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Therapeutic Effect of Intense Pulsed Light on Ocular Demodicosis

XiaoZhao Zhang[1, 2], Nan Song[2, 3*] and Lan Gong[1, 2*]

[1]Department of Ophthalmology and Vision Science, The Eye & ENT Hospital of Fudan University, Shanghai, China

[2]NHC Key Laboratory of Myopia (Fudan University); Laboratory of Myopia, Chinese Academy of Medical Sciences, Shanghai, China

[3]Department of Laser Plastic Surgery, The Eye & ENT Hospital of Fudan University, Shanghai, China

***Corresponding author:**

Lan Gong 13501798683@139.com; Nan Song greenkingsn@163.com

Correspondence: Lan Gong , The Eye & ENT Hospital of Fudan University Room 405 Building 10, No. 83 Fenyang Road Shanghai 200031 China Tel.: +86 13501798683 Fax: +86021 64310068 Email: 13501798683@139.com;

Nan Song, The Eye & ENT Hospital of Fudan University, No. 83 Fenyang Road Shanghai 200031 China Tel.: +86 13917039669 Email: greenkingsn@163.com

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

First author:

Xiaozhao Zhang

The Eye & ENT Hospital of Fudan University Room 405 Building 10, No. 83 Fenyang Road Shanghai 200031 China Email: zxz5360_1988@163.com

ABSTRACT

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

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

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

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

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

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

INTRODUCTION

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

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

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

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

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

METHODS

Subjects

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

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

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

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

Ocular demodicosis confirmation

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

Lid margin abnormalities

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

Conjunctival congestion assessment

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

Dry eye symptom assessment

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

Schirmer I test

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

Tear film stability

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

Corneal staining with fluorescein

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

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

MG expressibility

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

Meibum quality

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

5%TTO treatment

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

IPL treatment

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

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

Statistical analyses

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

RESULTS

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

Abbreviations:

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

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

Declarations:

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

Consent for publication:

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

Availability of data and material:

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

Competing interests:

The authors declare that they have no competing interests

Authors' contributions:

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

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

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

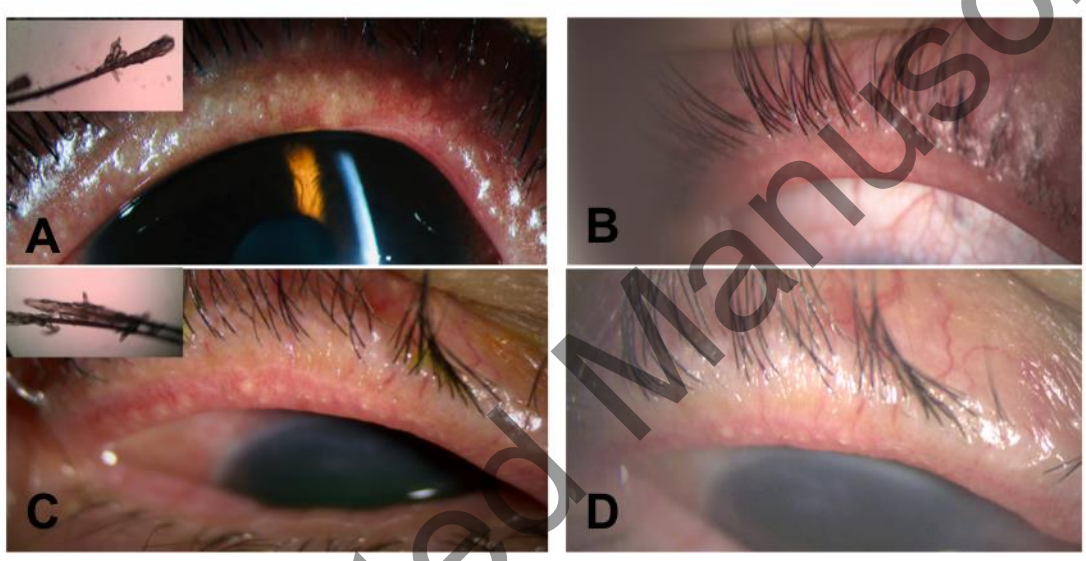

Table 1 Demographic datum in IPL group and the control(Mean±SD)

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

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

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

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

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

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