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ORIGINAL RESEARCH

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

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Purpose: To assess the effectiveness of a combination of intense pulsed light and low-level light therapy (IPL/LLLT) for the treatment of dry eye.

Study Design: Retrospective before-after single-center clinical study.

Materials and Methods: Patients diagnosed with dry eye, refractory to conventional treatment, underwent four sessions of combined IPL/LLLT over 3 months. The Ocular Surface Disease Index (OSDI) questionnaire, non-invasive breakup time (NIBUT), tear film osmolarity and meniscus height were measured 6 months before intervention, at baseline, post-intervention (3 months), 9 and 15 months.

Results: NIBUT, osmolarity and meniscus height significantly worsened during the 6 months before treatment, whereas symptoms did not change. OSDI scores significantly improved at post-intervention (MD = −44.0, 95% CI −38.1, −50.0), and then increased again until the at last follow-up, but still significantly different from baseline (MD = −30.0, 95% CI −23.4, −36.8). The three clinical signs showed a similar pattern, with one-year improvements of 3.6 seconds for the NIBUT (95% CI 3.1, 4.2, p <0.001), 28 mOsm/L for osmolarity (95% CI 23.6, 32.4, p <0.001) and 0.03 mm for meniscus height (95% CI 0.02, 0.04, p <0.001). No adverse effects were observed.

Conclusion: IPL/LLLT is safe and produces an important reduction in symptoms and signs of dry eye disease, still relevant one year after the end of treatment in a sample with high symptoms' severity. Therefore, it represents a promising treatment option for patients who do not improve with conventional treatment. Randomized trials are needed to determine the added benefit provided by LLLT.

Keywords: dry eye, meibomian gland dysfunction, intense pulsed light, low-level light therapy, retrospective study

Introduction

Dry eye disease (DED) affects millions of people worldwide.[1] Its symptoms include itching, stinging, burning, irritation, foreign body sensation, photophobia or pain, among others, affecting considerably patients' quality of life in severe cases.[2] One third of DED patients also show Meibomian Gland Dysfunction (MGD), a condition of the meibomian glands characterized by terminal duct obstruction and/or changes in their secretions, which is considered the leading etiologic factor of DED.[1–3]

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Conventional treatment for DED follows a stepwise approach,[4] starting with patient education, environmental and dietary modifications, and conservative treatments like lid hygiene, warm compresses, meibomian gland expression, and artificial tears. Medications include topical steroids, cyclosporine, leucocyte function–associated antigen-l antagonists, secretagogues, and topical or oral antibiotics. Refractory cases are treated with long-term topical corticosteroids, amniotic membrane grafting, or surgical interventions.

Intense Pulsed Light (IPL) therapy was developed and has been widely used to treat dermatologic diseases, but casual observations of its effects on Meibomian glands and symptoms of DED suggested that it could also be effective for this condition.[5] This technique consists in the application of a series of pulses of non-coherent polychromatic light in the periorbital region, with a wavelength spectrum ranging 500–1200 nm. This produces a selective thermal effect on the irradiated tissue, leading to coagulation and ablation of blood vessels and thus reducing vascularization.[6] Although its mechanisms of therapeutic action are still being investigated,[7–9] some randomized trials and several case series have shown that IPL is safe and effective in improving MGD and reducing symptoms of DED.[10–14]

Another kind of photobiomodulation is the Low-Level Light Therapy (LLLT). This technique uses light-emitting diodes (LEDs) at wavelengths insufficient to produce a thermal effect (often 590–633 nm), but that increases photon intensity and its capacity to penetrate below the skin, inducing cellular photoactivation.[15] In patients with DED, Toyos et al[16] observed a significant increase in Tear film Breakup Time (TBUT) after 3 months of red-light treatment, and Stonecipher et al[17] obtained significant improvements in symptoms, TBUT and MGD after 3 sessions over one week.

Recently, Stonecipher et al[18] published a retrospective analysis of 230 patients with MGD treated in one session with a combination of IPL and LLLT. One to three months after treatment, statistically and clinically significant improvements were observed in symptoms, such as TBUT and meibomian dysfunction grade, with no facial or ocular adverse effects. The aim of our study is to add new evidence on the effectiveness of this combined light therapy in the treatment of DED.

Materials and Methods

This study is a retrospective chart analysis of patients treated with IPL/LLLT in an ophthalmologic clinic in Gran Canaria (Spain), between January 2017 and June 2018. The Institutional Review Board of the Hospital La Paloma, Gran Canaria (ref: 2019/0037) approved the study, which was carried out in accordance with the tenets of the Declaration of Helsinki. Patients presented a diagnostic of evaporative dry eye, based on the criteria of the Tear Film and Ocular Surface Society (TFOS-DEWS II):[19] a score ≥13 in the Ocular Surface Disease Index (OSDI) questionnaire,[20] TBUT <10 seconds, osmolarity >308 mOsm/l or a difference between eyes higher than 8 mOsm/l, and the presence of lipid abnormalities. They were being treated with artificial tears, antibiotics or topical steroids (none with systemic treatment), showing no improvement or frequent relapses. All patients had Fitzpatrick skin types between I–V levels,[21] for whom IPL treatment is indicated. After being informed about IPL/LLLT, they signed informed consent and underwent the first session. They continued their conventional treatment during IPL/LLLT and follow up.

We included patients in the analysis if they were adults who had not been treated for other ocular problems, nor had any incident in the eyes during the IPL/LLLT period or follow-up, and who had completed the assessment of the dependent variables 6 months before treatment, at baseline, post-treatment (3 months) and last follow-up (12 months after the end of treatment).

Treatment

Treatment was applied with the CE-Marked Eye-light® device (Espansione Marketing S.p.A., Bologna, Italy). It consisted of 4 sessions over 3 months (weeks 0, 1, 4 and 12), and was applied following manufacturer's recommendations and as described in Stonecipher et al.[18] Patients were sitting or in supine position, wearing the protective opaque goggles recommended by the manufacturer. In each eye, five IPL pulses (wavelength 600 nm, 10–16j/cm^2) were applied, in this order: three along the inferior orbital rim, with the device in a vertical position trying to cover all the area close to the eyewear's edge, one behind the lateral canthus, and one along the inferior orbital rim with the device placed horizontally.

After the IPL treatment, the protective eyewear was removed and the LLLT mask was applied. It contains a series of LEDs at wavelengths of 633 ± 10 nm, with an emission power of 103 mW/cm^2. During the 15 minutes of treatment, a total fluence of 110 j/cm^2 is applied in the treated area. The periorbital area was treated with the patient keeping her/his eyes closed, to completely encompassing both lids. No manual gland expression was carried out after IPL/LLLT sessions.

Measures

The following outcomes were assessed at baseline, post-treatment (3 months), and 6 and 12 months after the end of treatment: the OSDI, a 12-item self-reported scale widely used to assess dry eye symptoms (range 0–100, higher scores indicate more severity); Tear film osmolarity was measured with the TearLab™ Osmolarity System (TearLab Corporation, USA); non-invasive break-up time (NIBUT) and meniscus height were measured with the Keratograph® 5M (OCULUS, Germany). For osmolarity, NIBUT and meniscus height, the average value of the two eyes was calculated for each patient and introduced in the analyses.

Statistical Analysis

Means and standard deviations of the dependent variables were calculated at baseline and for each follow-up. A repeated-measures analysis of variance (ANOVA) was carried out for each outcome, and paired *t*-tests were used to compare means at each time point, with Bonferroni's adjustment for multiple comparisons. For the OSDI, an exploratory interaction analysis was carried out using two-way repeated-measures ANOVA, with the conventional treatment (topical antibiotics, topical steroids, both treatments, none) as the between-subject factor, in order to assess whether the intervention effect differed between conventional treatments.

For the OSDI, the rate of patients with a score ≥33 (severe symptoms) was calculated at 6 months pre-baseline, baseline, post- and last follow up, and compared by means of χ^2-test. Pearson's correlations among the four dependent variables were calculated. Finally, we performed two multiple linear regressions on the OSDI scores' change from pre- to post-intervention and 12-month later, respectively, with age, sex, duration of DED, antibiotic and steroid treatment, and baseline OSDI, NIBUT, osmolarity and meniscus height (as well as their changes from baseline to each time point, in separate models) as independent variables.

Results

Two hundred and thirty-one patients underwent the procedure at the clinic, from which 156 met the inclusion criteria for analysis. Table 1 shows their sociodemographic and clinical characteristics. Mean age was 54.0 (sd = 14.1, range 30–77) and 79.5% were women. Mean duration of DED was 5.9 years (sd = 3.6) and mean OSDI score was 58.3 (sd = 26.5).

Table 1 Sociodemographic and Clinical Characteristics at Baseline

	n = 156
Age, (mean, sd, range)	54.0 (14.1) (30–77)
Female	124 (79.5%)
Fitzpatick skin type	
I	3 (1.9%)
II	4 (2.6%)
III	48 (30.8%)
IV	92 (59.0%)
V	9 (5.8%)
Duration of DED in years (mean, sd, range)	5.9 (3.6) (1–12)
Conventional treatment during study:	
- Artificial tears	156 (100%)
- Topical antibiotics	97 (62.2%)
- Topical steroids	52 (33.3)

Abbreviation: DED, dry eye disease.

There were no ocular or facial adverse effects in any patient during treatment or follow-up. Regarding effectiveness, Table 2 and Figures 1–4 show the results on the dependent variables at each time point. Repeated-measures ANOVA yielded significant results for the four variables (p-values < 0.001). Between 6 months before and baseline, the three physiological measures (ie, osmolarity, NIBUT and meniscal height) significantly worsened (p values <0.001), whereas the change in the OSDI was not significant (p = 1.000). At post-treatment, OSDI scores decreased by 44.0 points (95% CI 38.1, 50.0; p <0.001), and increased again until the last follow up, but maintaining a significant reduction compared to baseline (MD = −30.0, 95% CI −23.4, −36.8) (Table 2, Figure 1). The effect was not significantly different between groups of patients depending on their topical treatment (antibiotics, steroids, both or none) (F = 1.39, p = 0.200).

Six months before baseline, 125 patients (80.1%) had a score ≥33 in the OSDI. This percentage was similar at baseline (121, 77.6%), reduced to 0% at post-treatment (χ^2 = 197.6, p <0.001) and increased again to 39.1% at 12 months, but still significantly lower than the baseline rate (χ^2 = 84.2, p <0.001).

Table 2 Results of Repeated-Measures ANOVA on the Dependent Variables (n = 156)

Outcome	6 Months Before Baseline[a]	Baseline[a]	Post (3 Months)[a]	9 Months After Baseline[a]	15 Months After Baseline[a]	F (p-value)[b]	6 Months Before vs Baseline[c]	Baseline vs Post-Intervention[c]	Baseline vs 15 Months[c]
OSDI (0–100)	55.27 (23.42) (19–99)	58.29 (26.08) (15.40–100)	14.22 (6.28) (3.71–25.53)	21.14 (8.75) (5.36–37.36)	28.19 (12.54) (7.76–48.52)	213.97 (<0.001)	3.03 (1.000)	−44.08 (<0.001)	−30.10 (<0.001)
NIBUT (seconds)	4.30 (1.61) (1.64–7.11)	3.70 (1.77) (0.90–6.78)	8.85 (4.02) (2.21–15.56)	7.94 (3.49) (1.86–13.84)	7.34 (3.25) (1.80–12.68)	92.64 (<0.001)	−0.59 (0.018)	5.15 (<0.001)	3.63 (<0.001)
Osmolarity (mOsm/L)	319.17 (22.74) (281.0–358.0)	331.83 (21.61) (294.4–369.3)	278.96 (17.66) (246.0–308.9)	296.25 (19.73) (261.6.-328.1)	304.25 (18.02) (271.6–3.39.9)	160.15 (<0.001)	12.66 (<0.001)	−52.87 (<0.001)	−27.58 (<0.001)
Meniscal height (mm)	0.14 (0.04) (0.08–0.20)	0.12 (0.03) (0.07–0.18)	0.21 (0.05) (0.12–0.30)	0.16 (0.04) (0.09–0.23)	0.15 (0.03) (0.09–0.21)	119.45 (<0.001)	−0.02 (<0.001)	0.09 (<0.001)	0.03 (<0.001)

Notes: [a]Means (sd) (range). [b]F (p-values) from repeated-measures ANOVA within-subject effects. [c]Mean differences and p-values from paired *t*-tests, with Bonferroni adjustment for multiple comparisons.
Abbreviations: NIBUT, non-invasive break-up time; OSDI, Ocular Surface Disease Index.

The other three variables showed the same pattern of change than the OSDI, improving significantly at post-intervention and then deteriorating but maintaining significant clinical benefits 12 months after (all p-values <0.001, Table 2, Figures 2–4). Post-intervention and last follow-up improvements compared to baseline were, respectively, 5.2 (95% CI 4.1, 6.1) and 3.6 seconds (95% CI 2.8, 4.5) for the NIBUT; 53.0 (95% CI 46.8, 59.0) and 28 mOsm/L (95% CI 21.2, 34.0) for osmolarity, and 0.09 (95% CI 0.08, 0.10) and 0.03 mm (95% CI 0.02, 0.04) for meniscus height.

There were no significant correlations between outcome variables at baseline or last follow-up (Table 3). At post treatment, OSDI significantly correlated with meniscal height (r = 0.19, p = 0.02) and osmolarity with NIBUT (r = 0.17, p = 0.03). Table 4 shows the multiple regression models predicting the change in the OSDI. Higher (worse) scores on the OSDI at baseline significantly predicted a greater scores' reduction at post (B = 0.97, p <0.001) and 12 months follow up (B = 1.02, 95% CI 0.95, 1.10; p <0.001). Older age was significantly related to a greater change at 12 months, although with a small effect (B = −0.19, p = 0.003). None of the other variables obtained significant results.

Discussion

The results of this study show an important reduction of symptoms and signs of DED after four sessions of IPL/LLLT, in a sample with high symptoms' severity on average. Subsequently, outcomes worsened again but maintained significant benefits compared to baseline 12 months after the end of treatment. To our knowledge, the only published study that applied the combined IPL/LLLT is Stonecipher et al.[18] This study observed a reduction in the rate of patients with severe symptoms (OSDI ≥33) from 70.4% to 29.1%, a nearly doubled TBUT and lower MGD grade between 1 and 3 months after one treatment session. Our results on the OSDI and NIBUT after the fourth session, 3 months after starting treatment, were better (no patients with severe symptoms and 139% improvement in NIBUT), supporting the added benefit of successive sessions. Unfortunately, outcomes were not assessed between sessions in order to analyze the onset and evolution of improvement. Previous studies with IPL have shown immediate effects after the first session, and a peak of improvement between the last session (usually the third or fourth) and last follow-up, 1–2 months after.[11,12,22,23] Studies with longer follow-up have

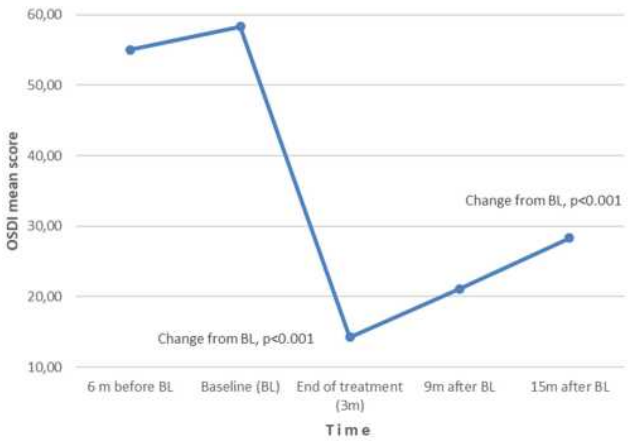

Figure 1 Change in OSDI scores.

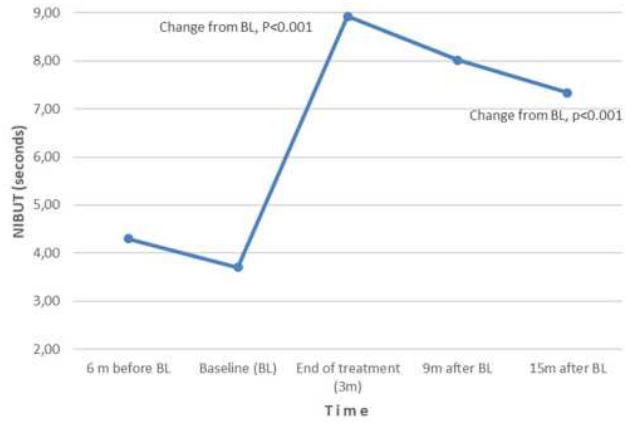

Figure 2 Change in NIBUT.

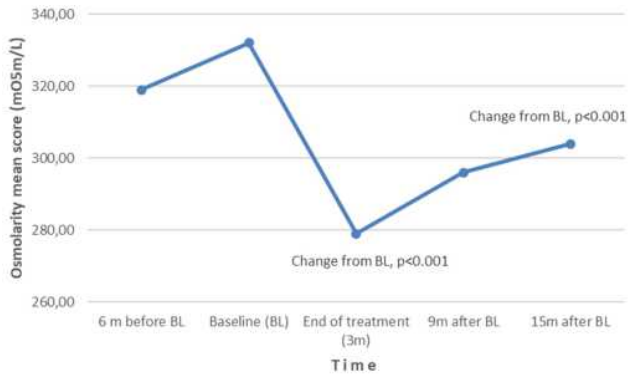

Figure 3 Change in osmolarity.

observed a decline of improvement 3–4 months after the last session,[24–26] as occurred in our study at 6 months. More research is needed to determine the optimal number and timing of sessions, or even the possibility of applying individualized protocols based on patient's response.

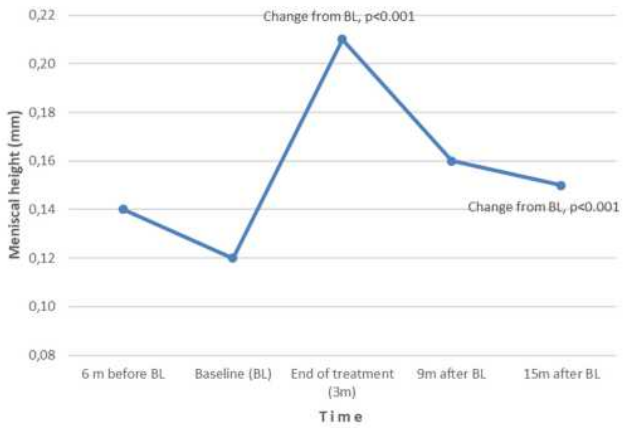

Figure 4 Change in meniscal height.

The study design does not allow to discriminate the differential effect of IPL and LLLT, a necessary aim since the effectiveness of the latter is currently supported by very limited evidence. We are only aware of two small studies that applied LLLT alone in patients with DED, obtaining significant improvements in the OSDI,[17] TBUT[16,17] and MGD[17] after 1–3 months. Regarding IPL, although there are several published case series,[13] the strongest evidence on its efficacy comes from some sham-controlled[10–12,24] and non-masked comparative[14,27] randomized trials. Results have shown significant improvements in TBUT,[10–12,14,27] lipid layer thickness,[10,14] lid margin parameters,[14] MGD measures[11,12,14,27] and symptoms,[11,14,24] some of which were maintained until 4.5 and 7 months after the end of treatment.[11,24] Comparing our results to the IPL within-group change of these studies, our increase in breakup time (139%) was lower than only two of them, which applied a similar IPL protocol to ours (167% in NIBUT[10] and 453% in fluorescein TBUT[11]). However, we obtained a significant reduction in tear film osmolarity not observed in these two studies. Furthermore, symptoms' reduction assessed by the OSDI was very intense in our study (75.6% at post-intervention and 51.6% one year later), compared to the range observed in all the mentioned trials (16–33%), except Arita et at[14] with the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire (reduction of 62%), who applied 8 sessions of IPL plus Meibomian gland expression. Several confounders could be affecting these differences. Our sample had greater severity in osmolarity and symptoms at baseline, and therefore a greater potential for improvement; indeed, baseline scores in the OSDI significantly predicted posterior improvement. Conventional treatment was not interrupted during IPL/

Table 3 Pearson's Correlations Between the Dependent Variables (n = 156)

	Baseline			Post-Treatment (3 Month)			Last Follow Up (15 Months)		
Outcome	**NIBUT**	**Osmolarity**	**Meniscal Height**	**NIBUT**	**Osmolarity**	**Meniscal Height**	**NIBUT**	**Osmolarity**	**Meniscal Height**
OSDI	−0.15	0.05	0.04	0.03	0.09	0.19*	−0.02	−0.04	0.09
NIBUT		0.06	−0.04		0.17*	0.06		−0.13	0.08
Osmolarity			0.09			0.13			−0.03

Note: *p<0.05.
Abbreviations: NIBUT, non-invasive break-up time; OSDI, Ocular Surface Disease Index.

Table 4 Multiple Linear Regression Models Predicting Change in the OSDI (n = 156)

	Change Baseline – Post Intervention[a]		Change Baseline – 15 Months[a]	
Age	−0.03 (0.421)	−0.03 (0.403)	−0.19 (0.010)	−0.19 (0.010)
Female	1.51(0.231)	1.70 (0.171)	2.41 (0.334)	2.29 (0.361)
Duration of DED	0.08 (0.585)	0.02 (0.881)	0.15 (0.594)	0.19 (0.504)
Treated with antibiotics	−1.08 (0.306)	−0.98 (0.341)	1.92 (0.359)	1.67 (0.424)
Treated with steroids	0.63 (0.568)	0.65 (0.552)	1.49 (0.493)	1.56 (0.478)
Baseline OSDI	−0.97 (<0.001)	−0.97 (<0.001)	−1.02 (<0.001)	−1.01 (<0.001)
Baseline NIBUT	−0.14 (0.637)	–	−0.36 (0.538)	
Change in NIBUT	–	0.03 (0.810)	–	−0.13 (0.639)
Baseline osmolarity	−0.01 (0.690)	–	−0.02 (0.700)	
Change in osmolarity	–	0.02 (0.424)	–	0.01 (0.816)
Baseline meniscal height	−29.2 (0.076)	–	24.4 (0.453)	
Change in meniscal height	–	21.1 (0.211)	–	7.64 (0.718)

Note: [a]Unstandardized coefficients (p-value).
Abbreviations: DED, dry eye disease; NIBUT, non-invasive break-up time; OSDI, Ocular Surface Disease Index.

LLLT, although their interaction with the intervention was not significant.

In summary, with the current evidence, it is not possible to draw definitive conclusions about the added effect of LLLT on signs' and symptoms' improvement, but our results, in a sample with severe refractory symptoms and one of the longest published follow-up, justify more research. Contrary to IPL, the mechanism of action of LLLT is supposed to be athermal and related to cellular photoactivation, which may induce activation of mitochondria and anti-inflammatory processes through the regulation of reactive oxygen species.[15,28–30]

DED is a heterogeneous disease and signs show a low correlation among them and with symptoms.[31] Tear film osmolarity has been shown to be an acceptable marker of DED,[32,33] but we have not found a significant correlation with symptoms, as occurred with the other outcomes.

This study has several limitations. First, a selection bias may be present since only patients with available measures were analyzed. Although our clinical experience shows that a great majority of treated patients were satisfied with the results of IPL/LLLT, we cannot discard this potential bias. Second, we did not assess the grade of MGD quantitatively, although the qualitative examination with meibography did not reveal clinically relevant changes in glands' macrostructure. However, this measure does not seem sensitive to IPL effects, since other studies that used meibography-based measures[11,12,14,25,34,35] have also not found statistically or clinically significant differences, even when they did it with measures of meibum quality and expressibility, or lid margin parameters. Third, the study did not have a parallel control group with sham treatment, in order to control for placebo effects. Nonetheless, the intensity and duration of treatment effects, compared to those observed in previous IPL studies in eyes treated with sham treatment,[10–12] suggest an actual clinically significant benefit.

Conclusions

Light therapy is safe, and its application is easy and quick, thus representing a promising treatment option for a prevalent condition like DED. Our study supports the efficacy of IPL in the treatment of severe DED symptoms; however, more research is needed to define the number and timing of sessions that maximize the intensity and durability of its effects, what patients will benefit most, and the possibility of developing individualized protocols. In the case of LLLT clinical research is still incipient, and future studies should compare its efficacy against sham treatment, IPL and their combination. At the same time, advances in the knowledge of the biologic mechanisms responsible for the therapeutic effects of each technique should help to refine their indication, based on patients' characteristics. The present study, despite its limitations, offers valuable preliminary evidence on the long-term effectiveness of this combined therapy for the treatment of DED.

Abbreviations

ANOVA, analysis of variance; DED, dry eye disease; IPL, intense pulsed light; LED, light-emitting diodes; LLLT, low-level light therapy; MGD, Meibomian Gland Dysfunction; MD, mean difference; NIBUT, Non-invasive Breakup Time; OSDI, Ocular Surface Disease Index; SPEED, Standardized Patient Evaluation of Eye Dryness; TFOS-DEWS, Tear Film and Ocular Surface Society; TBUT, Tear film Breakup Time.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval for the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

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