A Review on Evidence-Based Treatments for Meibomian Gland Dysfunction

Running Short Title: Treatment of Meibomian Gland Dysfunction

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Abstract

Objectives: To evaluate recent studies on available therapies for meibomian gland dysfunction

Methods: A literature search on recent publications, within the last five years, concerning treatment options for meibomian gland dysfunction was performed.

Results: A total of 35 articles reviewed after curation by the authors for relevance. In general, all modalities of treatments were shown to have clinical efficacy in alleviating dry eye signs and symptoms, although the extent of improvement and persistency of outcomes varied between the different treatments. Evidence from published studies demonstrate that thermal pulsation produces the longest-lasting effect per treatment, but it also incurs the highest per-treatment cost. Reusable methods for warm compress with lipid/semi-fluorinated alkane-containing eye drops are recommended as first-line treatment for mild to moderate dry eye patients, as this option is most technically feasible and cost-effective in clinical practice. Intense pulsed light therapy and thermal pulsation may be suitable as second line for patients unresponsive to warm compress therapy, however their respective limitations need to be considered. For refractory meibomian gland dysfunction with features of periductal fibrosis or severe blepharitis, supplementary treatment with meibomian gland probing or oral antibiotics may be used.

Conclusions: All eight forms of treatments, including self-applied eyelid warming, thermal pulsation, IPL, MG probing, antibiotics, lipid-containing eye drops, perfluorohexyloctane, were effective against MGD, though with varying extent of clinical improvements. A better understanding on the mechanisms of actions may guide physicians to make better treatment decisions targeting the root causes.

Word count: 250

Keywords: meibomian gland dysfunction; treatment, evidence-based; systematic review; thermal pulsation; intense pulsed-light therapy; warm compress; eyelid warming

Introduction

Dry eye disease is one of the most frequently encountered ophthalmic conditions in the clinical setting. It often causes gritty and painful eyes, with associated blurred vision, hindering activities of daily living. Depending on the population studied and how the diagnostic criteria used, dry eye disease is estimated to have a prevalence of between 5% to 35% [1-4], with a female preponderance [5]. Furthermore, its prevalence increases with age [6, 7], with up to 70% of elderly patients greater than 60 years of age suffering from symptomatic dry eye disease in one study conducted in Japan [8].

The causes of dry eye can be broadly classified into those with aqueous tear deficiency, excessive tear evaporation or a combination of both. The most common cause of aqueous tear deficiency is lacrimal gland dysfunction secondary to autoimmune disease, termed keratoconjunctivitis sicca. The most common cause of excessive tear evaporation is meibomian gland dysfunction (MGD) [9, 10]. This is a prevalent condition of the eyelids where there is a significant change in the consistency and quantity of meibum, causing inflammation of the eyelids and subsequent ocular surface dysfunction. While most cases are idiopathic, it may occasionally be secondary to dermatological conditions like acne rosacea and demodex infestation. MGD has a prevalence from 46.2% to 69.3% in several studies targeting Asian populations, with a trend of higher prevalence in the elderly [11]. Insufficient lipid secretion from meibomian gland undermines tear film stability, producing dry eye symptoms despite normal tear secretion. In a recent study, up to 70.3% of dry eye patients were found to have concurrent MGD [12].

The treatments for MGD can be classified into those that are heat-based versus non-heat-based. Eyelid warming, thermal pulsation and intense light therapy are three prevailing heat-based treatments for MGD-related dry eye disease. Eyelid warming usually involves the application of warm towels, commercialized eye masks (EyeGiene® or Blephasteam®) or eye bags (MGDRx Eye Bag) at least twice a day. Thermal pulsation (Lipiflow®) refers to the delivery of controlled heat together with gentle massage to the eyelids by the machine for 10-17 minutes. Intense pulsed light (IPL) therapy, which uses light energy on the skin surface, is widely used in dermatology to treat a variety of conditions including dermal vascular lesions, such as port wine stains and

hemangiomas, facial rosacea, and acne. In 2002, Dr. Toyos discovered the positive ophthalmic effects of IPL on his patients who underwent treatment for facial rosacea. Along with decreased facial erythema, his patients developed improvement in signs and symptoms of meibomian gland dysfunction (MGD) and dry eyes. Working alongside DermaMed Solutions, he helped to develop an IPL system that was geared towards treatment of dry eye disease [13]. Since that time, there has been a growing number of physicians across the USA and abroad using IPL to treat MGD and dry eye [14-16].

As for non-heat-based treatments, MG probing, antibiotics (either topical or oral), Manuka (Leptospermum species) honey, lipid-containing eye drops and perfluorohexyloctane are some common modalities used by physicians across the world. MG probing refers to the use of an intraductal stainless wire (usually 2mm-6mm long) to reopen the MG orifices mechanically. Topical anesthesia is applied during the procedure to minimize patient discomfort. Antibiotics are also very common in the treatment of MGD. Macrolides and tetracyclines are the mainstay antibiotics for MGD, either applied topically or orally. For honey, the medical field has been actively exploring its applications in modern medicine. [17-19] Its use in eye and wound healing have been documented in various studies. Manuka (Leptospermum species) honey can be applied on patients in the form of eye gel or eye drops as an adjunctive therapy.

This systematic review aims to summarize and compare the latest evidence for the management of MGD-related dry eye, focusing on the efficacy, safety and mechanisms of action of treatments, published within the last 5 years.

Methods

An Entrez Pubmed search was performed on the 24th February 2019 using the keywords ‘meibomian gland dysfunction’, ‘treatment’, ‘eyelid warming’, ‘intense pulsed light therapy’, ‘thermal pulsation’. The search was limited to papers published in the recent 5 years and those conducted on human subjects. A total of 44 entries were found using this search strategy. These papers were then manually curated (by KCS and PYL) to include only those concerning ocular surface treatment outcomes. Furthermore, papers investigating efficacy in other forms of dry eye disease were excluded. For example, papers including Sjogren syndrome related dry eye and chronic graft-versus-host disease related dry eye were excluded from the review. The results included both original studies and reviews, with the latter excluded from analysis. Keywords like ‘management’ or ‘therapy’ were also tested instead of ‘treatment’, but no extra result was generated. The references of individual papers from the curated results were checked to yield further articles.

Results

The search strategy yielded a total of 35 original articles for analysis after manual curation. Most of the papers cited the 2011 International Workshop on MGD guidelines for diagnostic criteria [20-22].

1. Warm compress and self-applied eyelid warming devices

Efficacy - A total of 8 articles investigating efficacy of warm compress in the treatment MGD-related dry eye disease were identified (**see Table 1**). All 8 of them were single-center studies. Five of them, including two by Arita et al and one by Bilkhu et al and one by Yeo at al and one by Ngo et al, were randomized control trials (RCTs) [23-27]. Two of papers, including one by Lam et al and one by Wang et al, were randomized non-controlled studies [14, 28]. The remaining one study, by Villani et al, is neither randomized nor controlled. Only five studies, including those by Wang et al, Artia et al, Bilkhu et al, Yeo et al and Ngo et al adopted investigator-masking [14, 23, 25-27]. Various techniques of eyelid warming were tested in these reports, including warm compress [23, 24, 26, 28, 29] EyeGeine eye masks [14, 26, 28], Blephasteam® eye masks [26, 28, 29] and MGDRx eye bags [14, 25, 27]. All 8 studies demonstrated the efficacy of warm compress in achieving clinical improvements in both dry eye symptoms and tear film metrics.

Conventional warm compress is usually done by applying warm towels on eyes for around 10 minutes. However, recent studies by Artia et al suggested that several modifications to traditional techniques would make the treatment more effective [23, 24]. Menthol was suggested to be added when using disposable eyelid warming devices [23] as it was postulated that it would activate the corneal cold-sensitive primary afferent neurons. On repeated uses of menthol-containing eyelid warmers, ocular outcomes, i.e. tear meniscus height (TMH) and TBUT improved in both healthy controls and dry eye patients. Similar improvements in tear film metrics were not seen in the non-menthol-containing group, although both groups showed improvements in the subjective dry eye symptoms. It was also important to note that the measurement was taken at least 8 hours after the application of eyelid warming, suggesting post-treatment persistence in therapeutic effect. A previous study

reported that menthol eyedrops alone were ineffective in improving dry eye symptoms. This suggests the combination of both menthol and eyelid warming may be required to achieve desirable effect.

Another modification suggested by Artia et al is related to the wetness of warm compress. Warm compress with the highest level of wetness (i.e. a hot towel compress) showed weakest improvements in ocular outcomes even after repeated administration [24]. This may be due evaporative cooling effect counteracting the eyelid warming effect. On the other hand, Arita et al demonstrated that eyelid warming with the Azuki no Chikara, a non-wet warming pad, had the greatest improvement in ocular outcomes, as well as a 9.6% increase in healthy meibomian gland area, after repeated usage for 1-month.

Eyelid warming with MGDRx eye bags, EyeGiene® masks and Blephasteam® masks all resulted in significant improvements in ocular outcomes [14, 25, 29], except in Ngo et al [27]. After 10 minutes application of MGDRx eye bags or EyeGiene® masks, the outer eyelid temperature rose to 36.8 ˚C and 35.6 ˚C respectively [14], which are both higher than the lower limit of melting range of the meibum in MGD patients (35 ˚C) [30, 31]. In another study comparing the effects of Blephasteam® and traditional warm towel compress [29], non-responders to traditional compress had significant improvements in Ocular Surface Disease Index (OSDI) scores and TBUT after receiving Blephasteam® treatment for 3 weeks. This possibly suggested a higher efficacy in Blephasteam® eye masks than traditional warm compress. However, it is important to note that this is a crossover study in which patients received 3 weeks of traditional compress immediately followed 3 weeks of Blephasteam® treatment. There might be insufficient washout time between the two treatments, and part of the ocular outcome improvements may be due to the residual effect of traditional warm compress instead of Blephasteam®. Nevertheless, the better efficacy of Blephasteam® and EyeGiene® over warm towel compress was confirmed in other studies as well [26, 29]. Both groups of patients using Blephasteam® and EyeGiene® achieved a reduction in tear evaporation rates (calculated by ocular thermography data), but similar change was not seen in the warm towel compress group [26]. One probable reason for this was the mean duration of eyelid warming, with temperature ≥ 38˚C, using these eyelid warming techniques were significantly higher than that achievable with warm towel compress.

Safety - Warm compress and self-applied eyelid warming are comfortable and safe to use, with no adverse effects reported in the articles reviewed. The subjective ocular discomfort score decreased in normal subjects after eyelid warming, despite no observable changes in objective ocular outcomes [24]. This showed that eyelid warming may give a sense of comfort to the patients on top of objective ocular improvements.

The duration of therapeutic effects is one of the major concerns with eyelid warming techniques. For instance, after single application of various commercially available warm compress products, the ocular effects started to diminish 10 minutes after device removal and mostly disappeared at 30 minutes after treatment [24]. On the contrary, longer lasting desirable ocular outcomes were observed after repeated administration of warm compress. Similar trends were also seen in MGDRx eye bag therapy. For example, patients who continued to eye bag treatment for 1–4 weeks had greater ocular comfort benefit (7.79/10, $p<0.001$) than single usage, with the highest ocular comfort scores (7.96/10, $p<0.001$) achieved in patients with continuous usage of eye bags for 1–8 times a month [25]. This shows that patient adherence to repeat treatment is an important determinant of long-term treatment efficacy. A single warming episode is insufficient for lasting improvement.

Mechanisms of Action - The mechanism of action of warm compress/eyelid warming was well discussed in the articles reviewed. The mean surface temperature of tarsal conjunctiva in MGD patients was found to be significantly lower (at least 1.5˚C lower) than that of normal subjects ($p<0.001$) [32]. Similar trends were also observed in corneal and eyelid temperatures [33]. The tarsal conjunctival or eyelid temperature of MGD patients measured in the two studies was lower than the meibum melting point of 35 ˚C. It was also important to note that the meibum melting point in MGD patients (35 ˚C) was higher than that in healthy subjects (32 ˚C) [30, 31]. As a result, most MGD patients have viscous meibum which obstruct the gland orifices. Warming the MGs liquefies the thickened meibum. The resulting fluid meibum increases aqueous tear film stability. This mechanism was proven by a study showing a significant and direct correlation between TBUT (in seconds) and tear lipid layer grading (LLG) [14].

A newer purposed mechanism of eyelid warming is its effect in changing tear lipid composition. Eyelid warming was shown to reduce molar fractions of major lysophospholipid classes ($p<0.001$) [28]. On the other

hand, amphiphilic lipids including O-acyl-ω-hydroxy-FAs (OAHFAs) increased in tears after eyelid warming, and these amphiphiles were found to be integral to the tear film stability. Lysophospolipids carry detergent-like properties and high polarity, which may compromise tear film stability. The significant correlation between reductions in the lyso-plasmalogen phosphatidylethanolamines (LpPE) level and improvements in ocular evaporation rate was highlighted by Lam et al. Further studies can be carried in this direction to consolidate our understanding of how eyelid warming may modify tear lipid profile.

2. **Thermal pulsation**

Efficacy - 5 articles on thermal pulsation (Lipiflow®) were reviewed (**see Table 2**). One of them was a systematic review of articles or abstracts documenting the ocular effects of a single 12-minute Lipiflow® thermal pulsation therapy [34]. Two studies, by Blackie et al and Finis et al, were RCTs [35, 36] and the remaining two, by Greiner et al and Satjawatcharaphong et al, were neither randomized nor controlled [37, 38]. Masking was only applied in one of the four studies [36]. The study by Blackie et al was a multicenter trial with a large sample size of 200 participants [35]. In all these studies, the duration of the thermal pulsation therapy was set at 12 minutes, and only the effect of single administration was investigated. In summary, thermal pulsation is an effective treatment modality in reducing both dry-eye-related symptoms and signs. In fact the Lipiflow® device has been approved for dry eye treatment by the US-FDA since 2016.

The systematic review [34] evaluated 31 articles and clinical abstracts on thermal pulsation published before January 2017. All except one reported significant improvement in ocular outcomes. The treatment group in that particular study may account for the lack of improvement as only patients with clinically significant dry eye for at least 5 years were recruited. Both RCTs included in the systematic review demonstrated that improvements in ocular outcomes after a single thermal pulsation session potentially lasted for up to 12 months after treatment, with superior outcomes when compared to twice-a-day traditional warm compress therapy.

From the studies by Blackie et al and Greiner et al, a single thermal pulsation session was sufficient to produce significant improvement in OSDI score, meibomian gland secretion (MGS) scores and number of meibomian glands yielding liquid secretion (MGYLS) [35, 37]. Blackie et al further noted that during the study period of 12 months [35], the majority of participants were satisfied with their improved ocular status and didn't seek additional treatment even the study protocol allowed them to do so. A significant increase in the number of expressible glands after a single thermal pulsation treatment was also noted by Finis et al [36]. In both RCTs comparing thermal pulsation to traditional warm compress or lid hygiene, more significant improvements in OSDI scores were observed in the thermal pulsation group.

Long-term ocular effects of a single thermal pulsation treatment were also examined. Despite the improvements in MGS, TBUT, OSDI and the Standardized Patient Evaluation of Eye Dryness (SPEED) scores at one-month time interval, only the improvements in MGS and SPEED scores persisted after 3 years [37]. The TBUT and OSDI scores returned to baseline level at 3-years after treatment. Although both SPEED AND OSDI scores measure dry eye symptoms, OSDI scores take into account the effect of environmental changes on severity of symptoms, and thus inherently have higher variability. Despite this, the results show that, with a single treatment of thermal pulsation, the majority of patients remained asymptomatic for at least one year, with more than half asymptomatic for at least 3 years.

The effects of baseline patient characteristics on subsequent treatment outcomes were also well discussed in a number of studies. Blackie et al demonstrated that patients with a milder baseline MGD and/or shorter duration of time from diagnosis to treatment were more likely to produce a greater MGS improvement [35]. However, another study by Satjawatcharaphong et al offered a contrasting view [38]. The study suggested that the degree of symptomatic relief achieved with treatment was directly correlated with a baseline severity of dry eye symptoms ($p<0.001$), number of MG yielding no secretion ($p=0.017$), and a grading of inferior conjunctival lissamine green (LG) staining ($p=0.019$). In other words, the study purposed an association between more severe baseline MGD and dry eye disease and better treatment outcomes (in terms of improvement in SPEED scores) after thermal pulsation. Owing to the contrasting views at the moment, the predictive effect of baseline patient characteristics on the efficacy of thermal pulsation may need to be answered by further multi-centre randomized controlled trials.

Safety - Out of all the articles reviewed, the potential for treatment to worsen of dry eye symptoms was reported in only one study [38]. In the paper by Satjawatcharaphong et al, 5% of the subjects experienced transient discomfort or soreness due to either an unusually short fornix or small palpebral aperture size compared to the Lipiflow® activator scleral shell, or meibum residual inflammatory materials remaining on the ocular surface after MG evacuation in patients with permanent punctal plugs. Apart from this transient adverse effect, the studies demonstrated that thermal pulsation had an excellent safety profile.

Mechanism of Action - Thermal pulsation (Lipiflow®) is a technology combining eyelid warming and massage. The proximal-to-distal peristaltic motion of the Lipiflow® activator aims to evacuate gland contents while a nominal therapeutic temperature of 42.5˚C is applied directly to the palpebral surfaces of upper and lower eyelids where MGs are located. There are multiple sensors to regulate the heat and pressure throughout the treatment.

The primary action of thermal pulsation is to liquefy the thickened meibum, similar to other self-applied warming techniques. However, it also focuses on the obstructive element of MGD and applies pressure to the eyelids to evacuate the stagnated gland contents. Moreover, owing to the design of the Lipiflow® activator, the heat is more precisely delivered to the MGs rather than to the ocular surface. The extra gland evacuating effect and more precise heating mechanism possibly explain the more persistent and significant effect of thermal pulsation when compared to self-applied eyelid warming as shown in various studies [26, 34-36].

The conventional method of evacuating stagnated gland contents is by manual meibomian gland expression (MGX) [39]. Despite the effectiveness of the procedure, it is painful and has to be carried out several times a year [35]. On the contrary, thermal pulsation provides a more comfortable alternative to MGX, but with extra eyelid warming effect.

3. **Intense pulsed light therapy**

Efficacy - A total of 10 articles concerning the use of IPL therapy in MGD-related dry eye were found (**see Table 3**). Two of them were double-masked RCTs, including the studies by Craig et al and Liu et al [40, 41]. There was also another investigator-masked controlled study, as reported by Yin et al, but this was conducted without randomization [42] Three prospective studies, by Albietz et al, Guilloto Caballero et al and Arita et al, were neither controlled nor randomized [43-45]. Finally, three were retrospective studies of patients receiving IPL treatment, and with a rather large sample sizes (80-100 subjects), including those by Toyos et al, Gupta et al and Vegunta et al [13, 15, 16]. Out of the three retrospective studies, two of them (Toyos and Gupta) were multicentered [13, 15]. The remaining one article, by Vegunta et al, was a single-centre retrospective study as well as a literature review of IPL-related articles [16]. MGX was performed after the application of IPL in all studies except two (Yin and Albietz) [42, 43]. In summary, IPL was useful in improving ocular outcomes in MGD-related dry eye of varying degrees of severity, with the treatment frequencies of every 2-4 weeks for at least 3 sessions proven useful in all prospective studies [39-43, 45]. It is important to note however that the meibomian gland dysfunction is not yet an approved indication for intense pulsed light therapy by the United States Food and Drug Administration (US-FDA).

In patients with mild to moderate dry eye, Craig et al demonstrated improvements in LLG, TBUT, VAS scores but not TMH and tear evaporation rate after IPL treatment when compared to placebo [40]. The improvement in LLG suggested that IPL treatment can facilitate meibum output through laser stimulation and help stabilize the tear film. Albietz et al and Arita et al demonstrated similar results for advanced MGD [43, 45]. In the study by Albietz et al, after 3 treatments in 8 weeks, significant improvements were observed in meibomian gland expressibility ($p = 0.002$), meibum quality ($p = 0.006$), TBUT ($p = 0.002$), corneal fluorescence staining (CFS) ($p = 0.001$) and redness ($p = 0.001$). The study by Arita et al also showed that two major lid margin abnormalities, i.e. the increased vascularity and plugging of MG orifices, improved after IPL-MGX treatment. Furthermore, the ocular effects brought about by IPL were also cumulative [40, 43], lasting for at least 6 weeks after the completion of treatment [43]. In the study by Toyos et al [13], odds ratios were calculated and pointed out that patients receiving 5 or more IPL sessions were 17.5 times more likely than those receiving 1-3 treatments to produce statistically significant improvement in TBUT ($p = 0.000$).

Therefore, repeated treatment with IPL potentiate its effects. However, the ideal number of treatments and duration between each of them remains to be determined by clinical trials.

On a molecular level, IPL is useful in reducing inflammatory markers in both tears and ocular surface [40]. IPL treated eyes had significant reduction in tear Interleukin-17A (IL-17A), Interleukin-6 (IL-6) and prostaglandin E2 (PGE2) when compared to controls after 3 IPL sessions. The level of inflammatory cytokines like IL-6 or IL-17 have been shown to strongly correlate with MGD-related dry eye disease severity [46, 47].

The effects of IPL in reducing postoperative dry eye after corneal surgery were also well discussed in the study by Guilloto Caballero et al [44]. Those undergoing phacoemulsification and photorefractive keratectomy (PRK) had significantly less dry eye if pre-treated with IPL. However, for those having surgeries with mechanical microkeratomes (MM) and femtosecond laser (FL), there was no significant differences between IPL treated eyes and controls.

The effects of Lipiflow® thermal pulsation and IPL were indirectly compared in the study by Vegunta et al [16]. A group of patients who did not show any improvement 3 months after thermal pulsation then underwent IPL therapy, and the majority of them showed significant improvement in SPEED2 scores, with some of them even showing an over 50% decrease in their SPEED2 scores. However, it is important to note that this study is not an RCT and therefore subjected to bias. In the future, an RCT can be carried out to effectively compare the clinical efficacy of IPL and thermal pulsation.

IPL was also compared to conventional eyelid warming and manual massage in the study by Yin et al [42]. OSDI, TBUT, MG expressibility, and meibum quality improved after treatment in both groups of patients ($p < 0.05$). The MG macrostructures, as revealed by MG dropout and meibomian gland acinar longest diameter (MGALD), also significantly improved in both groups. However, only the IPL group could maintain the improvement in MGALD 3 months after treatment. Regarding the microstructures, the improvement in meibomian gland acinar unit density (MGAUD) was only observed in the IPL group, suggesting the particular use of IPL in improving MG microstructures. This may be attributed to the purported photobiomodulatory effects of IPL.

Regarding the effects of patient factors on treatment outcomes, it was observed that the lower the initial MG expressibility score, the greater the improvement in OSDI after IPL [43]. Furthermore, it was discovered that IPL did not produce any significant improvements in patients with aqueous deficient dry eye [44]. Therefore, IPL is more of a specific treatment modality targeting MGD-related dry eye.

Two types of IPL devices (E>Eye; E-SWIN, Paris, France and Lumenis M22; Tel Aviv, Israel) were used in the studies. The E>Eye device produces a wavelength from 580nm to 1200nm, whereas the Lumenis M22 produces a wavelength from 400nm to 1200nm. The broader wavelength of Lumenis M22 can theoretically achieve a better bactericidal effect. *Proprionibacterium acnes,* a bacterium commonly found in MGD patients, absorb light between 400 and 700 nm with 415 nm from blue-light spectrum being most effectively absorbed. On the contrary, the red-light spectrum (580nm to 1200nm) delivered by the E>Eye device has poorer bactericidal effect but can potentially penetrate deeper into the skin and target the underlying sebaceous glands. [43] In addition, it was suggested that a treatment wavelength at around 500nm may induce photo-thermolysis of vessels and prevent the leakage of inflammatory cytokines to the ocular surface. [13, 15] The wavelength of 500-600nm was used in most of the reviewed studies and demonstrated significant improvements in ocular parameters. Regarding the power of the IPL, it should be inversely correlated with Fitzpatrick skin type grading, as demonstrated in various studies, in order to avoid skin depigmentation. [41, 44] An increase in treatment power may be indicated in older patients or those with MGD of greater severity. [13]

Safety - Adverse effects were reported by a number of studies. In one study, 14% of patients experienced adverse events after IPL treatment [13]. This included cheek swelling, conjunctival cyst, floaters, blistering (usually a red spot lasting less than one week), hair loss at brow and forehead, light sensitivity, and facial redness. These adverse effects usually resolved spontaneously without treatment within one week. Furthermore, no serious adverse effects were reported. However, pain associated with MGX immediately following IPL treatment may be a concern for some patients [16].

Although not reported in the studies reviewed, IPL-induced uveitis and iris damage have happened in patients who did not use ocular protection when applying cosmetic IPL therapy on the upper eyelids by

non-ophthalmologist healthcare workers [15]. Therefore, it should be noted that the IPL treatment for dry eye should adhere to lower eyelids for now and in the presence of ocular protection.

Mechanism of Action - There are generally 4 postulated mechanisms of actions of IPL purposed by the articles. First of all, IPL was purposed to induce local warming of MG and melting of the thickened meibum secretions. [13, 15, 43]. The MG is then manually expressed to ease the obstruction. Nevertheless, the temperature rise of the periocular skin after IPL was only 1 ˚C [16, 43], and possibly even less heat can reach the MG and liquefy the meibum. In addition, the use of protective eye goggles prevents IPL from directly acting on the gland openings. Thus, unlike warm compress and thermal pulsation, the eyelid warming effect of IPL is rather minimal and not a main mechanism of action.

The second postulated mechanism is through the reduction of bacterial and parasitic growth on eyelids. The targeted wavelengths of IPL may help in preventing bacterial overgrowth via the disruption of bacterial cell walls [41]. *Demodex folliculorum* and *Bacillus oleronius* are common inhabitants of human hair follicles and sebaceous glands. These organisms are occasionally found in ocular rosacea, causing inflammatory responses and contributing to dry eye diseases [15]. However, the evidence for this hypothesis may be insufficient as no significant reduction was observed in eyelid margin flora colony counts after IPL and MGX treatments [43].

Moreover, it was observed many MGD patients had telangiectasia at the eyelid margins [16, 41, 48]. This causes leakage of inflammatory cytokines like IL-17A and IL-6, which in turn may aggravate the original inflammation and MGD. The yellow wavelength of IPL can target the oxyhaemoglobin in superficial skin vessels, which have light absorption peaks of 578nm. This induces selective photothermolysis of the vessels when the light energy of IPL is converted into thermal energy. The vessels are then thrombosed, reducing cytokine leakage and inflammation. The sustained reduction in telangiectasia was observed in patients with rosacea-related MGD after repeated IPL administration [49].

The last hypothesis is related to the photomodulation effect of IPL [41]. The specific wavelengths of IPL can produce a stimulatory effect on the mitochondria of MGs. The photostimulatory effect has been proven to promote cell activity, such as photojuvenation and wound healing [50]. The optimal wavelengths for

photomodulation are 680, 730 and 880nm [51], which match the wavelengths of IPL treatment. It was suggested that that IPL may help improve the MG microstructure.

4. **Meibomian gland probing**

Efficacy - A total of 5 articles regarding the efficacy of MG probing were reviewed (**see Table 4**). The study by Ma et al. was a randomized controlled trial. [52] Two other papers, including prospective trials by Nakayama et al and Sik et al, that were neither randomized nor controlled. [53, 54] There were also two published retrospective studies, by Maskin et al and Syed et al. [55, 56] The exact procedures of MG probing were detailed in these articles. Operating microscope was used for visualization in two studies (Ma and Syed) [52, 56], whereas MG probing was conducted under slit lamp in the study by Maskin et al. [55] The other two studies (Nakayama and Sik) didn't specify the techniques used. [53, 54] In general, patients showed significant and immediate (i.e. within 1 week) improvements after MG probing.

Four of the studies targeted patients with refractory MGD that did not respond to conservative treatment, i.e. eyelid hygiene and warm compress. [52-54, 56] The only RCT by Ma et al [52] compared the ocular effect of the combined regimen of MG probing and 0.1% fluorometholone (FML) eyedrops, with the sole administration of 0.1% FML eyedrops. Although both groups showed significant improvement in ocular signs and symptoms ($p<0.001$), the improvements in the regimen with MG probing were greater than that of the control. The improvements were associated with increase in mean individual glandular area, reduction in eyelid margin vascularization ($P = 0.004$) and conjunctival hyperaemia ($P < 0.0001$), as observed in the studies by Sik et al and Maskin et al [54, 55].

Immediate relief of ocular symptoms was seen in most patients in the reviewed studies. [52, 55, 56] However, regarding the duration of treatment effect, a single session of MG probing was insufficient in 73.3% of patients in the study by Sik et al. [54] In contrast, for patients receiving 3 to 4 treatment sessions, ocular symptoms and signs improved up to 3-month post-treatment follow-up. A similar trend was demonstrated in the study by Syed et al. [56] Despite over 90% of patients showing immediate symptomatic relief 1 week after MG probing, dry eye symptoms recurred in 69.2% of patients who underwent over 6 months of follow-up. On average, the symptoms reappeared 38.2 weeks after the initial probing treatment. In addition, the initial increment in the number of expressible glands after probing was reduced upon 1-year follow-up. [55] Thus, multiple MG probing sessions are required to achieve best and long-lasting results.

Safety –Eyelid bleeding is the most common complication of probing. [52] Patients typically encountered bleeding when the orifice was covered by a membrane or there was ductal resistance during the procedure. However, most of the bleeding episodes were minor and self limiting without further treatment and didn't pose any risk to the patients.

Mechanism of Action - The effect of MG probing is rather immediate as it mechanically opens the MG orifices and ducts. Accumulated meibum can be promptly released, contributing to the instant reduction in intraglandular pressure and the immediate symptomatic relief. [52] Meibum clearance also helped to reduce inflammatory reactions in the MG and the associated dry eye symptoms. The study by Maskin et al stated that MG probing is more suitable for patients with unyielding fixed obstruction, such as periductal fibrosis. [55] For this type of patients, if heat and pressure are used to treat the MGD, the intraductal pressure may paradoxically increase and worsen the symptoms. Besides, MG probing may theoretically help to activate the stem cells in the ductal epithelium. This may account for the increase in healthy glandular area after probing.

Another study also provided possible explanation on MG probing in treating MGD. [53] Probing can lower the MG intraglandular pressure by alleviating the meibum obstruction. Improvements of meibum lipid level and viscosity were recorded in the study. The improved meibum quality may help to halt the vicious cycle of MGD progression, as altered meibum lipid composition was observed in MGD patients and had a positive correlation with MG atrophy. [57, 58] However, the sample size of the study by Nakayama was too small to generalize to all MGD patients. Further studies with a larger sample size on the possible beneficial effects of MG probing on meibum quality can be carried out in the future.

5. **Topical and oral antibiotics**

Efficacy - A total of 4 papers were reviewed under this topic (**see Table 5**). There were one RCT [59], one retrospective study [60], one literature review [61] and one in vitro study [62]. Macrolides and tetracyclines are the most common antibiotics for used in treating MGD. Macrolides (i.e. azithromycin, solithromycin) were investigated in three studies (De Benedetti, Balci and Liu) [59, 60, 62], while tetracyclines (i.e. doxycycline, minocycline) were included in two studies (De Benedetti and Doughty) [59, 61]. Topical application was used in the study by Balci et al [60]; while oral antibiotics were given in the studies by De Benedetti et al and Doughty et al [59, 61].

Daily topical 1.5% azithromycin for 30 days could produce significant improvements in patient symptom score and clinical signs in 1-month follow-up. [60] However, the improvements in clinical signs (CFS, TBUT, Schirmer score, meibum grade) failed to persist in 3-month follow-up. Previous studies have shown improvements in dry eye conditions after 30 days of topical azithromycin, but their study duration only lasted for 30 days. [63-65] Combining the results of the study by Balci et al and other studies, topical azithromycin was capable of producing short-term improvements, but the duration of the improvements after the cessation of antibiotic eye drops was not adequate. Although the study by Fadllalah showed that topical 1.5% azithromycin was effective 3 months after treatment, the study only included patients with anterior and posterior blepharitis, which are not seen in all MGD-related dry eye patients. [66] The differences in patient inclusion criteria may account for the discrepancies in the results. Current evidence suggested a limited role of topical azithromycin as a long-term solution to MGD-related dry eye, although an RCT with a longer follow-up period should be done to confirm this hypothesis.

On the other hand, oral form of antibiotics may have a role in dealing with MGD complicated with grade 2-3 posterior blepharitis. [59] Oral azithromycin and tetracyclines (doxycycline and minocycline) were both effective treatment for persistent MGD refractory to conservative treatments. [59, 61] Two to three months of relatively low doses of tetracyclines (100 mg for doxycycline or 50 mg for minocycline) were able to effectively reduce the abnormal appearance of MG (from -4% to -89%) and increase the tear film stability (from 21% to 273%). [61] However, amongst the two, oral azithromycin appears to be more effective than

oral doxycycline. [59] In the RCT by De Benedetti et al, a larger proportion of patients in the doxycycline group had to switch to azithromycin due to the lack of response. More importantly, the azithromycin group resulted in better improvements in symptoms and signs ($P<0.005$). It was also worth noted that the azithromycin therapy required a shorter duration and smaller dose than doxycycline, which help to improve treatment adherence and reduce side effects.

Safety – Topical antibiotics are safe to use, and no severe adverse events were reported in the studies. [60] However, minor ocular stinging sensation and redness were observed in a small number of patients. For oral antibiotics (both macrolides and tetracyclines), gastrointestinal disturbance was the most commonly encountered side effect. Doctors should however avoid tetracycline use in children and pregnant and lactating women. Minocycline was less preferable than doxycycline with study indicating a higher risk of developing systemic side effects. [67]

Mechanism of Action - Azithromycin is a lipophilic molecule, which penetrates conjunctival cells easily. Azithromycin molecule was found to remain in conjunctiva several days after the last topical administration. [68] Azithromycin was postulated to have a dual anti-bacterial and anti-inflammatory effect. It supresses the production of inflammatory cytokines through the blockage of nuclear factor kappa B activation in human corneal cells. [69] MGD was thought to have a complex pathogenesis that sometimes involves both bacterial colonization and inflammatory actions [70]. Therefore azithromycin can theoretically counteract its pathogenesis. Newer in vitro study showed the cationic amphiphilic drug nature of azithromycin could stimulate differentiation of human meibomian gland epithelial cells (HMGECs). [62] It also suggested another macrolide antibiotic, solithromycin, was even more potent than azithromycin in inducing HMGECs differentiation. Human clinical trials can be carried out in the future to compare the effect of solithromycin with azithromycin in treating MGD. For tetracycline antibiotics, they also had anti-inflammatory effect in addition to the bacteriostatic property. They were proven to induce a slight reduction in the activity of matrix metalloproteinase (MMP) on corneal surface. [71]

6. **Other topical treatments for MGD**

Efficacy - 3 papers related to non-antibiotic-containing topical treatments of MGD were identified and reviewed (**see Table 6**). The studies by Albietz et al and Mihaltz et al were RCTs [72, 73], while the study by Steven et al was a multicenter uncontrolled study. [74] Manuka (Leptospermum species) honey, lipid-containing eye drops and perfluorohexyloctane eye drops were discussed in these papers respectively. In summary, they were all effective in alleviating MGD-related dry eye symptoms and signs.

Antibacterial Manuka (Leptospermum species) honey was delivered in two formulations, namely Optimel Manuka Eye Gel (with 98% Manuka honey) and Optimel Eye Drop (with 16% Manuka honey). [72] Despite all groups (including the control) showing significant improvements in dry eye metrics (e.g. TBUT, redness), increased MG expressibility and reduced MMP 9 counts were only observed in the two groups treated with Manuka honey, showing that Optimel Manuka is an effective adjunctive therapy for MGD. The two formulations had their respective advantages. Optimel Gel was more effective in improving gland expressibility ($p=0.042$) and meibum quality ($p=0.005$). Optimel Eye Drop was the only group showing the reduction in total eyelid marginal bacterial colony counts ($p=0.03$). Another positive finding was the reduction of artificial tear or lubricant usage after Optimel Manuka as adjunctive therapy.

In the study by Mihaltz et al, lipid-containing eye drops were compared to sodium hyaluronate-based eye drops. [73] Both eye drops were proven to be equally effective in addressing dry eye symptoms and signs. However, lipid-containing eye drops were superior than its counterpart in reducing corneal higher-order aberrations and improving optical quality for patients with severe MGD (over 50% of MG loss). Semifluorinated alkanes (SFAs) containing eye drops were another type of eye drop targeting patients with MGD-related dry eyes. [74] Topical perfluorohexyloctane (a type of SFA) application for 6-8 weeks could lead to significant improvements in blepharitis and increase in the number of expressible MG.

Safety – Three treatments mentioned in this section are generally safe to use. Only temporary redness and stinging sensation were reported after the use of Optimel Manuka Gel and Eye Drops. [72] For lipid-containing eye drops, some patients may not tolerate it well. In the study by Mihaltz et al, two patients

opted to terminate the use of lipid-containing eye drops due to local irritation, burning and transient blurred vision. [73] A similar trend was not seen in the control group using sodium-hyaluronate eye drops. Regarding the use of perfluorohexyloctane, adverse events were observed in 5 out of 72 patients. [74] Adverse events mainly included application site reaction, foreign body sensation, hypersensitivity reactions and conjunctivitis.

Mechanism of Action – Pure raw honey was proven to suppress bacterial growth with its low pH, high osmolarity and low water content. [17] Moreover, some types of honey, i.e. the Leptospermum species, have extra antimicrobial effects, as a small amount of hydrogen peroxide can be produced from bee-derived glucose oxidase upon the dilution of the honey with water. [75] A recent study by Aragona et al also showed that the number of patients with elevated MMP 9 level was reduced after the use of honey product. [76] As MMP 9 is often elevated in MGD patients, this may account for the improvements in MG expressibility and meibum quality after Manuka honey application.

For the underlying mechanism of action of lipid-containing eye drops, it can form a lipid layer on the tear film, preventing the evaporation of tear. It performs better than the aqueous eye drops as aqueous drops will evaporate easily without the surface lipid layer.

Perfluorohexyloctane is also effective against MGD because of its superior spreading properties. It can spread into the MG orifices and interact with the meibum there. It was discovered that lipids which usually block the MG orifices can potentially dissolve in SFAs. [77] Thus, SFAs may help to resolve the obstruction occurring in MGD and prevent superimposed inflammation. This explained the alleviation of blepharitis after topical use of perfluorohexyloctane for 6-8 weeks in the study by Steven et al.

Discussion

In general, all eight types of treatments discussed, i.e. self-applied eyelid warming, thermal pulsation, IPL, MG probing, antibiotics, Manuka honey, lipid-containing and perfluorohexyloctane eye drops, had significant clinical efficacy in managing MGD-related dry eye disease. The mechanism of action of MGD treatments can be generalized into four aspects: (1) relieving the MG obstruction by heat or mechanical force, (2) anti-inflammatory effects, (3) anti-bacterial effects and (4) photo-modulatory effects. The choice of treatment depends on multiple factors, including the disease severity, associated pathological features, patient compliance, cost, availability and potential adverse effects of treatments.

The pathological features in MGD are an important criterion to decide on appropriate treatment modalities. Four pathologic processes were commonly found in MGD patients. (1) Hyperkeratinization in the lid margin. It was first mentioned in the study by Korb et al. [78] In patients with hyperkeratinization, manual expression of MG revealed the obstruction of the orifices by hyperkeratotic clusters with desquamated epithelial cells and thickened meibum. (2) The stasis of meibum due to meibum composition changes resulting in the obstruction of MG orifices. [70] (3) Obstruction caused by fixed and fibrotic changes such as multifocal periductal fibrosis. [9, 55] (4) Excessive bacterial colonization in MG. Bacterial products, such as lipase and toxins, were generated. The studies by Driver et al and Dougherty et al believed these products to be pathogenically relevant. [79, 80] Dougherty et al observed that the bacterial lipolytic activity was highest in patients with MG abnormality among six groups of chronic blepharitis patients. However, it is important to note that the impact of bacterial colonization is still controversial and plays a rather minor role in the understood pathogenesis of MGD. Despite differences in these pathologic processes, the end point of MGD is similar, resulting in MG atrophy and evaporative dry eye.

As increased meibum viscosity is a hallmark of MGD [81], heat-based therapy (i.e. warm compress, thermal pulsation and IPL, which can effectively melt thickened meibum) would be more likely to result in improvement in the majority of the patient population when compared to other treatment modalities. Although MG probing can remove both thickened meibum and fixed obstruction (i.e. periductal fibrosis) from the MG orifices, this

process has to be conducted by experienced ophthalmologists under topical anaesthesia. Patients may encounter minor eyelid haemorrhage during the process. [52] In light of the prevalence of MGD-related dry eye in our population and the invasiveness of the procedure, MG probing is not suggested as the first-line treatment for MGD. It can be reserved for the use against fixed obstruction, in which heat-based therapy may paradoxically raise the intraglandular pressure and cause additional discomfort.

With regard to the use of antibiotics, despite having anti-inflammatory and anti-bacterial effects, antibiotics are not regarded as the first-line treatment because it does not relieve meibum obstruction. However, oral antibiotics, preferably azithromycin, have a promising role in the treatment for refractory MGD with moderate to severe blepharitis, by lessening the inflammatory cytokines and bacterial count. [59, 61, 82] Topical antibiotics were believed to improve MGD symptoms and signs in various studies [63-66], but newly emerged evidence suggested that the improvement may be transient. [60] Further studies are required to better understand the role of topical antibiotics in treating MGD. Manuka honey (in form of Optimel Eye Gel and Eye Drops), lipid-containing eye drops and perfluorohexyloctane are effective in improving meibum quality and MG expressibility. [72-74] They can be used as adjunctive therapy with heat-based treatments to achieve the best clinical outcome.

In summary, for patients with MGD, heat-based therapy should be the mainstay of treatment. Out of the three different heat-based treatments discussed, conventional warm compress with warm towel is the least costly and most readily available treatment option for MGD-related dry eye. However, its efficacy, when used alone, is variable and dependent on patient persistent with repeated treatment. It is suggested that either menthol-containing or non-wet warm compress be used over hot towels. EyeGiene® and Belphasteam® eye masks were also shown to be more efficacious than traditional warm compress owing to the longer duration of heat retention. Nevertheless, EyeGiene® and Belphasteam® are rather costly options for patients. Given the large amount of dry eye patients in the clinical setting, it would not be economically viable for them to repeatedly use EyeGiene® and Belphasteam® products. Commercially available reusable non-wet compress like Azuki no Chikara is a more feasible option, with better treatment outcomes than warm towel compress and lower treatment costs than the mentioned commercial products. It is important to stress that patient adherence to daily and sustained treatment is important for the long-term efficacy of warm compress and eyelid warming devices.

Single administration only resulted in transient improvements. No matter regarding warm compress or even MGDRx eyebags, repeated administration was required to achieve long-lasting improvements in ocular parameters. Nevertheless, patients with only mild MGD-related dry eye may lack the incentive to apply warm compress twice a day repeatedly, resulting in minimal improvements in dry eye signs and symptoms.

Lipiflow® thermal pulsation and IPL therapy may incur significantly higher per-treatment costs compared to warm compress options. This particularly applies to thermal pulsation as the lip warmer and eyecup are for single use only and will be consumed after every treatment. However, the major advantage of thermal pulsation lies on its minimal requirement on patient compliance, with a single 12-minute session producing improvements lasting for at least 12 months, despite its greatest per-treatment cost. In contrast, IPL therapy has to be administered at a more regular interval, with patients receiving IPL every 2-4 weeks as demonstrated by most studies. IPL is not advised as a once-only treatment option. Only repeated administration (at least 3 continuous sessions) at regular interval can produce sustainable improvements.

With regard to the adverse effects, self-applied eyelid warming and thermal pulsation are rather safe and comfortable to use. IPL, which is usually followed by MGX, may be painful to some patients. Also, adverse effects like facial redness, blistering and light sensitivity were reported in over 10% of patients. Besides, the usage of IPL is limited to patients with a skin Fitzpatrick score of at most 5. IPL can be absorbed by melanin on skin, causing severe depigmentation in deeply pigmented patients. Furthermore, owing to the potential harm to the ocular structures, IPL is not used for the upper eyelids, so the improvement on MGs located in upper eyelids may be less significant.

Without the cost concern, thermal pulsation is the best treatment modality, given its long-lasting effects, minimal requirement on patient compliance and relatively uncommon adverse effects. However, considering the high per-treatment cost, reusable non-wet warm compress should remain the first-line option for MGD-related dry eye disease. Lipid or SFAs containing eye drops can be administered at the same time for better outcome. Only when patient compliance is low or when MGD is irresponsive to warm compress, IPL, thermal pulsation, MG probing (in cases with periductal fibrosis) or oral azithromycin (in cases with moderate to severe

blepharitis) may be considered. IPL may be more welcomed by healthcare providers as it does not involve disposable units and therefore no additional cost per treatment. Thermal pulsation usage may be restricted to patients with severe irresponsive MGD who are intolerable to the adverse effects of IPL.

Conclusion

This systematic review analysed 35 articles related to the eight treatment modalities for MGD-related dry eye disease. Although a number of these reviewed studies are not RCTs, the results consistently suggested that all eight treatments, including self-applied eyelid warming, thermal pulsation, IPL, MG probing, antibiotics, lipid-containing eye drops, perfluorohexyloctane, were effective against MGD, though with varying extent of clinical improvements. The long-term effectiveness of topical antibiotics and the mechanisms of action of some treatments, such as the effect of modified tear lipid profile on dry eye symptoms after eyelid warming as well as the photothermolytic and photostimulatory effects of IPL, should be further studied. A better understanding on the mechanisms of actions may guide physicians to make better treatment decisions targeting the root causes. The correlation between baseline patient characteristics, i.e. the severity of initial MGD, previous eye surgeries, and treatment outcomes can be another area for further inquiry. Hopefully, future double masked RCTs can be carried out to compare the treatment efficacy and persistence of different treatment modalities, especially between thermal pulsation and IPL.

List of Abbreviations

MGD: meibomian gland dysfunction; IPL: intense pulsed light; RCT: randomized controlled trial; TMH: tear meniscus height; TBUT: tear breakup time; OSDI: ocular surface disease index: LLG: lipid layer grading; OAHFA: o-acyl-ω-hydroxy-fatty acids; LpPE: lyso-plasmalogen phophatidylethanolamine; MGS: meibomian gland secretion; MGYLS: meibomian gland yielding liquid secretion; SPEED: standardized patient evaluation of eye dryness: LG: lissamine green; MGX: meibomian gland expression: VAS: visual analogue scale; CFS: corneal fluorescence staining; IL-17A: interleukin 17A; IL-6: interleukin 6; PGE2: prostaglandin E2: PRK: photorefractive keratectomy; MM: mechanical microkeratomes; FL: femtosecond laser; MGALD: meibomian gland acinar longest diameter; MGAUD: meibomian gland acinar unit density; FML: fluorometholone; HMGEC: human meibomian gland epithelial cell; MMP: matrix metalloproteinase; SFA: semifluorinated alkane

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The authors agree to make all materials, data and associated protocols promptly available to readers without undue qualifications in material transfer agreements.

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