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# Assessment of efficacy of topical azithromycin 1.5 per cent ophthalmic solution for the treatment of meibomian gland dysfunction

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**Background:** The aim was to evaluate the clinical efficacy of topical azithromycin 1.5 per cent ophthalmic solution in treatment of the clinical signs and symptoms associated with meibomian gland dysfunction (MGD).
**Methods:** In this retrospective study, 35 patients with MGD were treated with topical azithromycin 1.5 per cent ophthalmic solution for 30 days. Topical azithromycin 1.5 per cent ophthalmic solution was prescribed twice daily for two days and then once daily for a total of 30 days. Daily lid hygiene with dilute baby shampoo was instructed for all patients. Patient total symptom score, meibomian gland grading score, Schirmer score with anaesthetic, tear film break-up time (TFBUT) and corneal fluorescein staining score were evaluated at baseline and after one and three months.
**Results:** Patient total symptom score, meibomian gland grading score, Schirmer score with anaesthetic, TFBUT and corneal staining score reduced significantly from the baseline to the first month ($p < 0.05$, for each); however, at the third month, there was no significant difference from baseline in the meibomian gland grading score, Schirmer score with anaesthetic, TFBUT and corneal fluorescein staining score ($p > 0.05$, for each).
**Conclusion:** These results demonstrate that topical azithromycin 1.5 per cent ophthalmic solution appears effective in the short-term treatment of the clinical signs and symptoms associated with MGD.

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Blepharitis is a common ocular condition that can have a significant impact on quality of life. The two primary distinctions in blepharitis are anterior versus posterior blepharitis. Anterior blepharitis affects the anterior lamella of the eyelid and the eyelashes, whereas posterior blepharitis affects the posterior lamella of the eyelid and involves inflammation of the meibomian glands.

Meibomian gland dysfunction (MGD) is often used synonymously with posterior blepharitis; however, posterior blepharitis is a term describing inflammatory conditions of the posterior lid margin, which includes MGD and other causes, including conjunctivitis and acne rosacea. According to the International Workshop on MGD, MGD is a chronic, diffuse abnormality of the meibomian gland, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion. This may result in alteration of the tear film, symptoms of ocular irritation, clinically apparent inflammation and ocular surface disease.[1] With MGD, the meibomian gland orifices can become obstructed. Lipid composition of the meibum alters bacterial colonisation and inflammatory mediators are released following the obstruction of the meibomian glands. The inflammatory mediators are formed and released from lipolytic enzymes that are produced from bacteria. This results in highly irritating free fatty acids, which play an important role in the tear film. All of these changes contribute to further ductal obstruction, more inflammation and bacterial colonisation.[1–3] Eventually, all of these changes damage the ocular surface, resulting in patient symptoms.

Treatment of MGD varies greatly among eye-care professionals. There is no approved standard treatment regimen. Warm compress, lid hygiene, antibiotics, steroids, artificial lubricants, omega-3 essential fatty acids, intraductal meibomian gland probing, N-acetyl-cysteine (NAC) and cyclosporine A are suggested treatment options. Despite the several treatment options, it is still difficult to obtain the complete relief of symptoms and signs.

Azithromycin is a broad-spectrum second generation macrolide antibiotic with low-level anti-inflammatory properties that penetrate the conjunctiva and eyelids. The mechanism for the potential ocular anti-inflammatory activity of azithromycin is not completely understood, but the effect of azithromycin on blepharitis is thought to be dual: both antibacterial and anti-inflammatory.[4–7]

Recent reports have explored the efficacy of topical azithromycin ophthalmic solution in the treatment of posterior blepharitis.[8–14] Regarding the anti-inflammatory and antibacterial effect of azithromycin, it is valuable to evaluate its efficacy in the treatment of MGD. Therefore, in the present study, we performed a retrospective review of patients receiving topical azithromycin 1.5 per cent ophthalmic solution for MGD to determine its efficacy on relieving patient symptoms and signs.

| Symptom score | Description of score |
|---|---|
| 0 | None |
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |

*Patients' subjective symptoms, including itching, lacrimation and foreign body sensation, were graded on a scale ranging from 0 to 3. The sum of these three symptoms were recorded as total symptom score.

**Table 1. Patients' subjective symptoms***

## METHODS

This is a retrospective study. The medical records of all patients seen in the authors' clinical practice at Medipol University Hospital and who were treated with topical azithromycin 1.5 per cent ophthalmic solution for symptomatic MGD were reviewed. Patients with clinically apparent meibomian gland inflammation accompanied by symptoms of ocular irritation were considered as symptomatic MGD. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee.

### Data collection

Medical records of 35 patients diagnosed with symptomatic MGD who had no treatment before and had three months of follow-up were included. Patients with any of the following were excluded: patients younger than 18 years of age, any existing ocular inflammation, lid structural abnormalities, history of ocular trauma, intraocular inflammation or ocular surgery within the previous year. The following data were obtained from the records: patient demographic characteristics, medical and medication history, patient's subjective symptoms, visual acuity (VA) on Snellen chart, meibomian gland grading score, Schirmer score with anaesthetic, measurement of tear film break-up time (TFBUT), sodium fluorescein corneal staining score and adverse events.

At baseline and at the follow-up visit, patients were asked to fill out a questionnaire to grade their subjective symptoms, including: itching, lacrimation and foreign body sensation, on a scale ranging from zero to 3 (zero = none, 1 = mild, 2 = moderate to 3 = severe). The sum of these three symptoms was recorded as the patient's total symptom score (Table 1). The meibomian glands and their secretions were graded and recorded on a scale of zero to 4[12] (Table 2). The Schirmer test was performed after the instillation of a topical anaesthetic (proparacaine hydrochloride 0.5 per cent, Alcaine, Alcon Laboratories Inc, Puurs, Belgium). Sterilised strips of filter paper were placed in the inferior fornix, between the lateral third and the middle third of the eyelid, for five minutes with the patient looking straight ahead. Schirmer score was recorded in millimetres for each eye. TFBUT was measured using sterile sodium fluorescein strips, which were placed in each eye and the patient was asked to blink several times to ensure the fluorescein was distributed over the cornea. While looking straight ahead, the tear film was evaluated using cobalt blue filter during biomicroscopy. The TFBUT is defined as the interval between the last complete blink and the first appearance of a dry spot or disruption in the tear film. The appearance of the first tear break-up was recorded in seconds. The test was repeated three times and the average of the three consecutive measurements was then recorded for each eye as the TFBUT. Corneal fluorescein staining was conducted five minutes after the TFBUT measurements. Five areas of the cornea, that is the centre, nasal, temporal, superior and inferior regions, were evaluated with each area graded on a scale of zero to 3[15] (Figure 1). The type of staining was graded using the following grading scale: zero = normal–no staining, 1 = mild–superficial stippling micro-punctate staining, 2 = moderate–macropunctate staining with some coalescent areas, 3 = severe–numerous coalescent macropunctate areas and/or patches. The scores of the five regions were summed to obtain the total area of staining score for each eye.

On completion of the baseline visit, topical azithromycin 1.5 per cent ophthalmic solution (Azyter, Laboratoires Thea, Clermont-Ferrand, France) was prescribed twice a day for two days and then only before bed for a total of 30 days. Daily lid hygiene with dilute baby shampoo was instructed for all patients. Patients were re-evaluated on the same basis after one and three months.

| Meibomian gland score | Description of secretions | Digital pressure to express |
|---|---|---|
| 0 | Clear | Easily expressed |
| 1 | Cloudy fluid | Easily expressed |
| 2 | Cloudy fluid | Mild pressure |
| 3 | Cloudy, particulate fluid | Moderate pressure |
| 4 | Thick, toothpaste-like secretions | Hard pressure |

**Table 2. Meibomian gland grading scale**

### Statistical analysis

Statistical analyses were performed using SPSS 16.0 Software (SPSS Inc., Chicago, Illinois, USA). The data obtained from the worse eye of each patient were included in statistical analysis. Prior to the statistical application, the normality of data was confirmed using Shapiro–Wilk test. Data are presented as mean and standard deviation (SD). One-way analysis of variance for repeated measures was carried out for the mean Schirmer test score with anaesthetic and chi-square test was used to compare the following: mean patient total symptom score, mean meibomian gland grading score, mean TFBUT and mean corneal fluorescein staining score at different time intervals. The statistical significance level was set at $p < 0.05$.

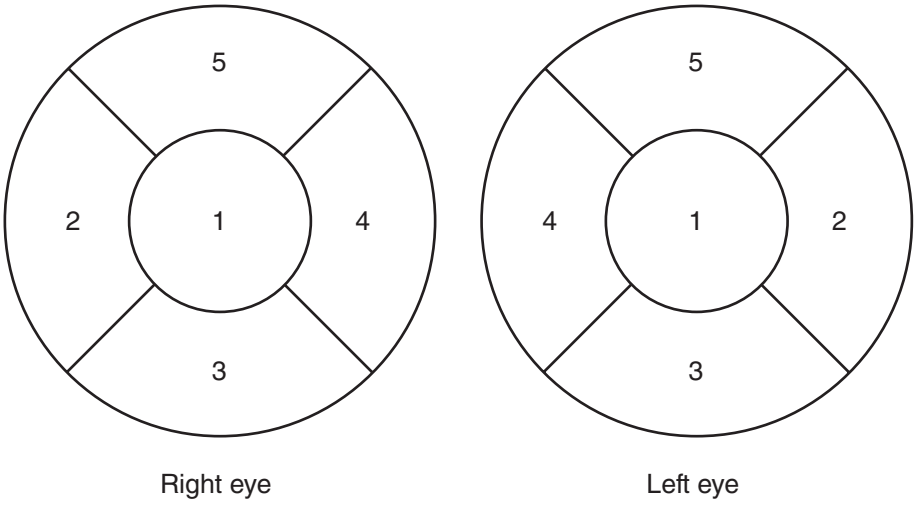


**Figure 1. Diagram of the five areas assessed for corneal staining. Each area was graded on a scale** of zero to 3 at baseline and after one and three months. **The type of staining was graded using the following grading scale: zero = normal–no staining, 1 = mild–superficial stippling micro-punctate staining, 2 = moderate–macropunctate staining with some coalescent areas, 3 = severe–numerous coalescent macropunctate areas and/or patches. The scores of the five regions were summed to obtain the total area of staining score for each eye.**

## RESULTS

Thirty-five patients with MGD were qualified based on inclusion and exclusion criteria. There were 18 male patients (51.4 per cent). Patient ages varied from 22 to 48 years with a mean of 40.5 ± 13.2 years. The mean VA was 6/6 for both eyes. The follow-up was three months.

Treatment responses are presented on Table 3. Subjective symptoms were analysed on patient total symptom scores. The mean total symptom score including itching, lacrimation and foreign body sensation decreased significantly from baseline to the first and third months (p = 0.022 and p = 0.030, respectively). The mean meibomian gland grading score reduced significantly from the baseline to the first month (p = 0.032); however, no significant difference was found in the reduction of meibomian gland score at the third month, when compared with the score at baseline (p = 0.61). The mean Schirmer score with anaesthetic improved significantly from the baseline to first month (p = 0.04) but there was no significant difference in the mean Schirmer score with anaesthetic from baseline to the third month (p = 0.06). The mean TFBUT and the mean corneal staining score demonstrated statistically significant improvements at the first month (p = 0.04 and p = 0.04, respectively); however, there was no statistically difference at the third month, when compared with the scores at baseline (p = 0.07 and p = 0.05, respectively).

| Variables | Mean at baseline | Mean at first month | Mean at third month |
|---|---|---|---|
| Total symptom score | 5.1 ± 1.4 | 3.3 ± 0.8 | 3.0 ± 0.8 |
| MG grading score | 2.2 ± 0.8 | 1.5 ± 0.6 | 2.0 ± 0.7 |
| TFBUT (seconds) | 8.0 ± 2.4 | 10.1 ± 2.1 | 9.0 ± 1.8 |
| Corneal staining score | 3.4 ± 1.4 | 2.1 ± 1.6 | 3.0 ± 1.2 |
| Schirmer score (mm) | 9.9 ± 3.6 | 12.3 ± 2.3 | 10.0 ± 1.8 |

MG: meibomian gland, mm: millimetre, TFBUT: tear film break-up time.

**Table 3. Treatment response**

### Adverse effect

Mild sensations of ocular stinging upon instillation were reported in five patients and moderate ocular redness after instillation in four other cases. All patients continued the treatment regimen. No systemic adverse effect was recorded. VA remained unchanged during the follow-up.

## DISCUSSION

In our study, significant improvements were achieved one month after topical azithromycin 1.5 per cent ophthalmic solution in all clinical signs and symptoms associated with MGD; however, the improvements in clinical signs did not persist during the three-month follow-up. Additionally, topical azithromycin 1.5 per cent ophthalmic solution was well tolerated and we did not record any adverse effect.

The underlying mechanism for MGD is complex, both inflammation and bacterial colonisation are thought to contribute to the development of the disease.[16] The azithromycin molecule is lipophilic, it can penetrate into conjunctival cells easily. Topical formulation of the azithromycin molecule has been found in conjunctival biopsies several days after the last drop.[17–22] The oral formulation of azithromycin is thought to suppress the production of pro-inflammatory mediators such as cytokines, chemokines and matrix metalloproteinases.[7,23,24] Li and colleagues[25] demonstrated that azithromycin suppresses production of pro-inflammatory mediators by blocking nuclear factor kappa B activation in human corneal epithelial cells. The effect of azithromycin on blepharitis is thought to be dual: both antibacterial and anti-inflammatory effects may contribute to the improvement of the signs of MGD.

Several studies have explored the efficacy of azithromycin in posterior blepharitis. In a study by Luchs,[9] 21 patients with posterior blepharitis were treated with topical azithromycin ophthalmic solution one per cent plus warm compresses twice a day for two days, then once daily for 12 days or warm compresses alone. At the end of treatment, patients using azithromycin demonstrated significantly greater improvements from baseline in meibomian gland

plugging, redness of the eyelid margins and quality of meibomian gland secretions compared to the patients using warm compresses alone (all comparisons, $p < 0.001$). Evaluations of lid debris and lid swelling showed greater numerical improvement in the azithromycin group but did not achieve statistical significance. Similarly in a study by Haque and colleagues,[10] patients with moderate-to-severe anterior and posterior blepharitis were treated with azithromycin ophthalmic solution one per cent twice a day for two days, then once daily for a total treatment duration of 28 days. At the end of treatment, significant ($p < 0.001$) decreases from baseline were noted in all subject-rated symptoms (eyelid itching, foreign body sensation/sandiness/grittiness, ocular dryness, ocular burning/pain and swollen/heavy eyelids). All improvements persisted for four weeks post-treatment. Additionally, eyelid margin culture showed significant decreases in the most commonly isolated organisms, including coagulase-negative staphylococci ($p = 0.037$) and *Corynebacterium xerosis* bacteria ($p < 0.001$). In another study by Foulks and colleagues,[11] the patients were treated with azithromycin ophthalmic solution one per cent one drop twice a day for two days, then once daily for a total treatment duration of four weeks. The authors achieved significant improvements in subject-rated symptoms from baseline ($p < 0.001$), as well as improvements in signs of eyelid margin disease. In an open-label study, Opitz and Tyler[12] treated 33 patients with posterior blepharitis with azithromycin ophthalmic solution one per cent twice a day for two days, then every evening for a total of 30 days. There were significant improvements from baseline in TFBUT, Schirmer test value and reductions in ocular surface staining, as well as improvements in lid margin scores, patient-rated symptom scores and ocular surface disease index scores. A recent study by Fadlallah and colleagues[13] found that treatment with azithromycin ophthalmic solution 1.5 per cent is an effective treatment option in chronic blepharitis. The authors demonstrated that twice daily for three days then once daily for a total of 30 days was more effective in improving eyelid redness/swelling and meibomian gland secretions than treatment administered twice a day for three days with moderate-to-severe chronic blepharitis.

Based on our study, significant improvements were achieved one month after topical azithromycin 1.5 per cent ophthalmic solution in all assessed parameters, including mean patient total symptom score, mean meibomian gland grading score, Schirmer test with anaesthetic, mean TFBUT and mean corneal fluorescein staining score. Our results are consistent with previously reported studies.[9–13] We suppose that these improvements may be related to the anti-inflammatory effect of azithromycin. By regulating the meibomian gland secretion, azitromycin may improve the tear film quality. Additionally, suppression of the inflammation may have caused more aqueous formation in the accessory lacrimal glands, which may explain the improvement in the corneal fluorescein staining score and Schirmer score with anaesthetic. Although we did not evaluate the microbiological analysis of the eyelid margin, the improvement could be related to the antibacterial effect of the molecule as demonstrated by a previous study.[10] Bacterial infection is probably not the primary pathophysiologic process in MGD but some clinical findings seen in MGD may be related to the effects of the bacteria. It is known that bacteria may have both direct and indirect effects on the ocular surface and on meibomian gland function. These include direct effects on the production of toxic bacterial products (including lipases) and indirect effects on the ocular surface.[26] One advantage of our study over former studies is the longer follow-up time.[9–12] In our study, significant improvements in the objective parameters were achieved at the first month but these improvements did not persist during the three-month follow-up. This finding is different from a previous study by Fadlallah and colleagues.[13] The authors demonstrated that a one month treatment with 1.5 per cent azithromycin (twice daily for three days then once at bedtime for the rest of the month) resulted in a pronounced improvement with no significant relapse until three months. Their study population included patients with anterior and posterior blepharitis. Differences in study populations may account for the different outcomes between our study and that of Fadlallah and colleagues.[13] Additionally, in our study, the improvement in the mean patient total symptom score was the only ongoing effect during the three-month follow-up. We think that this was probably related to the lid hygiene instructed during the follow-up.

The strengths of this study included that both subjective and objective parameters were assessed. On the other hand, there were some limitations. The limitations of this study were its retrospective nature, lack of control group and maybe the relatively small number of patients. Additionally, a microbiological analysis of eyelid margin was not performed.

In conclusion, topical azithromycin 1.5 per cent ophthalmic solution appears effective in the treatment of MGD but the long-term effect seems to be limited. Pulse therapy (using oral or topical azithromycin) may be necessary. Further prospective studies with long follow-up periods and different application routes would be justified to better assess the efficacy of topical azithromycin 1.5 per cent ophthalmic solution in MGD.

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