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REVIEW

Pulsed Light Therapy in the Management of Dry Eye Disease: Current Perspectives

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Purpose: To review the indications and efficacy of Intense Pulsed Light (IPL) application in the treatment of Meibomian Gland Dysfunction (MGD). Its main purpose is to describe its physiology, efficacy, indications, and adverse effects.

Patients and Methods: A two database (PubMed, EMBASE) search was performed from July 2017 to July 2022 using the MeSH terms ("Intense Pulsed Light" AND ("Meibomian Gland Dysfunction" OR "Dry Eye"). We included randomized studies and systematic reviews with meta-analysis. Exclusion criteria were non-randomized trials, studies enrolling non-MGD dry eye disease, and other works older than 5 years.

Results: Current literature shows that IPL is an effective and safe treatment modality for severe dry eye. Available evidence shows improvement of symptoms and objective indicators, such as noninvasive breakup time, thickness of lipid layer, and Schirmer test. However, our review concluded that the beneficial effects of IPL may lose some efficacy at 6-months after the initial session, and subsequent sessions may be required. Thus, IPL treatment should not be considered as first-line therapy for MGD but instead as an adjuvant option to the standard of care. The optimal treatment modality remains unknown and should be tailored according to each patient's phenotype, clinician's experience, and available technology. There is evidence that IPL treatment may down-regulate pro-inflammatory markers (such as interleukin (IL) 6, IL17a, IL-1) and Prostaglandin E2 (PGE2).

Conclusion: MGD is a multifactorial disease and IPL treatment seems a promising treatment modality. Despite this, more evidence is needed to study its benefits – since this is an emerging technology, it is expected an increase in comparative studies in the following years, with longer follow-up periods, which may enable more precise conclusions about this treatment modality.

Keywords: dry eye disease, meibomian gland dysfunction, intense pulsed light, low-level light therapy, near-infrared light therapy, ocular surface disease index

Introduction

Dry Eye Disease (DED) is a diverse pathology of the ocular surface which reflects a disturbance in the homeostasis of tear film. It is a chronic ocular surface disease that worldwide may affect up to 30% of the population aged over 50 years.[1] Symptoms may arise from tear film instability, ocular surface inflammation, hyperosmolarity, and neurosensorial changes.[2] Its risk factors include female gender, aging, drug effects, autoimmune disease, hormonal dysfunction, ocular surgery, and contact lens wear.[3] Therefore, careful evaluation of the ocular surface is of uttermost importance during preoperative evaluation, since DED is an important cause of decreased visual function and may negative influence the results of refractive, cataract and corneal surgery.[4]

The symptoms of dry eye disease include itchiness, dryness, foreign body sensation, photophobia, and intermittent blurring of vision. Although they frequently improve after treatment, it is usually a chronic disease, which may be influence physician and patient frustration. Thus, it is important to highlight the need for patient compliance and understanding of the disease.

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The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II Diagnostic Methodology report classifies DED as predominantly evaporative (given a reduction in lipid layer in Meibomian Gland Dysfunction (MGD)) or aqueous deficient (with diminished tear film volume).[5]

Meibomian gland dysfunction (MGD) is the main etiological factor of DED.[1,4,5] Its pathophysiology includes the obstruction of ducts and relative alterations in the biochemical composition of meibum. Although there are several standard treatment modalities for MGD (warm heat, lid margin hygiene, anti-inflammatory agents, antibiotics, omega-3 fatty acids supplementation), these agents may be insufficient in many patients. For this reason, efforts have been made in developing new treatment strategies for this entity, such as Intense Pulse Light (IPL) therapy.[6]

Literature reporting the effect of IPL treatment on MGD is quite recent. Its underlying mechanisms may include the thermal effect of IPL (which may enable the secretion of meibum by its softening), coagulation of abnormal telangiectasia (with subsequent decrease in pro-inflammatory markers) and reduced proliferation of bacteria and organisms at the eyelid margin.[7]

This work aims to review the efficacy and indications of IPL technology in the treatment of MGD. Its main purpose is to describe its physiology, efficacy, indications, and adverse effects.

Dry Eye Disease (DED)

Dry Eye Disease (DED) can be divided in two categories: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). The first describes insufficient lacrimal gland secretion and contributes to approximately 10% of cases, whereas the latter comprises approximately 80%, which results in ocular surface's excessive loss of tear film, mostly secondary to Meibomian Gland Dysfunction (MGD).[5]

There are several risk factors for DED – these include individual factors (such as aging, female gender, contact lens wear and Asian ethnicity), expositional factors (air-conditioning, air pollution, exposure to wind and low humidity, prolonged near activities), systemic conditions (Sjögren syndrome, diabetes, allergies, thyroid disease), medications and ophthalmological past history (eye surgery, eye trauma, blepharitis) and also nutritional deficiencies (such as vitamin A and fatty acids).[6]

Therefore, it is critical to understand the tear film's molecular composition and role of secretion of meibomian glands to understand the pathophysiology of DED.[7]

Current models state that the tear film consists of three independent but intertwined layers: an innermost mucin layer, an aqueous layer, and an external lipid layer. The mucin layer bathes the ocular surface and consists of glycocalyx intertwined with mucins. It has an important role in lowering the epithelial cells' hydrophobicity. The aqueous layer consists mostly of water-soluble proteins and provides lubricity and adequate osmolarity. The lipid layer is comprised of lipids and intercalated proteins and is responsible for preventing the loss of the aqueous layers through a mechanism of evaporation.[7,8]

Meibomian Gland Dysfunction

The meibomian glands are responsible for the production of lipids which will integrate the tear film. Its secretions comprise a mixture of several lipids with free fatty acids, phospholipids, among others.[1]

Under the broad category term, *meibomian gland dysfunction* (MGD) is a chronic, localized meibomian gland abnormality, functionally defined by ductular obstruction and defects in glandular production. MGD is a frequent condition, and it is commonly related to evaporative dry eye. Despite this, MGD has symptoms of its own, with mechanisms either generated at the eyelid margin or by its consequences at the ocular surface.[9]

The clinical signs include loss of meibomian glands, alterations in its secretion, and pathological disturbance in eyelid morphology; meibomian gland dropout implies either total or partial decrease in acinar glandular tissue, which can be diagnosed by enhanced noninvasive meibography by infrared photography. Meibomian gland secretion can be altered either by quantity (as detailed below) and quality (the expressed lipid may range from clear fluid to inspissated, viscous material).[9]

Morphological changes include but are not limited to eyelid margin's thickening and irregularity, with hyperkeratinization and increased vascularization; distortion of the mucocutaneous junction; and elevation and obstruction of meibomian gland orifices.[9]

Thus, MGD can be divided in two groups, accordingly to secretion by the meibomian glands – low-output and high-output.

Low-delivery MGD is characterized by obstruction of the terminal ducts secondary to epithelial keratinization and increased meibum viscosity. This leads to intraglandular dilation, gland atrophy and low secretion. This process is influenced by several factors, such as hormonal changes, gender, age, but also by drugs (eg systemic retinoids). It may be also associated with several skin conditions (eg acne rosacea, seborrheic dermatitis) and cicatricial conjunctivitis (eg trachoma).[2]

High-delivery MGD is characterized by accumulation of meibomian oil within the glands, which promotes bacterial growth and the release of toxic mediators, which may trigger the inflammatory cascade with subsequent atrophy of secretory acini.[9]

Intense Pulsed Light

Biophysical Principles

Intense Pulsed Light (IPL) systems are light sources of high-intensity that produce polychromatic and noncoherent light with wavelength ranging from 515 to 1200 nm, which corresponds to visible and infrared light.[10,11]

The ultimate principle of this technology is light induced thermolysis, in which light energy is selectively absorbed by a chromophore and converted to heat, targeting specific tissue without damaging its surrounding structures. The produced wavelength can interact with several chromophores within the human body, such as melanin (400–750 nm) and hemoglobin (578 nm), to generate heat.[10,11] The absorption of yellow light by hemoglobin can convert it to heat, therefore coagulating and ablating blood vessels, such as eyelid margin telangiectasias. The broad wavelength option is useful as it can be tailored to each patient's skin type, to minimize melanin absorption and subsequent hypopigmentation, as melanin absorption decreases with increasing wavelength.[6,10,11]

Thus, IPL-induced photothermy melts abnormal meibum more efficiently than conventional therapy, since heat is transmitted both inside and out, therefore promoting tear film stability and reduced evaporation. Selective photothermolysis also coagulates abnormal telangiectasia at the eyelid margin (by energy absorption by hemoglobin), which may interrupt the release of inflammatory markers and subsequent bacterial invasion to the meibomian glands.[10,11]

IPL technology may also induce a local thermal effect, which may warm meibomian gland secretions, which can improve viscosity, stabilize the tear film, and reduce the evaporative component of dry eye syndrome. Some studies suggest that IPL may also have a local antibacterial and anti-parasitic effect – Prieto et al reported the existence of coagulated *Demodex folliculorum* as well as reduced lymphocytic infiltration in patients submitted to this type of treatment.[11]

Historical Background

Intense Pulsed Light (IPL) therapy has been broadly used in the treatment of a wide variety of pathologies, like port-wine stains, hemangiomas, and rosacea. At the beginning of the 21st century, its beneficial effects in ophthalmology were discovered in patients treated for facial rosacea. Ever since new technologies were developed to apply this system to Dry Eye Disease (DED)'s treatment.[11]

Technique

The IPL device parameters, namely wavelength filter, pulse duration, fluency, are selected depending on the pathology to be treated, so that the target is reached. Each manufacturer has specific recommendations regarding each device.

After the diagnosis of MGD and DED has been made, and in the absence of contraindications for IPL treatment (namely periocular skin tattoos/piercings, skin malignancy anywhere or pigmented lesions on the surrounding skin, ocular trauma, previous eyelid or lacrimal surgery and inability to adhere to either the treatment or the follow-up regimen), the risks and benefits of the procedure are explained to every patient, and informed consent is obtained.

The patient's phototype is evaluated by the Fitzpatrick score (types I–VI), which helps determine the safest energy parameters since fair skin patients (ie lower Fitzpatrick score) require more energy than darker skin patients. This happens because melanin absorbs energy, which can result in temperature elevation and thermal burns, and damage of the

surrounding skin. Therefore, classically, for safety reasons, IPL treatment was not offered to patients with Fitzpatrick skin type higher than four.[11]

However, new technology devices have emerged – currently, the E>Eye® IRPL® technology (by ESW vision, France) is approved for use in Fitzpatrick skin type V, albeit with reduction of the flash intensity.[12] In addition, Thermaeye Plus®[13] (by MDS Medical Technologies, Spain) and Lumenis M22®[14] (by Lumenis Be Ltd, Israel) allow treatment in all skin types, including skin type VI.

At the beginning of every session, the patient removes any glasses, and the facial skin is cleaned. Protective eye shields are placed to avoid damage to intraocular structures. Hyperpigmented skin lesions are covered with a protective adhesive. Afterwards, ultrasound gel is then placed on the infraorbital and temporal skin (the area to be treated) to cool down the area and avoid thermal burns. It may also improve light transmission, allowing more efficacy in every treatment session. However, this is not always strictly required – the Optimal Power Energy® IPL (by Espansione Group, Italy), due to its technology, enables treatment without using any type of protective gel, with additional comfort for every patient.

Both the patient and the operator wear protection goggles during the emission of pulses. The pulse wavelength is calibrated, and the pulse settings are selected given every patient's skin type and tolerance. The number of pulses (most frequently 4–6) and treatment protocol vary according to each device manufacture's indications and the physician's experience. The pulses are applied on the inferior and temporal periocular zones. The gel is removed, and the skin cleaned and washed with water and a sunscreen and sun protection are advised on the following days.

At the end of the procedure, manual expression of the Meibomian glands at the slit-lamp can be performed.[11]

Each induction treatment cycle comprises more frequently 3–4 sessions, which can be, if necessary, followed by a maintenance session after 4–12 months.[11]

Materials and Methods

A two database (EMBASE, PubMed) search was performed from July 2017 to July 2022 using the MeSH terms ("Intense Pulsed Light" AND ("Meibomian Gland Dysfunction" OR "Dry Eye").

We included randomized studies and systematic reviews with meta-analysis.

Exclusion criteria were non-randomized trials, studies enrolling non-MGD dry eye disease, and other works older than 5 years.

Forty-two (42) results were obtained. After applying exclusion criteria and duplicates, 23 articles were selected. Two articles were excluded due to being written in the Chinese language. Two articles were excluded due to the inability to obtain the full manuscript. At the end of the selection, we included 16 original studies and 3 systematic reviews with meta-analysis.

We decided to use these relevant articles to answer practical questions about IPL treatment, rather than describing the results from each of the RCTs independently.

Finally, we also analyzed single-arm, non-randomized studies separately – this was meant to give new perspectives regarding novel treatment modalities, such as low-level light therapy (LLLT), quantum molecular resonance (QMR) electrotherapy and near-infrared light (NIL) therapy.

Results

What Have We Learned from RCTs?

What is the Effectiveness of IPL Treatment?

Based on the papers enrolled in our work, IPL treatment sessions were practiced in combination with meibomian Gland Expression (MGX), which will subsequently be referred to as IPL-MGX. The treatment arms submitted to IPL alone will be referred to as IPL. Thus, the summary of randomized studies is shown.

In 2021, Yan Shi et al conducted a randomized controlled trial composed of 123 patients comparing the efficacy of IPL-MGX versus MGX. The experimental group underwent a single treatment session. Their results show that IPL significantly improves eye symptoms, meibomian gland quality scores and 30-day tear secretion Schirmer test.[15]

A systematic review with the meta-analysis by Leng et al showed that, despite high heterogeneity, IPL-MGX treatment showed efficacy in the improvement of TBUT and Ocular Surface Disease Index (OSDI) of patients.[16]

A randomized trial enrolling 90 eyes of 45 patients published in 2019 by Arita et al assigned patients with refractory dry eye to either IPL-MGX or MGX. Each patient was submitted to eight sessions with intervals of 3-weeks. At 32 weeks of follow-up, the IPL-MGX group had significantly improved lipid layer thickness, noninvasive breakup time (NIBUT), fluorescein breakup time (BUT), and conjunctival fluorescein score (CFS). The Standard Patient Evaluation of Eye Dryness (SPEED) score showed a significant reduction compared with the MGX group.[17]

According to the results by Toyos et al after four sessions of IPL-MGX separated by 2-week intervals, patients showed statistically significant improvement in TBUT and meibomian gland secretion (MGS), compared to the MGX group. Regarding the OSDI score, despite improvement (decreased score), there were no differences between both treatment arms. No differences were also found regarding the daily use of artificial tears.[18]

Piyacomn et al reported improvement in TBUT and reduction of meibum quality and expressibility scores after the initial session, which persisted at 6-month follow-up.[19]

A systematic review with meta-analysis by Sambhi et al showed an important increase in TBUT albeit with a non-significant increase in Schirmer's test and SPEED score at subsequent post-treatment evaluations in the IPL+MGX group.[20]

Despite this evidence, a systematic review with the meta-analysis by Cote et al reported that there is lack of high-quality evidence regarding the role of IPL in MGD's treatment. This was mostly due to the fact that the authors considered the evidence grade to be very low or low as reported by the approach of Grading of Recommendations, Assessment, Development and Evaluation (GRADE). The main reason for this downgrading was due to the risk of bias (such as absence of masking), imprecision (limited number of studies with reduced sample size), and high heterogeneity.[21]

Are There Any Safety Concerns Regarding IPL Treatment?

A randomized controlled trial by Toyos et al reported no harmful adverse events. The only adverse reactions were light pain (1 patient) and moderate bacterial conjunctivitis (1 patient), with no statistically significant differences between groups.[18]

Arita and collaborators found no significant differences regarding intraocular pressure, visual acuity, lens opacity, and fundoscopy examination before and 32 weeks following treatment with IPL technology.[17] Similarly, no adverse events were reported by Yan Shi et. al.[15]

A randomized controlled trial by Piyacomn et al showed significantly higher reported pain scores in the IPL group (compared to sham group), albeit this difference was reduced after a few IPL sessions. The authors reported no adverse events related to the investigator's interventions.[19]

Regarding skin type, Li and collaborators showed that IPL is an effective and safe treatment modality in patients with Fitzpatrick types III/IV, particularly with low-energy settings (590 nm, 14 mJ/cm^2). Despite this, purpura, edema, erythema, blistering, and purpura were encountered in some patients, particularly in the higher-energy settings (560 nm, 16 mJ/cm^2). Therefore, caution is advised, especially in older patients which are more prone to hyperpigmentation.[22]

In order with the available literature, a systematic review with meta-analysis by Cote et al considered that IPL therapy is only applied to Fitzpatrick skin types I–IV, since patients with higher skin phototypes are at increased risk for adverse events. However, they also concluded that safety outcomes in this population may be uncertain.[21]

How Many Initial Treatment Sessions? How Long Does the Effect Last?

Current evidence suggests that the efficacy of IPL-MGX is positively correlated with the number of sessions and declines with increased observation time. Arita et al showed that after eight treatment sessions (every 3 weeks), patients in the IPL-MGX group achieved a significant reduction in SPEED score and improvement in NIBUT, BUT, meibum grade, lipid layer thickness, and eyelid abnormalities, comparing to MGX alone. These effects persisted at the 32-week follow-up (which corresponds to 11 weeks after the last session).[17]

In line with this evidence, Piyacomn et al described that the IPL-MGX group (3 sessions on days 1, 15, and 45) showed an increase in TBUT after the first treatment session, peaked at day 45 and persisted for at least 6 months after the initial treatment session.[19]

Similarly, Rong and collaborators described a significant increase in meibomian gland yield secretion score (MGYSS) and TBUT (after 3 sessions every 4 weeks), which persisted at the 6-month evaluation but regressed after 9-months (6 months after the last treatment session).[23]

Chen et al and Yan et al both submitted patients to 3 treatment sessions at 3-week intervals and reported the positive effects of IPL following 3-weeks and 3-months after the last treatment session, respectively.[12,21]

A systematic review with the meta-analysis by Leng et al concluded that at a 2-month follow-up, IPL was superior to MGX. However, the beneficial effects of IPL may wean at 6-months after the initial session. Therefore, with 3–4 sessions (at 3 or 4 week intervals), a follow-up appointment may be required after this period.[16]

Can IPL Be Used as a Single Treatment, or Should It Be Combined?

A systematic review with the meta-analysis by Leng et al showed that IPL-MGX treatment is more effective than MGX alone, albeit its efficacy declines over time. Despite this, some studies have not shown improve of TBUT, OSDI, or SPEED score in the arm of only IPL treatment, which highlights the synergistic effect of MGX with this technology. This suggests that MGX is of uttermost importance in the treatment of MGD and that IPL treatment alone might not be sufficient to achieve a sustained response in the treatment of MGD.[16]

A randomized crossover study by Shin et al allocated patients to 2 groups, each with 4 sessions at 2-week intervals (one group was submitted to two sessions of IPL-MGX followed by two sessions of IPL alone, and the other group underwent the same sessions in the reverse order).[24] They demonstrated the improvement in objective and subjective signs of MGD with IPL alone and that the addition of MGX to IPL improved only BUT. This was the first randomized study to compare IPL-MGX versus IPL alone. However, the last clinical evaluation was performed at 2 weeks following the last treatment session. Therefore, no conclusions could be taken on the long-term effects of IPL alone.[21]

Chen et al compared the efficacy of MGX, IPL, and IPL+MGX. Each group of patients was submitted to three sessions at 3-week intervals. Follow-up visits were performed at 1 and 3 months after the first session. In IPL+MGX group, OSDI, TBUT, and all indicators of meibomian gland secretion function improved at 1-month follow-up visit and sustained at the 3-month visit. In the IPL group, OSDI, TBUT, and all indicators of meibomian gland secretion function improved at 1-month follow-up visit, albeit only TBUT and meibomian gland secretion function sustained at 3-month follow-up. MGX also improved fewer parameters and for a shorter duration.[25]

Yan et al randomized patients to IPL+MGX or warm compresses + MGX. Each subject was submitted to 3 treatment sessions at 3-week intervals. Patients were subsequently evaluated at 3-weeks following the last treatment session. Despite both arms showing improvement in symptoms (SPEED) and signs of DED, IPL+MGX group improvement was more pronounced, especially for the primary outcome variable (TBUT – 0.5 s increase in control arm vs 2.3s increase in IPL+MGX group). This highlights the positive effect of IPL in the treatment approach for DED due to MGD, albeit its relative contribution remains unknown.[26]

What is the Most Effective Treatment Pattern?

Xue et al designed a randomized, double-blinding, randomized-controlled trial to evaluate the long-term effects of IPL therapy in patients with MGD. Patients were randomized to four or five light flashes or placebo treatment. Patients received 4 treatment sessions (on days 0, 15, 45, and 75). Patients were evaluated immediately before each treatment and at 4 weeks after completion of the last one. Light pulses were applied to four inferior periocular zones, and a fifth application was performed in the skin lateral to the lateral canthus. As expected, results showed the efficacy of both IPL arms. Sustained improvement in manifestations of DED was observed earlier in the five-pulse arm. Indeed, on day 45, only patients randomized to receive five flashes showed improvement of lipid layer thickness, meibomian gland capping, and OSDI symptoms score. Despite this, a consistent improvement in both IPL arms was not observed until 4 weeks following the final treatment session. This highlights the importance of four initial IPL sessions to achieve maximum beneficial effects.[27]

A randomized controlled trial by Wu et al randomized patients to treatment with either "Optimal Pulse Technology" (OPT), which comprised three sessions (10–14 J/cm^2) with three weeks in between. The second group was submitted to "Intense Regulated Pulsed Light" (IRPL) and received four sessions (9–13 J/cm^2) on days 1, 15, 45, and 75. The

investigators concluded that the OPT groups had superior improvement of MG secretion and performance in the inferior eyelid, comparing with the group submitted to IRPL. The OPT stabilizes IPL pulses and makes it more reproductible, minimizing the risk of unexpected energy rises and falls. Moreover, the OPT showed improvement of both the upper and lower eyelid margin, while IPRL only improved the lower lid margin.[28]

MGD can be effectively improved by IPL therapy. Standard sessions involve the infra-orbital and temporal skin, with the upper eyelid being excluded. Li et al conducted a randomized controlled trial to either standard IPL treatment (group A) or additional IPL pulse on the upper eyelid (group B). Results have shown that group B achieved improved BUT and decreased symptoms (OSDI), with better patient satisfaction. No harmful dermal or ocular complications were reported.[29]

What About Inflammatory Markers?

There is increasing evidence showing the role of inflammation in dry-eye disease.[19,20,30–33]

Interleukin (IL) – 17A is a cytokine with pro-inflammatory actions with origin in T-helper cells and has been studied in the dry-eye inflammatory cascade.[19] IL-1 has a predominant role in the cascade of inflammation and immunity by its pro-inflammatory actors (IL-1Ra and IL1b) and its increased levels have been reported in dry-eye disease.[30,31] It has been showed to play a relevant role in the induction of other cytokines with inflammatory action, such as TNF-A, IL-8, and IL-6.[32]

Prostaglandins are a well-known family of inflammatory mediators, synthesized by arachidonic acid by cyclooxygenase (COX), of which prostaglandin E2 (PGE2) is of particular interest. The association between PGE2 and dry-eye disease has been reported in some papers.[19,34]

Piyacomn et al found no statistically significant difference in IL-6 and IL-1Ra between both arms. Despite this, the authors found a substantial decrease in IL-1Ra levels in both arms at 3 months after the initial session.[19]

However, Choi et al found a significant decrease in tear inflammatory cytokines (TNF-A, IL-17A, IL-6 and IL-4) in the time period after three IPL sessions. They also found a small increase TNF-A, IL-17A, and IL-6 after the third treatment application, albeit not showing significant differences.[35]

Liu et al showed a substantial decrease in IL-6 and IL-17A after three IPL sessions. The investigators also found that IPL significantly downregulates the levels of prostaglandin E2, compared to control eyes, which correlates with a lower inflammatory response after IPL treatment.[33]

Discussion

Current literature shows that IPL is an effective treatment modality for severe dry eye. Available evidence shows improvement of symptoms and objective indicators, such as thickness of lipid layer, non-invasive breakup time, and Schirmer test.

Most studies show that both objective and subjective improvement appears after the initial session.

Based on the literature, IPL seems to be a secure option for Fitzpatrick skin types I–IV and skin type V with E>Eye® IRPL® technology (by ESW vision, France), and skin types V–VI with the Thermaeye Plus® (by MDS medical technologies, Spain) and Lumenis M22® (by Lumenis Be Ltd, Israel). There were no reported serious adverse events regarding this technology. Therefore, with the correct application of safety protocols, IPL is currently a safe technique. Despite this, continuous monitoring is required to evaluate potential hazards.

Current evidence demonstrates that MGX combined with IPL significantly increases TBUT, OSDI score, and symptoms and signs of dry eye. However, its efficacy decreases over time. Therefore, the synergism between MGX and IPL is of uttermost importance. MGX is a technique that promotes secretion and removal of blockage of the meibomian glands, which is an important part of evaporative DED. IPL therapy can improve symptoms by applying heat to promote drainage of abnormal meibum and coagulation of abnormal eyelid telangiectasia, breaking the inflammatory cycle and decreasing bacterial and Demodex proliferation.

IPL also exerts its mechanism by selective photothermolysis which coagulates eyelid margin's abnormal telangiectasia, interrupting the release of inflammatory markers and subsequent bacterial invasion. It may also stimulate meibomian gland secretion by exerting a local effect, improving meibum, promoting tear film secretion and reducing evaporation. Therefore, we cannot affirm that IPL treatment alone is superior to MGX due to the lack of evidence comparing both

treatment options. However, a more pronounced inflammatory component should favor IPL over MGX. Besides, MGX should difficult to perform in blepharitis and may enhance local inflammation, which could limit its applications.

Most studies studying IPL in the treatment of DED secondary to MGD submitted patients to 3–4 sessions of treatment at intervals of 3–4-weeks. It is shown that its benefits may begin to manifest after the first treatment session and correlate positively with increasing sessions. To our best knowledge, only Arita et al submitted patients to eight treatment sessions (compared to 3–4 sessions in most studies) – this can overestimate the positive effects of IPL in clinical practice, since prolonged treatments may be associated with fewer compliance by patients (due to follow-up losses).

In addition, our review concluded that the positive effects of IPL may lose some efficacy at 6-months after the initial session, and subsequent sessions may be required. Thus, IPL treatment should not be considered as first-line therapy for MGD but instead as an adjuvant option in addition to the standard of care.

There are differences between IPL light patterns for the treatment of DED secondary to MGD. As previously mentioned, Wu et al conducted a randomized controlled trial to determine the efficacy of "Optimal Pulse Technology" (OPT) and "Intense Regulated Pulsed Light" (IRPL). In summary, investigators found that OPT seemed more effective than IRPL. However, caution must be taken when concluding, as acknowledged by the authors. Firstly, both arms had different spot sizes (15x35 mm in OPT versus 14×40 in IPRL), with higher energy density in OPT. Secondly, both arms were submitted to different treatment schedules (eg day 1, 22, and 43 in OPT versus day 1, 15, 45, and 75 in IPRL), which may interfere with energy accumulation. And finally, OPT allows for stable energy flashes, while IPRL requires energy-storage intermission, which may lead to undesirable energy variation. Thus, more evidence is required to ascertain if there is a reproductible difference between these protocols.

Some studies[33,34] have reported increased tear inflammatory cytokines in patients suffering from DED secondary to MGD. IPL can target these pathways by selective photothermolysis, which accounts for selective ablation of eyelid margin telangiectasia and reduced extravasation of inflammatory markers and bacterial overgrowth. Therefore, decreased levels of IL-17A and IL-6 may have a significant correlation with the improvement in signs and symptoms and may (at least) partially explain them. There is also some evidence supporting the reduction of PGE2 after IPL therapy,[33] which supports its anti-inflammatory role. Despite this, more preclinical trials are needed to understand the effects of IPL in the treatment of DED due to MGD.

It should also be noted that there is significant heterogeneity between the available studies – most have few patients, with short follow-up periods and scarce evidence. Besides, nowadays, the large variety of available equipments (with different parameters and treatment protocols) greatly enhances the difficulty in the comparison of the efficacy between different treatment arms. Besides, there were other studies comparing different devices, which were not included in this review since they did not fulfill the inclusion criteria, which may also increase the risk of bias.

Despite being out of the scope of this review, the following paragraphs will approach novel technologies and treatment modalities in evaporative DED besides IPL, such as low-level light therapy (LLLT), quantum molecular resonance (QMR) therapy and near-infrared light (NIL) therapy. Therefore, the following section will also include non-randomized, single-arm, or retrospective studies.

LLLT consists of directional low-energy, high-fluence monochromatic light in the red or near-infrared wavelength (600–1000 nm) to transform biological tissues without inducing thermal or destructive interaction. Its biological principle requires the conversion of light in metabolic energy in a process called photobiomodulation. Therefore, LLLT differs from classical energy delivery systems such as lasers, which comprise larger amounts of energy, resulting in increased tissue temperature and coagulation, hence the label "low-level". Energy delivery in LLLT is insufficient to cause heating and tissue destruction but powerful enough to induce biomodulation.

Marta et al proved the efficacy of IPL+LLLT in 62 eyes of 31 patients with DED due to MGD. Each patient was submitted to 3 sessions at 1-week intervals. An improvement in the mean OSDI score was shown at 2–3 weeks and sustained at 6 months, with no adverse effects.[36]

Heitor-Marques et al have studied the efficacy of IPL (Eye-Light® with Optimal Power Energy®, Espansione Marketing S.p.A., Bologna, Italy) + LLLT (My Mask®, Espansione Marketing S.p.A., Bologna, Italy) versus IPL alone (E>Eye, E-SWIN, Paris, France). Every individual was submitted to 3 treatment sessions, as recommended by

the manufacturer. At 3-week follow-up, both groups showed a significant improvement in the OSDI-12 score and lipid layer thickness, compared to baseline.[37]

Despite this enthusiasm, current evidence regarding LLLT/IPL is still reduced, and high-quality randomized clinical trials (eg comparing IPL/LLLT and IPL/sham-LLLT) are needed to specify the contribution of LLLT in combination with IPL in the treatment of DED due to MGD.

Similarly, a retrospective study by Pérez-Silguero et al[38] showed significant decrease of DED manifestations after four sessions of IPL+LLLT (0, 1, 4, and 12 weeks). As previously mentioned, the positive effects of IPL are observed after the first treatment session, peak between the last session and subsequent follow-up (usually 1–2 months after the last treatment session), and start to fade afterwards (in this series, at 6-month follow-up after baseline). Despite this, improvement was sustained over baseline at 12-month follow-up. No adverse events were reported. Similar conclusions were taken by Stonecipher et al.[39]

Quantum Molecular Resonance (QMR) therapy (by Quantum Rexon-Eye® device (Resono Ophthalmic, Sandrigo, Italy)) is a novel technology that has successfully treated DED as well as patients with MGD. This modality employs electrical stimulation with low-intensity, high-frequencies (from 4 to 64 MHz) by the generation of electrical fields. These stimuli may enhance cellular metabolism and regeneration. Trivli et al studied the efficacy and safety of this technology in patients with mixed-type DED. Each patient underwent a 20-minute weekly session for 4 weeks. The investigators reported a significant improvement in meibum quality, NIBUT, OSDI score, NIBUT, Oxford staining, expressible meibomian glands number and a marked reduction of matrix metallopeptidase (MMP-9), with no reported adverse effects. Therefore, these results may suggest an improvement in inflammation and meibomian gland quality in patients suffering from MGD.[40]

Ren et al[41] developed a randomized clinical trial to evaluate the benefits of IPL+MGX and NIL+MGX. Patients underwent three sessions at 4-week intervals. Both groups showed an improvement in meibomian gland secretion quality and expressibility at 1- and 2-month follow-up. These results showed that both IPL and NIL can improve the secretion and quality of meibum, likely due to their thermal effects. The photothermal effect increases temperature and facilitates the liquefaction of meibum. When comparing both groups, the IPL group showed superiority over NIL regarding the improvement of symptoms of DED, but only at 2 months follow-up. One explanation might be the broad wavelength (500–1200 nm) of IPL, which covers the absorption peak of melanin, oxygenated and deoxygenated hemoglobin, the main chromophores of the human skin. Thus, the thermal effect generated by hemoglobin absorption can promote coagulation of abnormal eyelid telangiectasia with subsequent reduction in the secretion of pro-inflammatory molecules. These findings may support the theory that IPL contributes to the long-term improvement of meibomian gland function.

Conclusion

MGD is a large-spectrum disease, with MGX being a treatment modality, despite the benefits of IPL treatment. There are also several other treatment modalities for the treatment of DED, which are not included in the reviewed articles due to lack of inclusion criteria and, therefore, beyond the scope of this paper.

Thus, IPL should be performed in cases of DED refractory to conventional treatment modalities (such as palpebral hygiene, lid massage, ocular lubricants) – it is a very useful treatment option in patients with DED due to MGD, since it is an effective, quick, and safe procedure, without relevant adverse effects, as long as it is performed according to each device's manufacturer protocol. It should be also noted that IPL alone is also effective, and that despite the potential benefits of MGX, the latter is unpleasant to patients and, therefore, a significant proportion of them lack the appropriate motivation and collaboration.

It is important to highlight that MGX is a well-known, affordable procedure, which can be performed at the slit lamp, as long as it is enabled by the patient's cooperation and available material. This contrasts with other treatment modalities, which involve high level of investment by the institutions, with costly consumables in some devices. Therefore, on one hand, MGX may be an effective treatment with few costs. On the other hand, IPL may have added benefits, despite implying higher economical effort.

However, the ideal treatment schedule remains unknown – it is common belief that multiple treatment sessions yield higher efficacy than a single initial session, and several treatment regimens have been proposed (many of them being 3–4 sessions at 3–4 weeks interval). We also believe that the most effective technology should be tailored according not only to each professional's personal experience and comfort, but also to the patient's preference in view of the available technology. Therefore, according to the evaluated studies, we cannot state absolute superiority of one technology over one another.

There is compelling evidence that shows the up-regulation of pro-inflammatory markers in dry-eye disease. Our review includes evidence that shows an apparent decrease in IL-1, IL-6, IL-17a and PGE2 following several IPL treatment sessions. However, there are few results studying this hypothesis, and more evidence is required to sustain these findings.

Despite available literature pointing out the positive effects of IPL in the treatment of DED due to MGD, more evidence is needed to study its benefits – since this is an emerging technology, it is expected an increase in comparative studies in the following years, with longer follow-up periods, which may enable more precise conclusions about this treatment modality.

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Disclosure

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