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## ORIGINAL RESEARCH

# Comparative study to evaluate the efficacy of oral azithromycin and oral doxycycline in refractory meibomian gland dysfunction

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## ABSTRACT

**Aim: To assess the efficacy and safety profile or oral azithromycin with oral doxycycline in patients with refractory meibomian gland dysfunction.**

**Material and method: This prospective randomized control study comprised of 60 patients attending the outpatient Department of Ophthalmology at Subharti Medical College. All cases underwent a detailed evaluation including visual acquity, anterior segment slit lamp examination of lid margins, tear minuscus, conjunctiva, cornea and tear film. Patients aged 18-70 were included in the study and the age matched randomization was done in two groups i.e. Group A (Oral Azithromycin 500mg on day 1 and then 250mg per day for next 4 days) and Group B (Doxycycline 100mg twice a day for 7 days and then 100mg once a day for next 21 days). All patients underwent complete ophthalmic examination and the signs and symptom scores were recorded prior to the treatment subsequently at 1 month, 3 months and 6 months post treatment.**

**Results: At last follow-up, there was distinct improvement in all the symptoms and mean score of all the signs in both the groups. The decrease in mean score was more in group A as compared to group B, however statistically significant was found in bulbar conjunctival redness, meibomian gland plugging, eyelid margin redness and ocular surface staining. Side effects were more in Doxycycline group as compared to Azithromycin group.**

**Conclusion: Azithromycin group was proved to have better effect regarding symptoms, signs, cost and lower rates of the adverse effects.**

## INTRODUCTION

Dysfunction of the Meibomian gland (MGD) is a common eyelid condition which is responsible for developing evaporative dry eye.[1] MGD may be asymptomatic, only detectable by gland expression or more often, present with dry eye symptoms.[2] Common symptoms are foreign body and burning sensation, red eye, tearing and photophobia.[3] Common signs are loss of clarity and thickening of expressed meibum, pouting or plugging of meibomian gland orifices, meibomian gland drop out detectable by meibography, increased eyelid margin thickness and vascularity, eyelash loss, trichiasis and vascular invasion.[4,5]

Most cases usually require conservative management including warm compresses to provide appropriate meibum secretion, mechanical eyelid massage and cleansing with shampoo and cotton buds to remove excess debris, and artificial tears to continuously lubricate the ocular

surface.[6,7] In severe and refractory cases, however, antibiotics (topical and systemic) with anti-inflammatory properties are proposed.[8,9]

A few studies have shown the efficacy of azithromycin in chronic inflammatory diseases such as MGD.[10,11] Azithromycin inhibits pro-inflammatory cytokines and is potent against Gram-negative microorganisms.[12] Topical and oral azithromycin have recently been reported to improve the sign and symptoms of MGD and posterior blepharitis.

Azithromycin is a semi-synthetic macrolide antbiotic, chemically related to eythromycin and clarithromycin. A single dose of 1 g of azithromycin has been shown to provied prolonged high levels after 14days in drug targeted ocular tissues, to decrease inflammatory cytokines and suppress production of pro-inflammatory mediators. Good intracellular penetration and the long half-life of azithromycin can provide an effective antimicrobial, anti-oxidant and a favourable immunomoodulatory effect.[13].

Other antibiotics, particularly the Tetracyclines (mainly, doxycycline) were discovered in the 1940s, are a family of antibiotics that inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. Tetracyclines are broad-spectrum agents, exhibiting activity against a wide range of gram-positive and gram-negative bacteria, atypical organisms such as chlamydiae, mycoplasma and rickettsiae and protozoan parasites. The favorable antimicrobial properties of these agents and the absence of major adverse effects has led to their extensive use in the therapy of human and animal infections.[13] The present study has been undertaken to assess the efficacy and safety profile or oral azithromycin with oral doxycycline in patients with refractory meibomian gland dysfunction.

## MATERIAL AND METHOD

This was a prospective randomized control study comprised of 60 patients attending the outpatient Department of Ophthalmology at Subharti Medical College, Meerut. All cases underwent a detailed evaluation including visual acquity, anterior segment slit lamp examination of lid margins, tear minuscus, conjunctiva, cornea and tear film. This study was conducted over a period of 6 months. Patients aged 18-70 were included in the study and the age matched randomization was done in two groups i.e.

GROUP A was given Oral Azithromycin 500mg on day 1 and then 250mg per day for next 4 days.

GROUP B was given Oral Doxycycline 100mg twice a day for 7 days and then 100mg once a day for next 21 days.

The subjects were recruited according to the following inclusion and exclusion criteria:

Age 18–70 years, meibomian gland dysfunction not responding to conservative or topical management and at-least two signs and two symptoms of meibomian gland dysfunction with a score >2 were included in the study. Therapy with systemic or topical antibiotics within 1 month before selection, contact lens wearers, allergy to azithromycin or cyclins, allergic keratoconjunctivitis, ocular and orbital surgery of any kind, altered lid anatomy, nonadherence to follow up and pregnant women were excluded from the study.

Severity of five main symptoms was measured on a 4-point categorical scale (0–3) according to mild, moderate and severe. Slit lamp examination was performed to assess and record the severity of seven signs on a 4-point categorical scale. Meibomian gland plugging was graded as follows: 0, clear orifice of meibomian glands in the central part of the lower eyelid; 1, less than one-third of the orifices contained turbid or oily secretion; 2, between one-third and two-thirds of the orifices contained turbid or oily secretion; 3, more than two-thirds of the orifices contained turbid or oily secretion. Bulbar conjunctival redness was graded as none, pink, light red, and bright red based on slit lamp examination. Lid margin redness was also graded as none, pink, light red, and bright red based on the colour of the lower eyelid margin on slit

lamp examination. Lid margin debris was scored based on the number of crusts at the lower eyelid margin, included in this study even though it is mostly present in anterior blepharitis.
Each patient's symptoms or signs were given a score of 0 to 3. The symptom score of each subject was calculated by adding the score (0–3) of five symptoms which resulted in a range of 0–15. The sign score of each patient was also calculated by adding the score (0–3) of seven signs which resulted in a range of 0–21.
All patients underwent complete ophthalmic examination and the signs and symptom scores were recorded prior to the treatment subsequently at 1 month, 3 months and 6 months post treatment. The data was collected and subjected to statistical analysis.

## STATISTICAL ANALYSIS

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

## RESULTS

Females were slightly more as compared to males in our study. Mean age in group A and B was 40.38±14.91 and 41.19±16.58 years respectively. Most of the subjects were free from any kind of systemic disease.
As seen in table 1, most common chief complaint was dryness in both the study groups (71.33% in group A, 63.33% in group B). Least common complaint was lid swelling, found in 3.33% and 10% of the subjects in group A and B respectively.

**Table 1: Chief complaints among the study groups**

| Complaints | Group A (Azithromycin) | | Group B (Doxycycline) | | p value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Itching | 14 | 46.67 | 11 | 36.67 | 0.42 |
| Foreign Body Sensation | 10 | 33.33 | 12 | 40 | |
| Dryness | 22 | 71.33 | 19 | 63.33 | |
| Burning | 6 | 20 | 8 | 26.67 | |
| Lid Swelling | 1 | 3.33 | 3 | 10 | |

At the time of presentation, maximum score was observed for Eyelid margin redness 1.88 for group A and 1.82 for group B. Least common score was for Tear break up time 1.13 in group A and 1.26 in group B. All the signs were comparable among both the groups at the time of presentation as $p>0.05$ (Table 2)

**Table 2: Mean score (SD) of signs at presentation among the groups**

| Signs | Group A | | Group B | | p value$^{\beta}$ |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Eyelid Margin Redness | 1.88 | 0.58 | 1.82 | 0.63 | 0.77 |
| Eyelid Margin Debris | 1.21 | 0.45 | 1.14 | 0.42 | 0.59 |
| Bulbar Conjunctival Redness | 1.56 | 0.64 | 1.51 | 0.73 | 0.49 |
| Meibomian Gland Secretion | 1.62 | 0.41 | 1.69 | 0.48 | 0.39 |
| Meibomian Gland Plugging | 1.87 | 0.54 | 1.90 | 0.59 | 0.82 |
| Tear Break-Up Time | 1.13 | 0.31 | 1.26 | 0.43 | 0.47 |
| Ocular Surface Staining | 1.42 | 0.61 | 1.51 | 0.40 | 0.42 |

$^{\beta}$: unpaired t test

At first follow-up, there was marked improvement in lid swelling and burning followed by itching, foreign body sensation and dryness. The maximum decrease in mean score was observed for eyelid margin redness in group A which reduced to 1.41 from 1.88. In group B meibomian gland secretion showed the maximum decreased in mean score from 1.69 to 1.32. The decrease in mean score was more in group A as compared to group B, though statistically insignificant.

**Table 3: Mean score (SD) of signs at first follow-up (1st week)**

| Signs | Group A | | Group B | | p value$^{\beta}$ |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Eyelid Margin Redness | 1.41 | 0.48 | 1.53 | 0.61 | 0.62 |
| Eyelid Margin Debris | 1.07 | 0.41 | 1.09 | 0.38 | 0.78 |
| Bulbar Conjunctival Redness | 1.24 | 0.37 | 1.30 | 0.44 | 0.71 |
| Meibomian Gland Secretion | 1.21 | 0.56 | 1.32 | 0.51 | 0.46 |
| Meibomian Gland Plugging | 1.59 | 0.54 | 1.70 | 0.57 | 0.40 |
| Tear Break-Up Time | 0.99 | 0.28 | 1.11 | 0.46 | 0.11 |
| Ocular Surface Staining | 1.17 | 0.32 | 1.28 | 0.42 | 0.42 |

$^{\beta:}$ unpaired t test, *: statistically significant

At last follow-up, there was distinct improvement in all the symptoms and mean score of all the signs in both the groups. The decrease in mean score was more in group A as compared to group B, however statistically significant was found in bulbar conjunctival redness, meibomian gland plugging, eyelid margin redness and ocular surface staining (table 4).

**Table 4: Mean score (SD) of signs at last follow-up (2nd month)**

| Signs | Group A | | Group B | | p value$^{\beta}$ |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Eyelid Margin Redness | 0.92 | 0.60 | 0.98 | 0.61 | 0.23 |
| Eyelid Margin Debris | 0.73 | 0.50 | 0.84 | 0.44 | 0.15 |
| Bulbar Conjunctival Redness | 0.67 | 0.38 | 0.99 | 0.44 | 0.006* |
| Meibomian Gland Secretion | 0.83 | 0.56 | 1.04 | 0.52 | 0.08 |
| Meibomian Gland Plugging | 0.80 | 0.62 | 1.02 | 0.66 | 0.10 |
| Tear Break-Up Time | 0.55 | 0.38 | 0.68 | 0.49 | 0.13 |
| Ocular Surface Staining | 0.45 | 0.36 | 0.79 | 0.46 | 0.022* |

$^{\beta:}$ unpaired t test, *: statistically significant

Mean score of symptoms was 7.41±1.17 in group A which decreased to 0.6±0.21 at last followup was significant, p value (<0.01). Mean score of Pretreatment symptoms was 7.51±1.26 in group B which decreased to 0.61±0.38 at last followup which was statistically significant, p value (<0.01). Mean score of sign decreased from 8.62±1.19 to 1.2±0.74 on last follow up in group A. Mean score of Pretreatment signs was 8.29±1.78 in group B which decreased to 1.28 ± 0.76 which was statistically significant, p value (<0.01) (table 5).

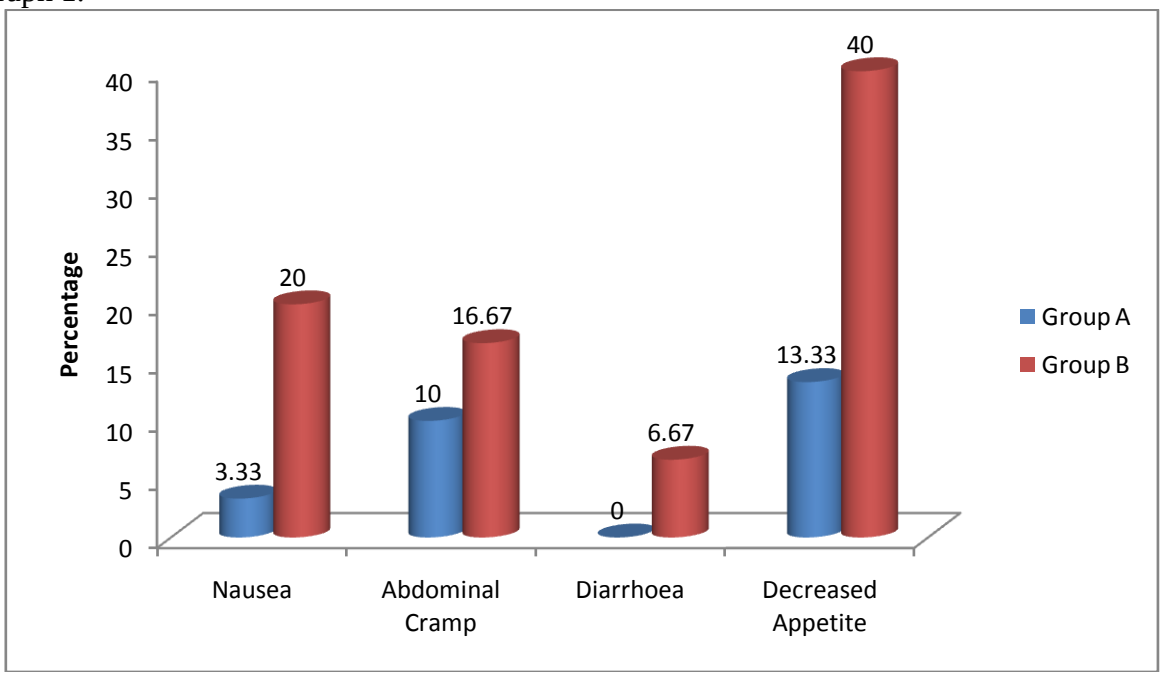
**Table 5: Comparison of pretreatment and post treatment symptoms and signs**

| Groups | Symptoms | | p value$^{\gamma}$ | Sign | | p value$^{\gamma}$ |
|---|---|---|---|---|---|---|
| | Pre Treatment Mean±SD | Last Follow up Mean±SD | | Pre Treatment Mean±SD | Last Follow up Mean±SD | |
| Group A | 7.41 ± 1.17 | 0.6 ± 0.21 | <0.01* | 8.62 ± 1.19 | 1.2 ± 0.74 | <0.01* |
| Group B | 7.51 ± 1.26 | 0.61 ± 0.38 | <0.01* | 8.29 ± 1.78 | 1.28 ± 0.76 | <0.01* |

$^{\gamma:}$ paired t test, *: statistically significant

Nausea was found in 1 patient (3.33%) in group A and 6 patients (20%) in group B. Abdominal cramp was seen in 10% of patients and 16.67% of patients in group A and group B respectively. Hence side effects were more in Doxycycline group as compared to

Azithromycin group with statistically significant difference, p value (0.003) as shown in graph 1.




**Graph 1: Comparison of side effects**

## DISCUSSION

Cleansing, warm compresses and massage are the three contemporary mode of treatment for MGD. Amongst the treatment modalities topical application of azithromycin eye ointment, artificial tear drops and systemic tetracyclines, (doxycycline being most frequently used) as well as systemic azithromycin are the treatment modalities available.[14] Keeping all this in mind, the aim was to assess the efficacy and safety profile or oral azithromycin with oral doxycycline in patients with refractory meibomian gland dysfunction.

Females were slightly more as compared to males in our study which comprised of 56.67% females in group A and 53.33% in group B in comparison to 43.33% males in group A and 46.67% in group B. Mean age in group A and B was 40.38±14.91 and 41.19±16.58 years respectively. **Kashkouli MB et al**[5] also reported similar findings in age and sex distribution among both the groups where 26 females were reported in group A and 24 males were reported in group A. A study published by **Kwan et al**[15] demonstrated association between sex and MGD in which females were found to have significantly higher frequency and intensity of dryness than males. In contrast **R N Kothari et al**[14] in their study reported that 59 (59%) were male and 41 (41%) were female.

The age was also comparable between both the groups and was congruous to the main study. **Nien et al**[16] studied and reported that older participants displayed significantly higher grades of MGD.

In our study most common chief complaint was dryness in both the study groups. It was observed in 71.33% patients in group A and 63.33% in group B followed by itching 46.67% and 36.67% in group A and B respectively. Findings in our study were consistent with that of Kashkouli MB et al[5] who also reported dryness as the most common complaint 34% and 26% in group A and B and least common was lid swelling. However, **R N Kothari et al**[14] in their study reported that most common chief complaints were Itching (100%) and foreign body sensation (100%) followed by burning (84%) and dryness (16%).

In our study at presentation, all the signs viz. eyelid margin redness, eyelid margin debris, bulbar conjunctival redness, meibomian gland secretion, meibomian gland plugging, tear

break-up time and ocular surface staining were comparable between both the groups at the time of presentation as p>0.05. Maximum score was observed for eyelid margin redness (p value 0.77) followed by meibomian gland plugging (p value 0.82) and least was observed for tear break up time (p value 0.47). At first follow-up, mean score of all the signs decreased in both the groups. The decrease in mean score was more in group A as compared to group B, though statistically insignificant. Maximum decrease in mean score was observed for eyelid margin redness in both the groups Similarly at 2nd and 3rd follow-up, mean score of all the signs decreased in both the groups. There was distinct improvement in all the symptoms and mean score of all the signs in both the groups.

Similar to our study R N Kothari et al[14], reported at the time of presentation that the maximum mean score was observed for eyelid margin redness (0.53 in group A and 0.48 in group B) .The p value of pretreatment symptoms (0.704) and signs (0.321) of both group indicate that there was no statistical significant difference among patients in both group. In azithromycin group mean of symptoms (7.50) and signs (8.70) at pretreatment clinically improved to mean of symptoms (0.62) and signs (1.22) at last visit. In doxycycline group mean of symptoms (7.60) and signs (8.38) at pretreatment clinically improved to symptoms (0.62) and signs (1.33) at last visit. Kashkouli MB et al[5] in their study found that symptoms significantly improved in both groups (p=0.001, 95% CI −2.2 to −0.7). However, there was no significant difference between the groups at all post-treatment visits. Both groups showed a significant improvement of clinical signs. Although the last follow-up mean score of all signs was less (better response) in the azithromycin than in the doxycycline group, the difference was statistically significant in only conjunctival redness and ocular surface staining. These results were approximately consistent with our study.

In out study overall mean pretreatment symptoms score was 7.41 ± 1.17 and 7.51 ± 1.26 in group A and B respectively while it decreased to 0.6 ± 0.21 and 0.61 ± 0.38 at last followup in group A and B respectively with statistically significant difference. Similarly overall mean sign score decreased to 1.2 ± 0.74 and 1.28 ± 0.76 from 8.62 ± 1.19 and 8.29 ± 1.78 in group A and B respectively with statistically significant difference. This can be due to the fact that Azithromycin is a semisynthetic macrolide antibiotic with a good intracellular penetration and long halflife; it has an anti-inflammatory and immunomodulatory effect that could help reduce eyelid and ocular surface inflammation. The oral formulation of azithromycin can suppress the production of some pro-inflammatory mediators like cytokines (TNFα, IL-1β), chemokines and metalloproteinases (MMP-1, MMP-3 and MMP-9). Its antibacterial and anti-inflammatory effects, coupled with a long half-life, make oral azithromycin a good treatment option for MGD.[5]

Similar to the present study **Giacomo De Benedetti et al**[17] in their study showed that azithromycin performed better throughout the study, showing a significant improvement in most patients (65%). This improvement appeared more quickly and was maintained throughout the period.

In our study; side effects were more in Doxycycline group as compared to Azithromycin group with statistically significant difference as p<0.05 in this study. Although the role of doxycycline in the treatment of MGD has been promising, its side effects and subsequently low compliance of the patients sometimes result in treatment abortion. Its side effects include dermatological effects (macula, papules), gastrointestinal effects (oesophagitis, dyspepsia, diarrhoea, vomiting), and hypersensitivity (allergy, urticaria). Similarly **R N Kothari et al**[14], reported more side effects in doxycycline group as compared to azithromycin group in all three follow ups. Decreased appetite was seen in 30% patients followed by nausea and abdominal cramps. The most common side effect was decreased appetitie, which was also reported by **Greene et al.**[18] Also, **Kashkouli MB et al**[5] in their study reported a few gastrointestinal side effects in the doxycycline group. They were reported by 15 patients

(30%) in the first week after starting the doxycycline, decreased to 26% (13/50) at the end of the 1-month treatment course, and then to 14% (7/50) at the end of the study. However, only mild and temporary side effects were seen in Azithromycin group.

Strengths of our study were its randomised masked trial design, using a grading system to quantify the qualitative measures. One limitation might be the absence of a control group without any systemic medication; there has been debate on whether clinical trials essentially require a placebo control instead of having an active treatment control. However, since enrolled patients had not responded to conservative management and had moderate to severe MGD (two signs and two symptoms of at least grade 2 severity, of which one had to be meibomian gland signs), systemic medication (doxycycline or azithromycin) was deemed to be required. Using one dosing regimen of oral azithromycin and doxycycline and not considering topical azithromycin is another limitation, which future studies are recommended to address.

## CONCLUSION

In conclusion, our study demonstrated beneficial effects for both oral azithromycin and oral doxycycline in cases of refractory meibomian gland dysfunction. Since MGD is a chronic disease, 5 day treatment with azithromycin would be cheaper than long term daily oral doxycycline. The cost of 1- month treatment with doxycycline is almost 50% more than 5-day treatment with oral azithromycin in our country. Azithromycin group was proved to have better effect regarding symptoms, signs, cost and lower rates of the adverse effects.

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