0.59 (0.65)	0.50 (0.67)
	Sham-IPL	1.36 (0.88)	1.19 (0.73)	1.03 (0.66)	1.03 (0.83)	1.12 (0.70)
	P-value	0.581	<0.001	<0.001	<0.001	<0.001
	Mean difference (95% CI)	0.08 (-0.23,0.39)	-0.48 (-0.74,-0.22)	-0.44 (-0.70,-0.18)	-0.45 (-0.72,-0.19)	-0.65 (-0.92,-0.39)
Schirmer's test	IPL	6.34 (4.03)	-	-	6.92 (4.34)	-
	Sham-IPL	7.20 (5.42)	-	-	8,25 (6.66)	-
	P-value	0.635	-	-	0.16	-
	Mean difference (95% CI)	-0.86 (-2.63,0.92)			-1.40 (-3.34,0.55)	
Tear osmolarity	IPL	294.02 (16.50)	-	292.14 (14.81)	290.54 (12.16)	300.39 (15.01)
	Sham-IPL	298.58 (15.14)	-	292.14 (12.20)	289.25 (10.21)	302.80 (18.50)
	P-value	0.130	-	0.975	0.588	0.517
	Mean difference (95% CI)	-4.56 (-10.49,1.37)		-0.08 (-5.42,5.25)	1.51 (-3.94,6.96)	-1.82 (-7.34,3.69)

Pain score immediately after IPL	IPL	0.98 (1.32)	0.65 (1.20)	0.38 (1.11)	-	-
	Sham-IPL	0.05 (0.23)	0.05 (0.29)	0 (0)	-	-
	P-value	<0.001	<0.001	0.02	-	-
	Mean difference (95% CI)	0.93 (0.58, 1.28)	0.60 (028,0.92)	0.38 (0.06,0.70)		
IL-1Ra	IPL	4215.58 (3418.07)	-	-	65.30 (59.11)	-
	Sham-IPL	3411.69 (3112.32)	-	-	75.47 (127.45)	-
	P-value	0.485	-	-	0.773	-
	Mean difference (95% CI)	803.89 (-1514.72,3122.504)	-	-	-10.18 (-81.48,61.13)	-
IL-6	IPL	39.80 (28.77)	-	-	10.22 (9.71)	-
	Sham-IPL	271.73 (464.84)	-	-	7.58 (1.82)	-
	P-value	0.350	-	-	0.669	-
	Mean difference (95% CI)	-231.93 (-810.79,346.93)	-	-	2.64 (-12.30,17.58)	-

Table 7 Outcomes in stage 1 subgroup (n=15)

Outcome parameters stage 1		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.78 (0.65)	6.60 (4.43)	9.07 (4.47)	7.26 (3.49)	7/07 (4.69)
	Sham-IPL	1.29 (0.48)	1.62 (0.65)	2.69 (0.93)	2.93 (1.34)	2.76 (0.77)
	P-value	0.720	<0.0001	<0.0001	0.001	0.002
	Mean difference (95% CI)	0.47 (-2.10,3.04)	4.97 (2.40,7.54)	6.38 (3.81,8.96)	4.30 (1.65,6.95)	4.27 (1.63,6.92)
OSDI score	IPL	42.50 (20.32)	37.74 (2.0.47)	33.69 (16.10)	30.95 (22.93)	30.36 (23.69)
	Sham-IPL	50.52 (19.44)	38.28 (27.14)	34.90 (23.98)	32.44 (17.67)	42.86 (21.68)
	P-value	0.441	0.958	0.907	0.773	0.183
	Mean difference (95% CI)	-8.02 (-28.39,12.36)	-0.54 (-20.92,19.83)	-1.21 (-21.58,19.16)	-3.04 (-23.73,17.64)	-14.06 (-34.74,6.62)

VAS	IPL	6.29 (2.56)	5.71 (2.29)	4.00 (1.41)	2.83 (1.72)	3.67 (1.75)
	Sham-IPL	4.5 (2.56)	4.29 (3.45)	3.43 (2.44)	4.63 (2.56)	5.00 (2.37)
	P-value	0.125	0.190	0.832	0.535	0.240
	Mean difference (95% CI)	1.79 (-0.49,4.06)	1.55 (-0.77,3.87)	0.27 (-2.18,2.71)	-0.82 (-3.42,1.78)	-1.45 (-3.88,0.97)
UCVA (logMAR)	IPL	0.41 (0.44)	0.39 (0.44)	0.39 (0..43)	0.31 (0.40)	0.41 (0.48)
	Sham-IPL	0.32 (0.36)	0.33 (0.41)	0.27 (0.27)	0.19 (0.24)	0.24 (0.31)
	P-value	0.618	0.742	0.524	0.877	0.700
	Mean difference (95% CI)	0.10 (-0.28,0.47)	0.06 (-0.31,0.44)	0.12 (-0.25,0.50)	0.03 (-0.35,0.41)	0.07 (-0.30,0.45)
BCVA (logMAR)	IPL	0.06 (0.06)	0.04 (0.05)	0.06 (0.09)	0.02 (0.06)	0.04 (0.06)
	Sham-IPL	0.10 (0.24)	0.04 (0.15)	0.06 (0.10)	0.06 (0.15)	0.04 (0.13)
	P-value	0.507	0.981	0.895	0.345	0.729
	Mean difference (95% CI)	-0.04 (-0.16,0.08)	0.00 (-0.12,0.12)	0.01 (-0.11,0.13)	-0.06 (-0.18,0.06)	-0.02 (-0.14,0.10)
Tear film lipid layer thickness	IPL	44.36 (18.98)	51.36 (20.31)	63.21 (19.79(	56.79 (26.54)	64.43 (31.25)
	Sham-IPL	54.94 (24.30)	66.31 (30.60)	64.93 (21.00)	76.64 (27.37)	62.21 (31.92)
	P-value	0.390	0.225	0.813	0.086	0.972
	Mean difference (95% CI)	-10.58 (-34.73,13.57)	-14.96 (-39.10,9.19)	-2.98 (-27.61,21.65)	-21.62 (-46.27,3.03)	0.45 (-24.20,25.10)
Meibography grade	IPL	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
	Sham-IPL	1.375 (0.52)	1.38 (0.52)	1.44 (0.50)	1.43 (0.53)	1.43 (0.53)
	P-value	0.039	0.039	0.016	0.041	0.041
	Mean difference (95% CI)	-0.38 (-0.73,-0.02)	-0.38 (-0.73,-0.02)	-0.44 (-0.79,-0.08)	-0.37 (-0.73,-0.02)	-0.37 (-0.73,-0.02)
Staining score (NEI grading system)	IPL	3.04 (1.70)	2.79 (1.63)	2.07 (1.92)	1.93 (1.06)	2.07 (2.28)
	Sham-IPL	3.21 (2.41)	1.88 (2.17)	1.64 (1.44)	2.36 (0.94)	2.71 (1.70)
	P-value	0.354	0.329	0.694	0.755	0.592
	Mean difference (95% CI)	0.89 (-0.99,2.77)	0.91 (-0.92,2.74)	0.38 (-1.50,2.26)	-0.30 (-2.18,1.58)	-0.51 (-2.39,1.37)
Meibum quality	IPL	12.42 (3.43)	3.21 (1.11)	2.64 (1.52)	5.00 (4.02)	5.50 (4.26)
	Sham-IPL	6.94 (3.83)	7.13 (5.15)	7.63 (4.15)	7.57 (2.71)	6.57 (1.62)

	P-value	0.429	0.024	0.004	0.044	0.244
	Mean difference (95% CI)	-1.37 (-4.75,2.02)	-3.91 (-7.30,-0.53)	-4.98 (-8.37,-1.60)	-3.55 (-7.01,-0.10)	-2.05 (-5.51,1.40)
Meibum expressibility grade	IPL	0.29 (0.49)	0.14 (0.38)	0.14 (0.38)	0.36 (0.48)	0.00 (0.00)
	Sham-IPL	0.44 (0.50)	0.38 (0.52)	0.63 (4.15)	0.57 (0.53)	0.57 (0.53)
	P-value	0.494	0.295	0.030	0.349	0.013
	Mean difference (95% CI)	-0.15 (-0.59,0.28)	-0.23 (-0.67,0.20)	-0.48 (-0.92,-0.05)	-0.21 (-0.66,0.23)	-0.57 (-1.02,-0.12)
Schirmer's test	IPL	7.29 (5.26)	-	-	7.83 (5.24)	-
	Sham-IPL	7.56 (5.39)	-	-	7.36 (2.76)	-
	P-value	0.904	-	-	0.951	-
	Mean difference (95% CI)	-0.28 (-4.79,4.24)	-	-	0.15 (-4.52,4.82)	-
Tear osmolarity	IPL	289.29 (14.33)	-	288.00 (9.02)	285.00 (8.52)	296.86 (11.57)
	Sham-IPL	294.63 (8.98)	-	291.25 (15.42)	286.71 (11.91)	302.29 (21.36)
	P-value	0.402	-	0.610	0.863	0.461
	Mean difference (95% CI)	-5.34 (-17.83,7.15)	-	-3.25 (-15.74,9.24)	-1.13 (-14.01,11.74)	-4.85 (-17.72,8.03)
Pain score immediately after IPL	IPL	1.43 (0.98)	1.14 (1.57)	1.00 (2.24)	-	-
	Sham-IPL	0.13 (0.35)	0.00 (0.00)	0.00 (0.00)	-	-
	P-value	0.018	0.039	0.071	-	-
	Mean difference (95% CI)	1.30 (0.22,2.39)	1.14 (0.06,2.23)	1.00 (-0.08,2.08)	-	-

Table 8 Outcomes in stage 2 subgroup (n=23)

Outcome parameters stage 2		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.70 (0.83)	4.36 (2.41)	8.01 (4.55)	6.56 (2.51)	5.27 (2.09)
	Sham-IPL	1.78 (0.65)	2.20 (0.58)	3.12 (0.88)	3.95 (2.15)	3.94 (0.72)
	P-value	0.918	0.007	<0.0001	0.001	0.095

	Mean difference (95% CI)	-0.08 (-1.65,1.48)	2.16 (0.59,3.72)	4.90 (3.33,6.46)	2.61 (1.04,4.17)	1.36 (-0.24,2.96)
OSDI score	IPL	38.99 (24.84)	21.49 (17.13)	25.14 (10.44)	26.44 (14.53)	22.74 (14.71)
	Sham-IPL	31.73 (20.80)	25.90 (20.53)	31.24 (18.74)	30.46 (16.31)	36.06 (19.97)
	P-value	0.301	0.402	0.385	0.602	0.058
	Mean difference (95% CI)	7.26 (-6.51,21.02)	-5.95 (-19.86,7.96)	-6.10 (-19.86,7.66)	-3.71 (-17.65,10.23)	-13.32 (-27.08,0.44)
VAS	IPL	5.42 (3.18)	3.58 (2.27)	2.73 (1.49)	2.82 (1.94)	2.29 (2.20)
	Sham-IPL	4.38 (3.20)	3.36 (2.38)	2.77 (1.92)	3.15 (2.15)	3.23 (2.52)
	P-value	0.244	0.888	0.929	0.781	0.410
	Mean difference (95% CI)	1.03 (-0.70,2.77)	0.13 (-1.65,1.91)	0.08 (-1.68,1.84)	-0.25 (-2.01,1.51)	-0.73 (-2.47,1.01)
UCVA (logMAR)	IPL	0.25 (0.23)	0.24 (0.24)	0.23 (0.21)	0.22 (0.25)	0.45 (0.42)
	Sham-IPL	0.34 (0.47)	0.36 (0.45)	0.38 (0.45)	0.35 (0.48)	0.36 (0.49)
	P-value	0.519	0.441	0.295	0.354	0.489
	Mean difference (95% CI)	-0.09 (-0.38,0.19)	-0.11 (-0.40,0.17)	-0.15 (-0.44,0.13)	-0.13 (-0.42,0.15)	-0.10 (-0.39,0.18)
BCVA (logMAR)	IPL	0.12 (0.11)	0.14 (0.16)	0.12 (0.15)	0.09 (0.13)	014 (0.14)
	Sham-IPL	0.05 (0.07)	0.08 (0.12)	0.03 (0.04)	0.04 (0.07)	0.05 (0.06)
	P-value	0.078	0.104	0.028	0.236	0.036
	Mean difference (95% CI)	0.07 (-0.01,0.16)	0.07 (-0.01,0.15)	0.09 (0.01,0.17)	0.05 (-0.03,0.13)	0.09 (0.01,0.17)
Tear film lipid layer thickness	IPL	61.75 (19.77)	64.42 (18.87)	56.14 (16.67)	59.83 (24.80)	72.37 (24.64)
	Sham-IPL	74.65 (24.02)	57.15 (21.15)	62.88 (24.37)	61.15 (24.57)	64.62 (25.14)
	P-value	0.141	0.408	0.725	0.880	0.132
	Mean difference (95% CI)	-12.90 (-30.09,4.28)	7.26 (-9.93,24.45)	-3.15 (-20.64,14.35)	-1.32 (-18.51,15.87)	-13.20 (-30.39,3.99)
Meibography grade	IPL	1.42 (0.63)	1.33 (0.62)	1.29 (0.62)	1.29 (0.62)	1.25 (0.62)
	Sham-IPL	1.15 (0.55)	1.08 (0.28)	1.08 (0.28)	1.00 (0.00)	1.04 (0.14)
	P-value	0.158	0.169	0.249	0.117	0.256
	Mean difference (95% CI)	0.26 (-0.10,0.63)	0.26 (-0.11,0.62)	0.21 (-0.15,0.58)	0.29 (-0.07,0.66)	0.21 (-0.15,0.58)

Staining score (NEI grading system)	IPL	2.50 (1.07)	1.21 (1.01)	1.00 (1.36)	1.38 (2.25)	1.59 (2.15)
	Sham-IPL	3.04 (1.70)	2.08 (1.11)	1.92 (1.06)	1.88 (1.28)	1.42 (0.67)
	P-value	0.328	0.115	0.114	0.355	0.715
	Mean difference (95% CI)	-0.54 (-1.62,0.54)	-0.87 (-0.95,0.21)	-0.88 (-1.98,0.21)	-0.51 (-1.59,0.57)	0.21 (-0.91,1.32)
Meibum quality	IPL	13.04 (2.60)	8.67 (3.77)	12.58 (4.54)	7.36 (4.03)	8.27 (3.89)
	Sham-IPL	12.42 (3.43)	13.38 (4.75)	5.71 (3.22)	11.58 (5.56)	13.46 (4.42)
	P-value	0.696	0.003	<0.0001	0.008	0.002
	Mean difference (95% CI)	0.62 (-2.48,3.72)	-4.72 (-7.82,-1.62)	-6.87 (-9.97,-3.77)	-4.20 (-7.30,-1.10)	-4.99 (-8.13,-1.85)
Meibum expressibility grade	IPL	1.08 (0.47)	0.50 (0.67)	0.42 (0.51)	0.33 (0.49)	0.36 (0.50)
	Sham-IPL	0.88 (0.65)	0.92 (0.51)	0.73 (0.60)	0.77 (0.93)	1.23 (0.60)
	P-value	0.398	0.076	0.182	0.064	0.001
	Mean difference (95% CI)	0.20 (-2.26,0.66)	-0.42 (-0.89,0.05)	-0.31 (-0.78,0.15)	-0.44 (-0.90,0.02)	-0.83 (-1.30,-0.36)
Schirmer's test	IPL	7.08 (4.54)	-	-	9.58 (5.92)	-
	Sham-IPL	6.47 (4.38)	-	-	7.92 (3.66)	-
	P-value	0.730	-	-	0.354	-
	Mean difference (95% CI)	0.62 (-2.90,4.13)	-	-	1.66 (-1.85,5.17)	-
Tear osmolarity	IPL	289.09 (9.87)	-	289.33 (10.55)	293.25 (7.80)	303.08 (15.17)
	Sham-IPL	300.62 (16.54)	-	291.00 (10.83)	289.92 (11.32)	298.85 (14.12)
	P-value	0.021	-	0.731	0.493	0.382
	Mean difference (95% CI)	-11.42 (-21.10,-1.75)	-	-1.67 (-11.17,7.84)	3.33 (-6.1812.83)	4.24 (-5.26,13.74)
Pain score immediately after IPL	IPL	0.42 (1.16)	1.08 (1.62)	0.58 (1.44)	-	-
	Sham-IPL	0.00 (0.00)	0.23 (0.60)	0.00 (0.00)	-	-
	P-value	0.285	0.029	0.134	-	-
	Mean difference (95% CI)	0.42 (-0.35,1.18)	0.85 (0.09,1.62)	0.58 (-0.18,1.35)	-	-

Table 9 Outcomes in stage 3 subgroup (n=34)

Outcome parameters stage 3		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.20 (0.74)	4.96 (1.33)	6.50 (2.57)	5.85 (2.53)	5.27 (2.33)
	Sham-IPL	1.42 (0.71)	2.00 (0.70)	2.96 (0.70)	3.14 (0.84)	2.9 (1.14)
	P-value	0.687	<0.0001	<0.0001	<0.0001	<0.0001
	Mean difference (95% CI)	-0.22 (-1.30,0.86)	2.95 (1.86,4,05)	3.53 (2.43,4.63)	2.71 (1.60,3.82)	2.39 (1.26,3.52)
OSDI score	IPL	29.34 (16.06)	21.78 (20.80)	16.60 (15.02)	21.17 (16.15)	19.40 (15.33)
	Sham-IPL	28.41 (14.24)	29.26 (16.79)	19.38 (14.84)	23.13 (16.06)	23.97 (16.26)
	P-value	0.866	0.177	0.679	0.929	0.482
	Mean difference (95% CI)	0.93 (-9.89,11.75)	-7.56 (-18.54,3.41)	-2.35 (-13.46,8.76)	-0.51 (-11.68,10.66)	-4.01 (-15.18,7.17)
VAS	IPL	3.87 (2.95)	2.70 (2.85)	1.77 (1.42)	2.79 (2.52)	2.50 (1.83)
	Sham-IPL	3.06 (2.59)	2.37 (2.24)	2.69 (2.70)	2.27 (2.10)	2.29 (2.20)
	P-value	0.326	0.702	0.526	0.282	0.585
	Mean difference (95% CI)	0.81 (-0.80,2.42)	0.33 (-1.34,1.99)	-0.54 (-2.19,1.12)	0.94 (-0.78,2.66)	0.47 (-1.23,2.18)
UCVA (logMAR)	IPL	0.40 (0.40)	0.36 (0.41)	0.34 (0.31)	0.34 (0.33)	0.31 (0.30)
	Sham-IPL	0.47 (0.40)	0.45 (0.38)	0.44 (0.42)	0.42 (0.40)	0.45 (0.42)
	P-value	0.566	0.471	0.431	0.565	0.247
	Mean difference (95% CI)	-0.07 (-0.33,0.18)	-0.09 (-0.35,0.16)	-0.10 (-0.35,0.15)	-0.07 (-0.33,0.18)	-0.15 (-0.40,0.10)
BCVA (logMAR)	IPL	0.16 (0.17)	0.12 (0.17)	0.15 (0.19)	0.16 (0.18)	0.12 (0.18)
	Sham-IPL	0.10 (0.10)	0.11 (0.12)	0.10 (0.11)	0.11 (0.22)	0.10 (0.14)
	P-value	0.310	0.683	0.307	0.392	0.559
	Mean difference (95% CI)	0.06 (-0.05,0.16)	0.02 (-0.09,0.13)	0.06 (-0.05,0.17)	0.05 (-0.06,0.16)	0.03 (-0.08,0.14)
Tear film lipid layer thickness	IPL	53.23 (22.54)	52.96 (22.82)	59.21 (22.58)	66.00 (28.05)	60.88 (29.66)
	Sham-IPL	69.88 (24.36)	68.15 (25.10)	67.84 (25.11)	73.63 (27.82)	72.37 (24.64)
	P-value	0.054	0.075	0.268	0.428	0.339
	Mean difference (95% CI)	-16.65 (-33.62,0.32)	-15.59 (-32.74,1.57)	-9.74 (-27.00,7.51)	-6.99 (-24.25,10.28)	-8.55 (-26.09,8.98)

Meibography grade	IPL	1.40 (0.74)	1.39 (0.63)	1.36 (0.63)	1.38 (0.65)	1.46 (0.66)
	Sham-IPL	1.53 (0.70)	1.53 (0.70)	1.53 (0.70)	1.34 (0.65)	1.23 (0.56)
	P-value	0.575	0.483	0.393	0.655	0.653
	Mean difference (95% CI)	-0.13 (-0.58,0.32)	-0.16 (-0.62,0.29)	-0.20 (-0.65,0.26)	-0.10 (-0.56,0.35)	0.11 (-0.35,0.56)
Staining score (NEI grading system)	IPL	5.97 (3.78)	4.07 (3.60)	2.07 (1.87)	2.50 (2.21)	1.82 (2.57)
	Sham-IPL	4.82 (2.97)	3.47 (4.18)	2.78 (2.55)	2.84 (2.59)	2.33 (2.44)
	P-value	0.258	0.551	0.499	0.705	0.539
	Mean difference (95% CI)	1.14 (-0.84,3.12)	0.62 (-1.41,2.65)	-0.70 (-2.73,1.33)	-0.39 (-2.42,1.64)	-0.64 (-2.69,1.41)
Meibum quality	IPL	15.53 (1.70)	9.71 (3.02)	7.36 (3.24)	7.46 (4.28)	8.46 (4.70)
	Sham-IPL	15.38 (3.94)	14.17 (3.88)	13.26 (4.00)	13.44 (3.96)	13.67 (4.20)
	P-value	0.907	0.001	<0.0001	<0.0001	<0.0001
	Mean difference (95% CI)	0.15 (-2.38,2.68)	-4.46 (-7.03,-1.89(	-5.91 (-8.48,-3.33)	-6.01 (-8.65,-3.37)	-4.97 (-7.60,-2.34)
Meibum expressibility grade	IPL	1.20 (0.56)	0.57 (0.51)	0.46 (0.78)	0.54 (0.66)	0.46 (0.63)
	Sham-IPL	1.21 (0.77)	1.12 (0.70)	0.94 (0.56)	0.97 (0.64)	1.13 (0.83)
	P-value	0.979	0.023	0.181	0.072	0.006
	Mean difference (95% CI)	-0.01 (-0.45,0.44)	-0.52 (-0.98,-0.07)	-0.31 (-0.76,0.14)	-0.43 (-0.89,0.04)	-0.64 (-1.10,-0.18)
Schirmer's test	IPL	5.50 (3.25)	-	-	5.39 (2.55)	-
	Sham-IPL	8.50 (7.00)	-	-	12.13 (9.80)	-
	P-value	0.178	-	-	0.004	-
	Mean difference (95% CI)	-3.00 (-7.37,1.37)	-	-	-6.70 (-11.21,-2.19)	-
Tear osmolarity	IPL	295.53 (21.19)	-	292.36 (15.53)	292.21 (15.32)	292.54 (13.13)
	Sham-IPL	294.53 (13.53)	-	293.47 (8.23)	286.19 (8.86)	306.27 (23.05)
	P-value	0.852	-	0.797	0.349	0.028
	Mean difference (95% CI)	1.00 (-9.52,11.52)	-	-1.40 (-12.09,9.29)	5.16 (-5.64,15.97)	-12.42 (-23.51,-1.32)
Pain score	IPL	1.13 (1.55)	0.43 (0.85)	0.46 (0.78)	-	-
	Sham-IPL	0.06 (0.24)	0.00 (0.00)	0.00 (0.00)	-	-

immediately after IPL	P-value	<0.0001	0.106	0.101	-	-
	Mean difference (95% CI)	1.07 (0.56,1.59)	0.44 (-0.09,0.96)	0.46 (-0.09,1.00)	-	-

Table 10 Outcomes in stage 4 subgroup (n=42)

Outcome parameters stage 4		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.17 (0.87)	4.84 (2.73)	7.44 (4.40)	6.25 (3.91)	4.59 (2.84)
	Sham-IPL	1.28 (0.76)	1.67 (0.80)	2.51 (1.10)	3.23 (1.35)	2.74 (0.72)
	P-value	0.883	<0.0001	<0.0001	<0.0001	0.017
	Mean difference (95% CI)	-0.11 (-1.58,1.36)	3.17 (1.71,4.64)	4.96 (3.48,6.45)	3.01 (1.43,4.58)	1.93 (0.35,3.52)
OSDI score	IPL	43.65 (21.40)	31.99 (20.43)	28.68 (16.84)	24.93 (17.08)	26.42 (16.83
	Sham-IPL	39.67 (24.84)	36.33 (24.05)	34.21 (23.93)	32.95 (17.95)	33.81 (21.39)
	P-value	0.520	0.482	0.412	0.275	0.395
	Mean difference (95% CI)	3.98 (-8.15,16.10)	-4.35 (-16.47,7.78)	-5.11 (-17.34,7.11)	-7.00 (-19.56,5.56)	-5.51 (-18.18,7.17)
VAS	IPL	4.72 (2.66)	4.15 (2.18)	2.90 (1.67)	3.15 (1.81)	2.60 (1.53)
	Sham-IPL	4.89 (3.27)	4.56 (3.33)	3.63 (2.58)	3.31 (2.39)	3.08 (2.50)
	P-value	0.989	0.646	0.623	0.478	0.495
	Mean difference (95% CI)	-0.01 (-1.47,1.45)	-0.35 (-1.83,1.14)	-0.38 (-1.88,1.13)	-0.56 (-2.12,0.99)	-0.54 (-2.10,1.02)
UCVA (logMAR)	IPL	0.35 (0.44)	0.33 (0.47)	0.37 (0.44)	0.34 (0.44)	0.32 (0.41)
	Sham-IPL	0.44 (0.57)	0.48 (0.62)	0.38 (0.59)	0.44 (0.65)	0.41 (0.63)
	P-value	0.596	0.341	0.981	0.543	0.794
	Mean difference (95% CI)	-0.08 (-0.39,0.22)	-0.15 (-0.30,0.31)	0.00 (-0.30,0.31)	-0.10 (-0.40,0.21)	-0.04 (-0.35,0.27)
BCVA (logMAR)	IPL	0.06 (0.10)	0.06 (0.10)	0.06 (0.08)	0.08 (0.11)	0.06 (0.11)
	Sham-IPL	0.20 (0.47)	0.10 (0.17)	0.06 (0.11)	0.08 (0.13)	0.04 (0.05)
	P-value	0.012	0.480	0.979	0.987	0.731

	Mean difference (95% CI)	-0.14 (-0.24,-0.03)	-0.04 (-0.15,0.07)	0.00 (-0.11,0.11)	-0.00 (-0.11,0.11)	0.02 (-0.09,0.13)
Tear film lipid layer thickness	IPL	72.17 (23.77)	65.91 (23.00)	64.52 (20.64)	75.74 (25.52)	71.82 (28.46)
	Sham-IPL	55.24 (25.20)	49.13 (20.50)	50.41 (23.38)	57.89 (26.81)	51.97 (24.93)
	P-value	0.020	0.021	0.041	0.008	0.006
	Mean difference (95% CI)	16.94 (2.69,31.18)	16.78 (2.54,31.02)	15.06 (0.58,29.53)	20.23 (5.29,35.17)	20.87 (6.03,35.71)
Meibography grade	IPL	1.57 (0.66)	1.50 (0.67)	1.48 (0.67)	1.32 (0.63)	1.38 (0.69)
	Sham-IPL	1.76 (0.63)	1.79 (0.63)	1.92 (0.69)	1.61 (0.66)	1.80 (0.68)
	P-value	0.323	0.148	0.025	0.187	0.020
	Mean difference (95% CI)	-0.20 (-0.59,0.19)	-0.29 (-0.68,0.10)	-0.45 (-0.84,-0.06)	-0.27 (-0.67,0.13)	-0.47 (-0.87,-0.07)
Staining score (NEI grading system)	IPL	5.74 (5.80)	3.65 (3.68)	2.48 (3.75)	2.19 (2.20)	2.10 (2.15)
	Sham-IPL	7.76 (7.44)	7.11 (7.36)	5.22 (5.71)	3.50 (3.58)	3.43 (4.57)
	P-value	0.200	0.029	0.046	0.101	0.046
	Mean difference (95% CI)	-2.02 (-5.12,1.07)	-3.45 (-6.55,-0.36)	-3.17 (-6.28,-0.06)	-2.67 (-5.85,0.52)	-3.26 (-6.47,-0.06)
Meibum quality	IPL	20.57 (2.04)	13.59 (3.79)	9.26 (3.97)	10.98 (5.46)	10.18 (4.97)
	Sham-IPL	21.42 (1.57)	19.61 (2.75)	16.94 (2.94)	17.80 (3.30)	15.76 (4.84)
	P-value	0.454	<0.0001	<0.0001	<0.0001	<0.0001
	Mean difference (95% CI)	-0.86 (-3.10,1.38)	-6.02 (-8.26,-3.78)	-7.64 (-9.90,-5.37)	-6.63 (-9.00,-4.27)	-5.65 (-8.07,-3.24)
Meibum expressibility grade	IPL	2.13 (0.41)	1.07 (0.48)	0.80 (0.40)	0.83 (0.72)	0.76 (0.77)
	Sham-IPL	2.21 (0.42)	1.76 (0.48)	1.50 (0.62)	1.53 (0.83)	1.29 (0.61)
	P-value	0.650	<0.0001	<0.0001	<0.0001	0.006
	Mean difference (95% CI)	-0.08 (-0.43,0.27)	-0.70 (-1.04,-0.35)	-0.70 (-1.05,-0.35)	-0.67 (-1.04,-0.30)	-0.54 (-0.92,-0.16)
Schirmer's test	IPL	6.22 (3.95)	-	-	6.22 (3.53)	-
	Sham-IPL	6.33 (4.51)	-	-	4.80 (3.22)	-
	P-value	0.922	-	-	0.380	-
	Mean difference (95% CI)	-0.12 (-2.44,2.21)	-	-	1.09 (-1.34,3.53)	-

Tear osmolarity	IPL	296.95 (16.27)	-	294.74 (17.65)	289.78 (11.86)	304.68 (15.68)
	Sham-IPL	302.47 (17.18)	-	292.11 (15.31)	293.13. (9.33)	303.00 (16.51)
	P-value	0.253	-	0.582	0.603	0.655
	Mean difference (95% CI)	-5.34 (-14.52,3.83)	-	2.59 (-6.63,11.80)	-2.57 (-12.27,7.13)	2.23 (-7.55,12.01)
Pain score immediately after IPL	IPL	1.04 (1.30)	0.38 (0.92)	0.04 (0.21)	-	-
	Sham-IPL	0.05 (0.23)	0.00 (0.00)	0.00 (0.00)	-	-
	P-value	<0.0001	0.075	0.835	-	-
	Mean difference (95% CI)	0.99 (0.58,1.40)	0.38 (-0.04,0.80)	0.04 (-0.37,0.46)	-	-

Table 11 Poor compliance subgroup (n_{IPL} = 17, $n_{sham\text{-}IPL}$ = 18)

Outcome parameters poor compliance		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.48 (0.80)	6.43 (3.44)	8.28 (3.93)	5.97 (2.14)	5.83 (3.59)
	Sham-IPL	1.64 (0.78)	1.94 (0.76)	2.91 (0.97)	2.97 (1.21)	3.17 (0.96)
	P-value	0.832	<0.0001	<0.0001	<0.0001	0.001
	Mean difference (95% CI)	-0.16 (-1.65,1.32)	4.49 (3.01,5.98)	5.37 (3.89,6.86)	3.02 (1.51,4.53)	2.64 (1.10,4.18)
OSDI score	IPL	41.80 (19.38)	35.90 (20.29)	31.77 (16.00)	31.40 (18.74)	28.76 (17.05)
	Sham-IPL	32.76 (22.28)	29.77 (21.36)	30.48 (19.45)	30.97 (14.79)	36.81 (18.00)
	P-value	0.145	0.435	0.856	0.857	0.293
	Mean difference (95% CI)	9.05 (-3.12,21.21)	4.89 (-7.40,17.18)	1.13 (-11.12,13.39)	1.13 (-11.16,13.43)	-6.64 (-19.01,5.74)
VAS	IPL	5.66 (2.45)	4.63 (2.67)	3.41 (1.33)	3.82 (1.59)	3.22 (1.52)
	Sham-IPL	4.44 (2.90)	3.85 (2.83)	3.07 (1.87)	3.57 (2.10)	3.62 (2.22)
	P-value	0.092	0.255	0.584	0.818	0.642
	Mean difference (95% CI)	1.22 (-0.20,2.64)	0.87 (-0.62,2.35)	0.41 (-1.06,1.88)	0.18 (-1.32,1.67)	-0.36 (-1.86,1.15)
	IPL	0.40 (0.47)	0.41 (0.52)	0.38 (0.44)	0.36 (0.44)	0.33 (0.41)

UCVA (logMAR)	Sham-IPL	0.29 (0.52)	0.37 (0.59)	0.29 (0.49)	0.29 (0.51)	0.29 (0.47)
	P-value	0.469	0.843	0.573	0.743	0.624
	Mean difference (95% CI)	0.12 (-0.20,0.43)	0.03 (-0.28,0.35)	0.09 (-0.23,0.41)	0.05 (-0.26,0.37)	0.08 (-0.24,0.40)
BCVA (logMAR)	IPL	0.14 (0.16)	0.11 (0.16)	0.10 (0.16)	0.10 (0.17)	0.12 (0.17)
	Sham-IPL	0.16 (0.50)	0.10 (0.18)	0.03 (0.05)	0.03 (0.09)	0.03 (0.06)
	P-value	0.791	0.790	0.285	0.366	0.204
	Mean difference (95% CI)	-0.02 (-0.15,0.12)	0.02 (-0.12,0.15)	0.07 (-0.06,0.21)	0.06 (-0.07,0.20)	0.09 (-0.05,0.22)
Tear film lipid layer thickness	IPL	51.50 (17.72)	51.39 (15.94)	54.76 (18.13)	52.58 (22.00)	53.17 (24.51)
	Sham-IPL	64.97 (29.72)	63.25 (23.70)	63.00 (22.75)	63.00 (26.87)	57.67 (24.88)
	P-value	0.070	0.111	0.298	0.259	0.611
	Mean difference (95% CI)	-13.47 (-28.06,1.12)	-11.86 (-26.44,2.73)	-7.84 (-22.60,6.92)	-8.61 (-23.58,6.35)	-3.87 (-18.76,11.02)
Meibography grade	IPL	1.18 (0.51)	1.18 (0.51)	1.18 (0.51)	1.19 (0.52)	1.18 (0.53)
	Sham-IPL	1.41 (0.71)	1.34 (0.60)	1.34 (0.60)	1.29 (0.61)	1.33 (0.59)
	P-value	0.228	0.386	0.386	0.782	0.404
	Mean difference (95% CI)	-0.22 (-0.58,0.14)	-0.16 (-0.52,0.20)	-0.16 (-0.52,0.20)	-0.05 (-0.41,0.31)	-0.15 (-0.52,0.21)
Staining score (NEI grading system)	IPL	3.89 (3.66)	2.34 (2.84)	1.47 (1.74)	2.08 (2.41)	1.76 (2.32)
	Sham-IPL	5.60 (5.55)	4.75 (4.83)	3.41 (4.11)	3.23 (3.75)	2.87 (4.47)
	P-value	0.200	0.045	0.107	0.283	0.267
	Mean difference (95% CI)	-1.55 (-3.92,0.82)	-2.41 (-4.76,-0.06)	-1.93 (-4.28,0.42)	-1.30 (-3.67,1.07)	-1.36 (-3.75,1.04)
Meibum quality	IPL	14.55 (5.92)	8.82 (4.55)	5.82 (3.78)	8.08 (4.71)	8.18 (4.63)
	Sham-IPL	17.22 (5.37)	16.66 (5.36)	14.84 (5.35)	16.10 (5.33)	15.13 (5.68)
	P-value	0.109	<0.0001	<0.0001	<0.0001	<0.0001
	Mean difference (95% CI)	-2.67 (-5.92,0.59)	-7.84 (-11.10,-4.58)	-9.03 (-12.29,-5.77)	-8.28 (-11.58,-4.98)	-7.05 (-10.37,-3.73)
Meibum expressibility grade	IPL	1.16 (0.78)	0.58 (0.69)	0.42 (0.51)	0.50 (0.62)	0.35 (0.49)
	Sham-IPL	1.63 (0.79)	1.53 (067)	1.25 (0.77)	1.53 (0.83)	1.33 (0.72)
	P-value	0.040	<0.0001	<0.0001	<0.0001	<0.0001

	Mean difference (95% CI)	-0.47 (-0.91,-0.02)	-0.95 (-1.40,-0.51)	-0.83 (-1.27,-0.38)	-1.05 (-1.50,-0.59)	-0.96 (-1.42,-0.50)
Schirmer's test	IPL	7.37 (4.23)	-	-	7.58 (3.85)	-
	Sham-IPL	5.24 (4.71)	-	-	7.07 (4.90)	-
	P-value	0.148	-	-	0.728	-
	Mean difference (95% CI)	2.13 (-0.75,5.02)	-	-	0.51 (-2.37,3.40)	-
Tear osmolarity	IPL	290.56 (10.86)	-	288.68 (11.31)	289.63 (11.51)	300.67 (13.26)
	Sham-IPL	299.19 (15.31)	-	290.25 (13.49)	293.33 (10.61)	298.73 (15.21)
	P-value	0.044	-	0.709	0.435	0.631
	Mean difference (95% CI)	-8.53 (-16.85,-0.22)	-	-1.57 (-9.79,6.66)	-3.33 (-11.69,5.03)	2.07 (-6.38,10.52)
Pain score immediately after IPL	IPL	1.32 (1.57)	1.11 (1.57)	1.00 (1.73)	-	-
	Sham-IPL	0.00 (0.00)	0.06 (0,25)	0.00 (0.00)	-	-
	P-value	0.001	0.009	0.011	-	-
	Mean difference (95% CI)	1.32 (0.54,2.09)	1.05 (0.26,1.83)	1.00 (0.23,1.77)	-	-

Table 12 Good compliance subgroup (n_{IPL} = 19, $n_{sham\text{-}IPL}$ = 27)

Outcome parameters Good compliance		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.42 (0.88)	4.83 (2.19)	7.46 (4.15)	6.88 (4.23)	5.29 (2.70)
	Sham-IPL	1.32 (0.64)	1.88 (0.70)	2.81 (0.84)	3.46 (1.20)	3.16 (1.65)
	P-value	0.894	<0.0001	<0.0001	<0.0001	0.002
	Mean difference (95% CI)	0.09 (-1.27,1.46)	2.95 (1.59,4.31)	4.65 (3.29,6.01)	3.38 (1.97,4.78)	2.18 (0.78,3.58)
OSDI score	IPL	37.72 (23.55)	24.79 (21.32)	23.80 (14.51)	21.01 (14.50)	25.30 (17.75)
	Sham-IPL	39.77 (21.71)	33.75 (22.83)	29.44 (22.59)	27.00 (17.83)	28.12 (21.93)
	P-value	0.724	0.123	0.332	0.532	0.743

	Mean difference (95% CI)	-2.05 (-13.45,9.34)	-8.96 (-20.35,2.44)	-5.64 (-17.03,5.76)	-3.69 (-15.28,7.90)	-1.92 (-13.39,9.55)
VAS	IPL	4.23 (3.10)	3.54 (2.55)	2.13 (1.46)	2.22 (1.98)	2.38 (1.61)
	Sham-IPL	4.16 (3.40)	3.44 (2.97)	2.88 (2.62)	2.73 (2.37)	2.66 (2.83)
	P-value	0.792	0.748	0.538	0.884	0.931
	Mean difference (95% CI)	0.19 (-1.23,1.62)	0.24 (-1.23,1.71)	-0.46 (-1.92,1.00)	-0.22 (-1.60,1.38)	-0.07 (-1.54,1.41)
UCVA (logMAR)	IPL	0.39 (0.39)	0.34 (0.37)	0.36 (0.36)	0.32 (0.37)	0.35 (0.38)
	Sham-IPL	0.55 (0.57)	0.51 (0.57)	0.51 (0.60)	0.50 (0.60)	0.55 (0.61)
	P-value	0.237	0.215	0.275	0.212	0.194
	Mean difference (95% CI)	-0.16 (-0.44,0.11)	-0.17 (-0.44,0.10)	-0.15 (-0.42,0.12)	-0.17 (-0.45,0.10)	-0.18 (-0.45,0.09)
BCVA (logMAR)	IPL	0.07 (0.10)	0.09 (0.12)	0.09 (0.12)	0.10 (0.11)	0.08 (0.12)
	Sham-IPL	0.09 (0.12)	0.12 (0.15)	0.10 (0.11)	0.14 (0.21)	0.11 (0.14)
	P-value	0.685	0.370	0.860	0.308	0.365
	Mean difference (95% CI)	-0.02 (-0.09,0.06)	-0.03 (-0.11,0.04)	-0.01 (-0.08,0.07)	-0.04 (-0.11,0.04)	-0.03 (-0.11,0.04)
Tear film lipid layer thickness	IPL	67.79 (22.77)	70.40 (18.84)	63.98 (19.46)	76.15 (24.61)	69.96 (28.40)
	Sham-IPL	65.88 (23.19)	59.60 (27.33)	60.14 (28.88)	70.63 (24.11)	63.37 (26.48)
	P-value	0.786	0.126	0.661	0.388	0.352
	Mean difference (95% CI)	1.92 (-11.93,15.76)	10.80 (-3.04,24.65)	3.14 (-10.90,17.18)	6.13 (-7.79,20.06)	6.63 (-7.33,20.60)
Meibography grade	IPL	1.44 (0.59)	1.37 (0.58)	1.38 (0.59)	1.22 (0.50)	1.31 (0.57)
	Sham-IPL	1.40 (0.58)	1.43 (0.59)	1.53 (0.62)	1.18 (0.38)	1.31 (0.57)
	P-value	0.801	0.722	0.402	0.878	0.737
	Mean difference (95% CI)	0.04 (-0.29,0.37)	-0.06 (-0.39,0.27)	-0.14 (-0.47,0.19)	-0.03 (-0.36,0.30)	-0.06 (-0.39,0.27)
Staining score (NEI grading system)	IPL	4.90 (4.22)	2.90 (2.87)	2.02 (2.29)	1.92 (1.74)	1.56 (1.90)
	Sham-IPL	4.08 (3.07)	2.68 (3.38)	3.03 (2.90)	2.32 (2.03)	2.19 (1.65)
	P-value	0.304	0.755	0.206	0.662	0.206
	Mean difference (95% CI)	0.83 (-0.75,2.41)	0.25 (-1.34,1.85)	-1.03 (-2.61,0.56)	-0.36 (-1.97,1.25)	-1.04 (-2.66,0.57)

Meibum quality	IPL	17.02 (5.35)	11.20 (5.05)	8.27 (4.28)	8.87 (5.28)	8.67 (4.88)
	Sham-IPL	15.33 (5.54)	14.82 (5.56)	13.30 (4.64)	12.95 (4.84)	12.64 (3.73)
	P-value	0.241	0.012	<0.0001	0.006	0.004
	Mean difference (95% CI)	1.69 (-1.14,4.52)	-3.63 (-6.46,-0.80)	-5.03 (-7.86,-2.20)	-4.02 (-6.87,-1.16)	-4.28 (-7.16,-1.41)
Meibum expressibility grade	IPL	1.63 (0.78)	0.88 (0.52)	0.72 (0.56)	0.73 (0.67)	0.60 (0.80)
	Sham-IPL	1.30 (0.92)	1.15 (0.67)	0.98 (0.73)	0.97 (0.82)	1.00 (0.59)
	P-value	0.108	0.202	0.225	0.233	0.026
	Mean difference (95% CI)	0.33 (-0.07,0.74)	-0.27 (-0.67,0.14)	-0.25 (-0.66,0.16)	-0.25 (-0.66,0.16)	-0.47 (-0.89,-0.06)
Schirmer's test	IPL	5.75 (3.50)	-	-	6.54 (4.90)	-
	Sham-IPL	6.73 (4.59)	-	-	8.13 (7.37)	-
	P-value	0.513	-	-	0.296	-
	Mean difference (95% CI)	-0.98 (-3.90,1.95)	-	-	-1.60 (-4.58,1.39)	-
Tear osmolarity	IPL	292.76 (12.71)	-	296.54 (17.73)	290.23 (13.67)	300.00 (14.52)
	Sham-IPL	298.50 (16.16)	-	293.00 (11.11)	288.26 (9.10)	303.05 (20.61)
	P-value	0.212	-	0.416	0.723	0.574
	Mean difference (95% CI)	-5.47 (-14.06,3.11)	-	3.54 (-4.99,12.06)	1.56 (-7.07,10.19)	-2.49 (-11.18,6.19)
Pain score immediately after IPL	IPL	0.92 (1.20)	0.48 (1.05)	0.04 (0.20)	-	-
	Sham-IPL	0.05 (0.22)	0.00 (0.00)	0.00 (0.00)	-	-
	P-value	<0.0001	0.019	0.850	-	-
	Mean difference (95% CI)	0.87 (0.47,1.27)	0.48 (0.08,0.88)	0.04 (-0.36,0.44)	-	-

Table 13 Excellent compliance subgroup (n_{IPL} = 21, $n_{sham\text{-}IPL}$ = 11)

Outcome parameters		Day 0	Day 15	Day 45	Month 3	Month 6
Excellent compliance						

TBUT	IPL	1.11 (0.71)	2.86 (1.29)	6.41 (4.01)	5.82 (1.87)	4.17 (2.01)
	Sham-IPL	1,39 (0.69)	1.84 (0.75)	2.74 (4.71)	3.55 (1.93)	3.00 (1.13)
	P-value	0.636	0.083	<0.0001	<0.0001	0.049
	Mean difference (95% CI)	-0.28 (-1.43,0.88)	1.02 (-0.13,2.18)	3.69 (2.53,4.86)	2.30 (1.10,3.49)	1.21 (0.00,2.42)
OSDI score	IPL	37.03 (19.90)	21.44 (13.89)	20.21 (16.50)	23.22 (17.23)	13.65 (9.67)
	Sham-IPL	34.94 (20.58)	32.53 (21.82)	27.71 (21.10)	29.73 (18.33)	34.32 (19.76)
	P-value	0.761	0.106	0.290	0.213	0.004
	Mean difference (95% CI)	2.09 (-11.35,15.53)	-11.09 (-24.53,2.35)	-7.29 (-20.80,6.22)	-8.72 (-22.45,5.01)	-20.63 (-34.67,-6.60)
VAS	IPL	4.63 (2.91)	2.80 (1.93)	2.70 (2.11)	3.09 (2.17)	2.40 (1.35)
	Sham-IPL	3.95 (2.77)	3.76 (3.13)	3.30 (2.70)	3.04 (2.42)	3.33 (2.32)
	P-value	0.456	0.334	0.662	0.878	0.269
	Mean difference (95% CI)	0.68 (-1.11,2.48)	-0.90 (-2.72,0.92)	-0.41 (-2.23,1.42)	-0.15 (-2.03,1.73)	-1.05 (-2.92,0.81)
UCVA (logMAR)	IPL	0.18 (0.17)	0.16 (0.15)	0.20 (0.17)	0.19 (0.17)	0.20 (0.21)
	Sham-IPL	0.37 (0.25)	0.37 (0.27)	0.32 (0.20)	0.31 (0.25)	0.29 (0.28)
	P-value	0.024	0.012	0.152	0.080	0.088
	Mean difference (95% CI)	-0.19 (-0.36,-0.03)	-0.21 (-0.38,-0.05)	-0.12 (-0.29,0.04)	-0.15 (-0.31,0.02)	-0.15 (-0.31,0.02)
BCVA (logMAR)	IPL	0.07 (0.10)	0.07 (0.10)	0.09 (0.14)	0.09 (0.12)	0.07 (0.12)
	Sham-IPL	0.12 (0.19)	0.05 (0.10)	0.06 (0.11)	0.06 (0.10)	0.03 (0.05)
	P-value	0.243	0.723	0.450	0.731	0.596
	Mean difference (95% CI)	-0.05 (-0.14,0.04)	0.02 (-0.07,0.11)	0.03 (-0.06,0.12)	0.02 (-0.07,0.11)	0.02 (-0.07,0.12)
Tear film lipid layer thickness	IPL	65.86 (31.08)	53.00 (29.74)	66.64 (23.32)	72.95 (28.79)	66.68 (33.45)
	Sham-IPL	61.45 (24.97)	55.31 (22.49)	59.16 (21.89)	64.47 (30.84)	66.97 (28.42)
	P-value	0.650	0.812	0.361	0.321	0.773
	Mean difference (95% CI)	4.41 (-14.64,23.47)	-2.31 (-21.37,16.75)	8.97 (-10.26,28.20)	9.84 (-9.60,29.28)	2.88 (-16.67,22.43)
Meibography grade	IPL	1.82 (0.84)	1.73 (0.75)	1.55 (0.79)	1.59 (0.80)	1.60 (0.84)
	Sham-IPL	1.67 (0.66)	1,67 (0.66)	1.70 (073)	1.56 (0.68)	1.53 (0.64)

	P-value	0.561	0.816	0.515	0.878	0.957
	Mean difference (95% CI)	0.15 (-0.36,0.66)	0.06 (-0.45,0.57)	-0.17 (-0.68,0.34)	-0.04 (-0.55,0.47)	0.01 (-0.50,0.53)
Staining score (NEI grading system)	IPL	6.64 (6.11)	5.00 (3.93)	3.00 (4.63)	2.32 (2.37)	2.95 (2.63)
	Sham-IPL	6.00 (6.21)	5.02 (6.84)	3.33 (4.71)	2.74 (1.71)	2.43 (2.31)
	P-value	0.739	0.990	0.732	0.368	0.680
	Mean difference (95% CI)	0.64 (-3.11,4.38)	-0.02 (-3.77,3.72)	-0.66 (-4.43,3.11)	-1.74 (-5.52,2.05)	-0.80 (-4.61,3.01)
Meibum quality	IPL	15.18 (3.89)	10.59 (4.05)	7.05 (3.13)	8.82 (5.73)	9.77 (4.82)
	Sham-IPL	14.45 (6.43)	13.40 (5.75)	12.58 (4.51)	11.65 (4.94)	12.00 (5.36)
	P-value	0.692	0.126	0.002	0.061	0.137
	Mean difference (95% CI)	0.73 (-2.88,4.34)	-2.81 (-6.42,0.79)	-5.71 (-9.34,-2.09)	-3.53 (-7.22,0.16)	-2.82 (-6.53,0.90)
Meibum expressibility grade	IPL	1.41 (0.74)	0.50 (0.59)	0.55 (0.52)	0.41 (0.66)	0.50 (0.53)
	Sham-IPL	1.21 (0.90)	0.95 (0.76)	0.90 (0.45)	0.65 (0.61)	1.06 (0.77)
	P-value	0.426	0.067	0.145	0.277	0.019
	Mean difference (95% CI)	0.19 (-0.28,0.67)	-0.45 (-0.93,0.03)	-0.36 (-0.84,0.12)	-0.27 (-0.77,0.22)	-0.61 (-1.13,-0.10)
Schirmer's test	IPL	5.59 (4.75)	-	-	6.64 (4.00)	-
	Sham-IPL	9.05 (6.20)	-	-	9.41 (7.33)	-
	P-value	0.108	-	-	0.192	-
	Mean difference (95% CI)	-3.46 (-7.67,0.76)	-	-	-2.87 (-7.19,1.45)	-
Tear osmolarity	IPL	303.36 (27.43)	-	287.73 (9.81)	292.82 (10.03)	300.82 (19.73)
	Sham-IPL	298.19 (14.75)	-	292.80 (12.64)	286.76 (10.54)	306.31 (19.04)
	P-value	0.367	-	0.370	0.254	0.454
	Mean difference (95% CI)	5.17 (-6.07,16.42)	-	-5.18 (-16.51,6.15)	6.77 (-4.88,18.42)	-4.50 (-16.28,7.28)
Pain score	IPL	0.45 (1.04)	0.27 (0.47)	0.10 (0.32)	-	-
	Sham-IPL	0.10 (030)	0.10 (0.44)	0.00 (0.00)	-	-
	P-value	0.035	0.297	0.575	-	-

immediately after IPL	Mean difference (95% CI)	0.36 (0.03,0.69)	0.18 (-0.16,0.51)	0.10 (-0.25,0.45)	-	-

Table 14 Comparison over time within group (p value is the comparison with the baseline level at day 0)

Outcome parameters		Day 0	Day 15	Day 45	Month 3	Month 6
TBUT	IPL	1.36 (0.82)	4.99 (2.83)	7.53 (4.03)	6.35 (3.20)	5.23 (2.91)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	1.44 (0.70)	1.88 (0.72)	2.81 (0.92)	3.34 (1.48)	3.11 (0.99)
	P-value when compared to day 0	N/A	0.009	<0.001	<0.001	<0.001
OSDI score	IPL	38.76 (21.11)	27.90 (20.28)	25.69 (15.77)	25.04 (16.97)	24.29 (16.92)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	36.02 (21.28)	32.23 (21.72)	29.12 (20.85)	29.12 (16.89)	32.71 (20.07)
	P-value when compared to day 0	N/A	0.127	0.002	0.002	0.159
VAS	IPL	4.83 (2.87)	3.79 (2.54)	2.68 (1.63)	2.94 (1.99)	2.67 (1.56)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	4.16 (2.98)	3.68 (2.92)	3.10 (2.42)	3.11 (2.27)	3.17 (2.47)
	P-value when	N/A	0.076	<0.001	0.001	0.002

	compared to day 0					
UCVA (logMAR)	IPL	0.35 (0.39)	0.33 (0.41)	0.34 (0.37)	0.31 (0.37)	0.31 (0.36)
	P-value when compared to day 0	N/A	0.181	0.374	0.052	0.318
	Sham-IPL	0.41 (0.47)	0.42 (0.48)	0.38 (0.46)	0.38 (0.48)	0.39 (0.49)
	P-value when compared to day 0	N/A	0.604	0.199	0.295	0.721
BCVA (logMAR)	IPL	0.10 (0.13)	0.09 (0.13)	0.09 (0.14)	0.10 (0.13)	0.09 (1.37)
	P-value when compared to day 0	N/A	0.684	0.824	0.882	0.572
	Sham-IPL	0.12 (0.30)	0.09 (0.14)	0.06 (0.10)	0.08 (0.15)	0.06 (0.10)
	P-value when compared to day 0	N/A	0.225	0.053	0.190	0.051
Tear film lipid layer thickness	IPL	61.58 (23.79)	60.54 (22.17)	61.33 (20.07)	67.53 (26.51)	63.69 (28.76)
	P-value when compared to day 0	N/A	0.691	0.998	0.058	0.602
	Sham-IPL	63.99 (25.41)	59.04 (24.39)	60.61 (24.33)	66.40 (26.97)	62.81 (26.37)
	P-value when compared to day 0	N/A	0.065	0.197	0.731	0.295
Meibography grade	IPL	1.42 (0.65)	1.38 (0.61)	1.35 (0.61)	1.29 (0.59)	1.32 (0.62)
	P-value when compared to day 0	N/A	0.167	0.037	<0.001	0.004
	Sham-IPL	1.50 (0.65)	1.49 (0.62)	1.54 (0.66)	1.34 (0.58)	1.39 (0.59)

	P-value when compared to day 0	N/A	0.844	0.327	0.015	0.166
Staining score (NEI grading system)	IPL	4.90 (4.46)	3.13 (3.19)	2.03 (2.76)	2.06 (2.09)	1.92 (2.23)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	5.21 (5.09)	4.15 (5.32)	3.24 (3.87)	2.73 (2.55)	3.48 (2.93)
	P-value when compared to day 0	N/A	0.003	<0.001	<0.001	<0.001
Meibum quality	IPL	15.82 (5.29)	10.27 (4.74)	7.20 (4.00)	8.60 (5.11)	8.74 (4.74)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	15.54 (5.85)	14.81 (5.63)	13.48 (4.81)	13.44 (5.24)	13.19 (5.01)
	P-value when compared to day 0	N/A	0.189	<0.001	0.001	<0.001
Meibum expressibility grade	IPL	1.44 (0.79)	0.71 (0.61)	0.58 (0.54)	0.59 (0.65)	0.50 (0.67)
	P-value when compared to day 0	N/A	<0.001	<0.001	<0.001	<0.001
	Sham-IPL	1.36 (0.88)	1.19 (0.73)	1.03 (0.66)	1.03 (0.83)	1.12 (0.70)
	P-value when compared to day 0	N/A	0.079	0.001	0.002	0.051
Schirmer's test	IPL	6.34 (4.03)	-	-	6.92 (4.34)	-
	P-value when compared to day 0	N/A			0.344	

	Sham-IPL	7.20 (5.42)	-	-	8,25 (6.66)	-
	P-value when compared to day 0	N/A	-	-	0.275	-
Tear osmolarity	IPL	294.02 (16.50)	-	292.14 (14.81)	290.54 (12.16)	300.39 (15.01)
	P-value when compared to day 0	N/A		0.378	0.117	0.070
	Sham-IPL	298.58 (15.14)	-	292.14 (12.20)	289.25 (10.21)	302.80 (18.50)
	P-value when compared to day 0	N/A	-	0.080	0.060	0.106
Tear osmolarity ≥ 308 mOsm/L at day 0	IPL (n=11)	324.89 (16.10)	-	295.11 (19.93)	303.33 (17.13)	303.63 (16.01)
	P-value when compared to day 0	N/A		<0.001	0.001	0.003
	Sham-IPL (n=9)	322.18 (12.89)	-	298.55 (12.69)	293.90 (9.61)	311.70 (14.83)
	P-value when compared to day 0	N/A		<0.001	<0.001	0.045
Pain score immediately after IPL	IPL	0.98 (1.32)	0.65 (1.20)	0.38 (1.11)	-	-
	P-value when compared to day 0	N/A	0.111	0.004		
	Sham-IPL	0.05 (0.23)	0.05 (0.29)	0 (0)	-	-
	P-value when compared to day 0	N/A	1.000	0.192	-	-
IL-1Ra	IPL	4215.58 (3418.07)	-	-	65.30 (59.11)	-

	P-value when compared to day 0	N/A			<0.001	
	Sham-IPL	3411.69 (3112.32)	-	-	75.47 (127.45)	-
	P-value when compared to day 0	N/A	-	-	<0.001	-
IL-6	IPL	39.80 (28.77)	-	-	10.22 (9.71)	-
	P-value when compared to day 0	N/A			0.071	
	Sham-IPL	271.73 (464.84)	-	-	7.58 (1.82)	-
	P-value when compared to day 0	N/A	-	-	0.182	-

Adverse event

There was no eyelid/lash burn, conjunctival burn/erosion, corneal burn/erosion/opacity or other adverse events after the IPL. Two patients in sham-IPL group developed adverse event and were excluded during the study. One patient developed macular hemorrhage due to Polypoidal choroidal vasculopathy (PCV) in one eye and the visual acuity dropped to counting finger 1 foot. This patient received standard treatment of care. The other patient developed viral blepharoconjunctivitis and was healed one week later. These adverse events did not result from the investigator's treatments or interventions.

Chapter 5 Discussion and Conclusion

This study is a prospective randomized double-masked sham-controlled clinical trial to determine the effectiveness, safety and the change in inflammatory cytokines after

intense pulsed light treatment in patients with meibomian gland dysfunction. Moreover, this study is the first to see effects of the stage of the disease as a subgroup analysis and we propose the 6month follow-up to see the effect in the long run.

Regarding our primary outcome variable or tear film break-up time (TBUT), we found significant increase in tear film break-up time in every visit in almost all stages of the disease. This is consistent with previous studies[2, 3, 5, 6, 8, 9, 11, 12]. Furthermore IPL could increase TBUT in any kinds of compliance. This implies that IPL can help stabilize the tear film even though the patients lack warm compression and lid scrub

Considering dry eye symptoms we found that IPL could significantly reduced both OSDI score and VAS over time. Similar results were found in previous studies.[2, 3, 5, 6, 8, 9, 11, 12] This effect began after the first session of IPL. On the contrary, those who received only conventional treatment required more time to lessen their symptoms. Moreover, the dry eye symptoms (OSDI) in IPL group reduced more than those in sham-IPL group in every stage of the disease. However, when comparing between two groups the scores were not statistically different. This might be because of the high value of standard deviation of the data.

Considering the ocular surface staining, we found that after IPL treatment ocular surface staining began to significantly decrease at day 15. Yin et al. and Craig et al. found in previous comparative studies that IPL does not reduce ocular surface staining when compared to not-received-IPL group.[2, 12] Interestingly, in our study, staining in IPL group significantly reduced more than that in sham-IPL group in stage 4. This emphasizes the IPL effect on inflammation reduction in severe stage of the disease. Probable explanations to this result are followings. Firstly, in Yin's study the IPL treatments were administered once a month for 3 months whereas in our study the IPL treatments were performed on day 0, 15 and 45. The duration between each session of IPL might have an effect on the effectiveness. Secondly, in Craig's study the number of IPL shots for one eye were four shots while in our study we performed five shots per side of eye. Lastly, neither Yin's nor Craig's study evaluated stage subgroup analysis.

Considering meibum quality score, IPL treatment can improve the quality of meibum at every visit and every stage of the disease when compared to sham group. This is consistent with Yin et al.'s prospective comparative study.[12] In Yin et al.'s study, three sessions of IPL were performed to the patients every one month and the data analysis was done after all three sessions so they lacked the data about when exactly the IPL could significantly decrease the meibum quality scores during the study. Additionally, we found that IPL can improve the meibum quality after the first session of IPL while the patients receiving only conservative treatment need more time to achieve this effect. Furthermore, we found that those who were not strictly complied with the warm compression and lid scrub could decrease their meibum quality scores by IPL.

Regarding meibum expressiibility score, IPL treatment can improve the expressibility of meibum at every visit especially in stage 4 when compared to sham group. This is in accordance with previous studies.[6, 8, 11, 12] We also found that IPL could decrease the meibum expressibility scores after the first session of IPL while the patients receiving only conservative treatment need more time to acheive this. Furthermore, patients with poor compliance significantly decreased their meibum expressibility scores. This implies that IPL can help improve the meibum expressibility despite lacking warm compression and lid scrub. There are some proposed mechanisms that might explain this result. IPL generates heat and thus liquefies the meibum.[19] In mathematical model, the temperature in small (60 microns) blood vessels may reach 45 -70 degree Celsius.[20] This temperature elevation is insufficient to cause the destruction of the blood vessels but it is probably enough to raise the eyelid skin temperature above the phase-transition temperature.[19] In addition, IPL activates fibroblasts and enhances collagen synthesis. [19] Red photons from IPL stimulates cytochrome C oxidase (Cox) which is a key enzyme in the electron transport chain embedded within the mitochondrial membrane. As a result, this prompts the photochemical cascade and increase in Adenosine triphosphate (ATP) production.[21] ATP activates pumps and membrane transporters leading to calcium ion influx. Intracellular calcium activates fibroblasts. Thus, collagen synthesis commences.[22]

Consequently, better apposition of the lid margins and more complete blinks occur. This leads to increased meibum pumping out of the meibomian glands.[19]

Considering tear film lipid layer thickness (TFLLT), previous studies showed controversy. Dell et at. found in prospective non-comparative study that IPL could not improve lipid layer thickness.[6] On the contrary, Craig et al. also found in prospective randomized placebo-controlled paired-eye study that IPL could improve lipid layer grade.[2] In our study, IPL could not increase TFLLT while comparing to the sham group. Noticeably, Craig et al.'s study used Tearscope Plus (Keeler, Berkshire, UK) to measure tear film lipid layer grade whereas we use LipiView interferometer (TearScience Inc, Morrisville, NC) to measure the thickness in nanometers. Different measurement methods and different machines may give different results.

Regarding meibomian gland structure, Yin et al. proposed in a prospective comparative study that IPL could improve gland dropout.[12] In our study we found that in stage 4 of the disease IPL could improve the meibography grade. Moreover, the gland structure began to alter faster than those who received only conventional treatment. This helps us understand more in mechanisms of IPL. Not only can IPL help in meibomian gland secretory function, but also improve the meibomian gland structure in severe stage of the disease.

As a result, for patients with stage 4 MGD which is known to be difficult to cure, we suggest that IPL are one of the promising methods to initiate. This is consistent with previous study that suggested IPL therapy combined with meibomian gland expression could ameliorated symptoms and improved the condition of the tear film in patients with refractory MGD.[23]

Considering Schirmer's test and tear osmolarity, we found that IPL did not alter the value of Schirmer's test and tear osmolarity in all stages of the disease. This is consistent with previous studies.[2, 5, 9, 12] IPL treatment theoretically improves MGD so it should not alter Schirmer's test which is an aqueous tear production measurement. Nonetheless, Dell et al. reported in prospective non-comparative study that IPL could reduce tear osmolarity in patients whose tear osmolarity more than 310 mOsm/L.[6]

According to our results, if we only focused on those patients whose tear osmolarity was more than 308 mosm/L, we found that both IPL and sham groups also diminished tear osmolarity over time. However, when compared between these two groups, there was no statistical difference. From our point of view, the number of patients whose tear osmolarity was more than 308 mOsm/L was not enough to detect the difference between two groups.

Moreover, IPL treatment is considered as a safe procedure since there is no adverse event after IPL for at least six months. The visual acuity both UCVA and BCVA remained unchanged throughout the study. The safety index was more than 1.00 at every visit. Regarding the pain from the procedure, even though the pain from IPL group was statistically higher than the other group, the absolute amount of pain score in the IPL group was approximately 1 out of 10. We considered this as a very low value. This reflects the cooling effect of the gel applying to the treated area before the procedure.

Considering the tear cytokines after IPL, Liu et al. found in randomized clinical trial that IPL could reduce the level of IL-6, IL-17A and PGE2 in tear.[10] However, in our study we measured the level of IL-1Ra and IL-6. We found that even though tear IL-1Ra levels at month 3 were statistically significantly lower than baseline levels, there was no statistically different in level between two groups. This may be attributable to the effects of warm compression, lid scrub and artificial tear. Regarding our results, IL-6 level was not significantly altered after IPL. According to previous studies, there are several factors influencing the cytokines analysis.[24-26] Cytokines may be degraded overtime. In peripheral blood samples, IL-6 was degraded up to 50% within 2-3 years.[24] However, there is no current data for tear samples. In our study, we collected the tear samples at day 0. The tear samples were frozen in -80 C for 3 months and then the immunoassays were analyzed. On the contrary, the tear samples at month 3 were frozen for only a few days when the immunoassays were analyzed. This might be the reason why the IL-6 level at baseline was not significantly more than that at month 3. As a result, we presumed that if the tear cytokines were perfectly measured at the time when the tear samples were collected, the IL-6 level might show significant decrease. Moreover, comparing with Liu et al.'s study, we proposed a larger sample size and longer follow-up study. Also, the skin

type of the Thai patients was mostly darker than that of Chinese patients so the amounts of power used were different.

The exact mechanisms of IPL effect on MGD remain unknown. There are several proposed mechanisms. For example, thrombosis of abnormal vessels[19] heating and liquefying the meibum[19, 20], reducing the epithelial turnover and decreasing the risk for gland obstruction[19], activating fibroblasts and enhancing collagen synthesis[19, 21, 22], eradicating Demodex[19], modulating the secretion of pro- and anti- inflammatory molecules[27-29], and suppressing matrix metalloproteinases.[19, 30]

Since IPL are known to help in telangiectasia and rosacea and one of the proposed mechanisms of IPL for MGD treatment is that IPL induces thrombosis of telangiectasia, the duration of the effects of IPL in telangiectasia or rosacea may help us predict the duration of the effects in MGD.[31] One study reported the duration of IPL effect on rosacea. In this study, the patients were treated with an average of 4.1 treatments.[32] The mean success rate in clearance was 77.8%. Patients were followed up for an average of 51.64 months. This suggests long-term results of IPL. In our study, we found that IPL has effect at least 4.5 months (after the last session of the treatment).

There are several limitations to our study. The time duration between tear collection and cytokine analysis might affect the cytokine level. So our study might not be able to conclude the true effect of IPL on these cytokine. Another limitation is that notwithstanding our 6-month results of IPL, the true duration of effects of IPL in patients with MGD is still unknown. Further longer follow-up studies are needed. Also, future direction may be to figure out how many sessions needed for different stages of the disease.

We excluded the patients who wore contact lens and those who recently had their eye surgery within 6 months. As we know that meibomian gland dysfunction is more prevalent among contact lens user and after the lid surgery.[33] Contact lens are found to be associated with duct obstruction and glandular atrophy.[33] Furthermore, we also excluded the patients who use antiglaucoma medication eye drops. MGD is also common in this population. Excluding these patients might limit the applicability of IPL.

Our population is all Asians with Fitzpatrick's skin type 2-4. This might limit the applicability of our findings to other races or skin types.

In conclusion, IPL is effective and safe to manage patients with meibomian gland dysfunction in any stage especially stage 4 in which other methods may have limit efficacy. These effects begin after the first treatment. IPL has advantage in patients who lack compliance with warm compression and lid scrub.

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