

Low-Level Light Therapy Versus Intense Pulsed Light for the Treatment of Meibomian Gland Dysfunction: Preliminary Results From a Prospective Randomized Comparative Study

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Purpose: The purpose of this study was to evaluate and compare the safety and efficacy of low-level light therapy (LLLT) and intense pulsed light (IPL) for the treatment of meibomian gland dysfunction (MGD).

Methods: Forty eyes of 40 patients with MGD were randomized to receive either LLLT or IPL. Four weekly sessions of LLLT (MY MASK-E, Espansione Marketing S.p.A., Bologna, Italy) and IPL (Eye-light device, Espansione Marketing S.p.A., Bologna, Italy) were performed. The following parameters were evaluated before and 2 weeks after the last session for each treatment: Standard Patient Evaluation of Eye Dryness questionnaire, noninvasive break-up time, tear meniscus height, redness score, meiboscore, and meibomian gland loss.

Results: All patients completed regularly all the scheduled sessions, and no adverse events were reported in any of the groups. The Standard Patient Evaluation of Eye Dryness score significantly decreased after both LLLT and IPL ($P < 0.001$) although the improvement was significantly greater in the LLLT compared with the IPL group (-9.9 ± 3.2 vs. -6.75 ± 4.5 ; $P = 0.014$). Patients in the LLLT group showed a significantly higher increase in tear meniscus height compared with those in the IPL group (0.06 ± 0.10 mm vs. -0.01 ± 0.014 ; $P = 0.040$). In both groups, the noninvasive break-up time, redness score, meiboscore, and meibomian gland loss did not vary significantly after treatment (all $P > 0.05$).

Conclusions: Both LLLT and IPL were safe and effective in improving ocular discomfort symptoms in patients with MGD; however, the former determined a greater improvement in symptoms and an improvement of tear volume.

Key Words: dry eye disease, meibomian gland dysfunction, low-level light therapy, intense pulsed light

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Dry eye disease (DED) is a chronic multifactorial disease of the tears and ocular surface that affects millions of people worldwide.^{1–3} Its symptoms include foreign body sensation, stinging, itching, and photophobia, all of which can restrict daily activity and affect quality of life.⁴ Meibomian gland dysfunction (MGD), a condition characterized by terminal duct obstruction and/or changes in the secretions of the meibomian glands, is considered the main cause of evaporative DED.^{5,6} Moreover, MGD is recognized as the most important factor contributing to the severity of ocular discomfort symptoms.⁷

Conventional treatment of MGD involves the application of warm compresses followed by self-administered lid margin massage to restore the normal release of meibum lipids into the tear film.⁸ However, patients often perceive eyelid hygiene as tedious and time-consuming, and this may result in poor compliance with treatment.⁹ In recent years, novel devices have emerged to allow in-office MGD management: Among these, intense pulsed light (IPL) is a technology based on a polychromatic light source with a wavelength spectrum of 500 to 1200 nm, which is directed to the periocular skin. The thermal effect on the irradiated tissue leads to ablation of blood vessels and liquefaction of meibum. Several studies have demonstrated that IPL is safe and effective in reducing MGD signs and symptoms.^{10–16}

Low-level light therapy (LLLT) is a newer technology using emitting near-infrared light to elicit mitochondrial light absorption and induce cell photoactivation with changes in inflammatory protein expression.¹⁷ This technology has been used in dermatology for over a decade for the treatment of atopic dermatitis, acne, and rosacea.¹⁷ More recently, LLLT has been used for MGD, and devices allowing combined treatment with IPL and LLLT have become available in the market.^{18–22} Nevertheless, to date, there has been no comparative study of IPL versus LLLT in the MGD population.

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Therefore, the purpose of this randomized controlled trial was to investigate and compare the safety and efficacy of LLLT versus IPL in patients with MGD.

MATERIALS AND METHODS

This prospective randomized comparative study was conducted at the University Hospital of Catanzaro (Italy) between September 2020 and June 2021. This study was approved by the local Institutional Review Board (Comitato Etico Regione Calabria—Sezione Area Centro) and was conducted in accordance with the principles of the Declaration of Helsinki. Consecutive patients attending the ocular surface clinic were screened for enrollment. Inclusion criteria were as follows: age ≥ 18 years; presence of signs consistent with MGD; presence of at least 1 MGD-related ocular symptom such as dryness, foreign body sensation, irritation, and burning; and ability to comply with the treatment/follow-up schedule. Exclusion criteria were as follows: previous ocular surgery, use of hypotensive eye drops, contact lens wearing, skin pigmented lesions in the treatment area, pregnancy, breastfeeding, and any uncontrolled ocular or systemic disease. Enrolled patients were randomized to receive LLLT or IPL in a 1:1 ratio by means of computer-generated random number allocation. Patients and investigators conducting the clinical examinations were blinded to allocation.

All treatments were conducted by the same physician (M.B.) using the Eye-light device (Espansione Marketing S.p.A., Bologna, Italy) and the MY MASK-E (Espansione Marketing S.p.A., Bologna, Italy) for IPL and LLLT, respectively. In both groups, each patient underwent 4 treatment sessions, once weekly over 4 weeks. For IPL treatment, protective eye shields were placed over the eyes and 5 flashes of light were applied for each eye (3 along the inferior orbital rim, 1 at the lateral canthus, and 1 applied horizontally along the inferior orbital rim). An automated software adjusted the therapeutic energy level (10–16 joules/cm²) based on the degree of skin pigmentation. In patients belonging to the LLLT group, the treatment was performed applying a special mask for 15 minutes. No eye shields were used for this treatment, and patients were instructed to keep their eye closed to ensure a complete treatment of the upper and lower eyelids. During the entire duration of the study, patients of both groups were instructed to instill unpreserved tear substitutes 4 times daily.

Ophthalmic evaluation including ocular surface workup was performed at baseline (0–14 days before the first session of treatment) and 2 weeks after the last session. The Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire was used to evaluate ocular discomfort symptoms. The Keratograph 5M (OCULUS, Germany) was used to measure noninvasive break-up time (NIBUT), tear meniscus height (TMH), and redness score and to acquire infrared images of the meibomian glands after everting the upper and lower eyelids. The digital images of the meibomian glands were subjectively evaluated using the meiboscore.²³ Moreover, meibomian gland loss (MGL), defined as the percentage of gland loss in relation to the total tarsal area, was calculated

using ImageJ software (National Institutes of Health; <http://imagej.nih.gov/ij>).²⁴

Sample size was calculated based on the previously published study of Piyacomn et al.¹³ A total of 20 patients in each group were required to detect a final difference of 2.12 seconds in break-up time with a power of 0.90 and a *P* value of 0.05.

Statistical analysis was performed using R (version 4.0.0) and RStudio (version 1.2.5042) software. Although both eyes were treated, only data derived from the right eye were used for statistical analysis. The normality of quantitative data was checked using the Kolmogorov–Smirnov tests of normality. The Wilcoxon test was used to compare the change in ocular surface parameters before and after treatment. The Mann–Whitney *U* test was used to compare the changes in ocular surface parameters between IPL group and LLLT one. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Overall, 40 patients fulfilling the study criteria were enrolled and randomized to receive LLLT (*n* = 20) or IPL (*n* = 20). All patients completed regularly all 4 treatment sessions and underwent the final evaluation. No protocol deviations were registered in the study. The baseline demographic and clinical characteristics of patients enrolled are reported in Table 1. There were no significant differences for all parameters between the 2 groups (all *P* > 0.05).

In both groups, the treatment was well-tolerated, with no significant adverse events reported. Periocular skin, visual acuity, intraocular pressure, lens transparency, and retina features showed no changes after treatment.

The ocular surface parameters in the LLLT group and IPL group before and after treatment are summarized in Table 2. The SPEED score significantly decreased after treatment in both groups (both *P* < 0.001). However, the improvement in the SPEED score was significantly greater in the LLLT compared with the IPL group (-9.9 ± 3.2 vs. -6.75 ± 4.5 ; *P* = 0.014). The TMH significantly increased in the LLLT group (*P* = 0.003) (Fig. 1), but not in the IPL group (*P* = 0.948). Patients in the LLLT group showed a

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients Enrolled in the Study According to the Type of Treatment

Parameter	LLT	IPL	<i>P</i>
Age (yr)	55.3 \pm 17.2	60.9 \pm 16.0	0.401
Sex (M/F)	14/6	8/12	0.112
Ethnicity			0.598
European	18 (90%)	19 (95%)	
Other	3 (15%)	1 (5%)	
Rosacea	4 (20%)	6 (30%)	0.715
Ocular allergy	2 (10%)	1 (5%)	1.000
Duration of MGD (yr)	2.4 \pm 1.5	3.2 \pm 1.9	0.106
History of MGX	8 (40%)	12 (60%)	0.527
History of MGP	1 (5%)	0 (0%)	1.000

TABLE 2. Ocular Surface Parameters in the LLLT Group and IPL Group Before and 2 weeks After the Last Session of Treatment

Parameter	Group	Before Treatment	After Treatment	P
SPEED	LLLT	16.8 ± 4.6	6.9 ± 3.2	<0.001
	IPL	16.4 ± 3.2	9.7 ± 4.1	<0.001
TMH (mm)	LLLT	0.27 ± 0.12	0.33 ± 0.10	0.003
	IPL	0.26 ± 0.11	0.25 ± 0.9	0.948
NIBUT (s)	LLLT	5.5 ± 3.3	5.4 ± 2.9	0.717
	IPL	6.1 ± 4.4	9.4 ± 7.7	0.193
Redness score	LLLT	1.2 ± 0.5	1.3 ± 0.6	0.527
	IPL	2.2 ± 3.8	1.4 ± 0.4	0.569
Meiboscore	LLLT	1.4 ± 0.7	1.4 ± 0.8	0.484
	IPL	1.8 ± 0.7	1.5 ± 0.5	0.182
MGL (upper eyelid) (%)	LLLT	73.8 ± 13.0	78.3 ± 12.1	0.306
	IPL	75.7 ± 10.0	76.0 ± 10.3	0.989
MGL (lower eyelid) (%)	LLLT	73.0 ± 12.3	75.6 ± 14.5	0.154
	IPL	75.3 ± 18.9	73.5 ± 21.4	0.570

Numbers in bold indicate values of significance less than 0.05.

significantly higher increase in TMH compared with those in the IPL group (0.06 ± 0.10 vs. -0.01 ± 0.014 ; $P = 0.040$). In both groups, the NIBUT, redness score, meiboscore, and MGL of the upper and lower eyelids did not vary significantly after treatment (all $P > 0.05$). Moreover, there was no significant difference in the change of these parameters between the LLLT group and the IPL one (all $P > 0.05$).

DISCUSSION

This randomized controlled trial compared IPL treatment versus LLLT in the setting of patients with DED owing to MGD. After 4 sessions of each treatment, ocular discomfort symptoms significantly improved in both groups. Nevertheless, a significantly higher reduction was observed in the LLLT group. Moreover, LLLT allowed a significant improvement of TMH, whereas this parameter did not change in patients who received IPL treatment. The safety of both treatments was excellent, with no adverse event reported. These results suggest a therapeutic potential of LLLT as a new tool in the armamentarium of MGD treatments.

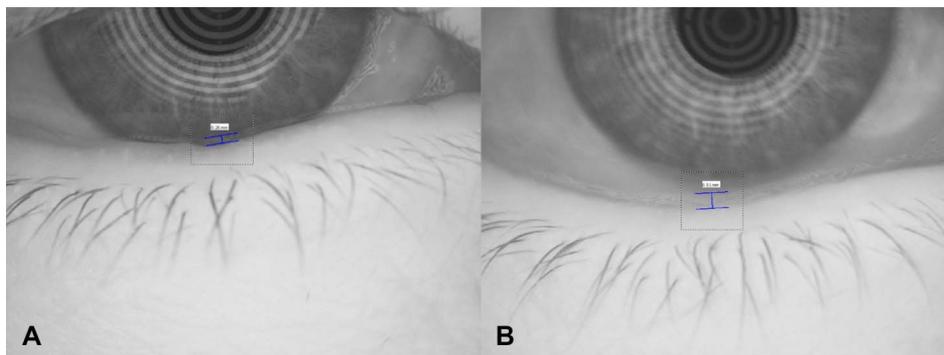
All previous studies evaluated LLLT in combination with IPL and reported a significant improvement of ocular discomfort symptoms after treatment^{18–22}; some of these studies also reported an increased tear production or tear volume.^{19,21,22} Because IPL alone is known to have little effect on tear production,^{10–13} Marta et al²¹ hypothesized that the tissue photobiomodulation induced by LLLT could affect the function of the lacrimal gland. This is supported by a study in a mice model, showing fewer neutrophils and inflammatory cytokines in the lacrimal gland after LLLT.²⁵ In agreement with this hypothesis, we documented an improvement of tear volume only in patients treated with LLLT.

The other ocular surface parameters investigated, such as tear film stability and meibomian gland area, did not change after treatment. For these metrics, no consistent results have been reported in previous studies after combined LLLT and IPL. Some authors reported after treatment an increase of BUT^{18–20,22} and meiboscore,²⁰ whereas others failed to demonstrated any effects on both tear instability and meibomian gland area.²¹ This lack of significance has been attributed by the authors to the relatively preserved NIBUT values and meibomian gland area at baseline. However, because the mechanism(s) of action of the LLLT treatment is/are still not completely known, it cannot be excluded that this treatment could exert its therapeutic action with minimal effects on these parameters.

To the best of our knowledge, this is the first study comparing LLLT with IPL. Several aspects of the study design, such as the originality, the randomization, the masking of the investigators, and absence of loss to follow-up, contribute to the validity of the results. Nevertheless, the study suffers from some limitations that include the short-term duration of the therapeutic scheme and the relatively small sample size. Moreover, although ocular discomfort symptoms improved, most of the objective outcomes did not change after treatment. The lack of a control arm with a sham treatment makes it difficult to rule out whether the subjective improvement was at least partially related to the placebo effect. Further studies with greater sample and different timing of the therapeutic sessions are warranted for better evaluating the potential role of LLLT in the management of MGD.

In conclusion, both LLLT and IPL resulted in improved ocular discomfort symptoms in patients with MGD. **When**

FIGURE 1. Images of the tear meniscus height obtained using Keratograph in a representative patient who underwent low-level light therapy. The tear meniscus height measured was 0.26 mm before treatment (A) and 0.51 mm after 4 sessions of treatment (B), showing a significant improvement. (The full color version of this figure is available at www.corneajrnl.com.)



comparing the efficacy of LLLT versus IPL, the former was associated with an increased tear volume and with a greater improvement in ocular discomfort symptoms.

REFERENCES

- Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15:276–283.
- Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf.* 2017;15:334–365.
- Aragona P, Giannaccare G, Mencucci R, et al. Modern approach to the treatment of dry eye, a complex multifactorial disease: a P.I.C.A.S.S.O. board review. *Br J Ophthalmol.* 2021;105:446–453.
- McDonald M, Patel DA, Keith MS, et al. Economic and humanistic burden of dry eye disease in Europe, north America, and Asia: a systematic literature review. *Ocul Surf.* 2016;14:144–167.
- Sabeti S, Kheirkhah A, Yin J, et al. Management of meibomian gland dysfunction. *Surv Ophthalmol.* 2020;65:205–217.
- Vigo L, Pellegrini M, Bernabei F, et al. Diagnostic performance of a novel noninvasive workup in the setting of dry eye disease. *J Ophthalmol.* 2020;2020:5804123.
- Teo CHY, Ong HS, Liu YC, et al. Meibomian gland dysfunction is the primary determinant of dry eye symptoms: analysis of 2346 patients. *Ocul Surf.* 2020;18:604–612.
- Thode AR, Lasky RA. Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction (MGD). *Drugs.* 2015;75:1177–1185.
- Alghamdi YA, Camp A, Feuer W, et al. Compliance and subjective patient responses to eyelid hygiene. *Eye Contact Lens.* 2017;43:213–217.
- Craig JP, Chen YH, Turnbull PR. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci.* 2015;56:1965–1970.
- Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. *Ocul Surf.* 2019;17:104–110.
- Vigo L, Taroni L, Bernabei F, et al. Ocular surface workup in patients with meibomian gland dysfunction treated with intense regulated pulsed light. *Diagnostics (Basel).* 2019;9:147.
- Piyacomn Y, Kasetsuwan N, Reinprayoon U, et al. Efficacy and safety of intense pulsed light in patients with meibomian gland dysfunction—a randomized, double-masked, sham-controlled Clinical Trial. *Cornea.* 2020;39:325–332.
- Giannaccare G, Taroni L, Senni C, et al. Intense pulsed light therapy in the treatment of meibomian gland dysfunction: current perspectives. *Clin Optim (Auckl).* 2019;11:113–126.
- Vigo L, Giannaccare G, Sebastiani S, et al. Intense pulsed light for the treatment of dry eye owing to meibomian gland dysfunction. *J Vis Exp.* 2019;146. doi: 10.3791/57811.
- Vigo L, Pellegrini M, Carones F, et al. Short-term effects of a novel eye mask producing heat and vibration for the treatment of meibomian gland dysfunction: a pilot study. *J Ophthalmol.* 2021;2021:1370002.
- Kim WS, Calderhead RG. Is light-emitting diode phototherapy (LED-LLLT) really effective? *Laser Ther.* 2011;20:205–215.
- Stonecipher K, Abell TG, Chotiner B, et al. Combined low level light therapy and intense pulsed light therapy for the treatment of meibomian gland dysfunction. *Clin Ophthalmol.* 2019;13:993–999.
- Pérez-Silguero MA, Pérez-Silguero D, Rivero-Santana A, et al. Combined intense pulsed light and low-level light therapy for the treatment of dry eye: a retrospective before-after study with one-year follow-up. *Clin Ophthalmol.* 2021;15:2133–2140.
- Solomos L, Bouthour W, Malclès A, et al. Meibomian gland dysfunction: intense pulsed light therapy in combination with low-level light therapy as rescue treatment. *Medicina (Kaunas).* 2021;57:619.
- Marta A, Baptista PM, Heitor Marques J, et al. Intense pulsed plus low-level light therapy in meibomian gland dysfunction. *Clin Ophthalmol.* 2021;15:2803–2811.
- Di Marino M, Conigliaro P, Aiello F, et al. Combined low-level light therapy and intense pulsed light therapy for the treatment of dry eye in patients with sjögren's syndrome. *J Ophthalmol.* 2021;2021:2023246.
- Kim S, Yoo YS, Kim HS, et al. Changes of meibomian glands in the early stage of post hematopoietic stem cell transplantation. *Exp Eye Res.* 2017;163:85–90.
- Bernabei F, Versura P, Pellegrini M, et al. Longitudinal analysis of infrared meibography in patients undergoing hematopoietic stem cell transplantation. *Cornea.* 2020;39:812–817.
- Goo H, Kim H, Ahn J, et al. Effects of low-level light therapy at 740 nm on dry eye disease in vivo. *Med Lasers.* 2019;8:50–58.