 doi:10.20944/preprints202205.0237.v1

Article

Combination Treatment of Intense Pulsed Light Therapy and Meibomian Gland Expression for Evaporative Dry Eye

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Abstract: Dry eye disease (DED) most commonly caused by evaporative subtypes and mainly induced by meibomian gland dysfunction (MGD). Intense pulsed light (IPL) combined with meibomian gland expression (MGX) is noninvasive treatment for improvement of ocular discomfort symptoms and MGD. In this prospective study between November 2020 and May 2022, the patients met the criteria of both ocular surface disease index (OSDI) ≥13 scores and standardized patient evaluation of eye dryness (SPEED)≥ 8 scores were enrolled in Kaohsiung Veteran General Hospital. Three separate treatment sessions of IPL therapy combined with MGX administered to the lower lids with an interval of 28 days. Further tear film assessment included lipid layer thickness (LLT), tear meniscus height (TMH), non-invasive tear break-up time (NIBUT), meibomian gland loss (MGL) either beforeor after 1st and 3rd IPL therapy combined with MGX. Besides, lissamine green staining and pain scores were also recorded. We totally enrolled 37 patients of 74 eyes. Men accounted for 18.92% (7/37). The mean age was 54.51 ± 11.72 years. The mean OSDI scores were 58.12 ± 22, while the SPEED scores were 17.03 ± 5.98. The mean Schirmer's test was 3.66 ± 2.43 mm. After three sessions IPL treatment with MGX, the OSDI, SPEED, LLT, TMH, MGL, MGXS and pain scores were significantly improved. For the MGX scores (MGXS) ≤20 group, MGL and lissamine green scores showed significant improvements. For the MGXS >20 group, TMH and dry spot rate revealed statistically improvement. Noninvasive IPL therapy with MGX statistically improved not only dry eye symptoms but also tear film assessments.

Keywords: dry eye; intense pulsed light therapy; meibomian gland; tear

1. Introduction

Dry eye disease (DED) is a multi-factorial ocular surface diseases characterized by inadequate or unstable tear film, resulting in disruption of lacrimal homeostasis due to impairment of one or more of its components [1]. Most DED cases are caused by evaporative subtypes, mainly induced by meibomian gland dysfunction (MGD). DED manifests as ocular surface burning and irritation, fluctuating visual acuity, red eye, and epiphora [2].

In patients with MGD, the glands narrow, acini atrophy and hyperkeratosis occur [3], and meibum viscosity increases [4]. The reduced meibum outflow may encourage proliferation of commensal bacteria [5], which secrete lipases that can change the lipid composition in the meibum, increasing the esterified cholesterol levels and consequently reducing meibomian gland (MG) output [4,6]. Some patients with plugged or capped MG orifices may present with lid margin thickening, irregularity, telangiectasia and hyperemia [7]. In severe MGD, solidified toothpaste-like secretions can be observed [6,8]. Forced MG expression (MGX), conceptualized in 1921 by Gifford [9], is an effective method for rehabilitating MG and improving dry eye symptoms.

Intense pulsed light (IPL) therapy is widely used in cosmetic skin treatments andfor removing hypertrichosis, benign cavernous hemangiomas, benign venous malformation,

 doi:10.20944/preprints202205.0237.v1

telangiectasia, port-wine stains, and pigmented lesions [10]. IPL therapy (high-intensity light source consisting of visible light; wavelength 515-1200 nm) postulates that oxyhemoglobin in blood vessels located on the surface of the skin absorbs light emitted from the flash lamp. This absorption generates heat that coagulates red blood cells, leading to blood vessels thrombosis [11-14]. In addition to reduction in telangiectasia and facial erythema severity, concurrent ocular surface health improvements were observed in patients undergoing IPL for rosacea dermatologic manifestations [15]. This study aimed to assess the performance of combination IPL with MGX in altering tear film characteristics and improving subjective symptoms associated with *DED* and *MGD.*

2. Methods

2.1. Patient Recruitment

This prospective study followed the tenets of the Declaration of Helsinki and was approved by ourinstitutional review board. After explaining the informed consent requirements, all enrolled patients provided written consent. In this study, all 37 patients enrolled in Kaohsiung Veteran General Hospital between November 2020 and May 2021 and met the inclusion criteria: an ocular surface disease index (OSDI) score ≥13 and standardized patient evaluation of eye dryness (SPEED) score ≥ 8. A MGD diagnosis was based on lid margin abnormalities (orifice plugging, lid margin hyperemia, telangiectasia, anterior or posterior shift of the mucocutaneous junction) determined by an experienced ophthalmologist. The exclusion criteria were as follows: patients with contraindications for light therapy (pregnancy, Fitzaptrick skin type 6, sunburn, sunlight allergy, ultraviolet radiation exposure, infectious skin disorders, diabetes, hemophilia, epilepsy, photosensitive therapy, pacemaker, defibrillation, cutaneous purpura, cutaneous disorders [including acne, birthmarks and eczema]). Nevus and tattoos should be protected during IPL treatment. Participants who received clinical skin treatment within 2 months before this study were also excluded.Wearing contact lenses within 48 hours of commencement or during the study,intraocular surgery within 6 months,intraocular or periocular injection within 6 months; any acute infectious or non-infectious ocular condition in either eye within 30 days, and ocular surface disease or condition associated with clinically significant scarring or destruction of conjunctiva or cornea also resulted in exclusion.

2.2. Pre-treatment Evaluation

We evaluated several enrolled patients characteristics (age, sex, pre-treatment vision, OSDI and SPEED questionnaires, Schirmer test) and tear film assessment (lipid layer thickness [LLT], tear meniscus height [TMH], non-invasive tear break-up time [NIBUT], blinking interval, dry spot rate, MG loss [MGL] including upper [UMGL] and lower lids [LMGL]) using the IDRA ocular surface analyzer (SBM SistemiSrl, Orbassano, Italy), and lissamine green scores. For the dry spot rate, we calculated the difference in the dry spot percentage divided by the time interval between the start of the first dry spotand complete blinking. For MGL, we calculated the sum of UMGL and LMGL, which was then divided by two. We stained the lower tarsal conjunctiva of each eye using lissamine green strips under saline drops and took external pictures of each eye in anterior and everted lower and upper tarsusviews after waiting five minutes to expose thestained area of the lid margins. We modified the 2010 SICCA-Ocular staining score [16] and graded the nasal and temporal conjunctiva with lissamine green staining as follows: 0-9 staining spots, grade 0;10-30, grade 1; 30-100, grade 2; and > 100, as grade 3. Each staining patch was considered as one point. Subsequently, we graded the eyelid margins with lissamine green staining of the horizontal length and vertical percentage over the upper and lower eyelid margins, respectively, according to the Korb grading system for lid wiper epitheliopathy [17, 18]. Lissamine green scores of each eye were graded as the sum of nasal, temporal conjunctiva,and upper and lower lid margins.

2.3. Treatment Strategy and Evaluation

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Both eyes of patients were assessed over an 84-day period, with IPL treatment applied to the skin area immediately below the lower eyelid during three separate treatment sessions on days 0, 28 and 56 with a 28-day interval between each session. Five pulses were applied to four periocular zones inferior to the eye and one periocular zone temporal to the eye; both eyes were protected by opaque goggles. The five pulses were approximately 12 J/cm^{2}each, based on individual skin appearance, as determined by the Fitzpatrick skin type.

After each of the first three IPL treatments, MGX were applied over the bilateral lower lids. We further graded and recorded the meibum status using the MGX score (MGXS). We modified the international workshop-MGD staging as follows [18]. Dysfunctions were graded as 0-3 according to qualitative changes in expressed meibum: complete gland obstruction, grade 0; toothpaste-pattern meibum, grade 1; turbid meibum with debris, grade 2; and clear meibum, grade 3. Fifteen visible main duct orifices of the bilateral lower lids were assessed on biomicroscopy. We recorded the sum of the 15 orifices'lower lidsMG grades as MGXS. Subsequently, all patients would give pain scores during MG expression from the bilateral lower lids (from 0-10, 0 indicating no pain and 10 indicating severe pain).

OSDI, SPEED, and tear film assessments (LLT, TMH, NIBUT,blinking interval, dry spot rate and MGL) were all assessed and recorded again 28 days after the first and third IPL treatments. We further divided patients into two groups according to MGXS after the first IPL treatment. Those with a score ≤20 were classified into the MGXS ≤20 group; those with a score >20 were classified into the MGXS >20 group.

2.4. Data and Statistical Analysis

We analyzed the relationship between general data and tear film assessment before IPL treatment using OSDI and SPEED scores. Categorical variables were analyzed using independent *t*-test; continuous variables were analyzed using the Pearson correlation test. Comparisons of pre- and post- IPL data were performed at different time points using a paired *t*-test. We further analyzed the general pre-IPL data and improvements from pre-IPL to post-third IPL treatment of the two MGXS groups using independent and paired *t*-test, respectively. Data were analyzed using IBM SPSS software v 20.0 (Armonk,NY). A *P* level < 0.05 was considered significant.

3. Results

Ultimately, 37 patients met the inclusion criteria: OSDI score >13 and a SPEED score >8. Men accounted for 18.92% (7/37) of the cohort. The mean age was 54.51 ± 11.72 years (24-76, median: 55) years. The mean OSDI and SPEED scores were 58.12 ± 22 (18.75-95, median: 59.38) and 17.03 ± 5.98 (8-28, median: 17), respectively. The mean Schirmer's test result was 3.89 ± 2.81 mm. The mean LLT, TMH, NIBUT, blinking interval, dry spot rate, MGL, and lissamine greens scores was 34.78 ± 26.31 nm, 0.18 ± 0.06 s, 4.75 ± 0.98 s, 13.01 ± 3.57 s, 5.80 ± 3.25 %/s, 42.40 ± 16.74 % and 9.03 ± 4.45, respectively. Table 1 summarizes the baseline information before IPL therapy. Among these data, the factors that correlated with OSDI were sex (*P*=0.009), SPEED scores (*P*=0.020), LLT (*P*=0.012), MGXS (*P*=0.035), pain scores (*P*=0.020), and lissamine green scores (*P*=0.028). The factors that correlated with SPEED score were age (*P*=0.034), and OSDI (*P*=0.001) and lissamine green scores (*P*=0.037).The mean OSDI score of female patients (30/37) was 62.58 ± 20.94; that of male patients (7/30) was 37.3 ± 15.55.

 doi:10.20944/preprints202205.0237.v1

Table 1. The baseline information of patients before IPL treatment.

N: 37 persons (74 eyes)	N (%), Mean ± SD	OSDI correlation	SPEED correlation
Age, years	54.51± 11.72	0.530[b]	0.034[b]*
Sex (M)	7 (18.92%)	0.009[a]*	0.097[a]
BCVA	0.89 ± 0.25	0.070[b]	0.065 [b]
OSDI, scores	58.12 ±22.17		0.001[b]*
SPEED, scores	17.03 ± 5.98	0.001[b]*	
Schirmer test, mm	3.89± 2.81	0.728[b]	0. 125[b]
Lipid layer thickness, nm	34.78± 26.31	0.012[b]*	0.194[b]
Tear meniscus height, mm	0.18±0.06	0.051[b]	0.281[b]
Noninvasive tear break-up time, s	4.75±0.98	0.357[b]	0.865[b]
Blinking time, s	13.01 ± 3.57	0.180 [b]	0.183 [b]
Dry spot rate, %/s	5.80 ± 3.25	0.538 [b]	0.360 [b]
Meibomian gland loss, %	42.40±16.74	0.957[b]	0.182[b]
Meibomian gland expression scores	19.84 ± 6.06	0.035[b]*	0.535[b]
Pain scores	6.18 ± 2.22	0.020[b]*	0.085[b]
Lissamine green scores	9.03 ± 4.45	0.028[b]*	0.037[b]*

*P<0.05, [a] independent t-test; [b] Pearson correlation test; N: number; %: percentage; SD: standard deviation;M: male; BCVA: best-corrected visual acuity; OSDI: ocular surface disease index; SPEED: standardized patient evaluation of eye dryness; s: seconds

Table 2 summarizes the OSDI and SPEED score, tear film assessment, MGXS, pain score, and lissamine green scored at as, pre-IPL and post-first and third IPL therapies. The mean OSDI scores decreased from 58.12 ± 22.16 pre-IPL to 41.19 ± 20.86 and 36.89 ± 18.31 (P< 0.001, both) post-first and third IPL therapies, respectively, which was significant. The mean SPEED scores decreased from 17.03 ± 5.93 (pre-IPL) to 13.06 ± 6.96 and 11.53 ± 6.51 (P< 0.001, both) after the first and thirdtreatments, respectively; which was statistically significant. The mean LLT increased from 34.74 ± 26.31 nm (pre-IPL) to 51.49 ± 29.17 nm and 53.99 ± 31.19 nm (P< 0.001, both); the mean TMH mildly increased from 0.18 ± 0.06s (pre-IPL) to 0.21 ± 0.07 s (P= 0.008) and 0.22 ± 0.14 s (P= 0.014); the mean NIBUT mildly increased from 4.75 ± 0.99 s (pre-IPL) to 4.94 ±1.18 s and 4.88 ± 0.98 s; and the blinking interval decreased from 13.01 ± 3.57 s (pre-IPL) to 10.62 ± 3.03 s and 11.38 ± 1.92 s (P< 0.001, both) after the first and third IPL treatments, respectively. These differences were statistically significant. The mean dry spot rate remained the same before 5.80 ± 4.65 %/s and after the first IPL treatment (5.81 ± 7.58 %/s) and mildly increased 5.84 ± 4.82 %/s following the third therapy. The mean MGL decreased 41.91 ± 20.30 (pre-IPL) to 32.80 ± 14.17 (P= 0.006) and 28.11 ± 11.08 (P< 0.001) after the first and third treatments, respectively. The mean MGXS mildly increased from 19.84 ± 6.06 following the first IPL treatment to 23.48 ± 6.42 (P< 0.001) following the third IPL treatment; moreover, the mean pain scoredecreased from 6.18± 2.22 (post-first IPL therapy) to 3.58 ± 1.85 (post-third IL therapy); this improvement was significant (P<0.001). The mean lissamine green scores mildly decreased from 9.03 ± 4.44 (pre-IPL) to 8.70 ± 3.72 (post-first IPL therapy).

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Table 2. The complete data before IPL and after the first and the third IPL therapies.

N: 37 persons (74 eyes)	Pre-IPL therapy Mean (SD)	Post-1st IPL therapy Mean (SD)	*P*	Post-3rd IPL therapy Mean (SD)	*P*
OSDI, scores	58.12 (22.16)	41.19 (20.86)	<0.001*	36.89 (18.31)	<0.001*
SPEED, scores	17.03 (5.93)	13.06 (6.96)	<0.001*	11.53(6.51)	<0.001*
LLT, nm	34.74(26.31)	51.49 (29.17)	<0.001*	53.99 (31.19)	<0.001*
TMH, mm	0.18 (0.06)	0.21 (0.07)	0.008*	0.22 (0.14)	0.014*
NIBUT, s	4.75(0.99)	4.94 (1.18)	0.233	4.88 (0.98)	0.333
Blinking time, s	13.01 (3.57)	10.62 (3.03)	<0.001*	11.38 (1.92)	<0.001*
Dry spot rate, %/s	5.80 (4.65)	5.81 (7.58)	0.594	5.84 (4.82)	0.862
MGL, %	41.91 (20.30)	32.80 (14.17)	0.006*	28.11 (11.08)	<0.001*
MGXS, scores		19.84 (6.06)		23.48 (6.42)	<0.001*
Pain scores		6.18 (2.22)		3.58 (1.85)	<0.001*
Lissamine green, scores	9.03 (4.44)	8.70 (3.72)	0.576		

*P<0.05, Paired t-test;N: number; IPL: intense pulse light; SD, standard deviation; OSDI: ocular surface disease index; SPEED: standardized patient evaluation of eye dryness; LLT: lipid layer thickness; TMH: tear meniscus height; NIBUT: non-invasive tear break-up time; s: seconds; %: percentage; MGL: meibomian gland loss; MGXS: meibomian gland expression scores

Table 3 summarizes the pre-IPL and post-first IPL general data of the MGXS ≤20 and MGXS >20 groups. The mean OSDI scores was higher in the MGXS ≤20 group (64.29 ± 18.05 vs. 54.91 ± 23.55); the mean SPEED scores were similar (17.74 ± 5.11) and 17.38 ± 6.54) between groups. However, the mean LLT was mildly higherin the MGXS ≤20 group (34.49 ± 25.55 nm vs. 33.52 ± 26.69 nm). The mean TMH was significantly higher in the MGXS ≤20group (0.19 ± 0.06 mm vs. 0.16 ± 0.06 mm) (P= 0.029), while the mean NIBUT was nearly identicalin both groups (4.75±0.89 s and 4.75± 1.07 s) groups. The mean blinking interval was longer in the MGXS ≤20 group (13.28 ± 3.35 s vs. 12.97 ± 3.64 s), while the mean dry spot rate was mildly lower in the MGXS ≤20 group (5.72 ± 5.71 %/s vs. 6.32 ± 12.13 %/s). Nevertheless, the mean MGL was higher in the MGXS ≤20 group (34.53 ± 11.08 % vs. 32.38 ± 12.13 %). Furthermore, the mean MGXS was significantly higher (P<0.001) in the MGXS >20 group (25.55 ± 3.50 scores vs. 15.11 ± 2.69); pain scores were approximately the same in both groups (6.06 ± 2.17 and 6.14 ± 2.42). However, the mean lissamine green scores were higher in the MGXS ≤20 group (10.12 ± 4.69 vs. 8.56 ± 4.08).

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Table 3. The pre-IPL and post-first IPL general data of the MGX scores ≤20 and MGX scores >20 groups.

Pre-IPL therapy	MGX scores ≤20 (Mean ± SD), n=35	MGX scores >20 (Mean ± SD), n=29	*P*
Age, years	53.34 ±13.11	55.62 ± 8.83	0.412
OSDI, scores	64.29± 18.05	54.91 ±23.55	0.094
SPEED, scores	17.74±5.11	17.38±6.54	0.811
LLT, nm	34.49 ±25.55	33.52±26.69	0.883
TMH, mm	0.19± 0.06	0.16± 0.06	0.029*
NIBUT, s	4.75±0.89	4.75± 1.07	0.987
Blinking time, s	13.28 ± 3.35	12.97 ± 3.67	0.721
Dry spot rate, %/s	5.72 ± 5.71	6.32 ± 3.77	0.498
MGL, %	34.53 ±11.08	32.38 ±12.13	0.584
MGXS, scores	15.11±2.69	25.55±3.50	<0.001*
Pain scores, scores	6.06± 2.17	6.14±2.42	0.892
Lissamine green, scores	10.12 ± 4.69	8.56 ± 4.08	0.190

*P<0.05, Independent t-test; IPL: intense pulse light; SD, standard deviation; n: number; OSDI: ocular surface disease index; SPEED: standardized patient evaluation of eye dryness; LLT: lipid layer thickness; TMH: tear meniscus height; NIBUT: non-invasive tear break-up time; s: seconds; %: percentage; MGL: meibomian gland loss; MGX: meibomian gland expression; MGXS: Meibomian gland expression scores

Table 4 shows the improvements between the first and third IPL therapy treatments combined with MGX in both groups. OSDI (P= 0.004/0.002) and SPEED scores (P= 0.04/<0.001), LLT (P= 0.003/<0.001), MGL (P= 0.023/0.005), and pain scores (P< 0.001 /<0.001) significantly improved in both groups. The significant improvements observed only in the MGXS ≤20 group were decreased blinking interval (P=0.005), increased MGXS (P<0.001) and decreased lissamine green scores (P=0.056), while those observed only in the MGXS >20 group were increased TMH (P=0.025) and decreased dry spot rate (P=0.021). However, NIBUT showed mild increases in the MGXS ≤20 group, but was nearly the same in the MGXS >20 group between the first and third IPL therapies combined with MGX. Figure 1 shows the changes in OSDI score, LLT and TMH after three sessions of IPL-MGX therapy in the MGXS ≤20 and >20 groups.

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Table 4. The data of post-1st IPL and post-3rd IPL therapy in two groups of MGXS ≤ 20 and MGXS > 20.

MGXS ≤20, n=35 MGXS>20, n=29	MGXS ≤20 Pre-IPL therapy Mean (SD)	MGXS ≤20 Post-3rd IPL therapy Mean (SD)	MGXS ≤20 *P*	MGXS >20 Pre-IPL therapy Mean(SD)	MGXS >20 Post-3rd IPL therapy Mean (SD)	MGXS >20 *P*
OSDI, scores	64.29 (18.05)	40.86 (20.36)	0.004*	54.91 (23.55)	32.32 (14.99)	0.002*
SPEED, scores	17.74 (5.11)	13.28 (6.09)	0.019*	17.38 (6.54)	9.79 (5.42)	<0.001*
LLT, nm	34.49 (25.55)	48.86 (32.74)	0.003*	33.52 (26.69)	60.17(28.95)	<0.001*
TMH, mm	0.19 (0.06)	0.25 (0.18)	0.087	0.16(0.06)	0.21 (0.07)	0.025*
NIBUT, s	4.75 (0.89)	5.04 (1.11)	0.126	4.75 (1.07)	4.79 (0.82)	0.856
Blinking time, s	13.28 (3.35)	11.57 (2.01)	0.005*	12.97 (3.67)	11.53 (1.70)	0.329
Dry spot rate, %/s	5.72 (5.71)	7.16 (5.79)	0.289	6.32 (3.77)	4.07 (3.25)	0.021*
MGL, %	34.53 (11.08)	29.57 (8.00)	0.023*	43.23 (16.13)	28.56 (10.78)	0.005*
MGXS, scores	15.11 (2.69)	20.43 (6.04)	<0.001*	25.55 (3.50)	27.17 (4.76)	0.074
Pain scores	6.06 (2.17)	3.81 (1.79)	< 0.001*	6.14 (2.41)	3.21 (1.88)	< 0.001*
Lissamine green, score	10.12 (4.69)	8.57 (3.47)	0.056	8.56 (4.08)	8.92 (3.66)	0.859

*P<0.05, Paired t-test; n: number; MGXS: meibomian gland expression scores; IPL: intense pulse light; SD: standard deviation; OSDI: ocular surface disease index; SPEED: standardized patient evaluation of eye dryness; LLT: lipid layer thickness; TMH: tear meniscus height; NIBUT: non-invasive tear break-up time; s: seconds; %: percentage; MGL: meibomian gland loss; MGX: meibomian gland expression

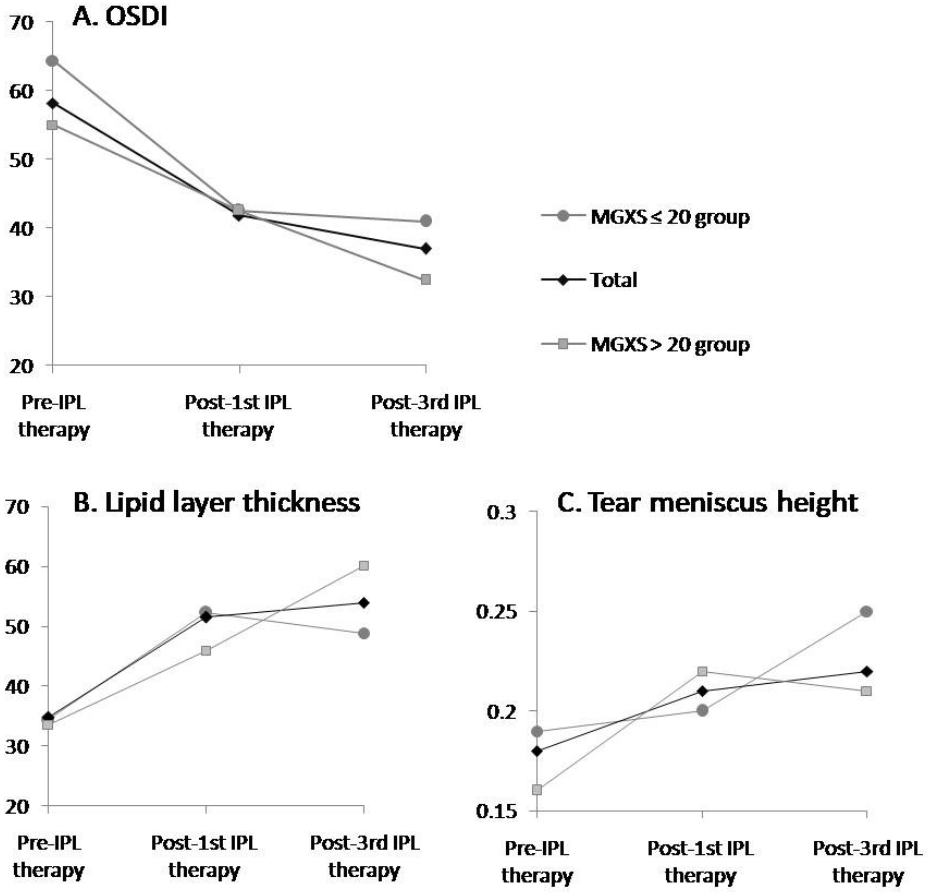

Figure 1. The improvement of OSDI scores, lipid layer thickness (LLT) and tear meniscus height (TMH) after three sessions of IPL-MGX combined therapy in two groups. OSDI scores were overall higher in the MGXS ≤20 group (A). The improvements of LLT showed better after third treatments

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in the MGXS>20 group (B). The improvements of TMH showed better after third treatments in the MGXS ≤20 group (C).

4. Discussion

MGD is a chronic, diffuse abnormality of the MG, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion [19]. AlthoughMG microstructures can currently be evaluated using in vivo confocal microscopy [20, 21], the etiology and pathogenesis of MGD remain unclear.

Warm compresses combined with lubricants the most common recommended supplementarytherapiesfor MGD-related evaporative dry eye.However, MGD management in clinical practice remains challenging as patient compliance with physician-recommended self-administered therapies is notoriously poor [22]. IPL therapy is a high-intensity light source which is directed toward the skin tissue and is subsequently absorbed by the targeted structure, resulting in heat production (>80 ℃), which destroys pigmented skin lesions. A third-generation IPL device designed specifically for periocular application with multiple homogenously sculpted light pulses has recently become commercially available and is currently the only medically certified IPL device for treating MGD [23].

In our study, the significant collaborative related factors of OSDI were SPEED, LLT, MGXS and pain scores. Regarding the correlation between OSDI scores and LLT,there was a negative correlation between OSDI and LLT; the higher the OSDI scores, the thinner the LLT. This was possibly due to the fact that dry eye symptom severityincreased because of the lower lipid content to protect the tear film from evaporation. Regarding the correlation between OSDI scores and MGXS and pain scores, there was also a negative correlation between OSDI scores and MGXS. However, a positive correlation between OSDI and pain scores was noted. These results indicated that increased dry eye symptom severity was associated with, stickierand cloudier meibum was and more pain during therapeutic MG expression.

Craig et al. reported that the lipid layer grade and NIBUT significantly improved after three separate sessions of IPL, with four pulses appliedfor patients with mild to moderate MGD. However, in their prospective, double-masked, paired-eye study, the tear evaporation rate and TMH were not differentbetween treated and control eyes [23]. In our study, LLT, TMH and MGXS significantly improved after three sessions of IPLtherapy combined with MGX in both eyes. However, NIBUT and the dry spot rate remained the same before and after treatment, even though LLT and MGXS significantly improved. The mean NIBUT beforeand after IPL treatment was much shorter than those obtained by Craig et al. [23]. Furthermore, stickier and harder meibum were found during compression in 47.30% (35/74) of patients with MGXS ≤20. This may explain why our patients had severer dry eye symptoms than the patients in the study of Craig et al. study, along with quick NIBUT, less aqueous production, and severe MGD.

According to Vegunta et al. [24], SPEED scores significantly decreased in 89% of 81 patients, and MG evaluations in 77% of patients significantly increased after four IPL treatments combined with MGX at four-week intervals. Tang et al. [25] further reported that combination IPL-MGX therapy was significantly more effective than warm compresses followed by MGX. In their study, SPEED score was reduced by 38% and 22% in the IPL-MGX and warm compress with MGX groups ($P<0.01$), respectively; and MG yielding secretion score improved by 197% in the IPL treatment group and 96% in the warm compress with MGX group [25]. In our study, there were significant improvements in the OSDI and SPEED scores, LLT, TMH, MGL, MGXS and pain scores after the first and the third IPL combined with MGX treatments. All studies showed the same results not only in relieving dry eye symptoms, but in improving lipid conditions, consistent with our results.

Aritaet al. [26] reported a study of 45 patients with 90 eyes who were randomly assigned to receive either IPL-MGX or MGX alone as a control. Each eye underwent eight sessions at 3-week intervals. TheIPL-MGX group had significantly improvedSPEEDscores, 14 to 5.5; LLT, 46 to 66 nm; NIBUT, 2.5 s to 7.0 s; BUT, 2.9 to 6.6 s;

 doi:10.20944/preprints202205.0237.v1

meibum grade, 2.2 to 0.3 from pre-IPL to after the eighth session. NIBUT (2.5 ± 1.2 s) and BUT(2.4 ±1.2 s) were approximately identical, however were much lower than those (5.28±1.42 s /5.29 ±1.42 s) observed by Craig et al. [23], consistent with our NIBUT results. Studies of Craig et al. [23] (from 5.28 ± 1.42 s to 14.11 ± 9.75 s) and Arita et al. [25] (from 5.28 ± 1.42 s to 7.0 ±2.7 s) showed significant improvements in NIBUT, which differed from our results. Although NIBUT in our study didn't improve significantly after IPL-MGX treatment, the mean NIBUT was slightly longer following the third treatment than pre-IPL; the NIBUT in our study following the third treatment was similar to that in the study by Arita et al. [24] which showed that the NIBUTcurve after IPL-MGX treatment revealed steady improvements within eight treatment sessions. Furthermore, we analyzed MGXS and pain scores as MGX. MGXS did improve significantly from the first to third IPL treatment, while pain scores showed a significant decrease following the third treatment compared to those following the first treatment, indicating that the meibum softened after IPL treatment and that the pain experienced during MGX decreased. The easier secretion of a clearer meibum after IPL-MGX therapy significantly thickened LLT and statistically increased TMH. However, LLT was not thickened enough to cover the whole cornea, leading to longer NIBUT, a slower dry spot rate and longer blinking interval. Even lissamine green scores in our study were lower after IPL-MGX compared therapy to pre-treatment values, but the difference was statistically insignificant.

We further divided patients who underwent the first IPL-MGX treatment into two groups by MGXS. Regarding pre-IPL therapy data, TMH and MGXS were significantly different between the groups. After the third treatment session, OSDI and SPEED scores, LLT, MGL and pain scoressignificantly improved in bothgroups. Furthermore, MGL and lissamine green scores showed improved significantly in the MGXS ≤20 group which presented severe MGD. Regarding severe MGD, IPL-MGX therapy may improve meibum quality and ocular surface conditions. However, NIBUT and TMH only mildly and insignificant improved, and even the dry spot rate was quicker post-treatment. Nevertheless, TMH and the dry spot rate significantly improved in the MGXS >20 group, indicating mild to moderate MGD, which has an LLT that is sufficient to cover the whole cornea. For mild to moderate MGD, IPL therapy combined with MGX is conducted with the purpose of maintaining a more aqueous tear film and delaying the dry spot rate. However, LLT was not sufficient to allow NIBUT to increase.

This study has some limitations. First, we did not choose one eye as a placebo control, which was critical in the study design to reduce risk bias from the patient's knowledge of which eye had been treated. However, bilateral eye treatment met the actual treatment effect in clinical settings. Second, the skin type of most Taiwanese individuals is classified as Fitzpatrick type 3-4; skin reactivity to light or ultraviolet rays may differ between individuals of other ethnicities. Third, most of our patients were female, which may have reduced the representativeness of our findings. Additionally, this study had a small sample size.

5. Conclusion

After three sessions IPL treatment with MGX, the OSDI, SPEED, LLT, TMH, MGL, MGXS and pain scores significantly improved compared to pre-treatment values. For severe MGD, blinking interval, MGXS and lissamine green scores has shown significant improvements after IPL therapy. For mild and moderate MGD, TMH and dry spot rate also revealed statistically improved. Noninvasive IPL therapy with MGX statistically improved dry eye symptoms as well as tear film stability.

Author Contributions: CJC and PSH did exams for patients including lissamine green staining and slit-lamp photo taking. JLC and KLP were responsible for clinical treatment of the patients. YCL and KLP collected clinical data. HIT searched and sorted related papers. KLP analyzed the statistical data, wrote the main manuscript and prepared table 1, 2, 3 and 4. JLC revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate: This study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics Committee of the Kaohsiung Veteran General Hospital's Institutional Review Board. The number of Ethics Committee approval registered as KSVGH20-CT10-23. This is a prospective study.

Funding: This research and all authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Acknowledgments: The authors wish to express their sincere gratitude for their cooperation to the staff of the Forest Service of Xanthi. This synergy contributed to a great extent to the implementation of the current research project. We hope that the research will contribute to the existing body of knowledge and raise awareness among forest managers. The authors also wish to thank Mrs. Malivitsi Zoe for editing the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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