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# Oral azithromycin versus doxycycline in meibomian gland dysfunction: A hospital-based study at Nepal eye hospital

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## ABSTRACT

**Background:** Meibomian gland dysfunction (MGD) involves posterior blepharitis, which includes a disruption of the tear and meibum lipids and thereby produces an evaporative dry eye. The most common cause is obstruction of the meibomian glands, which causes inflammatory changes and increases bacterial colonization along the lid margins. Conservative management consists of warm compresses, mechanical eyelid massage, and artificial tears; when severe, an oral antibiotic with anti-inflammatory properties can be suggested. **Aims and Objectives:** The aims and objectives of the study are to compare the effects (symptom and sign scores) and safety (side effects) of oral azithromycin compared with oral doxycycline in patients with posterior blepharitis. **Materials and Methods:** This is a prospective, comparative, and randomized hospital-based study conducted at Nepal Eye Hospital from June 2016 to December 2017. This study recruited patients having severe MGD. Convenience sampling technique was used for the selection of patients. **Result:** A total of 60 patients with 30 in each group ranging in age from 21 to 74 years were included. Both groups experienced a significant improvement in symptoms and indicators (P = 0.001). Ocular surface staining (P = 0.04) and bulbar conjunctival redness (P = 0.02) were significantly better in the azithromycin group, but symptom improvement was not different between the groups. When the doxycline group experienced more side effects in the 3rd week, there was no discernible difference in the mild gastrointestinal side effects between the groups. **Conclusion:** This study showed that oral doxycycline and azithromycin are beneficial to patients with MGD patients. Due to superior clinical improvement, shorter treatment duration, low cost, and side effects, 5-day oral azithromycin is recommended in comparison to 1-month oral doxycycline.

**Key words:** Meibomian gland dysfunction; Meibum lipids; Azithromycin; Doxycycline

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## INTRODUCTION

Meibomian gland dysfunction (MGD) is a common cause of posterior blepharitis, a condition where the tear film and meibum lipids are compromised, leading to an evaporative dry eye.[1,2] The leading cause is obstruction of the meibomian gland (MG), which can result in inflammation and increased bacterial colonization of the lid margins.[3] MGD can be asymptomatic or present with dry eye symptoms. Conservative management includes warm compresses, mechanical eyelid massage, and artificial tears.[4] In severe cases, "a chronic, diffuse abnormality

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of the MGs commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion" antibiotics with anti-inflammatory properties are proposed. Tetracycline and its derivatives are antimicrobials that decrease inflammation and inhibit matrix metalloproteinase.[5] Doxycycline, a long-acting analog of tetracycline, has been used to treat MGD due to its antimicrobial, anti-inflammatory, and anti-metalloproteinase properties.[6] Azithromycin, potent against Gram-negative microorganisms, has been reported to improve the signs and symptoms of MGD and posterior blepharitis.[5,7]

This prospective, randomized hospital-based study aims to evaluate the efficacy and safety of oral azithromycin and doxycycline in treating MGD in patients with posterior blepharitis.

### Aims and objectives

#### *General objective*

To compare the effects (symptom and sign scores) and safety (side effects) of oral azithromycin compared with oral doxycycline in patients with posterior blepharitis.

#### *Specific objectives*

To study the age and gender distribution of MGD.
To study efficacy of oral doxycycline in MGD.
To study efficacy of oral azithromycin in MGD.
To study the safety of oral azithromycin in MGD treatment.
To study the safety of oral doxycycline in MGD treatment.

Compare the effects (symptom and sign scores) and safety (side effects) of oral azithromycin compared with oral doxycycline in patients with posterior blepharitis.

## MATERIALS AND METHODS

This study is a hospital-based randomized prospective study conducted from June 2016 to December 2017, i.e., for 18 months at the Nepal Eye Hospital general ophthalmology outpatient department. Patients with severe MGD were recruited in the study using convenience sampling method. Total sample size of the study was 60. A questionnaire-based assessment of the symptom severity and grading of symptom score was done as outlined in the pro forma. Signs were assessed by single person, using standard Zeiss slit lamp. Corneal examination was further enhanced by the use of fluorescein strips and visualization of epithelial defects using cobalt blue light.

### Inclusion criteria

#### *All chronic cases of posterior blepharitis*

Clinical symptoms include burning, grittiness, dryness or a foreign body sensation, redness, crusty eyelids, heavy eyelids, or fluctuating vision.

Clinical signs include lid margin hyperemia, crusting of the lashes, plugging of the MG orifices, abnormal, thickened MG secretions, foamy tears, and tear film debris or an unstable tear film.

### Exclusion criteria

- Taking systemic or topical antibiotic within 1 month before inclusion
- History of liver disease, pregnancy, and breastfeeding
- Contact lens wearing, allergy to azithromycin or cyclins
- Vernal and atopic keratoconjunctivitis, ocular and ocular adnexal surgery
- Altered lid anatomy for any reason and incomplete follow-up (missing any of three pre-scheduled visits).

Diagnosis and grading of signs and symptoms of MGD were made on the basis of symptoms and signs at presentation and at each follow-up. Participants in the studies answered a questionnaire to assess symptom score and subjective score based on categorical scale (0–3). The questioner evaluated the symptoms of itching, burning, foreign body sensation, dryness, and eyelid swelling.[8] Sign score was evaluated objectively and graded 0–3 on categorical scale by the examiner. Seven signs were evaluated which include meibomian secretion, plugged gland orifices, injection of conjunctiva, redness of lid margin, debris of lid margin, tear breakup time (TBUT), and staining of corneal surface by fluorescein. Further, the total score and the sum of sign and symptom scores were calculated.

Ocular surface staining was immediately performed after recording the TBUT using a four-point categorical scale panel which was a modification of panels introduced in the Oxford grading scale.[9]

MGD was diagnosed based on having at least two symptoms and two signs (one must be the presence of MG signs) with a minimum severity score of 2 for each. All pre-treatment and post-treatment assessments and examinations were performed by one observer who was masked to the type of treatment. Patients were randomly assigned to either a 5-day oral azithromycin (500 mg on the 1$^{st}$ day then 250 mg/day for following 4 days) course or a 1-month oral doxycycline course (100 mg twice a day).

The symptom and sign scores were recorded before treatment and three times after treatment: First visit (1 week after 5-day azithromycin and 1 week of 1-month doxycycline), second visit (3 weeks after 5-day azithromycin and 3 weeks of 1-month doxycycline), and third visit (1 month after 1-month doxycycline and 5-day azithromycin).

Each patient's symptoms or signs were given a score of 0–3. 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. The total score (0–36) of each patient was calculated and recorded by adding the scores of symptoms (0–15) and signs (0–21) at each visit. Overall clinical responses were categorized based on the percentage of reduction of total score into four groups: Excellent (76–100%), Good (51–75%), Fair (26–50%), and Poor (1–25%).

Side effects of treatments were also recorded at each visit. Data were coded and entered into standard SPSS (the Statistical Package for the Social Sciences) version 21.0. After results had been obtained, data were decoded and interpreted in the final results. Qualitative data were analyzed using the Chi-square test and quantitative data by means of t-test.

## RESULTS

A total of 60 participants with MGD, meeting the inclusion criteria, were included in the study, with ages ranging from 21 to 74 years. More than half of the participants were male. Majority of the participants were from the age group 56 to 70. Among 30 patients in each group, most of the participants were from the age group 41 to 70 in azithromycin group and doxycycline group had same number of patients in age group 25–40 and 56–70, respectively.

The above table shows mean of signs severity score at the presentation and 4$^{th}$ week after treatment with doxycycline and azithromycin groups which shows significant decrease in severity of symptoms in both the groups and statistically significant improvement in symptoms among the both groups.

The above shows mean of signs severity score at the presentation and 4$^{th}$ week after treatment with azithromycin and doxycycline which shows statistically significant improvement in symptoms among the group.

The above table shows the comparison of side effects of azithromycin and doxycycline at 1$^{st}$, 3$^{rd}$, and 4$^{th}$ week which shows that there is statistical significance in nausea, abdominal cramp, and decreased appetite in all 3 weeks whereas diarrhea is statistically insignificant in 1$^{st}$ and 4$^{th}$-week follow-ups.

The above table shows the comparison of signs on azithromycin and doxycycline at the date of presentation, 1$^{st}$ week, 3$^{rd}$ week, and 4$^{th}$ week. The severity of the signs decreased in all the weeks. P-value is significant for MG secretion (central lower eyelid) plugged and MG orifice (middle lower eyelid) in the 1$^{st}$ week and bulbar conjunctival redness is significant in 1$^{st}$ week and 2$^{nd}$ week likewise ocular surface staining is statistically significant in the 3$^{rd}$ week.

The above table shows the comparison of signs on azithromycin and doxycycline at the date of presentation, 1$^{st}$ week, 3$^{rd}$ week, and 4$^{th}$ week. P-value for the itching is significant in the 4$^{th}$ week.

The trend in symptom severity scores over four weeks shows a significant reduction in both groups (Table 1). The trend in sign severity scores over four weeks shows a significant reduction in both groups (Table 2). The comparison of side effects between azithromycin and doxycycline across different weeks (Table 3). The comparison of symptoms between azithromycin and doxycycline across different weeks (Table 4). The comparison of signs between azithromycin and doxycycline across different weeks (Table 5).

## DISCUSSION

This study is the first randomized clinical trial comparing oral doxycycline and azithromycin in treating MGD in a Nepalese population. This study found that patients with severe MGD aged 21–74 years which age group is comparable to what Kashkouli reported.[8]

The study compared itching symptoms in 30 patients treated with azithromycin and doxycycline. Results showed itching severity decreased in the 1$^{st}$ week but not in the 3$^{rd}$ or 4$^{th}$ week. The 4$^{th}$ week showed no significant improvement, suggesting azithromycin and doxycycline may be effective in treating posterior blepharitis. These findings were similar to a study by Igami et al., which found significant improvement in itching symptoms 30 days after treatment.[7]

The study compared foreign body sensation in patients treated with azithromycin and doxycycline, both groups experienced similar symptoms. The severity of sensation decreased after 3 weeks, but improvement was statistically insignificant. A separate study showed significant improvement in blepharitis symptoms after a 4-week course.[10]

Dryness was present in both doxycycline and azithromycin groups at presentation, with varying severity levels, at 1$^{st}$ week, dryness severity was decreased in both groups. However, late presentation of dryness symptoms may be a factor. Treatment of dry eye sensation was statistically insignificant in both groups. Similar studies have shown

**Table 1: Trend of mean symptom severity Score: Doxycycline group and azithromycin group at date of presentation and 4 weeks**

| Symptoms | Doxycycline | | | Azithromycin | | |
|---|---|---|---|---|---|---|
| | DoP | 4 weeks | P-value | DoP | 4 weeks | P-value |
| Itching | 2.17 | 0.93 | 0.00 | 2.60 | 0.47 | P<0.001 |
| Foreign body sensation | 2.47 | 0.87 | 0.00 | 2.60 | 0.63 | P<0.001 |
| Dryness | 2.23 | 0.90 | 0.00 | 2.20 | 0.90 | P<0.001 |
| Burning | 2.0 | 0.73 | 0.00 | 2.00 | 0.77 | P<0.001 |
| Lid swelling | 1.93 | 0.83 | 0.00 | 1.63 | 0.70 | P<0.001 |

**Table 2: Trend of mean sign severity score: Doxycycline group and azithromycin group at date of presentation and 4 weeks**

| Signs | Doxycycline | | | Azithromycin | | |
|---|---|---|---|---|---|---|
| | DoP | 4 weeks | P-value | DoP | 4 weeks | P-value |
| MG secretion (central lower eyelid) | 2.03 | 0.90 | 0.000 | 2.17 | 0.97 | P<0.001 |
| Plugged MG orifice (middle lower eyelid) | 1.90 | 0.90 | 0.000 | 2.20 | 0.93 | P<0.001 |
| Bulbar conjunctival redness | 1.37 | 0.40 | 0.000 | 1.70 | 0.60 | P<0.001 |
| Eyelid margin redness | 1.80 | 0.77 | 0.000 | 2.00 | 0.70 | P<0.001 |
| Eyelid margin debris | 1.87 | 0.83 | 0.000 | 2.03 | 0.80 | P<0.001 |

**Table 3: Comparison of the side effects of azithromycin and doxycycline**

| Week | Side effects | P-value |
|---|---|---|
| 1st week | Nausea | 0.011 |
| | Abdominal cramp | 0.005 |
| | Diarrhea | 0.129 |
| | Decreased appetite | 0.020 |
| 3rd week | Nausea | 0.04 |
| | Abdominal cramp | 0.002 |
| | Diarrhea | 0.038 |
| | Decreased appetite | 0.005 |
| 4th week | Nausea | 0.389 |
| | Abdominal cramp | 0.038 |
| | Diarrhea | 0.228 |
| | Decreased appetite | 0.020 |

**Table 4: Comparison of signs on azithromycin and doxycycline at DoP (date of presentation), 1st week, 3rd week, and 4th week**

| Signs | P-value | | | |
|---|---|---|---|---|
| | DoP | 1st week | 3rd week | 4th week |
| MG secretion (central lower eyelid) | 0.261 | **0.032** | 0.305 | 0.24 |
| Plugged MG orifice (middle lower eyelid) | 0.279 | **0.039** | 0.483 | 0.945 |
| Bulbar conjunctival redness | 0.161 | **0.033** | **0.047** | 0.28 |
| Eyelid margin redness | 0.5 | 0.85 | 0.553 | 0.56 |
| Eyelid margin debris | 0.674 | 0.723 | 0.406 | 0.711 |
| Tear breakup time (second) | 0.172 | 0.491 | 0.185 | 0.581 |
| Ocular surface staining | 0.746 | 0.3 | **0.026** | 0.683 |

MG: Meibomian gland, *Statistically significant at p <0.05

similar results regarding the effects of oral doxycycline in patients with MGD.[7,10-12]

**Table 5: Comparison of symptoms on azithromycin and doxycycline at DoP (date of presentation), 1st week, 3rd week, and 4th week**

| Symptoms | P-value | | | |
|---|---|---|---|---|
| | DoP | 1st week | 3rd week | 4th week |
| Itching | 0.063 | 1 | 0.349 | **0.012** |
| Foreign body sensation | 0.496 | 0.697 | 0.06 | 0.135 |
| Dryness | 0.961 | 0.246 | 0.147 | 0.546 |
| Burning | 0.875 | 0.181 | 0.432 | 0.327 |
| Lid swelling | 0.409 | 0.26 | 0.322 | 0.238 |

* Statistically significant at p <0.05

The study found that azithromycin and doxycycline effectively reduced burning symptoms in patients with moderate-to-severe blepharitis, with improvements persisting for 4-week post-treatment similar to the results shown by other studies.[5,7] The study found that azithromycin and doxycycline were equally effective in improving MG secretion with doxycycline showing significant improvement in the 1st week. Further studies have shown that oral doxycycline is slightly less effective than topical azithromycin in improving MG secretion.[5,10]

Although there was no discernible difference in the long-term follow-up outcomes, the study indicated that doxycycline was more effective in the 1st and 3rd weeks and that azithromycin and doxycycline treatments both successfully decreased bulbar conjunctival redness in patients which is similar to that reported in study done by Kashkouli et al.[8]

The study found that both azithromycin and doxycycline treatments were comparable in treating eyelid margin

redness. However, the study found no statistically significant difference in the signs of redness after treatment. In contrast, a study by Igami et al., showed significant improvements in eyelid itching and hyperemia after oral azithromycin treatment for posterior blepharitis, with no significant decrease in severe cases.[7]

The study found that azithromycin and doxycycline were effective in treating plugged MG orifice. In the 1st week, doxycycline showed a significant improvement in plugged glands, while azithromycin showed no significant improvement. However, in the 3rd and 4th weeks, both drugs were equally effective.[5] A study by Kashkouli et al., found that both azithromycin and doxycycline groups significantly improved symptoms and clinical signs in patients with posterior blepharitis. The study supports the beneficial effects of oral azithromycin on symptoms and signs, possibly due to its antibacterial and anti-inflammatory effects.[8]

The study found that azithromycin and doxycycline had few side effects, though doxycycline caused more, including nausea, abdominal cramps, diarrhea, and decreased appetite. Quarterman et al., and Sobolewska et al., studied ocular rosacea patients with doxycycline, finding, side effects and gastrointestinal side effects were reported.[13,14]

The cost of a 1-month treatment with doxycycline is nearly 50% higher than a 5-day treatment with oral azithromycin in our country. As MGD is a chronic disease, a 5-day course of oral azithromycin is recommended due to better clinical improvement, shorter treatment duration, lower cost, and fewer side effects. However, a longer-term regimen is often required due to the chronic nature of MGD.

### Limitations of the study

The lack of a control group that received no systemic medicine may be one of the study's limitations. Another restriction would be to use the same value for all signs when calculating and analyzing the mean sign score. Using a single dosage of doxycycline and oral azithromycin without taking topical azithromycin and other lubricating agents is another limitation.

## CONCLUSION

This study showed that all of the signs and symptoms were statistically significant between the groups from the day of presentation until the last follow-up, except the groups taking doxycycline and azithromycin showed statistically negligible differences. However, the effect of azithromycin was comparatively better with regard to fewer side effects than doxycycline.

Despite being a chronic illness, MGD necessitates a long-term regimen. A longer doxycycline regimen resulted in higher systemic adverse effects. As a result, a 5-day oral azithromycin course is advised due to its superior clinical improvement, shorter treatment duration, reduced cost, and fewer adverse effects.

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**Authors' Contribution:**
**SD-** Definition of intellectual content, literature study, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **SS-** Review manuscript; **PK-** Coordination and manuscript revision; **SUD-** Data analysis and interpretation, preparation of tables, editing, and manuscript revision.

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