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REVIEW

Emerging treatment options for meibomian gland dysfunction

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Abstract: Meibomian gland dysfunction (MGD) is one of the most common diseases observed in clinics; it influences a great number of people, and is the leading cause of evaporative dry eye. Given the increased recognition of the importance of MGD, a great amount of attention has been paid to therapies targeting this condition. The traditional treatments of MGD consist of warm compresses and lid hygiene for removing an obstructed meibum, as well as antibiotics and anti-inflammatory agents to improve the quality of the meibum. However, each of these treatments has a different shortcoming and the treatment of MGD remains challenging. Despite the numerous possible treatment options for MGD, it is still difficult to obtain complete relief of signs and symptoms. This review focuses on current emerging treatment options for MGD including intraductal meibomian gland probing, emulsion eye drops containing lipids, the LipiFlow® thermal pulsation system, N-acetyl-cysteine, azithromycin, oral supplementation with omega-3 essential fatty acids, and cyclosporine A.

Keywords: meibomian gland dysfunction, dry eye, emerging treatment

Introduction

Meibomian gland dysfunction (MGD) is a common disease that is often overlooked in clinic; the disease may involve inflammation, hypersecretion, and abnormal excreta of the meibomian glands.[1,2]

It is documented that MGD is the leading cause of evaporative dry eye,[3] and it is also frequently found in aqueous-deficient dry eye.[4]

The goal of all the treatments of MGD is to improve the flow of meibomian gland secretions, thus leading to normal tear film stability. The traditional treatments of MGD consist of warm compresses and improved eyelid hygiene for removing obstructed meibum, as well as antibiotics and anti-inflammatory agents aiming at improving the quality of the meibum. However, these treatments may be frustrating to patients and ophthalmologists. Warm compresses and lid hygiene are shown to be effective for MGD for a long time;[5] however, heat and massage of the eyelid could not cure the disease completely, especially in advanced forms of the condition. Massage of the eyelid provides only partial and temporary relief of obstruction of the meibomian glands and this could be painful. Conventional approaches for warm compresses apply heat to the outer surface of the eyelid, therefore the heat is frequently of limited effectiveness. The use of topical antibiotics and corticosteroids to suppress the bacterial colonization and inflammation of the eyelid margin associated with MGD has been shown to be effective in the relief of symptoms and the signs of MGD.[6] However, the success of this treatment may have nothing to do with the changed meibum. Oral antibiotics, particularly

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the tetracyclines (including doxycycline, tetracycline, and minocycline) are used to suppress bacterial colonization and reduce inflammation of the lid margin, as well as suppress some of the lipase breakdown of the meibum leading to decreased free fatty acids and diglycerides. However, drug intolerance and prolonged therapy have limited the clinical application of oral antibiotics.[7]

MGD is one of the most common disorders encountered with ophthalmologists.[4] Despite the numerous possible treatment options for MGD, it is still difficult to obtain the complete relief of symptoms and signs. Patients with severe MGD often complain that their quality of life is significantly adversely affected by MGD symptoms. It is the purpose of this review to present the emerging treatment options for MGD, which serve to help alleviate the symptoms and signs of MGD.

Intraductal meibomian gland probing

Intraductal meibomian gland probing proposed by Maskin[8] is a relatively nontraumatic method to relieve the symptoms of MGD, which could mechanically open and dilate the natural orifices and ducts of the meibomian glands to remove abnormal meibum secretions.

After topical anesthesia, patients were treated with the 2 mm probe initially at the slit lamp. The lid chosen to be probed was slid to each side by tension, and then the probe was passed through the orifices of the meibomian glands, which were perpendicular to the lid margin. It is advised that the angle or placement of the probe is adjusted during the procedure for penetration. Then, the 4 mm probe was subsequently used for deeper probing.[9]

Maskin[8] reported that most cases (24 of 25 cases; 96%) had immediate post probing relief of symptoms, and all the patients had relief by 4weeks after probing. Lasting rapid relief of MGD symptoms, which may be due to the reestablishment of orifice and central ducts by probing, has been found. In addition, orifice penetration and intraductal probing could remove abnormal meibum to relieve the lid congestion and inflammation.

As a new optional treatment for MGD, intraductal meibomian gland probing may also have some disadvantages, such as variable discomfort and orifice hemorrhage during the procedure. More severe discomfort was noted in patients with greater lid tenderness and chronic inflammation, which resolved with the additional application of 4% topical lidocaine to the lid margin. Orifice hemorrhage resolved without treatment.[8,9]

Emulsion eye drops containing lipids

In evaporative dry eye, the inflammatory process is related to the meibomian glands, leading to tear film changes.[10] Therefore, some emulsion eye drops containing lipids have been introduced as optional treatments for MGD.

A kind of metastable oil-in-water emulsion drop containing lipids was documented to dissociate the tear film.[11] It was noticed that lipid-containing metastable oil-in-water emulsion may be beneficial to the lipid layer thickness.[12] The use of emulsion eye drops containing lipids also has a measurable beneficial effect on tear stability and may bring relief of symptoms.[13,14] More recently, one study about a kind of cationic emulsion eye drop has reported that these drops may improve tear spreading, facilitate lipid layer replenishment, and decrease tear evaporation due to better penetration through the membranes, which results in enhanced bioavailability.[15]

LipiFlow® thermal pulsation system

MGD often involves obstruction of the meibomian gland. It is recognized that relieving meibomian gland obstruction is vital to successful treatment of obstructive MGD.[16–21] This suggests that it is not sufficient to treat lid margin and ocular surface inflammation and/or infection alone, without clearance of the obstruction. The common traditional approaches for clearance of obstruction involve warm compresses, self-administered lid massage, and/or more aggressive, practitioner-administered manual expression.[22] Unfortunately, warm compresses and self-administered lid massage are usually ineffective.[23] As a time consuming and labor-intensive therapy, warm compress therapy has many compliance issues, leading to lower efficacy. Besides, conventional approaches for warm compresses that apply heat to the outer surface of the eyelid results in low efficacy, as the heat has to penetrate the layers of eyelid skin, muscle, and the insulating tarsal plate prior to reaching the meibomian glands and their contents.[24] Despite the limitations of warm compress therapy, this treatment could result in improvement in meibomian expression.[25]

LipiFlow® treatment (TearScience®, Morrisville, NC, USA), which could apply heat to both the upper and lower palpebral conjunctival surfaces in addition to pressure to the external eyelid at the same time to express the meibomian gland, has been shown to successfully address the limitations of current treatments in clearing meibomian gland obstruction.[26] The automated treatment device has two main components: a lid warmer and an eye cup.[18] The lid warmer resembles a large scleral lens designed to vault the cornea

and heat the internal surface of the upper and lower eyelids at the same time. The eye cup contains an inflatable air bladder that massages the eyelids to express the meibomian glands in the upper and lower eyelids simultaneously. As a single 12-minute treatment, it is much more convenient than conventional warm compress therapy, which usually takes more time to complete. As a temperature- and pressure-controlled device, this novel treatment for obstructive meibomian gland dysfunction has combined the benefits of both heat therapy and physical expression.[27]

This treatment is novel, as heat and pressure are simultaneously applied directly to the eyelids to influence the meibomian gland. Heat transfer is minimized by applying heat directly to the inner surface of eyelids, which obviously increases its efficacy. Expression pressure and heat to the eyelids and meibomian glands are applied simultaneously during the treatment procedure, thereby expressing the meibomian glands during heating, leading to minimal discomfort. Besides, no expression pressure is transferred directly onto the eyeball.

LipiFlow® may also have some adverse events including eyelid pain (three eyes of 138 eyes), moderate conjunctival vascular injection (one eye of 138 eyes), ocular burning symptoms (two eyes of 140 eyes), which were reported as being resolved in 4 weeks without treatment. Immediate post treatment increased corneal staining was observed in the study, which could be improved at a subsequent follow-up visit. In addition, a statistically significant mean decrease in corneal staining from baseline to 2 weeks and 4 weeks was observed.[26]

As a novel treatment heat and pressure can be applied to the eyelid tissue simultaneously to affect the meibomian glands, LipiFlow® has demonstrated obvious safety and effectiveness in treating MGD. A recent study had documented that the LipiFlow® thermal pulsation system gave rise to significant improvement in both signs (based on tear break-up time, corneal fluorescein staining, and meibomian gland secretion scores) and symptoms (based on Ocular Surface Disease Index and standard patient evaluation of eye dryness scores).[17,27]

N-acetyl-cysteine

N-acetyl-cysteine (NAC) is an acetylated derivative of the natural amino acid, l-cysteine. It has mucolytic, anti-collagenolytic, and antioxidant properties. It also modulates the cellular redox status to influence several inflammatory pathways, leading to decreased nuclear factor-kappa B activity, which regulates several proinflammatory genes that regulate the inflammation pathways.[28,29]

The role of inflammation in the etiology of MGD is uncertain since inflammation may be present or absent in MGD.[3] Classic anti-inflammatory treatments that are used in combination with hygiene, warm compresses, and topical antibiotics are often performed for a short time in MGD with posterior eyelid margin inflammation.[30] Topical anti-inflammatory therapy with corticosteroids has shown to be effective in the treatment of MGD by suppressing migration of inflammatory cells and inhibiting the release of several cytokines.[31,32] However, corticosteroids might induce some complications such as cataracts, steroid-induced ocular hypertension, and opportunistic superinfections.[33] Thanks to its mucolytic property, topical 5% NAC has shown to be effective in treating dry eyes.[34] Its systemic and topical administrations have been investigated to determine the treatment's possible role in the management of MGD.[35] Topical 5% NAC therapy has been shown to be effective and well tolerated in the management of the signs and symptoms of MGD.[35] NAC treatment gave rise to significant improvements in tear film break-up time and Schirmer scores, as well as in the symptoms of ocular burning, itching, and intermittent filmy or blurred vision. It is noted that topical administration of NAC is likely as effective as betamethasone–sulfacetamide sodium, a topical steroid–antibiotic combination therapy in treating MGD.[36]

Topical azithromycin

Topical azithromycin has been shown to be a potentially effective and well tolerated treatment for meibomian gland dysfunction in recent studies. Topical azithromycin therapy could lead to clinical control or relief of symptoms and signs of MGD, as well as improvement in lipid behaviors of meibomian gland secretion.[37] It has also been noted that topical azithromycin management could lead to improvement in meibomian gland orifice plugging.[38]

Since the underlying mechanism of MGD is not completely understood, the role of bacteria in the pathophysiology of MGD is still controversial. However, some clinical findings in MGD may be related to the bacterial colonization.[39] Azithromycin is a broad-spectrum macrolide antibiotic, which has great treatment advantages such as high efficacy spectrum, favorable tissue penetration to the eyelid, good pharmacokinetics for daily dose, and a sustained delivery mechanism system, which makes topical azithromycin favorable for the antibacterial treatment of MGD.[40] Furthermore, azithromycin has potent ocular anti-inflammatory properties. The mechanism for its potential anti-inflammatory activity

is not completely understood. It has been demonstrated that azithromycin could block the activation of nuclear factor-kappa B, leading to decreased inflammatory cytokine levels such as interleukin-6 and interleukin-8.[41] Besides, azithromycin has been shown to suppress the production of proinflammatory mediators by inhibiting human corneal epithelial cells.[42] This proven anti-inflammatory activity of azithromycin further confirms that it is rational to treat MGD with topical azithromycin. In general, this antibacterial and anti-inflammatory effect may contribute to the improvement of the signs of MGD, such as redness and swelling of the lid margin.[37]

Meibomian gland secretion in normal people mainly consists of neutral sterols and wax esters (which are nonpolar lipids), with lesser amounts of polar lipids (free fatty acids), diesters, triesters, triglycerides, and free sterols.[43] Many changes in meibomian lipid composition, such as increased monounsaturated fatty acids[44] and different fatty acid composition,[45] have been documented to contribute to abnormal lipid behaviors and clinical symptoms. Abnormal meibum has a higher melting temperature, which results in thicker meibum, ductal plugging, stagnation, and pouting of the meibomian gland orifices.[46] Topical azithromycin treatment could suppress the tissue or bacterial lipases, which are thought to degrade the lipid and successfully bring about improvement in lipid ordering, contributing to differences in the phase transition temperature of meibum.[37] Due to this change, relief in meibomian gland orifice plugging and improvement in the lipid properties of the meibomian gland secretion can be demonstrated.[37]

Oral supplementation with omega-3 essential fatty acids

Various studies have demonstrated that the meibum in MGD is often abnormal, and it seems feasible that the meibum lipid composition can be influenced by changing dietary lipid intake to manage MGD. Therefore, it is recommended that oral supplementation with omega-3 essential fatty acids could be evaluated as a possible therapeutic option for patients with MGD.[47] Omega-3 essential fatty acid supplements have been reported to improve some clinical symptoms and signs of MGD, as well as changes in meibum content.[48]

There are two hypotheses that may clarify how supplementation with omega-3 essential fatty acids can alleviate MGD. It has been demonstrated that the breakdown of omega-3 essential fatty acids may lead to suppression of inflammation, whereas the breakdown of omega-6 essential fatty acids produces molecules promoting inflammation.[49,50] Omega-3 and omega-6 fatty acids compete for the same enzymes in order to influence the inflammatory pathway, which are mediated by the anti-inflammatory agents aspirin and COX-2 inhibitors. So the first hypothesis is that metabolism of omega-3 essential fatty acids could inhibit the metabolism of omega-6 essential fatty acids, thus leading to decreased inflammation of the eyelid.

The second hypothesis is that supplementation with omega-3 essential fatty acids may influence fatty acid composition and, subsequently, the lipid properties of meibum.[48] This change may contribute to promoting tear stabilization and suppressing inflammation to avoid blocked meibomian gland ducts and stagnated meibum.[48]

Cyclosporine A

It is suggested that cyclosporine A may be valuable for the treatment of MGD.[51,52] More recently, the efficacy of cyclosporine 0.05% eye drops was conducted on a group of subjects with MGD.[51] The result was quite encouraging, as it demonstrated that cyclosporine A could decrease meibomian gland inclusions to ameliorate the objective signs of MGD. However, the researchers did not find obvious improvement in symptoms. Conversely, Rubin and Rao[52] noted an improvement in both the symptoms and signs of MGD. This contradiction may due to the complex mechanisms involved in how cyclosporine A treats MGD. Moreover, the numbers of subjects in these studies were relatively small, which may lead to some unavoidable contradictions when establishing the role of cyclosporine A.

Cyclosporine A is a highly specific immunomodulator, which has been used topically for the management of postkeratoplasty allograft rejection and corticosteroid-induced glaucoma,[53] herpes simplex virus stromal keratitis,[54] vernal keratoconjunctivitis,[55] dry eye syndrome,[56] and so on by primarily affecting T-lymphocytes. Cyclosporine A has many advantages for ocular use. First of all, it seldom influences intraocular pressure.[51] Secondly, compared to corticosteroids, cyclosporine A produce less inhibition of the phagocytic system, which ensures normal antimicrobial function of the immune system.[57] Moreover, cyclosporine A has demonstrated that it does not suppress wound healing or have an influence on the lens, which suggests that cyclosporine A is safe for ocular use.[56,57]

There may be two mechanisms through which cyclosporine A manages MGD. First, cyclosporine A, which is a highly specific immunomodulator affecting T-lymphocytes, may decrease the inflammation of the meibomian glands, leading to relief in the symptoms of MGD and in meibomian gland

plugging.[51] Second, cyclosporine A has been shown to ameliorate the ocular symptoms and signs of dry eyes by modulating the immune cell populations of both the conjunctiva and the lacrimal gland.[56] It has been noted that MGD usually coexists with dry eye, so alleviating dry eye may play a role in the treatment of MGD when using cyclosporine A.

Conclusion

MGD is one of the most common disorders encountered by ophthalmologists, and it may involve inflammation, hypersecretion, and abnormal excreta of the meibomian glands. Given increased recognition of the importance of MGD, great attention has been paid to the therapy of MGD. Although there are a number of traditional treatment options, such as warm compresses and lid hygiene for alleviating an obstructed meibum, and antibiotics and anti-inflammatory agents used to improve the quality of meibum; unfortunately, the treatment of MGD remains challenging. These emerging treatment options for MGD may play an important role in alleviating the clinical symptoms and signs of this disease.

Intraductal meibomian gland probing could produce lasting rapid relief of MGD symptoms, which may be due to the reestablishment of the orifice and central duct, as well as a result of removal of abnormal meibum. Some emulsion eye drops containing lipids may be viewed as optional treatments for MGD. As a novel treatment, LipiFlow® applies heat and pressure to the eyelid tissue simultaneously to affect the meibomian glands. In addition, the LipiFlow® thermal pulsation system appears to be safe and effective in treating MGD. Systemic and topical administrations of NAC have been investigated for their possible role in the management of MGD. Topical azithromycin therapy could lead to clinical control or relief in the symptoms and signs of MGD, and it can also result in improvement in the lipid behaviors of meibomian gland secretion; thus, it could be a potentially effective and well tolerated treatment for MGD. Nutritional supplementation with omega-3 essential fatty acids could also be an alternative treatment for MGD. Finally, cyclosporine A may be valuable for the treatment of MGD, although the results are somewhat contradictory in different studies.

Disclosure

The authors report no conflicts of interest in this work.

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