Efficacy of Oral Azithromycin Versus Doxycycline in Treatment of Meibomian Gland Dysfunction

Ashesh Koirala[1], Samiksha Bhattarai[2], Sangeeta Shah[2], Bhuwan Govind Shrestha[2], Poonam Lavaju[2]

[1]Mechi Eye Hospital, Birtamode, Jhapa,
[2]B.P. Koirala Institute of Health Sciences, Dharan, Sunsari, Nepal

ABSTRACT

Introduction: Meibomian gland dysfunction (MGD) is usually treated with conservative methods. Adjunct therapy with oral Doxycycline has played a vital role in its treatment. Recently Azithromycin has also been introduced as a newer agent.

Objective: To compare the efficacy, safety and compliance of oral azithromycin with doxycycline over one year period in patients with Meibomian gland dysfunction (MGD).

Methodology: A randomised comparative clinical trial was performed among 284 subjects (age >35 years) with MGD. They were randomly divided into two groups A and B. Along with standard conservative management, Group A received oral 9-day azithromycin (500 mg for 3 consecutive days for 3 consecutive weeks) and group B received 14 days doxycycline (200 mg/day). A score comprising seven symptoms and seven signs (primary outcome) was recorded before and at first and second follow up after treatment and further analyzed.

Result: The mean symptoms and signs treated by Azithromycin group was lesser as compared to Doxycycline group in the first follow up ($p < 0.001$). However it was statistically insignificant at second follow-up ($p=0.043$). The group taking azithromycin had a much better overall response ($p = 0.006$). Gastrointestinal symptoms were the major side effects encountered, the group taking doxycycline experienced significantly more side effects ($p \leq 0.001$).

Conclusion: Both antibiotics were effective and safe for treating persistent MGD, but azithromycin was more effective. It required a lower dose, worked faster, and had a shorter treatment duration compared to doxycycline.

Key words: Azithromycin; doxycycline; meibomian gland dysfunction.

Financial Interest : Nil
Conflict of Interest : Nil

Received : 30.06.2023
Accepted : 30.10.2023

Corresponding Author
Dr Ashesh Koirala
Lecturer/ Consultant, Department of Ophthalmology
B.P. Koirala Institute of Health Sciences, Dharan, Nepal
E-mail: ashesh5522936@gmail.com

Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v16i1.46383

ISSN: 2072-6805, **E-ISSN:** 2091-0320

INTRODUCTION

Meibomian gland dysfunction (MGD) is one of the most common issues encountered by ophthalmologists. It is also a very common cause of chronic dry eye disease which is often missed easily. MGD is a very common and significant cause of posterior blepharitis, and its true frequency is likely underestimated (Foulks GN et al, 2003).

Prevalence of the disease around the world is found to be 38.9% (Hom et al, 1990), whereas the prevalence is higher (56.3%) in the Asian population as compared to the rest of the world (Siak JJK et al, 2012).

MGD is more common in the older age group due to related anatomical/histological changes. But it can also present in the younger age group with prevalent systemic or ocular dysfunction. (Hykin PG et al, 1992).

The 2011 International Workshop on MGD highlighted the significance of MGD in evaporative dry eye disease and also noted that it can occur on its own, without being associated with dry eyes. (Nichols KK et al, 2011)

MGD can be asymptomatic and detected only through gland expression, but it often presents with dry eye symptoms. Common symptoms include a foreign body sensation, burning, redness, tearing, and light sensitivity. Common signs include unclear or thickened meibum, pouting or plugging of meibomian gland openings, meibomian gland loss visible on meibography, increased eyelid margin thickness and redness, eyelash loss, misaligned eyelashes, and increased blood vessels in the eyelid. (Arita R et al, 2016)

Most cases of MGD can be managed conservatively with warm compresses to help with meibum secretion, mechanical eyelid massage and cleansing with shampoo and cotton buds to remove excess debris, and artificial tears to keep the eye lubricated. For severe or persistent cases, antibiotics with anti-inflammatory properties, either topical or systemic, may be recommended. Tetracycline and its derivatives being protein synthesis inhibitor acting on 30S ribosomal unit, has the ability to decrease inflammation and inhibit matrix metalloproteinase. Doxycycline, a long-acting derivative of tetracycline, is used to treat MGD due to its antimicrobial, anti-inflammatory, and anti-metalloproteinase effects. It also tends to have fewer side effects than tetracycline. Azithromycin, a macrolide antibiotic, inhibits protein synthesis by targeting the 50S ribosomal subunit and is particularly effective against Gram-negative bacteria. Both topical and oral azithromycin have been reported to improve the signs and symptoms of MGD and posterior blepharitis. (Kashkouli MB et al, 2015).

Oral azithromycin reduces the levels of proinflammatory mediators IL-1, IL-8, and MMP-9, while increasing the expression of TGF-β1, which helps alleviate MGD symptoms. (Zhang Lili Su et al, 2015)

Similarly, a low dose treatment with doxycycline significantly improved symptoms and signs in patients with chronic blepharitis in association with a decrease in MMP-9 activity by possible up regulation of TIMP-1 (Iovieno A et al, 2009)

Although previous studies have demonstrated the effectiveness of both oral doxycycline and oral azithromycin in treating MGD, there has yet to be a study in our country comparing their efficacy and patient compliance. Thus,

this study was carried out to evaluate efficacy (symptom and sign scores) and compliance of oral doxycycline and oral azithromycin in meibomian gland dysfunction

METHODOLOGY

This was a hospital based randomized comparative clinical trial conducted at the Department of Ophthalmology, B.P. Koirala Institute of Health Sciences (BPKIHS) from December 30, 2018 to December 31, 2019 after obtaining an ethical clearance from the Institutional Review Committee (IRC). All patients aged ≥35 years who were diagnosed with MGD were enrolled in the study. Those with pre-existing systemic comorbidities, pregnancy, lactation, and previous ocular surgery, presence of other ocular surface disease and history of drug allergy were excluded from the study. After taking informed consent detailed history and examination was done according to the proforma. Total of 284 patients (142 in each group) were assigned in two groups A and B by simple randomization (envelope technique). Apart from the standard conservative management of MGD in both groups like eyelid massage, maintenance of eyelid hygiene, warm compression twice a day (4-5 minutes) and frequent lubricating drops etc. Group A received oral Azithromycin (500 mg OD for three successive days in a week for 3 successive weeks) and Group B received oral Doxycycline (100mg BD for 14 successive days) as an adjunct therapy.

The parameters of the study included symptoms and signs as follows: The severity of the main symptoms like; itching, foreign body sensation, burning sensation, dryness, eyelid swelling was measured on 4-point categorical scale (0-3).

Table 1: Severity of the symptoms was graded into 4 grades (0-4) by slit lamp examination

Symptoms	Grade 0	Grade 1	Grade 2	Grade 3
Itching	None	Awareness	Desire to rub	Frequent rub
Foreign body sensation	None	Awareness	Desire to rub	Desire to close eyelids
Dryness	None	Awareness	Need eyedrops	Need frequent drops
Burning sensation	None	Awareness	Desire to rub	Frequent rub
Eyelid swelling	None	Noticeable	Obvious	Decrese in palpebral fissure

**Geerling G et al., 2011*

Table 2: Severity of the signs was graded into 4 grades (0-4) by slit lamp examination

Signs	Grade 0	Grade 1	Grade 2	Grade 3
Bulbar conjunctival redness	None	Pink	Light red	Bright red
Eyelid margin redness	None	Pink	Light red	Bright red
Lid margin debris	None	1-5	6-10	>10
Meibum expressibility*	All glands expressible	3-4 glands expressible	1-2 glands expressible	no glands expressible
Meibum quality*	Clear fluid	Cloudy fluid	Cloudy particulate fluid	Inspissated, like toothpaste material

**Geerling G et al., 2011*

The sum of these symptoms and signs were recorded as total symptom score and total signs score and evaluated and compared at each follow up.

Tear film break up time: less than 10 sec was considered abnormal. (Geerling G et al., 2011). Schirmer test I: Normal: ≥15mm, Mild :10-15 mm, Moderate: 5-10 mm, Severe :<5 mm. (Abelsdorff G et al, 1904). Blink rate: > 15/min was considered abnormal. (Geerling G et al, 2011)

For first follow up, Group A was called in the eye OPD after 10th day of receiving treatment and Group B after 7th day of receiving treatment (At the middle of the treatment) and the above-mentioned parameters were reevaluated and data were recorded. Second Follow-up was after 21 days for group A and 14 days for group B (After completion of the treatment). .

RESULT

In this comparative study, there were total of 284 patients equally divided into two groups by randomization. The mean age was 61.3 ±14.45 years in group A and 64.8 ±11.23 years in group B with male: female ratio of 1:1.46.

Clinical characteristics: Most of the patients had more than one symptom. The main presenting symptoms were itching, foreign body sensation, dryness, burning sensation, watering. These symptoms were seen in all the patients in both the groups.

Out of 284 patients enrolled in study mean symptoms and signs at the time of presentation were significantly decreased over successive follow-up after receiving treatment with both groups of drugs. It was also found that the mean value of symptoms and signs treated by Group A (Azithromycin) were much lesser as compared to Group B (Doxycycline) in the first follow up indicating faster recovery. However, there was no difference in mean value of symptoms and signs treated by both the drugs in second follow-up indicating almost similar final outcomes.

Side-Effects of the two drugs: Various side effects were experienced by the patients during treatment in both the groups (35.21%). The most common side effect experienced by Group A (Azithromycin) was abdominal discomfort found in eight (5.6%) patients, followed by diarrhea in six (4.2%) patients and decreased appetite in three (2.1%) The rest of the group didn't have any complaints throughout the treatment period. The most common side effect experienced by Group B (Doxycycline) was diarrhea in 28 (19.7%) patients followed by heartburn in 24 (17%), decreased appetite in 11 (7.8%), abdominal discomfort in nine (6.3%) and abdominal cramps in six (4.2%) patients, while 61 (43%) of patients did not have any side effects. Doxycycline had more side effects than azithromycin. The difference in the side effects between the two groups was statistically significant. ($p < 0.001$)

Compliance of Drugs between two groups: Patients receiving Group A drug (Azithromycin) 99 number of patients (69.71%) had good compliance to drug while the rest had poor drug compliance. Poor compliance in those patients due to longer duration and confusing dosing technique. But patients receiving Group B drug (Doxycycline) had good drug compliance as 111 patients (78.16%) found drug easy to be used and never missed the drug during the

Table 3 : Mean comparision of symptom,sign and total score(SD) of meibomian gland dysfunction at three follow ups

		Group A (n=142)	Group B (n=142)	p-value	CI (95%)	
					Lower	Upper
Pre-treatment	Symptoms	1.72(0.35)	1.72(0.33)	0.901	-0.07	0.08
	Sign	2(0.36)	1.87(0.36)	0.308	-0.04	0.13
	Total	1.81(0.32)	1.79(0.31)	0.511	-0.05	0.09
At First Follow-up	Symptoms	0.75(0.39)	1.26(0.30)	<0.001	-0.60	-0.43
	Sign	0.66(0.48)	1.33(0.40)	<0.001	-0.78	-0.57
	Total	0.70(0.41)	1.30(0.31)	<0.001	-0.68	-0.51
At 2nd Follow-up	Symptoms	0.73(0.36)	0.82(0.34)	0.043	-0.167	-0.002
	Sign	0.64(0.48)	0.81(0.47)	0.003	-0.28	-0.057
	Total	0.69(0.39)	0.82(0.37)	0.006	-0.22	-0.037

entire course, while the rest had poor drug compliance. Poor compliance in this group was due to some serious gastrointestinal side effects. But the results were statistically not significant (p>0.001)

Comparison of cost of two drugs: The total cost of tablet Azithromycin was found to be a bit more expensive than tablet Doxycycline the mean cost of Azithromycin was Rs 240 ($ 2.18) and that of Doxycycline was Rs 230 ($ 2.09), which was statistically significant (p<0.001).

DISCUSSION

In this study, mean age of the population treated was 64.852±11.23 yrs, which showed MGD more common among elderly age groups. This finding is consistent with various studies indicating that 33% of patients under 30 years old and 72% of patients over 60 years old had MGD (Baudouin C et al, 2016)

In our study, 58.5% of females over 65 years of age presented with symptoms of MGD, and this result was statistically significant (p=0.033). It was supported by a study that showed prevalence of MGD commonly to be found in females approaching menopause. It was thought that common denominator in both menopause and aging is androgen deficiency which was responsible and also with a possibility that hormonal deficit may promote both meibomian gland dysfunction and evaporative dry eye in these diverse conditions. (Sullivan DA et al., 2002)

We found a significant improvement in sign and symptoms of both group from pre- treatment signs (p=0.38) and symptoms (p=0.901) to post treatment at first follow up signs (p<0.001, 95% CI -0.78 to -0.57) and symptoms (p<0.001, 95% CI -0.60 to -0.43). Both were statistically significant. However, mean sign and symptom in group A (Azithromycin) showed significant improvement pre-treatment and at first follow up as compared to group B (Doxycycline). But not significant improvement in sign and symptoms of both groups from first and second

follow-up. In general, the effect of azithromycin was seen to be sooner and consistent throughout the period of treatment showing significant improvement in most patients.

Similar to our study, a study done by Kashkouli MB et al, (2015) showed statistically significant improvement with azithromycin when compared with doxycycline (p=0.001)

In this study, at the end of treatment course gastrointestinal side effects were reported by 81 patients (57%) receiving oral doxycycline. Most common side effect being diarrhea (19.7%), followed by heartburn in 24 (17%), decreased appetite in 11 (7.8%), abdominal discomfort in 9 (6.3%) and abdominal cramps in 6 (4.2%) patients. These side effects did not necessitate discontinuing the treatment, but some patients chose to stop taking the medication, which resulted in poor drug compliance. Dougherty JM et al, (1991) showed that the side effects of doxycycline in the treatment of MGD led to low compliances and even treatment abortion. Other studies by Kashkouli M et al., (2015) and Bakar et al., (2009) also reported similar GI side effects which were more in the patients receiving doxycycline group.

In our study, only 13.4% patients receiving oral azithromycin developed gastrointestinal side effect, abdominal discomfort being the common (5.6%) among them followed by diarrhea in 6 (4.2%) patients and decreased appetite in 3 (2.1%), which didn't require discontinuation of treatment.

In our study, it was found that the compliance of doxycycline group (52.9%) was slightly better than azithromycin group (47.1%) but the result was not significant (p=0.33). It was thought to be due to cheaper rate of doxycycline and easy to use as compared to azithromycin (cap Doxycycline 100mg twice a day for 14 days). However, in contrast to our findings, Kothari RN et al. (2017) observed that patients in the azithromycin group had better compliance compared to those in the doxycycline group, attributing this to the shorter duration of the treatment and fewer side effects. (Kothari RN et al, 2017)

The limitations of this study were: i) small sample size. In order to extrapolate the results of this study, a larger sample size would improve the external validity of the study and representativeness of the sample; ii) non-blinded study design. Patients may develop reasoning bias.

CONCLUSION

While both oral doxycycline and azithromycin were effective and safe for treating persistent MGD, azithromycin was noted to act more quickly and effectively, with fewer side effects.

REFERENCES

Abelsdorff G et al (1904). O. Schirmer: Studies on the physiology and pathology of tear secretion and tear drainage. v. Graefe's archive for ophthalmology 52 (2), 197-291. *Journal of Psychology and Physiology of the Sense Organs,* 37

Arita R et al (2016). Development of Definitive and Reliable Grading Scales for Meibomian Gland Dysfunction. American Journal of Ophthalmology 169, 125–137. doi:10.1016/j.ajo.2016.06.025

Bakar Ö. et al (2009). Ocular signs, symptoms and tear function tests of papulopustular rosacea patients receiving azithromycin. Journal of the European Academy of Dermatology and Venereology 23, 544–549. doi:10.1111/j.1468-3083.2009.03132.x

Basak S.K et al (2012). Prevalence of dry eye diseases in hospital-based population in West Bengal, Eastern India. J Indian Med Assoc. 110(11,789-94). PMID: 23785913.

Baudouin C. et al (2016). Revisiting the vicious circle of dry eye disease: A focus on the pathophysiology of meibomian gland dysfunction. British Journal of Ophthalmology. doi:10.1136/bjophthalmol-2015-307415

Chen A. et al (2017). Asymptomatic Meibomian Gland Dysfunction and Cardiovascular Disease Risk Factors in a Middle-Aged Population in Taiwan - A Cross-sectional Analysis. Scientific Reports 7. doi:10.1038/s41598-017-05368-z

Dougherty J.M. et al (1991). The role of tetracycline in chronic blepharitis: Inhibition of lipase production in staphylococci, in: Investigative Ophthalmology and Visual Science. pp. 2970–2975.

Foulks G.N, Bron A.J (2003). Meibomian gland dysfunction: A clinical scheme for description, diagnosis, classification, and grading. Ocular Surface 1, 107–126. doi:10.1016/S1542-0124(12)70139-8

Geerling G. et al (2011). The international workshop on meibomian gland dysfunction: Report of the subcommittee on management and treatment of meibomian gland dysfunction. Investigative Ophthalmology and Visual Science 52, 2050–2064. doi:10.1167/iovs.10-6997g

Hom M.M. et al (1990). Prevalence of meibomian gland dysfunction. Optometry and Vision Science 67, 710–712. doi:10.1097/00006324-199009000-00010

Hykin P. G, Bron A. J (1992). Age-Related Morphological Changes in Lid Margin and Meibomian Gland Anatomy. Cornea, 11(4), 334–342. doi:10.1097/00003226-199207000-00012

Iovieno A. et al (2009). In Vivo Characterization of Doxycycline Effects on Tear Metalloproteinases in Patients with Chronic Blepharitis. European Journal of Ophthalmology, 19(5), 708–716. doi:10.1177/112067210901900504

Kashkouli M.B. et al (2015). Oral azithromycin versus doxycycline in meibomian gland dysfunction: A randomised double-masked open-label clinical trial. British Journal of Ophthalmology 99, 199–204. doi:10.1136/bjophthalmol-2014-305410

Kothari R.N (2017). Observational comparative study to evaluate the efficacy of oral azithromycin and oral doxycycline in management of meibomian gland dysfunction 3, 107–111.

Nichols K.K. et al (2011). The international workshop on meibomian gland dysfunction: Executive summary. Investigative Ophthalmology and Visual Science 52, 1922–1929. doi:10.1167/iovs.10-6997a

Schaumberg D.A. et al (2011). The international workshop on meibomian gland dysfunction: Report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. Investigative Ophthalmology and Visual Science 52, 1994–2005. doi:10.1167/iovs.10-6997e

Siak J.J. et al (2012). Prevalence and risk factors of meibomian gland dysfunction: The Singapore malay eye study. Cornea 31, 1223–1228. doi:10.1097/ICO.0b013e31823f0977

Sullivan D. A. et al (2002). Androgen Deficiency, Meibomian Gland Dysfunction, and Evaporative Dry Eye. Annals of the New York Academy of Sciences, 966(1), 211–222. doi:10.1111/j.1749-6632.2002.tb04217.x

Zhang L. et al (2015). Effects of azithromycin on gene expression profiles of proinflammatory and anti-inflammatory mediators in the eyelid margin and conjunctiva of patients with meibomian gland disease. JAMA Ophthalmology 133, 1117–1123. doi:10.1001/jamaophthalmol.2015.2326