Clinical outcomes and tear cytokine profiles of meibomian gland dysfunction treated with intense pulsed light

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Clinical outcomes and tear cytokine profiles of meibomian gland dysfunction treated with intense pulsed light

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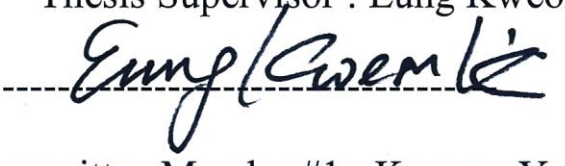

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ABSTRACT

Clinical outcomes and tear cytokine profiles of meibomian gland dysfunction treated with intense pulsed light

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Objective: To analyse the alteration in tear cytokine profiles, clinical outcome, and prognostic factors in meibomian gland dysfunction (MGD) patients treated with Intense Pulsed Light (IPL).
Methods: Participants with moderate to severe MGD were treated with 3 sessions of IPL. Bimicroscopic examinations of meibomian glands and lid margins, tear break-up time (TBUT), ocular surface staining, interferometry, Ocular Surface Disease Index (OSDI), and tear cytokine levels were evaluated.
Results: There was a significant improvement in clinical parameters including meibum quality, meibum expressibility, lid margin abnormality, TBUT, ocular surface staining, and OSDI. There was significant decrease in IL-6 and TNF-α. The decrease in tear cytokine levels were correlated with the improvement in clinical outcome (meibum quality, expressibility, lid margin abnormality, and ocular surface staining). Worse meibum expressibility, and low TBUT were associated with greater reduction in OSDI after treatment.
Conclusions: IPL lead to decreased inflammation, improved meibomian gland function, and ocular surface stabilization in MGD patients. Improvement in meibomian expressibility was associated with the significant reduction of inflammatory cytokines, IL-6 and TNF-α, and baseline meibum nonexpressibility and low TBUT was associated with decreased subjective symptom score after treatment. Therefore, patients with obstructive MGD are especially likely to benefit from IPL treatment.

Key words : meibomian gland dyfunction, intense pulsed light, tear cytokine

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I. INTRODUCTION

Meibomian gland dysfunction (MGD) is a common cause of evaporative dry eye and is a prevalent condition, affecting more than 50% of the Asian population.[1] The treatment options include self-administered management of lid hygiene, meibum expression, lubricants, oral tetracycline derivatives, and anti-inflammatory therapy.[2] There are many patients, however, who do not benefit from the treatment currently available.

Intense pulsed light (IPL) has been widely used to treat dermatologic conditions such as rosacea, benign vascular lesions, and pigmented lesions.[3] Moreover, it has also been used for skin rejuvenation and hair removal in the aesthetic field.[4] IPL is a noncoherent, polychromatic light source with a broad wavelength spectrum of 500-1200 nm.[5,6] Various convertible cut-off filters are employed to achieve appropriate

penetration to the target tissue, leading to selective photothermolysis in which the light energy is preferentially absorbed by a chromophore and converted into heat.[3,5]

Concurrent improvement of ocular surface conditions observed in patients treated for rosacea of their face, led to potential application of IPL for the treatment of MGD.[7] Previous studies have reported favorable outcome on the therapeutic effect of IPL on MGD patients.[8-13] However, the exact mechanism for the effect and the potential candidate who may benefit from this treatment have not been elucidated. The suggested hypothesis so far is that the coagulation of telangiectasia may lead to decrease of inflammation,[14] and the heat energy may liquefy the viscous meibum and dilate the clogged meibomian gland ducts.[13] Tear cytokines have been reported to be elevated in dry eye and MGD, and they were shown to correlate with symptoms and clinical parameters.[15,16] Therefore, a serial evaluation of the changes in tear cytokine levels and clinical assessment before, during, and after treatment would be helpful in explaining the anti-inflammatory effect of IPL, and in determining the correlation between the molecular mechanism and the clinical outcome. This study aimed to analyze the sequential alteration of tear cytokine profiles and the clinical outcomes in MGD patients treated with IPL to

help understand the mechanism of action. Furthermore, we analyzed the prognostic factors for the effective outcome to propose appropriate candidates who have the greatest potential to benefit from the treatment.

II. MATERIALS AND METHODS

1. Patient Selection

This prospective study adhered to the tenets of the Declaration of Helsinki, and was approved by the Severance Hospital Institutional Review Board, Seoul, South Korea (1-2016-0010). Written informed consent was obtained from all participants prior to enrollment.

Participants over 19 years of age, and diagnosed with moderate or severe MGD at Severance Hospital, Seoul, Korea, were screened for eligibility. MGD was staged according to the severity of symptoms including ocular discomfort, itching, or photophobia, and clinical signs including lid margin features, meibum secretions, expressibility, and corneal and conjunctival staining.[2] Moderate MGD was defined by moderate symptoms, moderate MGD clinical signs (plugging and vascularity of the lid margins, grade ≥8 to <13 secretions, expressibility 2), and mild to moderate corneal and conjunctival staining. Severe MGD was diagnosed by marked symptoms with limitation of activities, severe MGD signs

(dropout, displacement of lid margin, severely altered secretions grade ≥ 13, expressibility 3), increased corneal and conjunctival staining, and signs of inflammation (conjunctiva hyperemia, phylctenules). Patients with (1) Fitzpatrick skin type V, VI, (2) active allergy, infection, or inflammatory disease of the ocular surface unrelated to dry eye or MGD, (3) systemic diseases or medication use in which light therapy is contraindicated, (4) uncontrolled systemic disease, (5) tattoos, semipermanent makeup, or pigmented lesions in the treatment area, and (6) contact lens wear were excluded.

Thirty patients were enrolled. The eye with a higher stage of MGD was chosen as the study eye. If the MGD stage was equal in both eyes, the right eye was enrolled as the study eye.

2. Treatment technique

Patients received 3 sessions of IPL treatment of 3 weeks interval. All treatment adhered to the Toyo's protocol. IPL-Aid disposable eye shields (Honeywell Safety Products, Smithfield, RI, USA) were placed to protect the patient's eyes. Cooling ultrasound gel was generously applied to the treatment area, and homogenously sculpted light pulses of 590 nm wavelength and intensity ranging from 12~14 J/cm^2, appropriately

selected according to the patient's skin type, were delivered to the periocular skin inferior and lateral to the eye using M22 IPL machine (Lumenis Ltd., Israel). Approximately 15 overlapping pulses were applied from the preauricular area, across the cheeks and nose to the contralateral side, bordering close to the inferior boundary of the eye shields to make sure light pulses were delivered as close as possible to the lower eyelids. After the initial pass was completed, more ultrasound gel was applied, and the treatment is repeated for a second pass. After IPL treatment, manual expression of the meiboman glands of the upper and lower eyelids was performed with meibum expressor forceps. The patients were instructed to maintain lid scrub and use of artificial tears during the treatment period.

3. Clinical Assessments

The clinical assessments were performed at baseline, at each treatment session, and at 3 weeks after the final session. All evaluations were carried out before the IPL treatment at each visit. The order of the examination was arranged so that the influence of a preceding test on the sequential test was minimized. All patients underwent tear film lipid layer interferometry, followed by tear meniscus area measurement with

anterior segment optical coherence tomography. Then tear sampling was performed, followed by slit lamp examinations including a fluorescein tear break-up time (TBUT), measurement of ocular surface staining, and examination of lid margin and meibomian glands. All patients were instructed to fill out the Ocular Surface Disease Index (OSDI) questionnaire.

Lipid layer thickness (LLT) measurement and meibography were performed using interferometer (LipiView®, TearScience Inc, Morrisville, NC, USA) as previously described.[17] Images of the participant's eye with the pupil at center are captured while the patient is instructed to stare at the internal target. The LLT is derived from the reflected tear film image, and is presented in interferometric color units (ICU), where 1 ICU corresponds to approximately 1nm. The maximum LLT that can be measured is 100 nm. The images of the meibomian glands were obtained by everting the lower eyelids. Meibomian gland dropout was scored using a 0 to 4 meiboscale based on the area of gland loss (0, 0%; 1, <25%; 2, 25-50%; 3, 51-75%; and 4, >75%).[18]

The lower tear meniscus area was measured using Fourier-domain optical coherence tomography (FD-OCT; RTVue; Optovue, Inc., Fremont, CA, USA).[19] A 3-mm image was scanned vertically at the middle of the lower

eyelids twice for each eye. The tear meniscus area was measured using virtual calipers in the FD-OCT software. Tear meniscus area was defined as the area enclosed by the boundaries of the tear meniscus, the cornea, and the lower palpebral conjunctiva.

Tear film break-up time was measured by instilling a single drop of sterile saline onto a fluorescein-impregnated strip (Haag-Streit, Koeniz, Switzerland), and then applying it on the inferior palpebral conjunctiva. The mean time of the three attempts was calculated. Then, the corneal and conjunctival staining was graded from 0 to 5 according to the Oxford scheme.[20]

Meibum expressibility was evaluated by applying firm digital pressure to the central 5 glands in the lower lid, and was scored as 0, all 5 glands; 1, 3-4 glands; 2, 1-2 glands; and 3, 0 glands.[21] Meibum quality was assessed in the central third of the lower lid, and was scored from 0, clear fluid; 1, cloudy fluid; 2, cloudy particulate fluid; and 3, inspissated, like toothpaste.[22] The highest grade encountered from any of the expressed gland was recorded. Lid margin abnormalities were scored as the sum of the following 4 parameters: vascular engorgement, plugged meibomian gland orifices, irregularity of the lid margin, and anterior or posterior displacement of the mucocutaneous junction.[23]

Subjective symptoms were assessed using the Ocular Surface Disease Index (OSDI), which is a valid 12-item questionnaire on the symptoms related to dry eye disease and their effect on vision.[24]

4. Tear Sample Collection and Cytokine Analysis

Tear samples were collected by initially instilling 30 μL of phosphate-buffered saline into the inferior fornix, then 20 μL of the unstimulated tear fluid and buffer was collected with a micropipette at the lateral canthus. The samples were transferred into 0.5-mL Eppendorf tubes (Eppendorf, Fremont, CA, USA), and were stored at -70 ℃ until further analysis.

Cytokine concentrations were analyzed using a multiplex immunobead assay (BD™ Cytometric Bead Array Human Soluble Protein Flex Set; BD Biosciences, San Jose, CA, USA). The cytokines analyzed included IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α. The tear samples were incubated with antibody-coated capture beads and detector antibody-phycoerythrin agent for 3 hours at room temperature. The samples were washed to remove the unbound antibodies. Flow cytometry was performed using the BD LSRII system (BD Bioscience), and the data was analyzed using BD Cytometric Bead Array software (FCAP

Array™ v3.0 software). The cytokine concentrations were calculated based on the standard curves and a 4-parameter logistic curve-fitting model.

5. Statistical Analysis

Normal distribution of the data was evaluated with Shapiro-Wilk test ($p > 0.05$). Data which conformed to the normal distribution were evaluated with repeated measure analysis of variance (ANOVA) to assess the time course changes in the clinical parameters and cytokine levels over 3 treatment sessions. Nonparametric values were evaluated using Friedman test. If significant differences were observed, the Bonferroni post-hoc test for multiple comparisons was performed to compare the baseline and post-treatment data at individual time points. A post hoc analysis for nonparametric values was performed using Wilcoxon sign test. The correlations between changes in the significantly reduced tear cytokine concentrations, and the change in significantly improved ocular surface parameters following the final session were analyzed by Spearman's rank correlation coefficient. Univariate and multivariate regression models were constructed to identify baseline clinical parameters associated with the changes in OSDI scores after treatment. Statistical analyses were

performed with SPSS version 21.0 (SPSS Inc. Chicago, IL, USA). P values less than 0.05 were considered significant.

III. RESULTS

1. Clinical outcome

The changes in clinical parameters over the time period of 3 IPL sessions are outlined in Table 1. The meibum quality, meibum expressibility, and the lid margin abnormality improved with IPL treatment ($p<0.001$). TBUT increased ($p=0.005$), and ocular surface staining score decreased ($p=0.025$) serially with treatment. OSDI scores also decreased with IPL treatment ($p=0.002$). The change in lipid layer thickness, the grade of meibomian gland dropout, and the change in tear meniscus area was not significant. The serial changes in each clinical parameters with statistically significant changes between the treatment sessions are depicted in figure 1.

Table 1. Change in clinical parameters following each IPL session in MGD patients.

Clinical parameter	Baseline (Before session 1)	Between session 1&2	Between session 2&3	After session 3	p-value
Meibum quality					
Mean ± SD	2.47 ± 0.50	1.93 ± 0.58	1.80 ± 0.61	1.60 ± 0.56	**<0.0001** [a]
Median (range)	2 (2-3)	2 (1-3)	2 (1-3)	2 (1-3)	
Meibum expressibility					
Mean ± SD	1.90 ± 0.55	1.30 ± 0.54	1.33 ± 0.71	0.97 ± 0.61	**<0.0001** [a]
Median (range)	2 (1-3)	1 (0-2)	1 (0-3)	1 (0-2)	
Lid margin abnormality					
Mean ± SD	2.50 ± 0.57	2.00 ± 0.87	1.90 ± 0.88	1.77 ± 0.73	**<0.0001** [a]
Median (range)	2 (2-4)	2 (1-4)	2 (1-4)	2 (1-3)	
TBUT (sec)					
Mean ± SD	4.16 ± 2.11	4.84 ± 3.76	5.15 ± 2.89	6.05 ± 3.71	**0.005** [b]
Median (range)	4.15 (0.5-9.0)	3.8 (1.2-18.0)	4.4 (1.6-13.0)	5.15 (1.9-21.0)	
Ocular surface staining					
Mean ± SD	0.93 ± 0.87	0.80 ± 0.92	0.67 ± 0.96	0.47 ± 0.82	**0.025** [a]
Median (range)	1 (0-3)	1 (0-3)	0 (0-3)	0 (0-3)	
OSDI					
Mean ± SD	58.18 ± 21.76	47.39 ± 24.68	47.00 ± 21.57	46.47 ± 22.35	**0.002** [b]
Median (range)	60.4 (4.2-92.0)	43.48 (4.2-92.5)	46.95 (4.2-83.3)	47.60 (8.3-91.7)	
Lipid layer thickness (nm)					
Mean ± SD	78.48 ± 21.01	74.24 ± 26.43	72.60 ± 22.44	75.20 ± 23.36	0.939 [a]
Median (range)	81 (37-100)	78.5 (29-100)	72 (34-100)	77 (30-100)	
Meibomian gland dropout					
Mean ± SD	2.21 ± 1.03	2.21 ± 1.03	2.18 ± 1.06	2.18 ± 1.02	0.753 [a]
Median (range)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	
Tear meniscus area ($\mu L/mm^2$)					
Mean ± SD	0.02 ± 0.02	0.02 ± 0.02	0.03 ± 0.03	0.03 ± 0.03	0.286 [a]
Median (range)	0.02 (0.00-0.11)	0.02 (0.00-0.08)	0.02 (0.01-0.13)	0.02 (0.01-0.15)	

[a] Friedman test
[b] Repeated measure ANOVA
TBUT = Tear break-up time; OSDI = Ocular Surface Disease Index
Bold fonts indicate statistically significant results.

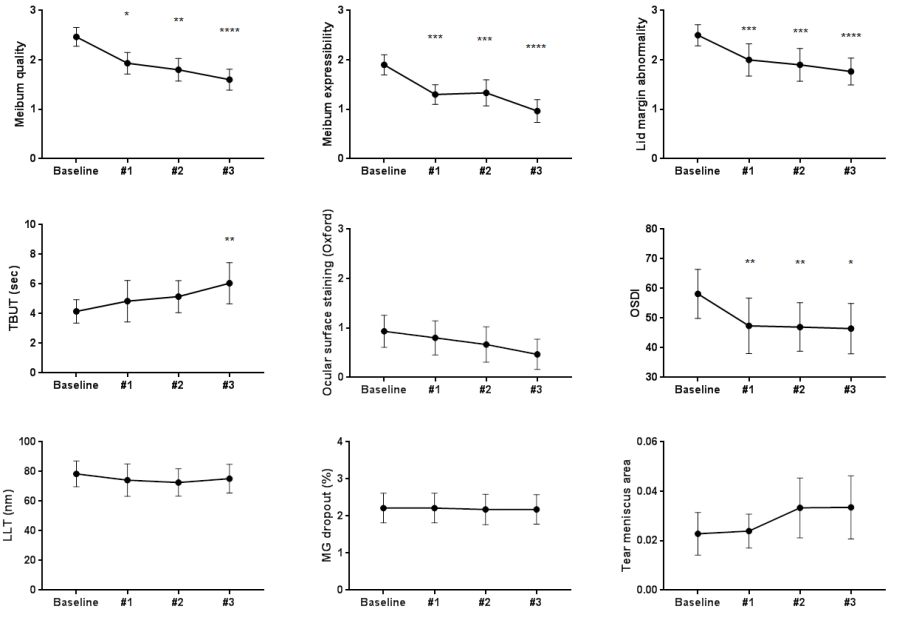

Figure 1. Change in clinical parameters following each IPL session in MGD patients. (A) meibum quality, (B) meibum expressibility, (C) lid margin abnormality, (D) TBUT, (E) Ocular surface staining score using Oxford scheme, (F) OSDI, (G) lipid layer thickness, (H) meibomian gland dropout score; meiboscale, (I) tear meniscus area. The symbol "*" (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001) represents statistically significant post hoc analysis results in multiple comparison with the baseline value.

2. Tear cytokine analysis

The IL-6 and TNF-α concentrations showed significant decrease over the time course (p-value of 0.012 and 0.042, respectively) (Table 2). Although the concentrations of other cytokines tended to decrease, the statistical values were not significant.

Table 2. Change in tear cytokine profiles following each IPL session in MGD patients.

Clinical parameter	Baseline (Before session 1)	Between session 1&2	Between session 2&3	After session 3	p-value
IL-2	4.18 (0-31.2)	3.115 (0-9.1)	3.35 (0-13.18)	3.11 (0-12.15)	0.863
IL-4	0.019 (0-1.65)	0.00 (0-1.07)	0.00 (0-1.37)	0.00 (0-1.15)	0.332
IL-6	9.58 (1.13-747.85)	8.05 (0-271.01)	4.15 (0-288.72)	7.31 (0-107.92)	**0.012**
IL-10	0.66 (0-2.9)	0.50 (0-1.46)	0.58 (0-1.29)	0.34 (0-8.55)	0.268
IL-17A	2.07 (0-156.3)	1.89 (0-165.92)	0.97 (0-12.96)	0.89 (0-28.54)	0.071
TNF-α	16.70 (0.82-633.75)	5.74 (0.53-157.23)	6.64 (0.61-66.62)	7.89 (0.29-51.66)	**0.042**
IFN-γ	0.00 (0-4.19)	0.00 (0-7.93)	0.00 (0-1.14)	0.00 0 (0-0.58)	0.979

Nonparametric test variables are expressed as median (minimum – maximum).
[a] Friedman test
Bold fonts indicate statistically significant results.

3. Correlation between clinical outcome and tear cytokines

To investigate whether the change in tear cytokine levels were related to the change in clinical parameters, correlation analysis was performed between tear cytokines and clinical variables which showed statistically significant improvement with treatment (Table 3).There was a significant correlation between the change in IL-6 with the change in meibum quality (Spearman's correlation coefficient, r_s=0.470, p=0.018), meibum expressibility (r_s=0.532, p=0.023), and lid margin abnormality (r_s=0.591, p=0.003) (Figure 3). The change in TNF-α concentration was associated with the change in meibum expressibility (r_s=0.388, p=0.044), and the change in ocular surface staining score (r_s=0.449, p=0.018).

Table 3. The correlations between the changes in tear cytokine levels, and the changes in the clinical parameters, which showed significant improvement after IPL treatment.

	Meibum quality	Meibum expressibility	Lid margin abnormality	TBUT	Ocular surface staining	OSDI
IL-6	**r_s =0.470 p=0.018**	**r_s =0.532 p=0.023**	**r_s =0.591 p=0.003**	r_s =-0.157 p=0.363	r_s =0.299 p=0.114	r_s =0.088 p=0.736
TNF-α	r_s =0.252 p=0.328	r_s **=0.388 p=0.044**	r_s =0.118 p=0.651	r_s =0.004 p=0.989	**r_s =0.449 p=0.018**	r_s =0.346 p=0.174

Bold fonts indicate statistically significant results.
r_s = Spearman's correlation coefficient

4. Prognostic factors

Regression analysis was performed to analyze prognostic factors associated with the improvement in subjective symptom score. The clinical parameters which proved statistically significant in the previous analyses were investigated. In the univariate analysis, the higher baseline meibum expressibility score (ß=0.488, p=0.016) were associated with the degree of reduction of OSDI score after 3 treatment sessions (Table 4). In the multivariate analysis, higher baseline meibum expressibility (ß=0.645, p=0.001), and lower baselineTBUT (ß=-0.461, p=0.016) were significantly related to decreased subjective symptom score after treatment.

Potential complications and adverse events including uveitis and iris damage did not occur in any of the patients.

Table 4. Univariate and multivariate linear regression analysis of the association of the change in OSDI score with baseline clinical conditions.

Variable (Baseline value)	**Univariate Model**		**Multivariate Model**	
	Beta	**P value**	**Beta**	**P value**
Age	-0.134	0.532	-0.199	0.240
Sex	0.134	0.534	0.332	0.052
Meibum quality	0.122	0.571	-0.159	0.392
Meibum expressibility	**0.488**	**0.016**	**0.645**	**0.001**
Lid margin abnormality	-0.350	0.094	-0.226	0.188
TBUT	-0.240	0.259	**-0.461**	**0.016**
Ocular surface staining	0.247	0.245	0.049	0.798

Bold fonts indicate statistically significant results.

IV. DISCUSSION

There have been previously reported studies on the clinical outcome of IPL on MGD patients, however, this is the first study to provide evidence for the possible mechanism for the clinical effect of IPL on MGD, and propose appropriate candidate who may benefit from this treatment.

There is increasing evidence that inflammation is associated with the development of MGD. Increased tear concentrations of IL-1ß, IL-6, IL-8, IL-12, IFN-γ, TNF-α, IL-17, and MMP-9 have been reported to be associated with the chronic inflammatory status of MGD, and significant correlations were observed between tear inflammatory mediators and clinical parameters.[16,25-28] Altered cytokine balance in tear fluid has been associated with squamous metaplasia of the ocular surface epithelium and disruption of conjunctival goblet cell function, contributing to the ocular surface damage and compromising tear film stability.[29,30] Subsequent stimulation of proinflammatory cytokine secretion due to the desiccating stress further aggravates the ocular surface inflammation.[31,32] Therefore, evaluation of tear cytokine profile is useful in demonstrating the inflammatory status of MGD and the efficacy of treatment.

This study confirmed that the inflammatory tear cytokines, IL-6 and TNF-α, decreased significantly after IPL treatment, and it correlated with

the improvement in clinical parameters including meibum quality, expressibility, lid margin abnormality, and ocular surface staining. The decrease in tear cytokine with IPL treatment followed by the improvement in clinical symptoms and signs support the postulated hypothesis that the IPL leads to thrombosis of the abnormal blood vessels in the lid margin, thus decreasing the extravasation of the inflammatory mediators. The absorption peak at 578 nm by the oxyhemoglobin allows for selective photothermolysis, in which the converted heat energy leads to vasculature destruction.[3,5] In fact, Schroeter et al reported that 77.8% of 60 patients with facial rosacea showed clearance of telangiectasia after IPL treatment,[33] and Papagerogiou et al reported significant reduction in facial telangiectasia and erythema in subtype 1 rosacea patients after four IPL sessions.[14] Similar effect has been reported in MGD patients treated with IPL, as shown by the reports on the significant relief of eyelid telangiectasia and conjunctival injection,[11] and the decrease in lid margin vascularity.[12] Similarly in our study, vascular engorgement along the lid margin and the plugging of the meibomian orifices improved with IPL treatment, contributing to the reduction of the total lid margin abnormality score. However, the other two categories of the score, which were structural changes including lid margin irregularity and replacement

of the mucocutaenous junction, failed to respond to the treatment. The decrease in superficial vascular engorgement along the lid margin further strengthens the effect of IPL in decreasing ocular surface inflammation as shown by the reduction of the tear cytokine levels.

As well as alleviating inflammation, IPL also improved meibum quality, expressibility, lid margin abnormality, TBUT, ocular surface staining, and OSDI. Since the ocular surface parameters were associated with the change in cytokine concentrations, the stabilization of the ocular surface after IPL treatment are likely to be consequences of both decreased ocular surface inflammation and the direct effect of IPL on the meibomian glands. Another mechanism of IPL has been suggested as the local warming effect which liquefies the inspissated meibum and encourages more regular outflow. Improvement in parameters related to meibomian gland function including meibum quality, expressibility, and lid margin abnormality score which consists of the plugging of the gland orifices as one of its categories, can improve the quality of the tear film lipid layer and reinforce tear film stability. Significant improvements of TBUT and the ocular surface staining score indicate the stabilization of the ocular surface. The demonstrated restoration of ocular surface integrity and alleviation of eyelid inflammation leads to decrease in

patient reported symptoms, as shown by the reduction in OSDI. These results are consistent with the previous studies which reported improved TBUT, lipid layer grade, oil flow score, and subjective symptom scores.[9,12,34]

We also identified which baseline characteristics were correlated with a successful outcome. Those with a greater number of unexpressible meibomian glands, and short TBUT were significantly associated with the degree of reduction in posttreatment OSDI score. The treatment potential for subjects with reduced gland expression at baseline demonstrates the effectiveness of IPL in restoring meibomian gland function and improving ocular comfort, especially in obstructive MGD.

The limitations of this study include lack of a control group, and a risk for placebo effect and investigator bias. The follow-up period after treatment termination was short, and further investigation is needed to assess the long-term effectiveness and safety. Also, the clinical evaluations were limited to the lower eyelids only. Direct treatment of the upper eyelids was not possible due to the risk of light penetration and intraocular damage. However, it has been shown that there is an indirect effect on the upper eyelids and the meibomian gland function improved even when only the inferior lid margin was treated.[12]

V. CONCLUSION

In summary, IPL treatment on MGD patients lead to decrease in inflammation, and improved meibomian gland function and ocular surface parameters. The decrease in IL-6, and TNF-α were correlated with the improvement in meibomian gland function including meibum quality, expressibility, and lid margin abnormality, and ocular surface staining. Among these significant variables, the worse meibum expressibility was associated with the degree of reduction in subjective symptom score after treatment. Therefore, it may be assumed that IPL can decrease inflammation and improve meibomian gland function, eventually leading to the stabilization of the ocular surface and patient comfort. Additionally, patients with obstructive MGD are more likely to benefit from the treatment, and the tear cytokine levels, IL-6 and TNF-α, may be used as predictors for treatment response.

REFERENCES

1. Alghamdi YA, Mercado C, McClellan AL, Batawi H, Karp CL, Galor A. Epidemiology of Meibomian Gland Dysfunction in an Elderly Population. Cornea 2016;35:731-5.
2. Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci 2011;52:1922-9.
3. Raulin C, Greve B, Grema H. IPL technology: a review. Lasers Surg Med 2003;32:78-87.
4. Huang J, Luo X, Lu J, Chen J, Zuo C, Xiang Y, et al. IPL irradiation rejuvenates skin collagen via the bidirectional regulation of MMP-1 and TGF-beta1 mediated by MAPKs in fibroblasts. Lasers Med Sci 2011;26:381-7.
5. Babilas P, Schreml S, Szeimies RM, Landthaler M. Intense pulsed light (IPL): a review. Lasers Surg Med 2010;42:93-104.
6. Heymann WR. Intense pulsed light. J Am Acad Dermatol 2007;56:466-7.
7. Toys R BC, Youngerman S. Case report: Dry-eye symptoms improve with intense pulsed light treatment. [Accessed December 22 2016]
8. Toyos R, McGill W, Briscoe D. Intense Pulsed Light Treatment for Dry Eye Disease Due to Meibomian Gland Dysfunction; A 3-Year Retrospective Study. Photomedicine and Laser Surgery 2015;33:41-6.
9. Craig JP, Chen YH, Turnbull PR. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci 2015;56:1965-70.
10. Vegunta S, Patel D, Shen JF. Combination Therapy of Intense Pulsed Light Therapy and Meibomian Gland Expression (IPL/MGX) Can Improve Dry Eye Symptoms and Meibomian Gland Function in Patients With Refractory Dry Eye: A Retrospective Analysis. Cornea 2016;35:318-22.
11. Jiang X, Lv H, Song H, Zhang M, Liu Y, Hu X, et al. Evaluation of the Safety and Effectiveness of Intense Pulsed Light in the Treatment of Meibomian Gland Dysfunction. J Ophthalmol 2016;2016:1910694.
12. Gupta PK, Vora GK, Matossian C, Kim M, Stinnett S. Outcomes of intense pulsed light therapy for treatment of evaporative dry

eye disease. Can J Ophthalmol 2016;51:249-53.
13. Vora GK, Gupta PK. Intense pulsed light therapy for the treatment of evaporative dry eye disease. Curr Opin Ophthalmol 2015;26:314-8.
14. Papageorgiou P, Clayton W, Norwood S, Chopra S, Rustin M. Treatment of rosacea with intense pulsed light: significant improvement and long-lasting results. Br J Dermatol 2008;159:628-32.
15. Enriquez-de-Salamanca A, Castellanos E, Stern ME, Fernandez I, Carreno E, Garcia-Vazquez C, et al. Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease. Mol Vis 2010;16:862-73.
16. Lam H, Bleiden L, de Paiva CS, Farley W, Stern ME, Pflugfelder SC. Tear cytokine profiles in dysfunctional tear syndrome. Am J Ophthalmol 2009;147:198-205 e1.
17. Eom Y, Lee JS, Kang SY, Kim HM, Song JS. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. Am J Ophthalmol 2013;155:1104-10 e2.
18. Pult H, Riede-Pult B. Comparison of subjective grading and objective assessment in meibography. Cont Lens Anterior Eye 2013;36:22-7.
19. Han KE, Yoon SC, Ahn JM, Nam SM, Stulting RD, Kim EK, et al. Evaluation of dry eye and meibomian gland dysfunction after cataract surgery. Am J Ophthalmol 2014;157:1144-50 e1.
20. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640-50.
21. Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea 1998;17:38-56.
22. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye (Lond) 1991;5 (Pt 4):395-411.
23. Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Fukuoka S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. Ophthalmology 2009;116:2058-63 e1.
24. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis

BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615-21.

25. Acera A, Rocha G, Vecino E, Lema I, Duran JA. Inflammatory markers in the tears of patients with ocular surface disease. Ophthalmic Res 2008;40:315-21.
26. Jung JW, Han SJ, Nam SM, Kim TI, Kim EK, Seo KY. Meibomian Gland Dysfunction (MGD) and Tear Cytokines after Cataract Surgery according to Preoperative Meibomian Gland Status. Clin Exp Ophthalmol 2016; doi:10.1111/ceo.12744.
27. Solomon A, Dursun D, Liu ZG, Xie YH, Macri A, Pflugfelder SC. Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease. Investigative Ophthalmology & Visual Science 2001;42:2283-92.
28. Yoon KC, Jeong IY, Park YG, Yang SY. Interleukin-6 and tumor necrosis factor-alpha levels in tears of patients with dry eye syndrome. Cornea 2007;26:431-7.
29. Chen YT, Nikulina K, Lazarev S, Bahrami AF, Noble LB, Gallup M, et al. Interleukin-1 as a Phenotypic Immunomodulator in Keratinizing Squamous Metaplasia of the Ocular Surface in Sjogren's Syndrome. American Journal of Pathology 2010;177:1333-43.
30. Contreras-Ruiz L, Ghosh-Mitra A, Shatos MA, Dartt DA, Masli S. Modulation of conjunctival goblet cell function by inflammatory cytokines. Mediators Inflamm 2013;2013:636812.
31. Higuchi A, Kawakita T, Tsubota K. IL-6 induction in desiccated corneal epithelium in vitro and in vivo. Mol Vis 2011;17:2400-6.
32. Gamache DA, Dimitrijevich SD, Weimer LK, Lang LS, Spellman JM, Graff G, et al. Secretion of proinflammatory cytokines by human conjunctival epithelial cells. Ocul Immunol Inflamm 1997;5:117-28.
33. Schroeter CA, Haaf-Von Below S, Neumann HAM. Effective treatment of rosacea using intense pulsed light systems. Dermatologic Surgery 2005;31:1285-9.
34. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; a 3-year retrospective study. Photomed Laser Surg 2015;33:41-6.

ABSTRACT(IN KOREAN)

마이봄샘 기능이상 환자에서 Intense pulsed light의 임상적 효과 및 눈물내 사이토카인 분석

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최문정

목적: 마이봄샘 기능이상 환자에서 Intense Pulsed Light (IPL)의 효과 및 눈물내 사이토카인의 변화를 평가하고, IPL 치료 효과에 영향을 주는 요인을 알아보고자 하였다.
방법: 중등도 마이봄샘 기능이상 환자 30명을 대상으로 3주 간격으로 3회 IPL을 시행하였다. 마이봄샘기능평가, 눈물막 파괴시간, 각결막 형광염색, 안구표면질환지수 (OSDI), 마이봄샘 간섭계, 눈물 내 사이토카인의 변화를 분석하였다.
결과: 시술 후 IL-6와 TNF-α가 감소하였고, 마이봄 지질의 질과 분비 정도, 안검경계 이상, 눈물막파괴시간, 각결막 형광염색, OSDI는 호전 소견을 보였다. 눈물내 사이토카인 (IL-6, TNF-α)의 감소는 임상적 증상 (마이봄샘 지질의 질과 분비 정도, 안검경계 이상, 각결막형광염색)의 호전 정도와 상관관계를 보였다. 이 중 기존 마이봄샘 지질의 분비 정도가 낮을수록, TBUT가 낮을수록 시술 후 OSDI로 측정한 증상의 개선 정도가 큰 것으로 나타났다.
결론: 마이봄샘 기능이상 환자에서 IPL 치료는 염증을 감소시키고, 마이봄샘 기능 및 안구표면상태를 호전시켰다. 눈물내 사이토카인의 감소는 마이봄샘 분비정도의 호전과 연관이 있었고, 마이봄샘 분비가 잘 되지 않았던 환자에서 더 큰 증상의 호전을 보인 것으로 보아 IPL치료는 폐쇄성 마이봄샘기능이상에서 효과적일 것으로 사료된다.

핵심되는 말 : 마이봄샘 기능이상, Intense pulsed light, 눈물내 사이토카인