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ORIGINAL RESEARCH

Intense Pulsed Light Combined with Low Level Blue and Red Light Therapy for *Demodex*-Associated Blepharitis

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Purpose: *Demodex*-associated blepharitis is a chronic disease of the lid accounting for over 60% of all blepharitis. Although several therapies have been employed to address *Demodex* mites' infestation, there is no universal consensus about the most effective strategy. Purpose of this study was to evaluate the efficacy of combined intense pulsed light (IPL) and low-level light therapy (LLLT) in the treatment of *Demodex*-associated blepharitis and associated ocular surface disease (OSD).

Patients and Methods: Medical records of patients with *Demodex*-associated blepharitis resistant to first-line therapy who underwent IPL and LLLT (12 minutes of blue light followed by 12 minutes of red light) were retrospectively examined. The following data collected before treatment (T0) and at last follow-up (T1) were reviewed: collarettes (0–4 grade); saponification (presence/absence); lid margin telangiectasia (0–3 grade); conjunctival hyperemia (0–4 grade); corneal fluorescein staining (CFS) (0–5 grade); noninvasive tear break-up time (NITBUT), tear meniscus height (TMH), inter-blink interval (IBI), meibomian gland dropout (0–3 grade) and symptoms (5-item Dry Eye Questionnaire [DEQ-5]). Treatment-related adverse effects (TrAEs) were recorded.

Results: Data from 34 eyes of 17 patients (3 males, 14 females; mean age 64.6±10.0 years) were included. A mean of 7.6 ± 3.6 treatment sessions of IPL and LLLT was performed. Mean score of collarettes decreases significantly from 1.44 ± 0.83 at T0 to 1.00 ± 0.97 at T1 ($p = 0.007$). The rate of eyes with saponification decreases significantly (from 41.18% to 11.76%; $p = 0.002$). Conjunctival hyperemia significantly decreased from 2.00 ± 0.78 to 1.47 ± 0.61 ($p = 0.005$). Mean CFS score decreased significantly from 0.56 ± 1.16 to 0.24 ± 0.96 ($p = 0.031$). Symptoms' mean score improved significantly after treatment (from 12.00 ± 5.34 to 7.76 ± 4.92; $p = 0.003$). No patient reported TrAEs.

Conclusion: Combined light therapy with IPL and LLLT employing blue and red lights is an effective treatment strategy for patients with recalcitrant *Demodex*-associated blepharitis to reduce mites count and improve main ocular surface parameters along with patients' symptoms.

Keywords: *Demodex*, dry eye, IPL, LLLT, meibomian gland dysfunction, MGD

Introduction

Demodex-associated blepharitis is a chronic disease of the lid margin determined by *Demodex* mites' infestation, reported in approximately 58% of patients presenting to an outpatient clinic, and affecting around 25 million Americans.[1] *Demodex* mites are the most common ectoparasites living on human skin and eyelids; they can reside in clusters around the lash root and lash follicle where they feed on sebum and follicular epithelial cells.[2] *Demodex*-associated blepharitis may account for over 60% of all blepharitis.[3,4] Prevalence of *Demodex* increases with age, and it is estimated to affect approximately 80% of people older than 60 years reaching 100% by the age of 70,[5] with similar prevalence according to sex and ethnicity.[1,3]

Demodex mites may cause direct mechanical damage because of burrowing and laying eggs, together with irritation, inflammation and hypersensitivity reactions on the ocular surface due to the release of several chemicals, among which

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digestive enzymes, that break down epithelial cells used as food.[2] Additionally, *Demodex* mites may favor bacterial overgrowth from harboring and being vectors for bacteria,[2,6,7] and high numbers of mites have been associated with reactive conjunctivitis and keratitis.[8] Nearly all patients with *Demodex*-associated blepharitis are symptomatic, and the vast majority (>95%) experience three or more symptoms among itching, more frequently at night and/or early morning, dry eyes, foreign body sensation, contact lenses intolerance, redness, burning, tearing, discharge, pain, and blurred vision.[1,3,9–14]

Demodex blepharitis is frequently intertwined with dry eye disease (DED) since 60–70% of DED patients also have *Demodex* blepharitis. In fact, alterations in the tear film may make the ocular surface environment more hospitable for *Demodex* mites thus facilitating infestations; simultaneously, the overgrowth of *Demodex* mites may exacerbate symptoms of ocular surface disease (OSD).[1,14] Other common associations include meibomian gland dysfunction (MGD), ocular rosacea, chalaza, hordeola and pterygia.[15,16]

Over the years, several treatment strategies have been employed to address mites' infestation and provide symptoms relief, but none proved to be clearly effective for *Demodex* blepharitis.[9,17] The recent FDA approved lotilaner ophthalmic solution 0.25% has been reported to address *Demodex* mites' infestation, but no data regarding other ocular surface signs or symptoms are available.[18,19] However, given *Demodex* blepharitis is frequently associated with OSD, treatment strategies that address at the same time the overall ocular surface status and *Demodex* infestation may better and more comprehensively ameliorate patients' signs and symptoms.

Combined light therapies using intense pulse light (IPL) and light modulation (LM) low level light therapy (LLLT) with blue/red lights may potentially conjugate the well-known advantages of IPL in killing mites and improving MGD function,[20–23] with the advantages of blue light, which stimulates porphyrins and creates an anti-bacterial action,[24,25] and red light, which stimulates adenosine triphosphate (ATP) production by increasing and improving cellular activity, reducing inflammation and oedema.[24,25]

The purpose of the present study was to evaluate the outcomes of combined IPL and LLLT with blue/red lights on signs and symptoms of patients with *Demodex*-associated blepharitis in a real-life setting.

Materials and Methods

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Earlam and Christopher Optometrists Ltd, Taunton, United Kingdom, with a waiver of specific informed consent, as all patients had previously provided general written consent for the use of their clinical data in research. None of the authors participated in the approval process. All patient data were anonymized prior to analysis to ensure confidentiality, and no personally identifiable information was collected or stored. Data handling was conducted in full compliance with applicable data protection regulations.

Retrospective study in which medical records of patients who underwent combined light therapies with IPL and LM LLLT with blue and red lights for *Demodex*-associated blepharitis between June 2020 and October 2023 at Earlam and Christopher Optometrists Ltd (Taunton, UK) were examined to determine the efficacy of the treatment in reducing *Demodex* mites' counts and signs and symptoms of OSD.

The inclusion criterion was the presence of *Demodex*-associated blepharitis refractory to first line therapy consisting of over-the-counter topical medicine with a low concentration of tea tree oil or hypochlorous-based acid in the form of scrub, spray or cleansing wipe. The diagnosis was reached clinically through the detection at the slit-lamp examination of the pathognomonic collarettes that were defined as the presence of cylindrical, waxy debris located at the base of the eyelashes, typically formed by undigested material, epithelial cells, keratin, digestive enzymes, dead or living mites, and eggs and/or egg casings.[8,26–28] Patients were excluded in case of (1) systemic, facial or ocular acute inflammation, (2) systemic or ocular uncontrolled diseases, (3) ocular dermatosis within the previous month, (4) allergic diseases within the previous month, (5) eye surgery within the previous three months, (6) lid malposition or exophthalmos, (7) excessive sun exposure within the previous month, (8) Fitzpatrick skin types V and VI for the risk of skin depigmentation,[29,30] (9) pregnancy or breastfeeding, and (10) incomplete data from medical charts.

Treatment

The Eye-light® device (Espansione Marketing S.p.A., Bologna, Italy), which is CE marked for the treatment of MGD, was used in all patients while continuing their first-line tailored home regime.

Treatment protocols included both Optimal Power Energy OPE™ IPL and Light Modulation LM™ LLLT with blue and red light. Briefly, OPE™ IPL employed a polychromatic light (600–1200 nm) with energy range of 4.5–8.2 J/cm^2 and was performed without the use of a protective gel since the software-enabled technology and the thermal filter guaranteed the light impulse emission to be always at the right frequency, making the procedure safe and effective. Protective eye goggles were placed over the eyes and 5 flashes of light were applied for each eye without overlap (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 based on the degree of skin pigmentation chosen by the practitioner according to Fitzpatrick Scale. The LM™ LLLT treatment was performed applying first the blue light (465 ± 40 nm) delivered through the blue mask for 12 minutes, and then the red light (625 ± 40 nm) delivered through the red mask for additional 12 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. Treatment was repeated at variable frequencies according to patients' response.

Data Collection

Demographical and clinical data collected at baseline before treatment (T0) and at last follow-up (T1) were reviewed. Collarettes were graded clinically, and a 0–4 scale was used according to Gao et al and Hosseini et al[27,31] Specifically, eyes were given grade 0 if only 0–2 lashes per eyelid had collarettes, grade 1 if 3–10 lashes per eyelid had collarettes, grade 2 if >10 but < 1/3 of the lashes per eyelid had collarettes, grade 3 if ≥ 1/3 but < 2/3 of the lashes per eyelid had collarettes and grade 4 if ≥ 2/3 of the lashes per eyelid had collarettes. *Demodex* eradication was defined as collarettes grade 0 after treatment. Presence of saponification was recorded. It was defined as the presence of a foamy, soapy material at the eyelid margin and was considered a sign of poor quality meibum resulting from *Demodex* enzymes reacting with tear lipids.[32] Lid margin telangiectasia was graded on a 4-point scale. Specifically, grade 0 was used for no or mild redness in the lid margin conjunctiva and no telangiectasia crossing the meibomian gland orifices, 1 for redness in the lid margin conjunctiva and no telangiectasia crossing the meibomian gland orifices, 2 for redness in the lid margin conjunctiva and telangiectasia crossing the meibomian gland orifices involving less than ½ of the lid length, 3 for redness in the lid margin conjunctiva and telangiectasia crossing the meibomian gland orifices involving half or more of the lid length.[33]

The all-in-one MYAH device (Topcon, Visia Imaging, Japan) was used to collect data on: (1) noninvasive tear break-up time (NITBUT); (2) tear meniscus height (TMH); (3) inter-blink interval (IBI), defined as the mean time between two blinks; (4) inferior eyelid infrared meibography for scoring the extent of meibomian glands (MG) dropout a 0-3-point scale: 0 = no dropout; 1 = less than 1/3; 2 = 1/3–2/3; and 3 = more than >2/3.[34] Conjunctival hyperemia was graded clinically according to Efron scale (0–4 point).[35] Corneal fluorescein staining (CFS) was measured after instilling one drop of fluorescein into the lower conjunctival sac using a moist fluorescein strip according to the Oxford grading scheme.[36] The severity of ocular surface symptoms was measured using the 5-item Dry Eye Questionnaire (DEQ-5). It consists of 5 questions on frequency and severity of DED symptoms of ocular discomfort, dryness, and tearing over a one-month recall period. The total score ranges from 0 to 22 and a DEQ-5 score of ≥6 indicates pathological symptoms.[37] Treatment-related adverse effects (TrAEs) were recorded in patients' charts.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) with 95% confidence intervals [95% CI], median and interquartile (IQR) range or as percentages for categorical variables. Clinical data were compared before and after treatment. Shapiro–Wilk test was used to test for data distribution. Since not all data followed a normal distribution, matched-paired Wilcoxon signed rank test was used for continuous variables and McNemar test was used for dichotomous variables. All statistical analyses were performed using STATA 18.0 (StataCorp, College Station, TX) and a p-value of less than 0.05 was considered statistically significant.

Results

Seventeen patients (34 eyes) with a mean age of 64.6 ± 10.0 years [range 48–83 years; median (IQR): 63 (14.5)] and of whom 77.8% females (n =14) were included. Patients received a mean of 7.6 ± 3.6 IPL and LLLT treatment sessions performed 4.3 ± 3 months apart, and last follow-up visit (T1) was performed at 25.5 ±12.2 weeks from the last treatment session. Changes of clinical parameters from T0 to T1 are shown in Table 1. Mean score of collarettes decreases

Table 1 Means, Standard Deviations and 95% Confidence Intervals of Data Collected at Baseline (T0) and After Treatment at the Last Follow-Up Visit (T1)

Parameter	**T0 (n=34)** **Mean ± SD [95% CI]** **Median (IQR)**	**T1 (n=34)** **Mean ± SD [95% CI]** **Median (IQR)**	**p-value**
Collarettes (0–4)	1.44 ± 0.83 [1.15;1.73] 1 (0.75)	1.00 ± 0.97 [0.66;1.34] 1 (0.625)	0.007*
Saponification (presence)	41.18% [23.7%;58.6%] 0 (1)	11.76% [0.3%;23.2%] 0 (0)	0.002*
Telangiectasia (0–3)	1.91 ± 0.96 [1.58;2.25] 2 (1)	1.71 ± 0.91 [1.39;2.02] 2 (1)	0.187
Conjunctival hyperemia (0–4)	2.00 ± 0.78 [1.73;2.27] 2 (0.25)	1.47 ± 0.61 [1.26;1.69] 2 (1)	0.005*
CFS (0–5)	0.56 ± 1.16 [0.15;0.96] 0 (0.25)	0.24 ± 0.96 [−0.10;0.57] 0 (0)	0.031*
NITBUT (seconds)	6.07 ± 3.94 [4.70;7.45] 5.8 (6.55)	7.76 ± 6.53 [5.49;10.04] 6.92 (9.1)	0.166
TMH (millimeters)	0.34 ± 0.19 [0.27;0.40] 0.295 (0.19)	0.39 ± 0.26 [0.29;0.48] 0.34 (0.24)	0.763
Meibomian glands dropout (0–3)	2.09 ± 0.78 [1.82;2.36] 2 (0.375)	2.03 ± 0.77 [1.76;2.30] 2 (0.625)	0.406
Parameter	**T0 (n=17)**	**T1 (n=17)**	**p-value**
IBI (seconds)	2.55 ± 1.82 [1.62;3.49] 1.8 (2.05)	2.39 ± 1.77 [1.45;3.33] 1.9 (1.6)	0.696
DEQ-5	12.00 ± 5.34 [9.26;14.74] 11 (8.5)	7.76 ± 4.92 [5.24;10.29] 7 (7)	0.003*

Note: *Statistical significance.

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; CFS, corneal fluorescein staining; NITBUT, noninvasive tear break-up time; TMH, tear meniscus height; IBI, inter-blink interval; DEQ-5, 5-item dry eye questionnaire.

significantly from 1.44 ± 0.83, 95% CI [1.15;1.73] at T0 to 1.00 ± 0.97, 95% CI [0.66;1.34] at T1 (p = 0.007). At T0, all eyes showed *Demodex* collarettes, which were above grade 1 in 10 eyes (29.4%). At T1, *Demodex* mites' reduction of at least 1-point-scale was noted in 64.7% (n = 22) of eyes, while *Demodex* eradication was observed in 17.6% of cases. At T0, 41.18% (n = 14) 95% CI [23.7%;58.6%] of eyelid margins showed saponification; this rate significantly decreased to 11.76% [0.3%;23.2%] at T1 (p = 0.002). Although telangiectasia did not show significant changes from T0 to T1, its score improved in 17.6% of eyes (n = 6), while worsened in 5.9% (n = 2) and remained unchanged in all the other cases (76.5%). Conjunctival hyperemia significantly decreased from 2.00 ± 0.78 [1.73;2.27] at T0 to 1.47 ± 0.61 [1.26;1.69] after treatment (p = 0.005), improving in 35.3% of eyes (n = 12), while worsening in 5.9% (n = 2).

At T0, 23.5% of eyes had positive CFS with an overall mean CFS score of 0.56 ± 1.16 [0.15;0.96] that decreased to 0.24 ± 0.96 [−0.10;0.57]at T1 (p = 0.031), remaining positive in 5.9% (n = 2).

Although NIBUT did not show significant changes from T0 to T1, its value improved in 65% of eyes (n = 22) by an average of 1.7 ± 7.5 sec [−4.32; +0.94]. No significant changes were recorded for TMH, infrared meibography or inter-blink interval (always p > 0.406).

Mean score of symptoms measured by the DEQ-5 showed significant changes after treatment (from 12.00 ± 5.34 [9.26;14.74] at T0 to 7.76 ± 4.92 [5.24;10.29] at T1; p = 0.003), and overall symptoms' improvement was experienced by 82.4% (n = 14) of patients. No patient reported TrAEs during or after each session. Slit-lamp photographs taken in patients #5 and #12 before and after study treatment showing improvements in collarettes and saponification, respectively, are shown in Figure 1. Detailed demographical and clinical characteristics of each patient, number and frequency of treatments, length of observation and trend of changes for all parameters are shown in Table 2.

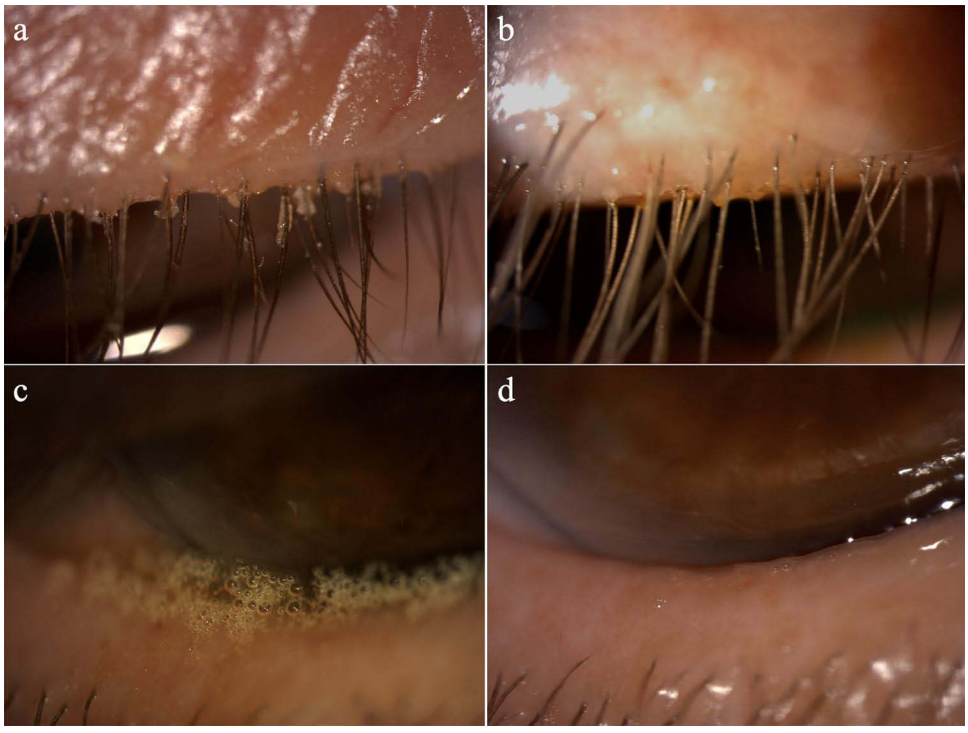

Figure 1 Slit lamp photographs of representative patients before and after treatment. (**a**) Collarettes of patient n.5 at T0 (grade 3). (**b**) Collarettes of patients n.5 at T1 (grade 1) after five sessions of intense pulsed light (IPL) and low level light therapy (LLLT). (**c**) Saponification of patient n.12 at T0. (**d**) Marked reduction in saponification in patient n.12 at T1 after six sessions of IPL and LLLT. Original magnification: ×16.

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Table 2 Demographical and Clinical Characteristics of Each Patient, Number and Frequency of Treatments, Length of Observation and Trend of Changes for All Parameters

Patient (n)	Age (y), Sex	Comorbidity	Sessions (n)	T0-T1 (Mos)	Frequency (Mos)	Collarettes	Saponification Resolution	Telangiectasia	Conjunctival Hyperemia	CFS	NITBUT	TMH	MGs Dropout	IBI	DEQ-5
1	53, F	Rosacea	16	42	2.6	Improved	N.A.	Stable	Improved	Improved	Improved	Worsened	Improved	Worsened	Improved
2	63, M	/	5	13	2.6	Improved	Yes	Stable	Stable	Stable	Worsened	/	Improved	/	Improved
3	63, F	Allergy to preservatives	7	22	3.1	Improved	N.A.	Stable	Stable	Stable	Improved	Worsened	Stable	Worsened	Improved
4	56, F	Eczema	14	28	2.0	Improved	N.A.	Improved	Improved	Improved	Improved	Stable	Stable	Improved	Improved
5	75, F	Epithelial corneal dystrophy	5	27	5.3	Improved	N.A.	Stable	Stable	Stable	Improved	Improved	Stable	Improved	Improved
6	61, F	Thyroid disease (Hashimoto)	14	46	3.3	Worsened	Yes	Stable	Stable	Stable	Improved	Worsened	Stable	Improved	Improved
7	68, F		8	44	5.5	Improved	Yes	Improved	Improved	Stable	Improved	Worsened	Stable	Improved	Improved
8	70, F	Atopy, hay fever, giant temporal arteritis	5	14	2.8	Improved	N.A.	Stable	Stable	Stable	Worsened	Worsened	Stable	Worsened	Improved
9	57, F	Breast cancer	5	51	10.2	Stable	Yes	Worsened	Worsened	Stable	Improved	Improved	Stable	Worsened	Improved
10	63, F	Breast cancer	6	9	1.5	Improved	Yes	Stable	Stable	Stable	Worsened	Improved	Stable	Worsened	Improved
11	53, F		8	22	2.8	Stable	N.A.	Stable	Stable	Stable	Worsened	Worsened	Worsened	Worsened	Improved
12	77, F		6	17	2.8	Improved	No	Stable	Improved	Stable	Worsened	Improved	Stable	Improved	Worsened
13	67, F	Graves	9	36	4.0	Improved	No	Stable	Stable	Stable	Improved	Improved	Stable	Worsened	Improved
14	48, M	GVHD	6	21	3.5	Improved	N.A.	Stable	Stable	Stable	Worsened	Improved	Stable	Stable	Improved
15	83, F	/	5	39	7.9	Worsened	N.A.	Stable	Stable	Stable	Improved	Worsened	Stable	Worsened	Worsened
16	80, F	/	4	48	12.1	Improved	N.A.	Stable	Improved	Improved	Worsened	Worsened	Stable	Improved	Worsened
17	61, M	/	6	11	1.9	Worsened	N.A.	Worsened	Improved	Stable	Improved	Improved	Stable	Improved	Improved

Notes: N, number; Y, years; Mos, months; CFS, corneal fluorescein staining; NITBUT, noninvasive tear break-up time; TMH, tear meniscus height; MGs, meibomian glands; IBI, inter-blink interval; DEQ-5, 5-item dry eye questionnaire; F, female; M, male; N.A., not applicable; GVHD, graft-versus-host disease.

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Discussion

Demodex blepharitis is a common clinical finding and more than 77% of patients reports a negative impact of this condition on their daily lives.[1,9,38] It is frequently intertwined with other OSDs, with 60–70% of DED patients and 85% of MGD patients suffering from *Demodex* blepharitis.[14,39]

The present study showed that the combined use of IPL and LLLT was able to significantly decrease *Demodex* mites' infestation, with a reduction of collarettes grade in 58.8% of cases. Saponification on the eyelid margin resolved in 71% of cases; in parallel, significant improvements were detected in other ocular surface parameters, as demonstrated by the significant improvement in CFS, conjunctival hyperemia and, most importantly, patients' symptoms.

IPL has previously been shown to be effective in reducing *Demodex* counts and improving MG function.[20–23] This technique was initially developed as in-office procedure to treat skin conditions, and it seemed to coagulate *Demodex* mites one week after treatment while preserving the hair follicle structure.[40,41] After the anecdotal finding that patients with rosacea receiving IPL showed improvements in ocular discomfort symptoms,[42] its use was then applied to the ophthalmic field, determining the reduction of mites counts and the improvement of MG function, among others.[20–23] The mechanism of action on MG function has not been fully elucidated; presumably, IPL provides thermal action by increasing the temperature in the vessels within the lid, thus heating meibum and facilitating its expression; simultaneously, it may also coagulate telangiectatic vessels thereby decreasing inflammatory mediators.[43]

The efficacy of IPL in the treatment of *Demodex* blepharitis was compared by Zhang et al to 5% tea tree oil (TTO) and, although no significant differences were noted between treatments, *Demodex* eradication rate was higher in the IPL group, being 55% one month after treatment and reaching 100% at 3 months.[23] Interestingly, ocular discomfort symptoms, break-up time and meibum quality showed better results after IPL, highlighting its preferably therapeutic potential for ocular Demodicosis. A few studies also employed a combination of IPL and MG expression (MGX) to improve MG function.[44–46] However, MGX may cause pain and can be scarcely tolerated by patients. Craig et al showed IPL alone to be effective in ameliorating signs and symptoms in patients with DED.[21]

More recently, LLLT demonstrated its potential as a treatment for ocular surface diseases, by acting through tissue photobiomodulation[47] and resulting in overall improvements in cellular function with impact on wound healing,[48] pain modulation[49] and normalization of cell function.[50,51] LLLT initial applications were studied in combination with IPL on recalcitrant MGD cases. Combined IPL/LLLT showed to improve patients' symptoms, break-up time, MG grading and MG expressibility score.[47,52] Additionally, combined IPL/LLLT showed to reduce tear fluid inflammatory markers such as interleukin-1β, interleukin-17F, MMP9 together with the MMP9/TIMP1 ratio and ocular surface B-cell proportions.[52] The comparison between IPL and LLLT in DED owing to MGD showed that LLLT determined significantly greater improvements in symptoms scores, being also the only treatment able to increase TMH.[53]

The above-mentioned studies employed LLLT protocols with the sole use of the red light, taking advantages of its ability to improve cellular metabolism by increasing ATP production within mitochondria, reduce inflammation by regulating antioxidant defenses, mitigate oxidative stress and activate transcription factors and signaling pathways.[54–56] Current LLLT protocols also employ the blue light to exploit its targeted action on *Demodex*-associated blepharitis due to its efficacy in bacteria elimination and microbiome stabilization.[57,58] In fact, the blue light energy is absorbed by porphyrins within bacteria, generating singlet oxygen radicals that cause damage to the cell wall of gram-positive bacteria leading to cell death.[24,25] In this context, the relatively weak bacterial defense mechanism against singlet oxygen-induced damage contributes to the high efficiency of the photodynamic inactivation.[59]

Several other treatment options may be considered in patients with *Demodex*-associated blepharitis; however, they may be uncomfortable, may come with side effects or may require daily use for 1–3 months to achieve both mites' death and mating prevention, thus making patients' compliance potentially suboptimal.[60] Daily scrubs with TTO and its derivatives, especially with terpinen-4-ol (T40), besides showing uncertain efficacy in mites' eradication, may be inconvenient for patients and contact dermatitis, ocular irritation, allergic reactions, epithelial cell toxicity, MG toxicity, strong odor and long treatment duration have all being reported with their use.[26,61–68] Ivermectin and metronidazole use may be limited due to hypersensitivity reactions, drug interactions and severe side effects reported with oral use.[63,69,70] Microblepharoexfoliation (MBE) alone do not reach mites' eradication, and its use should be combined with daily home-

based lid hygiene procedures.[61,71,72] Additionally, the recently FDA-approved lotilaner ophthalmic solution 0.25% demonstrated high efficacy in *Demodex* mites and collarettes eradication as well as erythema reduction, with most reported side effect being instillation site pain; however, no additional benefit on ocular surface signs and symptoms has been reported and it is not yet available worldwide.[18,19]

Considering the challenges of compliance and side effects across this vast armamentarium of therapies, the significant reduction in *Demodex* collarettes score, coupled with overall improvements in OSD signs and symptoms and the absence of reported side effects, makes combined light therapy with IPL and LLLT a promising option for patients with symptomatic *Demodex* blepharitis who are refractory to first-line treatments such as over-the-counter topical tea tree oil or hypochlorous acid, which still retain the advantage of wide availability. Additionally, although the mite eradication rate was low, the significant reduction in collarettes score following treatment appears clinically meaningful. Higher *Demodex* infestation levels have been positively correlated with more severe structural damage to the meibomian glands,[39] and it is hypothesized that *Demodex* must reach a certain threshold before causing a decrease in meibomian gland acinar density, thereby initiating glandular damage.[39] Furthermore, symptoms of ocular irritation have been shown to correlate with higher mean *Demodex* densities, whereas asymptomatic patients tend to exhibit lower mean densities.[73]

The main limitation of the present study lies in its retrospective, real-world design. Patients followed individualized home regimens without a standardized treatment schedule, and no sham treatment was included, an omission known to potentially account for minor observed improvements, especially when subjective assessments exceed objective clinical findings.[74,75] Both numbers and time-lapse in-between sessions varied on an individual basis based on clinical response. Without a fixed follow-up schedule, it is difficult to determine the precise duration of treatment efficacy; therefore, we can only estimate an approximate efficacy period of 4.3 ± 3 months per patient. Furthermore, last follow-up visit was not performed after a fixed interval from the last treatment session, and it is conceivable that the low eradication rate reached in our cohort may depend either on a too early or late assessment. On the one hand previous studies showed a *Demodex* eradication rate around 27% at 1 week after the last IPL treatment that increased further from 1 to 3 months post-treatment.[22,46] On the other hand, *Demodex* blepharitis is a chronic and recurrent disease, in which although mites may be eradicated, re-infestations can occur again.[10] The small number of eyes treated and analyzed represents another limitation and might have avoided reaching statistical significance for some parameters, such as NITBUT and TMH that showed non-significant increases. Furthermore, identification of *Demodex* mites and collarettes grading was performed through clinical examination only. Previous studies identified *Demodex* mites by eyelashes epilation followed by their exam under a light microscope or by in-vivo confocal microscopy.[22,46] However, these techniques are often impractical in routine clinical practice, and the detection of collarettes at the slit-lamp examination can be considered pathognomonic.[26]

Conclusion

Based on the results of the present study, combined light therapy with IPL and LLLT employing both blue and red lights seems an effective treatment strategy for patients with recalcitrant *Demodex*-associated blepharitis to reduce collarettes score and saponification while also improving main ocular surface parameters and patients' symptoms. Further well-designed prospective studies are required to better investigate and confirm these preliminary results.

Abbreviations

IPL, intense pulsed light; LLLT, low-level light therapy; DEQ-5, 5-item Dry Eye Questionnaire; CFS, corneal fluorescein staining; NITBUT, noninvasive tear break-up time; TMH, tear meniscus height; IBI, inter-blink interval; TaAEs, Treatment-related adverse effects; DED, dry eye disease; OSD, ocular surface disease; MGD, meibomian gland dysfunction; LM, light modulation; ATP, adenosine triphosphate; OPE, Optimal Power Energy; SD, standard deviation; TTO, tea tree oil; MGX, meibomian glands expression; MBE, microblepharoexfoliation.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Institutional Review Board of Earlam and Christopher Optometrists Ltd, Taunton, United Kingdom, with a waiver of specific informed consent, as all patients had previously provided general written consent for the use of their clinical data in research. None of the authors participated in the approval process.

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 of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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