

Comparison of anti-inflammatory effects of intense pulsed light with tobramycin/dexamethasone plus warm compress on dry eye associated meibomian gland dysfunction

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Abstract

• **AIM:** To compare the anti-inflammatory effects of intense pulsed light (IPL) with tobramycin/dexamethasone plus warm compress through clinical signs and cytokines in tears.

• **METHODS:** Eighty-two patients with dry eye disease (DED) associated meibomian gland dysfunction (MGD) were divided into two groups. Group A was treated with IPL, and Group B was treated with tobramycin/dexamethasone plus warm compress. Ocular Surface Disease Index (OSDI), tear film breakup time (TBUT), corneal fluorescein staining (CFS), meibomian gland expressibility (MGE), meibum quality, gland dropout and tear cytokine levels were evaluated before treatment, 1wk and 1mo after treatment.

• **RESULTS:** TBUT in Group A was higher ($P=0.035$), and MGE score was lower than Group B at 1mo ($P=0.001$). The changes of interleukin (IL)-17A and IL-1 β levels in tears were lower in Group A compared with that in Group B at 1wk after treatment ($P=0.05$, $P=0.005$).

• **CONCLUSION:** Treatment with IPL can improve TBUT and MGE and downregulate levels of IL-17A and IL-1 β in tears of patients with DED associated MGD better than treatment with tobramycin/dexamethasone plus warm compress in one-month treatment period.

• **KEYWORDS:** intense pulsed light; meibomian gland dysfunction; dry eye disease; interleukin-17A; interleukin-1 β

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INTRODUCTION

Meibomian gland dysfunction (MGD) is mainly characterized by terminal duct obstruction and abnormality in meibum secretion^[1], which alters the tear film and decreases its functional integrity^[2]. MGD may occur as an isolated disorder, but it may also be accompanied by dry eye disease (DED)^[3]. DED is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms^[4]. DED has been divided into evaporative and aqueous deficiency subtypes, and MGD is the most common cause of evaporative dry eye^[3-5]. According to some studies, the overall prevalence of MGD varies widely from 3.5% to 70% and the prevalence of DED ranges from 5% to 50%, both of which is related to age, race and district^[6-7]. It's reported by the Dry Eye Workshop II (DEWS II) that 32.9% of dry eye patients associates with MGD^[7].

Tear instability and tear hyperosmolarity associated with MGD, could activate stress signaling pathways in the ocular surface epithelium and resident immune cells, therefore trigger production of inflammatory cytokines. It's regarded as a self-perpetuating "dry eye inflammatory vicious cycle"^[8]. Several studies have reported the levels of interleukin (IL)-6, IL-17A and IL-1 β in tears of dry eye patients were higher than that in normal subjects^[9-13]. Moreover, IL-6 levels in tears have become one of the evaluation indexes for DED^[14]. Assessment based on inflammation will improve the selection of treatment. Treatments recommended for DED associated MGD includes warm compress, lid massage, antibiotic and anti-inflammatory ointments, and artificial tears^[15]. Unfortunately, warm compress is hard to standardize and its troublesome procedure reduces patients' compliance^[16-17]. Some anti-inflammatory ointments can't be used consecutively because of their side effects, which may decrease the treatment efficiency. To avoid the drawback of conventional treatment, a new therapy named intense pulsed light (IPL) was proposed by some

researchers^[18-23]. IPL devices could direct light extended from 515 nm to 1200 nm to the skin near the eye lid. The probable mechanisms of IPL treating DED associated MGD include heat transfer, antibiotic effect and preventing inflammatory mediators from the meibomian glands^[24]. Although the clinical effects of IPL on DED associated MGD has already been proved by several studies^[19,21-23], no one has compared the anti-inflammatory effects of IPL with tobramycin/dexamethasone plus warm compress. This study aimed at comparing IPL with tobramycin/dexamethasone plus warm compress on DED associated MGD from perspective of anti-inflammatory effects.

SUBJECTS AND METHODS

Ethical Approval The study continued for one year from November 2016 to November 2017. Patients who had been diagnosed as DED associated MGD were recruited. Informed consents were obtained from all patients before the study. The study was approved by the biomedical ethics committee of Peking University Third Hospital and adhered to the tenets of the Declaration of Helsinki. The study was registered at clinicaltrials.gov (NCT 02958514).

Patients were diagnosed as MGD on the basis of the criteria provided by the Tear Film and Ocular Surface Society (TFOS)^[25-26]: 1) ocular symptoms; 2) abnormal morphologic lid features; 3) alterations of meibomian gland secretion. Patients with either 1) + 2) or 1) + 3) could be diagnosed as MGD. Meanwhile, patients were also diagnosed as DED based on criteria provided by the Dry Eye Workshop (DEWS)^[27]: 1) the Ocular Surface Disease Index (OSDI) >13; 2) tear film breakup time (TBUT) ≤5s or 5s<TBUT≤10s with positive corneal fluorescein staining (CFS).

Patients were excluded from the study if they met each criteria as follow: 1) under the age of 18y; 2) ocular infection and allergy; 3) allergic to hormonal drugs; 4) abnormalities of anatomy or movements of eyeballs; 5) ocular surgical history or trauma within 3mo; 6) Fitzpatrick Skin Types IV, V and VI^[28]; 7) with tattoos, pigmented lesions or skin cancer in the treatment area; 8) radiotherapy or chemotherapy history within 1y; 9) pregnancy or lactation; 10) autoimmune disease.

Intervention Procedure Patients were divided into two groups randomly according to a computer-generated randomization program. Patients received bilateral treatment, but only the severer eye was enrolled in the study. Patients in Group A were treated with IPL once per month, and sodium hyaluronate eye drops (Hycosan, EUSAN GmbH, Germany) four times a day. Patients in Group B were given tobramycin/dexamethasone ointment (Tobradex, Alcon, Belgium) plus warm compress once every night and sodium hyaluronate eye drops four times a day. The IPL device (M22, Lumenis, USA) was used in this study. Pulse intensity ranged from 12 to 14 J/cm². Pulse width was 6ms. IPL treatment was performed by a same doctor and was

given as follow: 1) Clean the treatment area on both upper and lower eyelids with cotton swabs; 2) Apply compound lidocaine cream (Beijing Unisplendour Pharmaceutical Co., Ltd.) for anesthesia for 30min; 3) Protective shield was placed over the cornea and sclera, and the other eye was protected by an eyeshade; 4) IPL was administered to the periocular area on both upper and lower eyelids (8 mm×15 mm each); 5) Give the treatment area a 10-minute cold compress with a cold wash cloth.

As for Group B, patients received tobramycin/dexamethasone ointment and a 10-minute warm compress (45°C-50°C) once every night at home for one month. Data were obtained from patients in Group A and Group B before treatment (referred to as baseline), 1wk and 1mo after treatment.

Clinical Evaluation To compare the clinical effects of the two groups, tests were conducted in the same order that minimized the extent to which one test influenced the tests that followed.

1) Subjective symptoms of patients were evaluated by the OSDI questionnaire. 2) Measurement of TBUT was facilitated by viewing with a blue exciter filter after instilling sodium fluorescein onto the bulbar conjunctiva with a fluorescein sodium ophthalmic strip (Liaoning Meizilin Pharmaceutical Co., Ltd., China). TBUT was measured three times for each patient and made an average^[5]. 3) CFS score was quantified according to the system provided by National Eye Institute^[29]. 4) The central glands of eyelid were pressed to enumerate meibomian gland expressibility (MGE) score. It was scored according to the number of the five glands from which a meibum secretion could be expressed (0=5 glands expressing, 1=3 to 4 glands expressing, 2=1 to 2 glands expressing and 3= none gland expressing)^[30]. MGE of the upper and lower eyelids should be scored respectively and then the two scores were added. 5) Meibums quality from the upper and lower eyelids were scored respectively (0= clear and fluid-like, 1= cloudy and fluid-like, 2= cloudy and granular, and 3= whitish, toothpaste-like)^[31], and then the two scores were added as a meibum quality score. 6) The severity of gland dropout was scored by observing the morphology of meibomian glands with infrared meibography system (Topcon, Japan). Magnification was set at 10× and image resolution at 640×480. The upper and lower eyelids were scored respectively (0= normal, 1= dropout <1/3, 2= dropout between 1/3-2/3, and 3= dropout >2/3)^[30], and then the two scores were added.

Tear Sample Collection and Analysis Tear collection was performed before any other test at baseline, 1wk and 1mo after treatment. Tear samples were collected non-traumatically from the inferior tear meniscus. Glass capillary micropipettes (Drummond Scientific, Broomall, PA, USA) were used to collect 5 μL of tears. Tear samples were fully eluted into a sterile collection tube (Sigma-Aldrich, St. Louis, MO, USA) at once. Tubes with tear samples were kept cold (4°C) during

Table 1 Clinical outcomes in Group A and Group B at baseline, 1wk and 1mo

Parameters	Group	Baseline	1wk	1mo
OSDI	A	38.92±2.59	29.98±3.31 ^a	25.72±4.52 ^b
	B	38.14±2.39	31.07±2.44 ^b	21.48±4.79 ^b
TBUT(s)	A	4.17±0.31	5.34±0.37 ^b	5.87±0.44 ^{b,d}
	B	3.80±0.28	4.71±0.33 ^a	4.63±0.31 ^a
CFS	A	2.24±0.42	1.39±0.34 ^a	1.18±0.35 ^a
	B	2.85±0.49	1.68±0.41 ^b	1.24±0.38 ^a
MGE	A	3.71±0.20	2.63±0.19 ^c	1.61±0.15 ^{b,c}
	B	3.80±0.21	3.12±0.22 ^b	2.61±0.23 ^b
Meibum quality	A	2.22±0.22	2.00±0.20	2.53±0.32
	B	2.54±0.22	2.15±0.20	2.94±0.33
Gland dropout	A	3.80±0.17	3.80±0.13	4.18±0.21
	B	3.87±0.13	3.70±0.11	4.12±0.19

OSDI: Ocular surface disease index; TBUT: Tear film breakup time; CFS: Corneal fluorescein staining; MGE: Meibomian gland expressibility. ^a $P<0.05$, ^b $P<0.01$, ^c $P<0.001$, comparing with baseline. ^d $P<0.05$, ^e $P<0.01$, comparing Group A with Group B.

collection, and then stored at -80°C until activity assays were performed. The concentrations of IL-17A, IL-1 β and IL-6 in tears were analyzed using a Milliplex Map Kit (HSTCMAG-28SK, EMD Millipore Corporation, USA). Data acquisition and analysis were integrated seamlessly with the Bio-Plex Luminex 200 XYP instrument (Bio-Rad Laboratories). The threshold sensitivities of IL-17A, IL-1 β and IL-6 were >3.3 pg/mL, >1.4 pg/mL and >1.1 pg/mL, respectively.

Statistical Analysis SPSS 23 was used to analyze the data. Data were expressed as mean±standard error of the mean (SEM). As the concentrations of IL-17A, IL-1 β and IL-6 in tears vary greatly among individuals, changes of cytokines were compared between Group A and Group B. Analysis between baseline and 1wk or 1mo in the same group was performed by Wilcoxon signed rank test. Analysis between Group A and Group B was performed by Mann Whitney *U* test. Outcomes were considered significant if $P<0.05$.

RESULTS

Patients and Clinical Outcomes Eighty-two patients were included in this study. Forty-one patients were analyzed in Group A (10 males and 31 females), with a mean age of 54.44 ± 16.19 (range 22-80)y. Forty-one patients were analyzed in Group B (11 males and 30 females), with a mean age of 55.22 ± 16.71 (range 23-86)y. The visual acuity and intraocular pressure of patients were stable during treatment in both groups. Compared Group A with Group B, there was no difference in OSDI, TBUT, CFS, MGE, meibum quality, gland dropout and levels of IL-6, IL-17A, IL-1 β in tears at pre-treatment baseline ($P>0.05$).

OSDI, CFS, TBUT and MGE scores were improved in both Group A and Group B at 1wk and 1mo after treatment compared with baseline, which were of statistically differences (all $P<0.05$). However, there was no significant difference in meibum quality scores and gland dropout scores between each time point and baseline in both groups (all $P>0.05$; Table 1).

Compared Group A with Group B, there was no difference in TBUT and MGE score at 1wk ($P>0.05$). Compared with Group B, TBUT in Group A was higher than that in Group B at 1mo ($P=0.035$), and MGE score in Group A was lower than that in Group B at 1mo ($P=0.001$). However, there was no significant differences between Group A and Group B on OSDI, CFS, meibum quality scores and gland dropout scores at 1wk or 1mo (all $P>0.05$).

Changes of Tear Cytokine Levels The concentrations of IL-6, IL-17A and IL-1 β in tears at baseline, 1wk and 1mo were shown in Table 2. Changes of IL-6, IL-17A and IL-1 β were defined as the concentrations of IL-6, IL-17A and IL-1 β at 1wk or 1mo minus the concentrations of IL-6, IL-17A and IL-1 β at baseline, respectively.

The changes of IL-6 in Group A were -83.94 ± 36.55 pg/mL at 1wk and -61.74 ± 35.94 pg/mL at 1mo. The changes of IL-6 in Group B were -72.68 ± 23.39 pg/mL at 1wk and -84.16 ± 23.87 pg/mL at 1mo. In Group A, change of IL-6 at 1wk was lower than that at 1mo, though there was no statistical difference ($P=0.249$). In Group B, change of IL-6 was lower at 1mo compared with that at 1wk ($P=0.015$). Compared Group A with Group B, change of IL-6 did not differ significantly at either 1wk or 1mo ($P=0.556$, $P=0.104$; Figure 1).

The changes of IL-17A in Group A were -1.96 ± 1.52 pg/mL at 1wk and 0.18 ± 1.77 pg/mL at 1mo. The changes of IL-17A in Group B were 2.30 ± 1.68 pg/mL at 1wk and -1.07 ± 1.35 pg/mL at 1mo. In either Group A or Group B, change of IL-17A at 1wk did not differ significantly from that at 1mo (both $P>0.05$). Compared with Group B at 1wk, the change of IL-17A in Group A was lower, which was statistically different ($P=0.05$). Compared with Group B at 1mo, the change of IL-17A in Group A did not differ significantly ($P=0.534$; Figure 2).

The changes of IL-1 β in Group A were -0.61 ± 0.26 pg/mL at 1wk and -0.07 ± 0.33 pg/mL at 1mo. The changes of IL-1 β in Group B were 0.35 ± 0.26 pg/mL at 1wk and 0.39 ± 0.44 pg/mL

Table 2 Concentrations of tear cytokines in Group A and Group B at baseline, 1wk and 1mo

pg/mL

Parameters	Group	Baseline	1wk	Change	1mo	Change
IL-6	A	126.90±39.68	42.96±7.99	-83.94±36.55	65.16±18.71	-61.74±35.94
	B	129.21±27.21	56.52±12.8	-72.68±23.39	32.40±7.14	-84.16±23.87
IL-17A	A	17.31±2.09	15.35±1.98	-1.96±1.52	17.49±2.17	0.18±1.77
	B	15.81±1.89	18.11±2.28	2.30±1.68	14.74±1.87	-1.07±1.35
IL-1β	A	3.62±0.34	3.01±0.39	-0.61±0.26	3.55±0.35	-0.07±0.33
	B	3.18±0.33	3.53±0.34	0.35±0.26	3.57±0.56	0.39±0.44

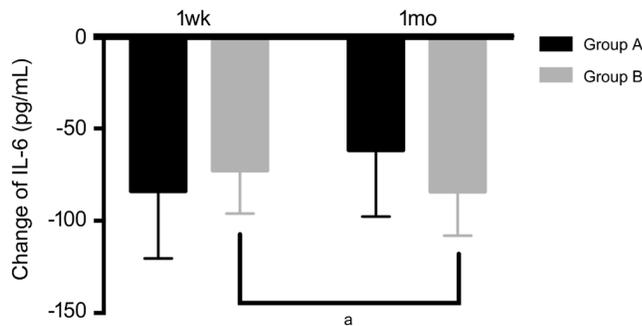


Figure 1 Changes of IL-6 at 1wk and 1mo in Group A and Group B IL: Interleukin. Change of IL-6: The concentration of IL-6 at 1wk or 1mo minus the concentration of IL-6 at baseline. ^a $P < 0.05$ comparing 1wk with 1mo in Group B.

at 1mo. In Group A, change of IL-1β was lower at 1wk than that at 1mo ($P = 0.027$). In Group B, there was no significant difference compared change of IL-1β at 1wk with that at 1mo ($P = 0.224$). Compared with Group B at 1wk, the change of IL-1β in Group A was lower, which differed significantly ($P = 0.005$). Compared with Group B at 1mo, the change of IL-1β in Group A did not differ statistically ($P = 0.626$; Figure 3).

DISCUSSION

IPL is a new treatment for patients with DED associated MGD. However, the mechanisms of IPL to treat DED associated MGD still remain uncertain currently. The probable mechanisms included heat transfer, antibiotic effect and anti-inflammatory effect. The light emitted from IPL device was selectively absorbed by chromophores in hemoglobin, subsequently releasing thermal energy, which heated and destructed the abnormal vasculature in the eyelid margin and adjacent conjunctiva, thus preventing inflammatory mediators from the meibomian glands^[24]. The probable mechanisms of IPL covered almost all the principles to treat DED associated MGD in classical therapy. Tobramycin/dexamethasone is widely used as an antibacterial and anti-inflammatory combination by ophthalmologist. Dexamethasone is a pure glucocorticoid agonist. It's already known that therapeutic doses of dexamethasone have been shown to inhibit influx of macrophage and neutrophil, accompanied by a substantial downregulation of inflammatory cytokine production such as IL-6^[32-33]. Several studies have reported the improvements of symptoms and signs of DED associated MGD after IPL^[19-20]. Some studies indicated that IPL treatment could downregulate

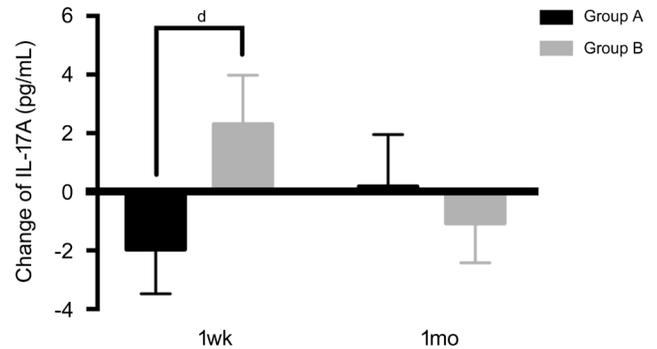


Figure 2 Changes of IL-17A at 1wk and 1mo in Group A and Group B Change of IL-17A: The concentration of IL-17A at 1wk or 1mo minus the concentration of IL-17A at baseline. ^d $P < 0.05$ comparing Group A with Group B at 1wk.

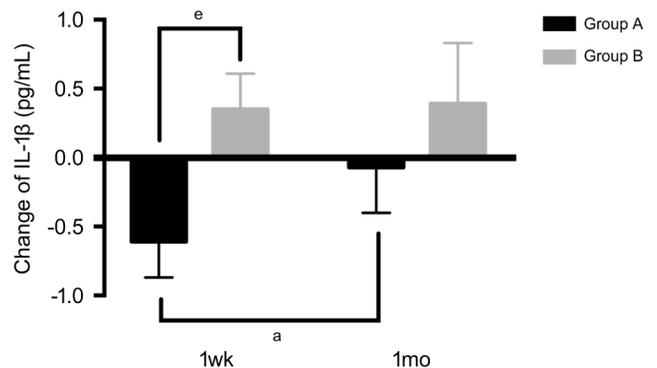


Figure 3 Changes of IL-1β at 1wk and 1mo in Group A and Group B Change of IL-1β: The concentration of IL-1β at 1wk or 1mo minus the concentration of IL-1β at baseline. ^a $P < 0.05$ comparing 1wk with 1mo in Group A. ^e $P < 0.01$ comparing Group A with Group B at 1wk.

levels of IL-6 and IL-17A in tears of patients with DED associated MGD, comparing with placebo group^[21]. However, the anti-inflammatory effects of IPL still remained unknown when comparing to tobramycin/dexamethasone plus warm compress. The clinical symptoms and signs for DED associated MGD after IPL were compared with tobramycin/dexamethasone plus warm compress in our study. OSDI, TBUT, CFS and MGE scores were all improved after treatment in both Group A and Group B, manifesting the clinical effects of both IPL and tobramycin/dexamethasone plus warm compress. These results coincided with previous reports^[19,22,34]. Our study manifested that IPL improved TBUT and MGE more than tobramycin/dexamethasone plus warm compress at 1mo after treatment.

The changes of tear cytokine levels after IPL were compared with tobramycin/dexamethasone plus warm compress in order to evaluate their anti-inflammatory effects. As proved in many studies, hyperosmolar stress could activate mitogen-activated protein kinases (MAPKs) on the ocular surface epithelium and stimulate secretions of IL-1 β and IL-6^[8]. IL-6 and IL-1 β are pro-inflammatory cytokines. IL-1 β stimulates the production of other inflammatory cytokines, and then lyse the tight junctions in the superficial corneal epithelium^[35]. IL-6 drive the production of IL-17A produced by T-helper cells, and IL-17A could causes corneal barrier disruption^[36-38]. These inflammatory mediators could upregulate each other, thus amplifying the inflammatory cascade^[39]. We speculated that the batter clinical effects of IPL were due to IPL downregulating more cytokines.

In this study, the effects of IPL and tobramycin/dexamethasone plus warm compress on the changes of IL-6, IL-17A and IL-1 β levels in tears were different. The reduction of IL-6 level in tears at 1wk was more than that at 1mo in Group A, but in Group B, the reduction of IL-6 level at 1wk was less than that at 1mo, though there were no statistical difference. It could be speculated that both IPL and tobramycin/dexamethasone plus warm compress could downregulate the level of IL-6 in tears, but the effect of IPL on IL-6 reduced as time went by. As for IL-17A and IL-1 β in tears, IPL downregulated the levels of IL-17A and IL-1 β at 1wk, while tobramycin/dexamethasone plus warm compress did not. But when time went to 1mo, IL-17A and IL-1 β levels in Group A went back to the same level as pre-treatment. It's manifested that IPL downregulated levels of IL-17A and IL-1 β in tears more than tobramycin/dexamethasone plus warm compress at 1wk, but the effect could not last for 1mo.

Interestingly, changes of IL-6, IL-17A and IL-1 β levels was lowest at about 1wk after IPL, which was earlier than the appearance of clinical outcome peaks at 1mo. It's speculated from this result that changes of tear cytokine levels may be more sensitive indexes than clinical signs to show effects of IPL. Changes of tear cytokine levels had the potential to be predictive indexes of clinical effects duration. When changes of tear cytokine levels were negative, it manifested the effect of IPL was on-going. However, when changes of tear cytokine levels went up to positive, it manifested the effect of IPL was over. This means the need of another time of IPL treatment. The result helped explain why prior researchers gave patients several times of IPL treatment at 4-week intervals.

The study also had some limitations. For the safety, tobramycin/dexamethasone ointment cannot be used consecutively because of its potential side effects such as ocular hypertension and cataract. Thus, Group B in this study was treated with tobramycin and dexamethasone ointment for only one month.

It could not be deduced from this study whether further benefit would be realized if tobramycin/dexamethasone was used in Group B for a longer time.

In conclusion, our study suggested that treatment with IPL could improve TBUT and MGE and downregulate levels of IL-17A and IL-1 β in tears of patients with DED associated MGD better than treatment with tobramycin/dexamethasone plus warm compress in one-month treatment period.

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