

Comparing Efficacy of Combined Intense Pulsed Light Therapy and Low-level Light Therapy Versus Intense Pulsed Light for the Treatment of Dry Eye Disease: A Retrospective Study

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Abstract

Introduction: Dry eye disease is a prevalent condition that impacts millions of individuals globally, with meibomian gland dysfunction (MGD) being a significant contributor to the development of this condition. In recent years, intense pulsed light (IPL) and low-level light therapy (LLLT) have emerged as promising treatments for MGD-related dry eye disease. Several studies have reported that a combined therapy of IPL with LLLT is effective in treating MGD patients. However, to date, there is a lack of research comparing the efficacy of IPL alone versus IPL in combination with LLLT in the treatment of dry eye patients.

Purpose: To compare the efficacy of Intense Pulsed Light therapy combined with Low-Level Light therapy Versus Intense Pulsed Light for the treatment of dry eye disease

Study design: Retrospective single-center clinical study

Materials and Methods: Patients presenting with a dry eye disease (DED) with MGD and having received treatment with IPL or IPL with LLLT at Thammasat University Hospital between February 2023 and November 2023 were included. The single IPL session and combined IPL and LLLT session was performed once weekly over 3 weeks. The end point was the mean difference of DEQ-5 score between baseline (0-14 days before the first session of the treatment) and 2 weeks after the last session. Data collection was done retrospectively. Statistical analysis was done using STATA 16.0.

Results: 51 patients were included (25 patients from IPL group, 26 patients from IPL with LLLT group). DEQ-5 score significantly decreased after the single IPL treatment and the combined IPL with LLLT treatment ($P < 0.001$). Patients in the combined IPL with LLLT group showed significant improvement in DEQ-5 score compared with the single IPL group (-10.2 ± 3.1 vs -7.8 ± 2.1 , $P < 0.05$). There was no adverse effect reported in both groups.

Conclusions: Both IPL and IPL with LLLT were safe and effective in improving ocular discomfort symptoms in MGD-related dry eye disease. However, the combined IPL with LLLT determined a greater improvement in symptoms.

Keywords: Intense pulsed light, Low-level light therapy, Meibomian gland dysfunction, Dry eye disease

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Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film.¹ It is a common condition that affects millions of people worldwide, and its prevalence continues to rise due to factors such as aging population, increased screen time, and environmental changes. One of the main contributors to DED is meibomian gland dysfunction (MGD), which is characterized by the blockage or alteration of the meibomian glands in the eyelids, leading to decreased oil production and subsequent instability of the tear film. This instability results in symptoms such as dryness, irritation, and blurred vision.²⁻³

Traditional treatments for MGD consist of warm compresses, lid hygiene, practitioner-administered manual expression, antibiotics and anti-inflammatory agents.⁴⁻⁵ Patients often find that the warm compression is inconvenient and time-consuming, resulting in poor compliance.⁶ Additionally, while practitioner-administered manual expression is effective, its application is limited due to the associated pain.⁷ Since traditional treatments for MGD have limitations in terms of convenience and effectiveness, intense pulsed light (IPL) therapy and low-level light therapy (LLLT) have gained popularity as treatment modalities for MGD in recent years.

IPL therapy involves the use of high-intensity polychromatic light to treat MGD by targeting the abnormal blood vessels and reducing inflammation around the meibomian glands, which are responsible for producing the oily layer of the tear film.⁸⁻¹⁰ Numerous studies have reported its effectiveness and safety in managing DED associated with MGD.¹¹⁻¹³ The positive outcomes from these studies have led to the acceptance and integration of IPL therapy in clinical practice for managing dry eye disease.

LLLT, on the other hand, utilizes low-energy, high-fluence monochromatic light to stimulate healing and reduce inflammation, and has also shown promise in improving dry eye symptoms. Several studies have demonstrated the effectiveness of LLLT therapy in the treatment of dry eye and meibomian gland dysfunction.¹⁴⁻¹⁵

More recently, the combined therapy of IPL with LLLT has been the subject of several studies, and has demonstrated significant improvements in symptoms and clinical parameters in patients with MGD.¹⁶⁻¹⁹

While both IPL and LLLT have individually shown efficacy in treating MGD, there is currently a lack of comparative research between IPL combined with LLLT versus single IPL in the treatment of dry eye related to MGD. Therefore, further research is needed to directly compare the effectiveness of these treatments in order to provide a more comprehensive understanding of their potential benefits for patients with MGD.

Materials and Methods

The retrospective, non-randomized observational and single-center study was conducted at Thammasat University Hospital between February 2023 and November 2023. The study was approved by the Institutional Review Board (IRB) and followed the ethical guidelines outlined in the Declaration of Helsinki for research involving human subjects.

Objectives

This study aimed to compare the efficacy of combined IPL with LLLT versus single IPL for the treatment of meibomian gland dysfunction (MGD) related dry eye disease by evaluating dry eye symptoms. The primary objective of the study was to assess the difference in dry eye symptoms, as measured by the Dry Eye Questionnaire-5 (DEQ-5) score, between baseline (0-14 days before the first session of the treatment) and 2 weeks after the last treatment session. The DEQ-5 is a valid and reliable instrument for assessing dry eye symptoms, and is especially useful in identifying severe dry eye patients. It is sensitive to both symptom intensity and frequency.²⁰ A higher score represents more frequency and/or more severe symptoms. Additionally, the study aimed to review the safety of IPL and LLLT treatment by monitoring and documenting any adverse events.

Patients

The inclusion criteria were as follows: adults aged ≥ 18 years old at time of treatment, documented diagnosis of dry eye disease with meibomian gland dysfunction (MGD), receive either IPL alone or combined IPL with LLLT at Thammasat University Hospital between February 2023 and November 2023, available DEQ-5 scores before and after treatment, no significant change in other dry eye therapies (e.g. artificial eye drops).

The exclusion criteria were as follows: patients who received both treatments sequentially without clear distinction (e.g. IPL first, then LLLT added later), patients who did not complete 3 treatment sessions, incomplete medical records or missing data outcome.

The patients in this study were allocated to each treatment group due to physician preference and health insurance coverage. The assessor was masked to the treatment allocation. Data collection was done retrospectively through electronic medical records (EPHIS program) and patients' records of Thammasat University Hospital. The term used to search through EPHIS includes 'MGD' 'DED'. Data gathered included patient demographic data (age, sex), underlying disease (diabetes mellitus, hypertension), history of ocular surgery, history of meibomian gland expression, current usage of artificial eye drops (both preservative-free and contain preservative).

Treatment

In this study, the Eye-Light device (Espansione Marketing S.p.A., Bologna, Italy) was utilized to administer the IPL and LLLT treatments. The use of the Eye-light device for both IPL and LLLT treatments was carefully controlled and applied consistently by the same physician, in order to ensure the accuracy and reliability of the treatment protocol. In both groups, each patient underwent 3 treatment sessions, once weekly over 3 weeks.

In the single IPL treatment, a protective eyeshield was placed over the eyes to safeguard them from the intense light, and a handpiece emitting pulses of light was applied onto the skin. The IPL component emitted polychromatic, non-coherent light filtered to a wavelength of 600 nm. Eye-Light devices from Espansione included built-in optical filters. Light below 600 nm was filtered out, and only 600-1200 nm

is used in treatment. During the procedure, five flashes of light with an energy density of 10-16 joules/cm² were administered for each eye. The flashes were administered in a specific pattern, with three flashes along the inferior orbital rim in the vertical position, one flash along the inferior orbital rim in the horizontal position, and one flash behind the lateral canthus. The same procedure was carried out in the contralateral eye.

In the combined IPL with LLLT treatment, patients underwent IPL, then followed by LLLT. After the IPL session, the protective eyeshield was removed, and the LLLT mask was applied over the patient's eyes. The LLLT device emitted red light at approximately 633 nm and had an emission power of 100 mW/cm². During a treatment session, the total fluence in the treated area was 100 J/cm². The LLLT treatment lasted for 15 minutes, during which time patients were instructed to keep their eyes closed to facilitate the application of the therapy to both the upper and lower eyelids. Throughout the study, patients were allowed to continue using their usual artificial tears. No manual gland expression was done after IPL or LLLT treatment sessions.

Sample size

Sample size was calculated by sample size formula for two independent means. We expected DEQ-5 score mean difference between group treatment to 4-point difference which is commonly considered clinically meaningful. We estimated standard deviation of 4.5 according to Kwan et al., 2021.²¹ With acceptable error of 5% and 80% power, the sample size was 20 patients per group. To account for 10-15% drop out rate, the minimum sample size was a total of 46 patients.

Statistical analysis

All statistical analyses were performed using Stata 16.0. Continuous variables were summarized as means and standard deviations (SD), and categorical variables as frequencies and percentages. A two-sample independent t-test was used to compare baseline characteristics and DEQ-5 scores between the IPL and combined IPL + LLLT groups. To evaluate treatment effectiveness within each group, paired t-tests were used to compare DEQ-5 scores before and after treatment. The difference in DEQ-5 score

reduction between the two groups was assessed using an independent t-test. To explore factors associated with symptom improvement, a linear regression model was constructed with the change in DEQ-5 score as the dependent variable. The model included baseline DEQ-5 score, treatment group, age, sex, history of meibomian gland expression, artificial eye drops and topical steroids usage as independent variables. Regression coefficients (β), 95% confidence intervals (CI), and p-values were reported. A p-value of < 0.05 was considered statistically significant in the study.

Results

Patient selection was shown on flowchart 1. A total of 73 patients were initially included. After applying the exclusion criteria, 51 patients were included in the final analysis. Specifically, 17 patients were excluded due to incomplete

treatment sessions, and 5 had received both IPL and LLLT sequentially without clear documentation of treatment phases. Among the 51 included patients, 25 patients received a single IPL treatment, while 26 patients received a combined IPL with LLLT treatment.

Baseline demographic characteristics of the enrolled patients were reported in Table 1 of the study. The analysis revealed that there were no significant differences between the two groups in terms of demographic characteristics, with all P-values exceeding 0.05. The mean age of the patients was found to be 58.7 ± 15.13 years, with a majority of 37 patients being female (72%). 24 patients (47%) had previously undergone ocular surgery. Concerning conventional treatment, 33.3% had previously done meibomian gland expression and artificial eye drop usage was present in 96% of cases.

Flowchart 1: Patient selection in the study

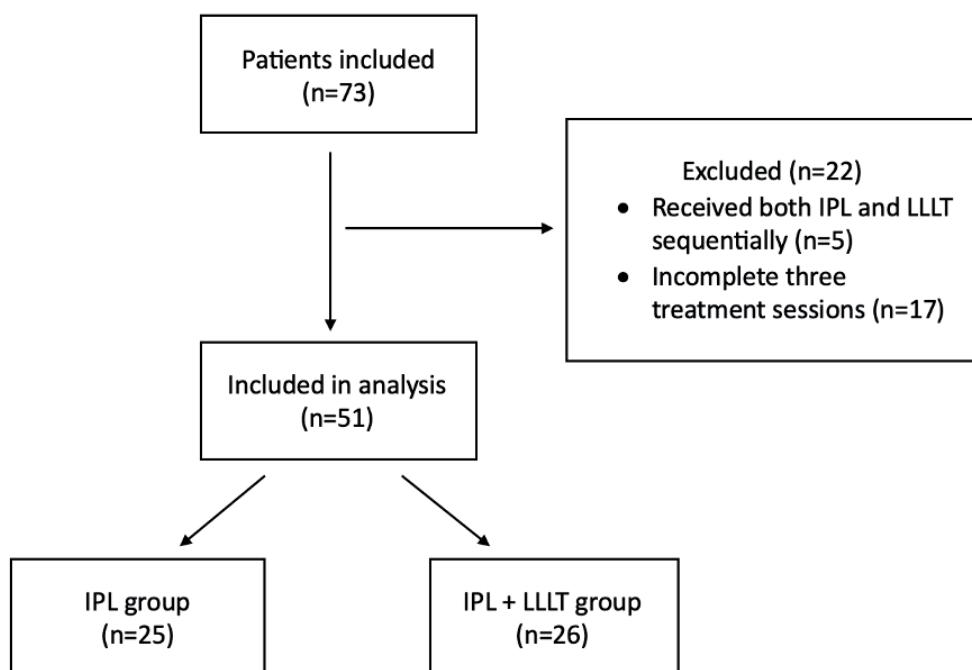


Table 1: Baseline demographic and clinical characteristics of patients enrolled in the study

Parameter	IPL	IPL with LLLT	P-value
Age(yr)	58.5 ± 14.6	58.8 ± 15.9	0.946
Sex(M/F)	7/18	7/19	0.589
DM	7 (28%)	2 (7.7%)	0.061
HT	6 (24%)	9 (34.2%)	0.301
History of ocular surgery	12 (48%)	12 (46.5%)	0.559
History of meibomian gland expression	8 (29.3%)	9 (37.5%)	0.569
Current usage of eye drops			
• Artificial tears	25 (100%)	24 (92.3%)	0.490
• Topical steroids	17 (68%)	12 (46.15%)	0.160
Baseline DEQ-5 score	15.48 ± 2.50	15.84 ± 2.41	0.597

The DEQ-5 score in the IPL group and combined IPL and LLLT group before and after treatment are summarized in Table 2. Prior to treatment, there were no statistically significant differences in the total DEQ-5 score between the two groups (15.5 ± 2.5 vs 15.8 ± 2.4 , $P = 0.597$). Both groups exhibited a statistically significant reduction in the DEQ-5 score following treatment (both $P < 0.001$). However, the combined IPL and LLLT group demonstrated a significantly greater improvement in the DEQ-5 score compared to the single IPL group (-10.2 ± 3.1 vs -7.8 ± 2.1 , $P = 0.0023$).

Factors associated with DEQ-5 score improvement were summarized in Table 3. Results showed that higher baseline DEQ-5 scores were significantly associated with greater DEQ-5 score improvement ($\beta = 0.96$; 95% CI: 0.75-1.17; $P < 0.001$). Additionally, patients treated with combined IPL and LLLT experienced a greater improvement in DEQ-5 scores compared to those treated with IPL alone, after adjusting for baseline severity ($\beta = 1.95$; 95% CI: 0.91-2.98; $p < 0.001$).

There were no device-related adverse events in both single IPL treatment and combined IPL with LLLT treatment.

Table 2: Comparison of the dry eye symptoms (DEQ-5 score) for both groups and between baseline and 2 weeks after treatment

	Before treatment	After treatment	Difference	P-value
IPL	15.48 ± 2.50	7.72 ± 1.67	7.76 ± 2.13	$P < 0.001$
IPL with LLLT	15.84 ± 2.41	5.65 ± 1.79	10.19 ± 3.15	$P < 0.001$
			$P = 0.0023$	

Table 3: Predictors of DEQ-5 score improvement at 2 weeks after treatment

Predictor	Coefficient	95% CI	P-value
Baseline DEQ-5 score	0.96	0.75-1.17	P < 0.001
IPL with LLLT	1.95	0.91-2.98	P < 0.001
Age	-0.16	-0.05-0.18	0.357
Male	-0.82	-1.96-0.32	0.152
History of meibomian gland expression	-0.29	-1.37-0.78	0.586
Current usage of artificial eye drops	-0.94	-3.69-1.80	0.492
Current usage of topical steroids	-0.28	-1.34-1.77	0.588

Discussion

At 2 weeks post-treatment, both the single IPL treatment and the combined IPL and LLLT showed statistically and clinically significant improvement (mean improvements > 4 points) in DEQ-5 scores. This study showed that both groups were able to relieve the dry eye symptoms of patients with MGD-related dry eye disease. The between-group difference of 2.43 points was statistically significant ($p = 0.0023$), meaning that the dry eye symptom was significantly improved in the combined IPL and LLLT treatment than the single IPL treatment. Since there was no Minimal Clinically Important Difference (MCID) directly to between-group difference. To apply in our study, this means a patient must improve by at least 4 points to feel a meaningful benefit. Therefore, the added benefit of combination therapy, though statistically supported, may be of modest clinical relevance.

The improvement of dry eye symptoms observed in the combined IPL and LLLT treatment group is consistent with previous findings, which reported enhanced symptom relief using the combined approach.^{16-19,22-23} Perez-Silguero et al.¹⁸ and Solomon et al.¹⁹ studies found that this combined treatment resulted in a significant improvement in the Ocular Surface Disease Index (OSDI) score and tear breakup time (TBUT) over a period of 3 months.

The combined use of IPL and LLLT may offer synergistic effects that improve MGD-related dry eye symptoms. There are several potential mechanisms by which LLLT provides additional benefits to IPL. First, LLLT directly targets cellular mitochondria and boosts

mitochondrial ATP production, supporting gland regeneration or repair through activation of cellular metabolism.²⁴ Second, LLLT reduces oxidative stress and inflammatory cytokines (e.g., IL-1 β , IL-6, TNF- α), supporting IPL by dual anti-inflammatory action.²⁵⁻²⁶ Third, LLLT can reach deeper glandular tissue than IPL. So, LLLT enhances healing of meibomian glands and potentially improves gland expression over time. Finally, LLLT targets broader periocular tissue by full-face exposure. LLLT may also have an effect on the meibomian glands in the upper eyelids, complementing the effects of IPL on the lower eyelids. In conclusion, IPL may act as a pre-treatment, clearing blockages, reducing inflammation, and improving meibum quality.²⁷ LLLT follows with cellular regeneration and deeper tissue healing post-IPL.

Our analysis also indicated that baseline symptom severity and treatment modality are important factors influencing dry eye symptom improvement following light-based therapies. Specifically, patients with higher baseline DEQ-5 scores experienced greater symptom relief. This aligns with previous findings indicating that patients with more severe disease may benefit more from multi-modal approaches.¹⁷ Although combined treatment significantly relieved dry eye symptoms, there was a patient from the IPL combined with LLLT group whose DEQ-5 score did not improve after treatment. This lack of improvement was attributed to the patient's lagophthalmos, a condition in which the eyelids do not fully close during sleep, leading to insufficient tear film distribution and subsequent dry eye symptoms.

However, the combined IPL and LLLT treatment carried some disadvantages when compared with the single IPL treatment. Firstly, the cost of the combined treatment was significantly higher, making it less accessible to some patients. Additionally, the combined treatment required a longer treatment time, which may be inconvenient for those with busy schedules. Even though combined IPL and LLLT were more expensive upfront, it provided greater symptom relief at a lower cost per unit of improvement, suggesting it may be more cost-effective especially in patients with moderate to severe dry eye.

For clinical practice recommendation in Thailand where resource allocation and patient affordability may vary, combined IPL and LLLT therapy can be recommended as an effective treatment option for moderate to severe dry eye disease, particularly in patients with meibomian gland dysfunction. While both IPL alone and combined therapy provided statistically and clinically significant symptom relief, the combined approach showed superior improvement in DEQ-5 scores. Despite the between-group difference being below the standard MCID threshold, the enhanced outcome may justify the additional cost in patients with more severe or refractory symptoms. For patients with milder disease or cost limitations, IPL alone remains a valid and effective alternative.

While the current study on the use of IPL and LLLT for dry eye disease showed promising results, this study has several limitations inherent to its retrospective design. First, selection bias may be present, as treatment allocation was not randomized. Patients who received combined IPL and LLLT may have had more severe symptoms or different baseline characteristics compared to those receiving IPL alone, potentially influencing the outcomes. Although baseline DEQ-5 scores were similar, unmeasured confounders such as compliance, duration of symptoms, or socioeconomic status may have differed between groups. Second, information bias is a possibility due to reliance on medical records. Inconsistent documentation, missing data, or variability in how DEQ-5 scores were recorded may have affected the accuracy

of symptom measurement. In addition, the use of a subjective outcome measure (DEQ-5) without blinding may introduce observer or reporting bias, especially if patients or evaluators were aware of the treatment received. Third, confounding bias cannot be ruled out. Other factors such as use of adjunctive therapies (e.g., artificial tears, warm compresses), environmental exposures, or lifestyle differences may have influenced dry eye symptoms independently of the treatment modality. Lastly, the short follow-up period of 2 weeks limits the ability to evaluate long-term efficacy and sustainability of treatment effects. The generalizability of our findings may also be restricted to similar clinical settings in Thailand, and results may not apply to broader or more diverse populations. Regardless of these limitations, to the best of our best knowledge, this is the first study to compare single IPL versus IPL combined with LLLT in clinical study.

Conclusion

The single IPL treatment and the combined IPL with LLLT relieved the dry eye symptoms of the patients with MGD related dry eye disease compared with their baseline symptoms. The combined IPL with LLLT was associated with a greater improvement in ocular discomfort symptoms. Patients with more severe disease may benefit more from combined treatment. Future prospective, randomized controlled studies with longer follow-up durations and standardized outcome assessment are needed to confirm these findings and further assess the cost-effectiveness and long-term benefits of combined IPL and LLLT therapy in dry eye disease. Additionally, future studies should consider categorizing patients based on the severity of their MGD to better understand the impact of IPL and LLLT on different stages of the disease.

Disclosure statement

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