Open Access

Original Article

Comparison Between Efficacy and Safety of Oral Azithromycin (250mg) vs Oral Doxycycline (100mg) in Treatment of Meibomian Gland Dysfunction (MGD)

Waseem Yousuf, Fakhar Humayun, Teyyeb Azeem Janjua, Taimoor Ashraf Khan, Muhammad Haroon Sarfraz*, Mohammad Asim Mehboob

Department of Ophthalmology, Armed Forces Institute of Ophthalmology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Ophthalmology, Wah Medical College, Wah Cantt/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare the efficacy and safety of oral Azithromycin with oral Doxycycline in patients with Meibomian Gland Dysfunction.

Study Design: Quasi-experimental study.

Place and Duration of the Study: Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Apr 2021 to Apr 2022.

Methodology: The sample population comprised 172 subjects, including 86 cases in the oral Doxycycline-Group and 86 oral Azithromycin-Group. Meibomian Gland Dysfunction was diagnosed by a consultant ophthalmologist by slit-lamp examination. Schirmer-I test and Tear Break Up Time were performed. Signs and symptoms of Meibomian Gland Dysfunction were assessed before treatment and at six months follow-up.

Results: The study recruited equal numbers of cases and controls. Symptoms scores for burning sensation (2.04±0.5 vs 1.9±0.7) and foreign body sensation (1.8±0.6 vs 1.5±0.8) were significantly higher in patients taking Doxycycline as compared to the Azithromycin-Group (p<0.05). On comparing the signs score between the two Groups, it was seen that total scores (pre-treatment and post-treatment) were more significant in the Doxycycline-Group (p<0.05). Treatment with Doxycycline yielded more significant complications, such as diarrhoea (39.5%), nausea (46.5%), and cramps (48.8%). Headache was more associated with Azithromycin treatment (3.4%), whereas Rash (1.1%) and blurring of vision (1.1%) were seen in the Doxycycline-Group.

Conclusion: Meibomian Gland Dysfunction leads to tear film instability and direct damage to the ocular surface epithelium. This study supports the clinical efficacy and safety of oral Azithromycin and Doxycycline therapy for managing refractory or severe Meibomian gland disease.

Keywords: Azithromycin, Doxycycline, Meibomian gland dysfunction.

How to Cite This Article: *Yousuf W, Humayun F, Janjua TA, Khan TA, Sarfraz MH, Mehboob MA. Comparison Between Efficacy and Safety of Oral Azithromycin (250mg) vs Oral Doxycycline (100mg) in Treatment of Meibomian Gland Dysfunction (MGD). Pak Armed Forces Med J 2023; 73(Suppl-2): S312-315. DOI: https://doi.org/10.51253/pafmj. v73iSUPPL-2.8815*

INTRODUCTION

The term "anterior blepharitis" refers to inflammation of the lid margins before the grey line, which means inflammation of lash follicles, eyelashes, and skin.[1] The term "posterior Blepharitis" refers to inflammation of the structures posterior to the grey line, which includes the tarsal plate, Meibomian glands, blepharo-conjunctival junction, and Meibomian duct orifices.[2] In association with Meibomian gland dysfunction (MGD) glandular obstruction due to terminal duct obstruction or altered secretion is the most common cause of low lipid delivery.[3] This may lead to altered tear films, eye irritation, clinically visible inflammation, and blepharospasm.[4] MGD and dry eyes are often reported as the most common etiopathology of blepharospasm.[5] The slit-lamp examination must reveal structural and morphological changes.[6] A clinical score called Meibomian gland expressibility (MGE) helps to assess the severity of the disease at the time of presentation and how it improves with treatment.[7] There is no cure for meibomian gland expressibility at this time. An effective treatment aims to stop the progression of the disease. It is treated with warm compresses, artificial tears, and topical and systemic antibiotics.[8] Compressions with warm water may assist in liquefying the stagnant, partially solidified excretion of meibum lipids. Oral tetracycline and doxycycline also help in bringing the disease under control. The mechanism lies in its ability to inhibit bacterial protein synthesis and lipase action.[9] Studies have also demonstrated that azithromycin's anti-inflammatory properties can help reduce blepharitis pathogenesis by reducing inflammation of eyelids and ocular surfaces.[10] We, therefore, planned this study to compare the efficacy and safety of oral azithromycin and oral doxycycline in treating meibomian gland dysfunction.

METHODOLOGY

The quasi-experimental study was conducted at the Armed Forces Institute of Ophthalmology,

Correspondence: Dr Waseem Yousuf, Department of Ophthalmology, Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan

Received: 01 Jun 2022; revision received: 20 Jun 2022; accepted: 22 Jun 2022

Rawalpindi Pakistan, from April 2021 to April 2022. Approval was taken from the Hospital Ethical Review Committee (IRB No: 266/ERC/AFIO). Sample size was calculated using open-Epi sample size calculator version 3.0, considering the mean score of pre-treatment meibomian gland secretion in the azithromycin group to be 1.8±0.7 and 1.5±0.7 in doxycycline group.[11]

Inclusion Criteria: Patients of either gender, aged 18 to 80 years old, with posterior blepharitis that did not respond to conservative and topical therapy, with at least two symptoms and signs having a score >2 in the abovementioned scales were included in the study.

Exclusion Criteria: All those patients who had a history of wearing contact lenses, liver disease, pregnancy or lactation, allergy to Azithromycin or tetracyclines, allergic keratoconjunctivitis, abnormal anatomy of the eyelid, and previous orbital or ocular surgery, were excluded from the study.

All patients were advised conservative management. signs and symptoms of meibomian gland dysfunction were assessed before treatment and at six months follow-up. Eligible patients were randomized into equal-strength azithromycin and doxycycline groups (86 in each group) using the lottery technique after obtaining informed written consent. Patients' five main symptoms (burning, eyelid oedema, dryness, foreign body sensation, and itching) were recorded on the proforma, followed by the assessment of the six main signs (examination for the meibomian gland, including meibum quality, meibomian gland expression, and lid margin abnormality), tear condition (through tear break-up time and Schirmer test), and ocular surface condition (using corneal fluorescein staining). The symptom score was calculated by multiplying the sum of the scores (0–3) of five symptoms (range 0–15). The sign score was also calculated by summing the scores (0–3) of six different signs (ranging from 0 to 18). At the follow-up visit, the sum of each score (total score, range 0–33) was determined by adding the scores of signs (0–18) and symptoms (0–15).[12] Digital pressure was applied to release the meibum on the middle third of the lower eyelid. Depending on the worst secretion, it was graded as clear, hazy, turbid, or solid. Tear Break Up Time (TBUT) using a standardized fluorescein strip was measured and scored as 0 (over 10 seconds), 1(8–10 seconds), 2(5–7 seconds), and 3(less than 5 seconds). This score was computed by modifying panels from the oxford scale based on the ocular surface staining.[13] Schirmer-I test was also employed, and the results were rated as 0(>15 mm), 1(10–15 mm), 2(9–5 mm), and 3(>5 mm).[14] Clinical response at (6 months follow-up) was categorized into four Groups based on the reduction in total score (as a percentage): poor (1%–25%), fair (26%–44%), good (45%–75%), and excellent (76%–100%).[15] At a follow-up appointment, adverse effects were also noted.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Categorical variables were presented using percentage and frequency. Numerical variables such as age and scoring of signs and symptoms were shown as Mean and SD. Independent sample t-test and Chi-square test were applied to explore the inferential statistics. The *p*-value of 0.05 or less was taken as significant.

RESULTS

The mean age of the patients was 53.9±11.8 years, ranging from 26 to 79 years. Of the 172 participants, 82 (47.7%) were females, and 90(52.3%) were males. Detail of signs and symptoms and scoring in the study population are given in Table-I. Symptoms scores for burning sensation and foreign body sensation were significantly higher in patients taking Doxycycline compared to the Azithromycin Group (p=0.001). Dryness, eyelid oedema, and itching were also more in the Doxycycline Group, but this difference was not statistically significant (Table-II).

Table-I: Detail of Signs and Symptoms and Scoring in the Study Population (n=172)

Variables	Mean±SD	
	Male(n=90)	Female(n=82)
Burning	1.9±0.6	1.9±0.7
Itching	1.8±0.7	1.8±0.7
Foreign body sensation	1.7±0.6	1.6±0.8
Dryness	1.6±0.7	1.7±0.7
Eye lid edema	1.9±0.6	1.7±0.8
Lid margin abnormality	1.9±0.3	2.0±0.2
MG expression	1.6±0.5	1.6±0.5
Meibum quality	1.6±0.5	1.7±0.5
Ocular surface staining	1.2±0.6	1.3±0.6
Tear break up	1.1±0.7	1.2±0.7
Schirmer test result	1.1±0.7	1.1±0.7

On comparing the signs and their scoring between the two Groups, it was seen that total scores (pre-treatment and post-treatment) were more significant in the Doxycycline Group. Patients taking azithromycin showed lesser ocular surface staining, Schirmer test scoring, and more significant lid margin abnormalities (Table-III).

Table-II: Comparison of symptoms in Patients Having Meibomian gland Dysfunction Taking Azithromycin and Doxycycline (n=172)

	Azithromycin Group(n=86)	Doxycycline Group (n=86)	*p*-value
Burning	1.93±0.7	2.04±0.6	0.03
Itching	1.75±0.7	1.88±0.7	0.80
Foreign Body Sensation	1.56±0.8	1.81±0.7	0.001
Dryness	1.57±0.7	1.85±0.7	0.20
Eye lid edema	1.80±0.7	1.87±0.7	0.40
Total Score Pretreatment	8.67±2.0	9.42±2.0	0.90
Total Score Post Treatment	1.09±0.8	1.04±0.8	0.40

Table-III: Comparison of Signs in Patients Having Meibomian Gland Dysfunction Taking Azithromycin and Doxycycline (n=172)

	Azithromycin Group (n=86)	Doxycycline Group (n=86)	*p*-value
Lid Margin Abnormality	1.98±0.2	1.9±0.3	0.06
MG Expression	1.68±0.5	1.67±0.5	0.50
Meibium Quality	1.5±0.6	1.8±0.4	0.001
Occular Surface Staining	1.2±0.5	1.3±0.7	0.001
Tear Break up	1.1±0.7	1.2± 0.7	0.5
Schimmer Test Result	1.0±0.7	1.2± 0.7	0.2
Total Sign Score Pretreatment	8.7±2.0	9.3±2.5	0.01
Total Sign Score Posttreatment	1.1±0.7	1.2±0.9	0.02

No significant difference was seen in clinical response in patients of both Groups. Patients with a doxycycline treatment regime showed good clinical response with 45-75% improvement (Table-IV). Treatment with doxycycline yielded more significant complications, such as diarrhoea, nausea, and cramps. Headache was more associated with Azithromycin treatment, whereas Rash and blurring of vision were seen in the Doxycycline Group (Table-V).

Table-IV: Comparison of Clinical Response in Patients Having Meibomian Gland Dysfunction Taking Azithromycin and Doxycycline (n=172)

		Azithromycin Group (n=86)	Doxycycline Group (n=86)	*p*-value
Clinical Response	Poor (1-25%)	1(1.1%)	2 (2.3%)	0.3
	Fair (26-44%)	44(51.1%)	31(36.1%)	
	Good (45-75%)	39(45.3%)	51(59.3%)	
	Excellent (76-100%)	2(2.3%)	2(2.3%)	

DISCUSSION

General ophthalmic outpatient clinics commonly report chronic posterior blepharitis or meibomian gland dysfunction. Management of the meibomian gland includes lid hygiene, warm compresses, topical lubricants, and topical and oral antibiotics.[13,14] However, lid hygiene and warm compresses are the mainstay therapy for maintaining disease control. However, empirical oral antibiotic treatment is proposed if clinical symptoms are slow or inappropriate. Several antibiotics with anti-inflammatory properties may help control bacterial flora and inflammation of the eyelids.[15]

The clinical advantages of antibiotics, such as minocycline, doxycycline, and tetracycline, for treating meibomian gland dysfunction have been previously reported by aronowicz *et al.*[16] Dougherty *et al.*[17] Comparing our results about clinical efficacy and side effects of oral doxycycline with the study done by Yoo *et al.*[18] Doxycycline was equally effective in the management of blepharitis. However, it resulted in more gastrointestinal side effects, e.g. diarrhoea was found in 34(40%) out of 86(100%) patients in our study and abdominal cramps were found in 42(49%) out of 86(100%) patients.

Previous studies did not compare the systemic side effects of oral antibiotics used to treat blepharitis. These side effects include diarrhoea, abdominal pain, headache, blurred vision, and rashes. In papulopustular rosacea, Bakar *et al.*[19] explained the symptoms and side effects of systemic azithromycin for four weeks in the body. The margin of the eyelids and the inflammation of the eyes' surface were evaluated in its study. In a study by Al-Hity *et al.*[20] there were no side effects found with systemic Azithromycin for meibomian gland dysfunction. However, our study showed that 20(23%) out of 86(100%) patients had diarrhoea, and 30(35%) patients had nausea in the Azithromycin Group.

Table-V: Complications in Patients Having Meibomian Gland Dysfunction Taking Azithromycin and Doxycycline (n=172)

		Azithromycin Group (n=86)	Doxycycline Group (n=86)	*p*-value
Nausea	Yes	30(34.8%)	40(46.5%)	0.15
	No	56(65.2%)	46(53.5%)	
Diarrhea	Yes	20(23.3%)	34(39.5%)	0.02
	No	66(76.7%)	52(60.5%)	
Cramps	Yes	24(27.9%)	42(48.8%%)	0.007
	No	62(72.1%)	44(51.2%)	
Headache	Yes	3(3.4%)	0(0%)	0.08
	No	83(96.7%)	86(100%)	
Rash	Yes	0(0%)	1(1.1%)	0.09
	No	86(100%)	85(98.9%)	
Blurring of Vision	Yes	0(0%)	1(1.1%)	0.07
	No	86(100%)	85(98.9%)	

The clinical effects of both drugs on relieving ocular signs and symptoms are comparable. The main objective of MGD management is to stabilize the tear film, which is well-represented by fluorescein staining score, Schirmer I test, and Tear film break-up time analysis. Our study showed that oral azithromycin statistically improved Tear film break-up time and meibomian gland secretion patterns in patients with MGD after six months of treatment.

ACKNOWLEDGMENT

To all those who participated directly or indirectly in this study.

CONCLUSION

Meibomian gland dysfunction leads to tear film instability and direct damage to the ocular surface epithelium. This study supports the clinical efficacy and safety of oral Azithromycin therapy and doxycycline therapy for managing refractory or severe meibomian gland disease.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

WY & FH: Concept, data acquisition, drafting the manuscript, critical review, approval of the final version to be published.

TAJ & TAK: Data acquisition, data analysis, critical review, approval of the final version to be published.

MHS & MAM: Study design, drafting the manuscript, data interpretation, , approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Sabeti S, Kheirkhah A, Yin J, Dana R. Management of meibomian gland dysfunction: a review. Surv Ophthalmol 2020; 65(2): 205-217. https://doi.org/10.1016/j.survophthal.2019.08.007
2. Amescua G, Akpek EK, Farid M, Garcia-Ferrer FJ, Lin A, Rhee MK. Blepharitis preferred practice pattern. Ophthalmol 2019; 126(1): P56-93. https://doi.org/10.1016/j.ophtha.2018.10.019
3. Igami TZ, Holzchuh R, Osaki TH, Santo RM, Kara-Jose N, Hida RY. Oral azithromycin for treatment of posterior blepharitis. Cornea 2011; 30(10): 1145-1149. http://doi: 10.1097/ICO.0b013e318207fc42.
4. Bai Y, Ngo W, Khanal S, Nichols JJ. Characterization of the thickness of the Tear Film Lipid Layer in Meibomian Gland Dysfunction using high resolution optical microscopy. Ocul Surf 2022; 24:34-39. https://doi.org/10.1016/j.jtos.2021.12.011
5. Irfan S. Is Benign Essential Blepharospasm a "Benign" and/or an "Essential" Condition?. Am J Cosmet Surg 2018; 35(2): 83-91. https://doi.org/10.1177/0748806817740185
6. Adil MY, Xiao J, Olafsson J, Chen X, Lagali NS, Ræder S, et al. Meibomian gland morphology is a sensitive early indicator of meibomian gland dysfunction. Am J Ophthalmol 2019; 200: 16-25. https://doi.org/10.1016/j.ajo.2018.12.006
7. Xiao J, Adil MY, Chen X, Utheim ØA, Ræder S, Tønseth KA, et al. Functional and morphological evaluation of meibomian glands in the assessment of meibomian gland dysfunction subtype and severity. Am J Ophthalmol 2020; 209: 160-167. https://doi.org/10.1016/j.ajo.2019.09.005
8. Ngo W, Gann D, Nichols JJ. Impact of the 2011 International Workshop on Meibomian Gland Dysfunction on clinical trial attributes for meibomian gland dysfunction. Ocul Surf 2020; 18(1): 27-30. https://doi.org/10.1016/j.jtos.2019.10.003
9. Kimmitt BA, Moore GE, Stiles J. Comparison of the efficacy of various concentrations and combinations of serum, ethylenediaminetetraacetic acid, tetracycline, doxycycline, minocycline, and N-acetylcysteine for inhibition of collagenase activity in an in vitro corneal degradation model. Am J Vet Res 2018; 79(5): 555-561.https://doi.org/10.2460/ajvr.79.5.555
10. Ciloglu E, Özcan AA, Incekalan T, Unal F. The role of topical azithromycin in the treatment of meibomian gland dysfunction. Cornea. 2020; 39(3): 321-324. https://doi: 10.1097/ICO.000002233
11. De Benedetti G, Vaiano AS. Oral azithromycin and oral doxycycline for the treatment of Meibomian gland dysfunction: A 9-month comparative case series. Indian J Ophthalmol 2019; 67(4): 464-471. https://doi: 10.4103/ijo.IJO_1244_17.
12. Oliver C, Tadrous C, Docherty G, Warner S. Retrospective analysis of ophthalmology consults to a tertiary academic teaching centre. Can J Ophthalmol 2019; 54(4): 484-488. https://doi.org/10.1016/j.jcjo.2018.08.010
13. Ganesalingam K, Ismail S, Sherwin T, Craig JP. Molecular evidence for the role of inflammation in dry eye disease. Clin Exp Optom 2019; 102(5): 446-454. https://doi.org/10.1111/cxo.12849
14. Amescua G, Akpek EK, Farid M, Garcia-Ferrer FJ, Lin A, Rhee MK, et al. Blepharitis preferred practice pattern®. Ophthalmol. 2019; 126(1): P56-93. https://doi.org/10.1016/01254654556465j.ophtha.2018.10.019
15. Labro MT. Anti-inflammatory activity of macrolides: a new therapeutic potential?. J Antimicrob Chemother 1998; 41 (suppl_2): 37-46. https://doi.org/10.1093/jac/41.suppl_2.37
16. Aronowicz JD, Shine WE, Oral D, Vargas JM, McCulley JP. Short term oral minocycline treatment of meibomianitis. Br J Ophthalmol 2006; 90(7): 856-860. http://dx.doi.org/10.1136/bjo.2006.091579
17. Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. Invest Ophthalmol Vis Sci 1991; 32(11): 2970-2975.
18. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol 2005; 19(4): 258-263. https://doi.org/10.3341/kjo.2005.19.4.258
19. Bakar Ö, Demirçay ZE, Yuksel M, Haklar GO, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. Clin Exp Dermatol 2007; 32(2): 197-200. https://doi.org/10.1111/j.1365-2230.2006.02322.x
20. Al-Hity A, Lockington D. Oral azithromycin as the systemic treatment of choice in the treatment of meibomian gland disease. Clin Exp Ophthalmol 2016; 44(3): 199-201. http://dx.doi.org/10.1111/ceo.12666