

5-Day Oral Azithromycin Versus 1-Month Continuous Topical Azithromycin Ointment in Meibomian Gland Dysfunction: A Randomised Double-Masked Open-Label Clinical Trial

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Abstract

Background/aims: To assess the efficacy of 5-day oral azithromycin compared with 1-month continuous topical azithromycin ointment in patients with Meibomian gland dysfunction (MGD) who had failed to respond to previous conservative management. **Methods:** 100 patients (>40 years old) with MGD were randomly assigned to receive either oral 5-day azithromycin (500mg/day) or 1-month continuous topical azithromycin (1 % w/w preservative free with sterile base). They also continued eyelid warming/cleaning, lid massage and artificial tears. A score consisting five symptoms and seven signs of MGD was recorded prior to the treatment and at 1 week, and 15 days and 1 month after treatment. Total score was recorded afterwards which was sum of both scores (symptom score and sign score). The results were statistically analyzed and overall clinical improvement was compared in the two groups. **Results:** Symptoms and signs showed significant improvement in both groups. The group consisting of 1-month continuous topical azithromycin showed a significantly better clinical response ($p=0.008$). This group also didn't show any systemic side effects as compared to the group consisting of patients on oral azithromycin therapy. **Conclusions:** Although both oral and topical azithromycin improved the symptoms of MGD, continuous topical azithromycin is recommended for its better effect on improving the signs, better overall clinical response and nil systemic side effects as compared to oral azithromycin.

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I. Introduction

The secretions of meibomian glands (meibum) consists of a complex mixture of various polar and nonpolar lipids. The meibum spreads onto the tear film and functions to slow evaporation of the aqueous component, preserve a clear optical surface, and form a barrier to protect the eye from microbial agents and organic matter such as dust and pollen.^[1]

Meibomian gland dysfunction is caused primarily by terminal duct obstruction with thickened opaque meibum containing keratinized cell material. The obstruction, in turn, is due to hyperkeratinization of the ductal epithelium and increased meibum viscosity. The obstructive process is influenced by endogenous factors, such as age, sex, and hormonal disturbances, as well as by exogenous factors such as topical medication. The obstruction may lead to intraglandular cystic dilatation, meibocyte atrophy, gland dropout, and low secretion effects that do not typically involve inflammatory cells. The outcome of MGD is a reduced availability of meibum to the lid margin and tears film. The consequence of insufficient lipids may be increased evaporation, hyperosmolarity and instability of the tear film, increased bacterial growth on the lid margin, evaporative dry eye and ocular surface inflammation and damage.^[1]

Meibomian gland dysfunction (MGD) has been defined by the International workshop on MGD in the year 2011 as "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."^[1]

While conservative treatment methods like eyelid warming, massage, and cleansing combined with artificial tears are considered first-line therapy;^[2,3] severe and refractory cases require a more aggressive treatment.

In severe and refractory cases of MGD treatment with topical as well as systemic antibiotics with anti-inflammatory properties are proposed and tetracycline are the antibiotics with the ability to reduce the inflammation and inhibit matrix metalloproteinase.^[4,5,6]

Some studies have shown the efficacy of azithromycin in reducing the inflammation in MGD. It inhibits the pro-inflammatory cytokines and is quite effective against gram-negative bacteria. Azithromycin both topical as well as oral have shown to improve signs as well as symptoms of MGD.^[6,7,8]

Although many studies and research trials have shown the efficacy of both oral azithromycin as well as doxycycline in the treatment of MGD, to the best of our knowledge there has been no study comparing the efficacy of oral azithromycin and topical azithromycin in the treatment of MGD. Therefore, this clinical trial was designed to evaluate the efficacy (symptoms and sign scores) of oral azithromycin compared to topical azithromycin in patients of Meibomian gland dysfunction (MGD) who were not responding to the conservative treatment methods like eyelid warming, massage, cleaning and artificial tears.

II. Materials and Methods

This present study with a cross-over design has been done at a tertiary care center of Ophthalmology department at Rajindra Hospital, Patiala OPD between January 2019 to October 2019. In order to make up for the loss of patients during follow-up, 64 patients in each group were recruited.

At the beginning of the study, five patients per block, were assigned to one treatment or another by writing numbers (1–64) on sealed papers, which were randomly selected soon afterward. One masked observer secured the papers and another took care of scoring and examination. Participants were informed about the purposes of the study and after having consent were enrolled in this trial.

Various patients (age more than 40 years) with Meibomian gland dysfunction (MGD) who had not responded to conservative management like eyelid warming/massage/cleaning 4 to 5 minutes twice a day and artificial tears (ocular lubricants) (4 to 5 times a day) were included.

Exclusion criteria were: patients taking systemic or topical antibiotics within 1 month prior to the inclusion, patients with history of liver disease, pregnancy, breast feeding, contact lens wearers, patients allergic to azithromycin, vernal keratoconjunctivitis, patients with history of ocular surgery and incomplete follow-up (patients who missed any of pre-scheduled visits).

Various parameters were assessed namely, five main symptoms (burning, itching, foreign body sensation, dryness, and eyelid edema) and seven main signs [type of MG secretion, number of occluded gland orifices, conjunctival hyperemia, lid margin redness, ocular surface staining with fluorescein, tear break-up time (TBUT), as seen on slit lamp bio microscopy].

Symptom severity was measured on a 4-point scale (0-3) according to patients' response to questions: Itching, burning, foreign body sensation, dryness and swelling of eyelids. Signs of MGD were assessed by performing slit lamp examination and recorded based on 4-point scale (0-3) (Table 1)

Meibum was generated by applying digital pressure on the lower eyelid at its central third. The secretion was graded as clear, cloudy, turbid, or solid depending on the worst secretion.

Plugging of Meibomian glands was graded as 0 (clear orifices of Meibomian glands in the central part of lower eyelid); 1 (less than one third of the orifices contained turbid or oily secretion) ; 2 (between one third and two third of the orifices contained turbid or oily secretion) ; 3 (more than two third of the orifices show turbid secretion).

Redness of the bulbar conjunctiva was graded as none, pink, light red and bright red based on slit lamp examination.

Redness of the lid margins was also graded as none, pink, light red and bright red based on the color of lower eyelid margins as assessed on slit lamp examination.

Lid margins debris was evaluated based on number of crusts at the lower eyelid margins also assessed on slit lamp examination. TBUT was recorded and graded as 0 (over 10 s), 1 (8–10 s), 2 (5–7 s), and 3 (less than 5 s). A single fluorescein strip was used to make the measurement more repeatable. The time for first split was recorded and graded.

The staining of the ocular surface was done immediately after recording the TBUT using the 4-point scale (0-3). The patient's upper lid was elevated and entire cornea and ocular surface was observed and assessed. The nasal and temporal interpalpebral conjunctiva was assessed by asking the patient to look temporally and nasally respectively. The number and pattern of dots on the cornea and conjunctiva were recorded (table 1)

The diagnosis of MGD was made if patient has two symptoms and two signs with minimum severity score of 2 for each. All pretreatment and post-treatment observations, recordings and evaluations were done by an observer who was masked to the type of treatment given to that block of patients. Patients were randomly assigned to either oral azithromycin regimen or topical azithromycin ointment treatment regimen. Patients were

also instructed to continue conservative management; eyelid massage/ warming and cleaning twice a day along with ocular lubricants five times a day throughout the study period.

The symptoms and signs scores were recorded first before commencing the treatment and three times after the treatment: 7days, 15 days and 30 days (three follow up visits)

Each patient's symptom and signs were scored from 0 to 3. The symptom score was calculated by addition of individual score (0-3) of symptoms of five symptoms which resulted in a range of 0-15. The sign score was also calculated by adding the individual score (0-3) of seven signs which resulted in range of (0-21). Total score of each patient was calculated by adding the symptom and sign score of that patient. Same parameters were assessed of each patient at every follow-up. Results were tabulated and appropriate statistical comparison was done.

Table 1: Grading of five symptoms and seven signs in 50 patients with Meibomian gland disease

Symptom/Sign	Grade 0	Grade 1	Grade 2	Grade 3
1. Itching	None	Awareness	Desire to rub	Frequent rub
2. Foreign body sensation	None	Awareness	Desire to rub	Desire to close lids
3. Dryness	None	Awareness	Need drops	Frequent drops
4. Burning	None	Awareness	Desire to rub	Frequent rub
5. Eyelid Swelling	None	Noticeable	Obvious	Decrease in palpebral fissure
6. MG secretion	Clear	Cloudy	Turbid	Solid paste
7. Plugged MG orifice	None	< 1/3	1/3-2/3	>2/3
8. Bulbar conjunctiva redness	None	Pink	Light red	Bright red
9. Eyelid margin redness	None	Pink	Light red	Bright red
10. Eyelid margin debris	None	1-5	6-10	>10
11. TBUT	>10	8-10	5-7	<5
12. Ocular surface staining	No staining	Minor staining	Moderate staining	Marked staining

Statistical analysis

Chi-square test and Mann Whitney test were used for statistical analysis. The Mann Whitney test was used to compare symptoms, signs, and total mean scores. Chi-square test was applied to analyse the total clinical response. Statistical significance was set at P < 0.05; 95% confidence interval was applied as a measure of precision.

III. Results

There were 128 patients of which 28 did not complete the study according to the predetermined protocol. Therefore, only 100 patients were included for analysis who were studied between January 2019 to October 2019. The two groups were matched for demographics. (Table 2)

Table 2: Demographics of 100 patients with Meibomian gland dysfunction who were given treatment with oral azithromycin or topical azithromycin

	Oral Azithromycin group (50)	Topical Azithromycin group (50)
Male/Female	22/28	24/26
Mean Age	51 (17.5)	43 (15.3)
Mean Duration of Disease (weeks)	12.3	11.5
Chief Complaints		
Itching	9 (18%)	11 (22%)
Foreign Body Sensation	16 (32%)	13 (26%)
Dryness	15 (30%)	16 (32%)
Burning	7 (14%)	8 (16%)
Lid Swelling	3 (6%)	2 (4%)

Symptoms improved in both groups (p = 0.237) though not significant (Table 3). There was no significant difference between the groups at each post treatment follow-ups.

Both treatment groups however showed a significant improvement of signs (p= 0.008) (Table 3). While mean signs scores were not different significantly at first and second follow up visits, there was significant improvement in the 1-month continuous topical azithromycin ointment group (50 patients) at the last follow up. So there was improved (better response) mean total score in topical azithromycin group at the same last follow up.

The topical azithromycin ointment group patients also showed no gastrointestinal side effects (nausea, diarrhoea etc.) as compared to oral azithromycin group.

Table 3: Mean symptoms, sign and total scores of 100 patients with MGD at each visit

	Oral Azithromycin Group (50 patients)	Topical Azithromycin Group (50 patients)	p Value
Pretreatment			
Symptom	7.15 (2.08)	7.10 (2.29)	0.783
Sign	11.00 (2.51)	10.25 (2.77)	0.369
Total	18.15 (4.16)	17.35 (3.48)	0.606
First follow-up			
Symptom	5.80 (1.96)	5.70 (2.16)	0.902
Sign	8.25 (2.27)	7.50 (2.76)	0.300
Total	14.05 (3.72)	13.20 (3.02)	0.605
Second follow-up			
Symptom	5.10 (1.80)	4.75 (2.10)	0.459
Sign	7.20 (2.12)	6.40 (2.50)	0.199
Total	12.30 (3.54)	11.15 (3.08)	0.446
Last follow-up			
Symptom	4.90 (2.12)	4.10 (2.02)	0.237
Sign	6.25 (1.94)	4.25 (2.47)	0.008*
Total	11.15 (3.82)	8.35 (3.22)	0.038*

Mann-Whitney test: *p <0.05; Significant

IV. Discussion

Though, many clinical trials and studies have been done comparing the efficacy of oral azithromycin and oral doxycycline in the treatment of MGD in which there was improvement seen in both the groups.^[6] However to the best of our knowledge no clinical trial has been done comparing the efficacy of oral azithromycin versus 1-month continuous topical azithromycin ointment in the treatment of Meibomian gland dysfunction.

This clinical trial was done to compare the efficacy of oral azithromycin and topical azithromycin in the treatment of MGD. Though improvements were seen in both the groups so far as symptoms are concerned as seen from table 3, a significant (p = 0.008) improvement in the patients sign and total score was seen only in the group of patients on continuous 1-month topical azithromycin ointment. This may be attributed to the fact that continuous topical application of azithromycin ointment might be responsible for sufficient continued anti-inflammatory activity so as to give a significant improvement in this group with topical azithromycin (p=0.008). Main drawback of the study is that we don't know that the sterile ointment base used in the preparation is responsible for how much contribution towards the betterment of symptoms and sign score. Besides this, we could not give any consideration to the indoor versus outdoor life of enrolled patients as well as their living/working conditions i.e. use of air conditioners, mobiles and laptops etc.

V. Conclusion

Although both oral and topical azithromycin improved the symptoms of MGD, continuous topical azithromycin is recommended for its better effect on improving the signs, better overall clinical response and nil systemic side effects as compared to oral azithromycin.

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