e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(8); 222-229

Original Research Article

A Comparative Study between Oral Azithromycin and Doxycycline for the Treatment of Meibomian Gland Dysfunction.

Manoj Kumar Mishra[1], Vaidehi Kumari[2], R. K. Singh[3]

[1]Assistant Professor, Department of Ophthalmology, SKMCH, Muzaffarpur, Bihar, India.

[2]Eye Specialist, Muzaffarpur, Bihar, India.

[3]Associate Professor and Head, Department of Ophthalmology, SKMCH, Muzaffarpur, Bihar, India.

Received: 25-06-2022 / Revised: 20-07-2022 / Accepted: 10-08-2022

Corresponding author: Dr. Manoj Kumar Mishra

Conflict of interest: Nil

Abstract

Objectives: This present study was to compare the clinical outcome between oral azithromycin and oral doxycycline for the treatment of meibomian gland dysfunction. **Methods:** A total of 100 meibomian gland dysfunction patients were enrolled in this study. All enrolled patients were divided into two groups (group A & group B). Each group had 50 patients. Group A patients were treated with Oral five days azithromycin (500mg on day 1 and then 250 mg/day). Group B patients were treated with first week oral doxycycline (200 mg/day) then rest 3 weeks oral doxycycline (100mg/day). On every visit the patient had undergone a detailed eye examination and various visual parameters had been rechecked and recorded.

Results: In azithromycin group mean of symptoms (8.01) and signs (8.87) at pre-treatment clinically improved to mean of symptoms (0.86) and signs (1.65) at last visit. Similarly in doxycycline group mean of symptoms (8.98) and signs (8.23) at pre-treatment clinically improved to symptoms (0.66) and signs (2.24) at last visit. when pre-treatment and last follow up symptoms and signs were compared in both groups, they showed highly significant differences ($p < 0.0001$), which indicates that both the treatment was equally effective. **Conclusions:** This present study concluded that the both oral azithromycin and oral doxycycline are the effective treatment of meibomian gland dysfunction. While oral azithromycin is comparatively better choice of treatment as compared to oral doxycycline for meibomian gland dysfunction in terms of better clinical improvement, shorter treatment duration, lesser side effects and lower cost.

Keywords: Meibomian gland dysfunction, Oral azithromycin, oral doxycycline

Introduction

Meibomian gland (MGD) dysfunction is a common eyelid condition which is responsible for developing evaporative dry eye [1].

Meibomian gland dysfunction (MGD) is a chronic problem of the meibomian glands, commonly characterized by terminal duct obstruction and or qualitative/quantitative changes in the glandular secretion. This

may result in alteration of the tear film, clinically apparent inflammation, and ocular surface disease [2].

It is one of the leading causes of ocular surface disease. Inflammatory mediators such as interleukin 1, matrix metalloproteinases, collagen production, nitric oxide, and activated B cells seem to play a key role in the development of this condition, which leads to hyperkeratinisation of the ductal epithelium and, therefore, obstruction of the MGs. The subsequent accumulation of meibum is responsible for inflammation and subsequent increased bacterial colonization of the lid margins, as seen in posterior blepharitis [3,4].

Many treatment options have been proposed (topical compresses and cleansers, topical lubricants, immunomodulation, nutritional supplements, oral and/or topical antibiotics, laser and light-based treatments, and surgery), although the refractory nature of the disease makes it largely incurable, thus necessitating expensive and long treatments [5,6].

Macrolide antibiotics, which have dual effects, have been indicated to be effective in treating MGD and have been the traditional systemic management for acne rosacea and posterior blepharitis, but the severe side effects of first generation macrolides limit their clinical use [8]. Compared with former macrolides, azithromycin is a semi-synthetic macrolide antibiotic of the second generation, which is characterized by a long half-life, good intraocular penetration, and broad antibacterial scope [9,10]. Previous studies have verified prolonged high-level ocular concentrations could be achieved after administering either oral azithromycin (OA) or topical azithromycin (TA); even after discontinuing the medication, relatively high concentrations still can be maintained in the conjunctiva [8, 9]. Objectives of our study was to compare the efficacy of oral Azithromycin and Doxycycline for the treatment of Meibomian gland dysfunction.

Material and Methods

This study was conducted in Department of Ophthalmology of SKMCH, Muzaffarpur, Bihar India during a period from October 2021 to April 2022. Entire patients signed an informed consent approved by institutional ethical committee of Shri Krishna Medical College and Hospital (SKMCH), Muzaffarpur, Bihar, India was sought.

A total of 100 patients of meibomian gland dysfunction were enrolled in this study. Exclusion criteria consisted of altered lid anatomy for any reason, contact lens wearing, veneral or atopic kerato-conjunctivitis, ocular and ocular adnexal surgery, pregnancy and breastfeeding, history of liver diseases, allergy to azithromycin or cyclones, systemic/ topical antibiotic taken within 1 month prior to inclusion and history of antipsychotic, antihistaminic and antidepressant medication.

A complete assessment, general physical examination and routine haematological investigations were performed to all patients. Assessment of visual acuity (distant and near vision) was done. Fundus examination was done by using Direct and Indirect ophthalmoscope (Using 20D lens). Biochemical investigations (Blood Sugar- Fasting and Post Prandial, HbA1C level) were performed.

Follow up: Patients were called for routine follow up at interval of 1 month, 3 months and 6 months.

Methods:

Various visual parameters in accordance with the Study Performa had been recorded. These include uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA) were done using Snellen's Chart. Severity of five main symptoms were measured on a four-point categorical

scale (0–3) according to patient's response to questions: itching, burning, foreign body sensation, dryness and eyelid swelling. Slit lamp examination was performed to assess and record the severity of six signs on a four-point categorical scale: meibomian gland secretion, number of plugged gland orifices, conjunctival injection, lid margin redness, lid margin debris, tear break up time (TBUT). Schirmer test 1 and schirmer test 2 performed.

All enrolled patients were divided into two groups (group A & group B). Each group had 50 patients. Group A patients were treated with Oral five days azithromycin (500mg on day 1 and then 250 mg/day). Group B patients were treated with first week oral doxycycline (200 mg/day) then rest 3 weeks oral doxycycline (100mg/day). On every visit the patient had undergone a detailed eye examination and various visual parameters had been rechecked and recorded specially, TBUT.

Doxycycline was instructed to be taken with a full glass of water while sitting for a few hours before going to bed and keeping a couple of hours between any supplement and doxycycline. 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. The total score (0–36) of each patent was calculated and recorded by adding the scores of symptoms (0–15) and signs (0–21) at each visit.

Statistical Analysis

Data was analysed by using SPSS software. Mean ± Standard deviation were observed. P-value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Observations

A total 100 meibomian gland dysfunction patients were included in this study. Out of which 64(64%) were male and 36(36%) were female. 100 patients were divided into two groups. Each group had 50 patients of meibomian gland dysfunction.

In Azithromycin group, there were 30 (60%) males and 20(40%) females. In doxycycline group there were 32(64%) males and 18(36%) females. In both groups male patients were more than female patients.

The mean age in azithromycin group of males was 47.43 ±8.43 and that of female was 45.12 ±9.72 and the mean age in doxycycline group of male was 49.64 ±11.25 and that of female was 50.45±11.32). doxycycline group mean age of both male and female was more than in azithromycin group.

In azithromycin group there were Diabetic (16%) and hypertensive (21%). In doxycycline group there were Diabetic (22%) and hypertensive (19%). The chief complaints in azithromycin group were Itching (100%), foreign body sensation (100%), burning (91%) and dryness (18%). The chief complaints in doxycycline group were foreign body sensation (100%), Itching (100%), burning (88%) and dryness (15%). No patient in both group had complained about eye lid swelling.

Table 1: Comparison of symptoms and signs among Azithromycin and Doxycycline group at pre-treatment and in all follow up.

	Azithromycin	Doxycycline	P-value
	Mean ± S. D	Mean ± S. D	
Pre-treatment			
Symptoms	8.01±1.71	8.98±1.56	0.0038
Sign	8.87±1.34	8.23±1.76	0.0435

Total	16.88±3.05	17.21±3.32	0.6059
1st follow up			
Symptoms	2.12±1.52	2.74±1.75	0.0615
Sign	3.75±1.67	2.54±1.58	0.0003
Total	5.87±3.19	5.28±3.33	0.3678
2nd follow up			
Symptoms	1.02±0.76	0.74±0.65	0.0056
Sign	2.24±0.78	2.13±0.92	0.3629
Total	3.02±1.0	2.67±1.65	0.0712
Last follow up			
Symptoms	0.86±0.34	0.66±0.54	0.0023
Sign	1.65±0.92	2.24±1.06	<0.0001
Total	2.13±1.34	1.98±1.11	0.3897

In both Azithromycin group and doxycycline group mean of pre-treatment and last follow up symptoms and signs were all most same. The p value of pre-treatment symptoms (0.008) and signs (0.0435) of both groups indicate that there was statistically significant difference among patients in both groups. The p value of last follow up visit symptoms (0.0023) and signs (<0.0001) of both groups indicate that there was highly statistically significant difference among patients in both groups.

In azithromycin group mean of symptoms (8.01) and signs (8.87) at pre-treatment clinically improved to mean of symptoms (0.86) and signs (1.65) at last visit. In doxycycline group mean of symptoms (8.98) and signs (8.23) at pre-treatment clinically improved to symptoms (0.66) and signs (2.24) at last visit. When pre-treatment and last follow up of symptoms and signs were compared in both group of patients , they showed highly significant differences ($p < 0.0001$), which indicates that both the treatment was equally effective in MGD patients.

Table 2: Comparison of pre-treatment and last follow up signs in Azithromycin and Doxycycline group.

Group	MG Secretion (Central lower eyelid)	Plugged MG orifice (central lower eyelid)	Bulbar conjunctival redness	Eyelid margin redness	Eyelid margin debris	Tear breakup time (seconds)
Pre-treatment						
Azithromycin	1.87±0.76	2.96±0.65	1.89±0.67	1.54±0.78	1.97±0.76	0.88±0.67
Doxycycline	1.92±0.65	2.34±0.84	2.12±0.64	1.67±0.65	1.98±0.67	0.45±0.64
p – value	0.6176	< 0.0001	0.0139	0.2019	0.9215	<0.0001
Last follow up						
	Plugged MG orifice (central lower eyelid)	Bulbar conjunctival redness		Eyelid margin debris		Tear breakup time (seconds)
Azithromycin	0.96±0.54	0.42±0.21		0.56±0.48		0.08±0.30
Doxycycline	0.92±0.54	0.11±0.04		0.53±0.40		0.21±0.41
p-value	**0.6010**	**<0.0001**		**0.6317**		**0.0112**

The p value of Side effects in both azithromycin and doxycycline groups at first visit (0.002) and at last follow up (0.012) indicate that there was significant difference among group, indicating that azithromycin group had fewer side effects than doxycycline group.

Table 3: Comparison of pre-treatment and last follow-up symptoms and signs in azithromycin and doxycycline group.

Group	Symptoms		P-value	Sign		P-value
	Pre-treatment	Last follow-up		Pre-treatment	Last follow-up	
Azithromycin	8.01±1.71	0.86±0.34	< 0.0001	8.87±1.34	1.65±0.92	<0.0001
Doxycycline	8.98±1.56	0.66±0.54	< 0.0001	8.23±1.76	2.24±1.06	<0.0001

Table 4: Comparison of Side effects in azithromycin and Doxycycline group patients in all follow up visits.

Drugs	Nausea	Abdominal Cramp	Diarrhoea	Decreased Appetite
1st visit				
Azithromycin	6(12%)	4(8%)	1(2%)	9(18%)
Doxycycline	10(20%)	7(14%)	0	14(28%)
2nd visit				
Azithromycin	3(6%)	2(4%)	2(4%)	3(6%)
Doxycycline	6(12%)	9(18%)	0	9(18%)
Last visit				
Azithromycin	2(4%)	1(2%)	0	1(2%)
Doxycycline	4(8%)	5(10%)	0	4(8%)

The percentage of all the side effects in azithromycin group like nausea 6(12%), abdominal cramp 4(8%), diarrhoea 1(2%) and loss of appetite 9(18%) at first follow up were significantly less than in doxycycline group like nausea 10(20%), abdominal cramp 7(14%), loss of appetite 14(28%).

The percentage value of all side effects in azithromycin group like nausea (2%), abdominal cramps 1(2%) and loss of appetite 1(2%) at last follow up were significantly less than in doxycycline group like nausea 4(8%), abdominal cramps 5(10%), and loss of appetite 6(12%).

Discussions

Meibomian gland dysfunction (MGD) is one of the leading causes of OSD. Inflammatory mediators such as interleukin 1, matrix metalloproteinases, collagen production, nitric oxide, and activated B cells seem to play a key role in the development of this condition, which leads to hyper keratinization of the ductal epithelium and, therefore, obstruction of the meibomian gland. The subsequent accumulation of meibum is responsible for inflammation and subsequent increased bacterial colonization of the lid margins, as seen in posterior blepharitis [3, 4].

Tetracyclines (oral or topical) have been found to be effective,[11] owing to their ability to modulate the expression of inflammatory mediators in vivo and in vitro and thus reduce the severity of the signs and symptoms of MGD [12,13]. Topical administration of tetracyclines, frequently in combination with local corticosteroids and other drugs, is considered as the second-line therapy, as are oral tetracyclines, [14,15] with the caveat that adverse effects can lead to dermatologic and gastrointestinal

complications, as well as hypersensitivity [3].

Consistent with Kashkouliet al.,[4] azithromycin administered in a short regimen (5 days) proved to be very effective, with minimal adverse effects, and patients remained stable throughout the course of the study. Other articles have used different dosages of azithromycin: Igami et al. [16] administered three cycles of 500 mg/day for 3 days with a 1-week interval, while Bakar et al. [17] opted for the same dosage administered weekly for 4 weeks. In this study, our dosage of azithromycin was chosen according to the doses reported in the literature and to address another important issue such as number and time interval between each dose. Doxycycline was administered in a longer regimen (1 month) and according to our previous protocol, which differs from those reported elsewhere in that it was less aggressive. The drug was less well tolerated and resulted in a reduced duration of stability in most patients, even if it was as effective as azithromycin in 10% of initially treated patients, thus suggesting that there is a subgroup of the population in which both antibiotics are equally effective.

In our study, there was statistically significant (0<0.0001) improvement seen in between pre-treatment and last follow up signs and symptoms in within group and between group patients.

Although the role of doxycycline in the treatment of MGD has been shown previously in Dougherty J et al, [18] its side effects and subsequently low compliance of the patients sometimes result in stopping treatment by himself.

In our study, gastrointestinal effects were reported by 17 patients (34%) in the first week after starting the doxycycline, decreased to 12(24%) at the end of the 1-month treatment course, and then to 8(16%) at the last follow. Bakar et al [17] reported that the side effects of systemic azithromycin were minimal and well tolerated in most patients treated for papulo-pustular rosacea. This study showed mild and temporary side effects which did not require treatment to be discontinued. The most common side effect was decreased appetite, which has also been reported by Greene et al. [19) However, we found 4(8%) patients still having decreased appetite 8 weeks after stopping the medication oral doxycycline which cannot be explained. As per Kashkouli M et al [4] side effects observed in azithromycin and doxycycline group at first follow up were almost equal (p=0.24), at 2nd follow up doxycycline group had significantly higher side effect (p=0.002) and at last follow up again both groups should similar side effects. (p=0.11). In this study, occurrence of side effects is more in doxycycline group compared to azithromycin group in all three follow up.

Thus, this present study was based on real-life situations and empirical experience and, in the present case, scientific hypotheses from the literature. Our study is limited by the absence of a control group.

Our study is also limited by the fixed dosages of both oral antibiotics administered. However, we tried to learn from previous experience to replicate experimental models based on randomization and masking that can provide practical clinical data for ophthalmologists.

Conclusions

This present study concluded that the both oral azithromycin and oral doxycycline are the effective treatment of meibomian gland dysfunction. While oral azithromycin is comparatively better choice of treatment as compared to oral doxycycline for meibomian gland dysfunction in terms of better clinical improvement, shorter treatment duration, lesser side effects and lower cost.

References

1. Jester JV, Parfitt GJ, Brown DJ. Meibomian gland dysfunction: hyperkeratinization or atrophy? BMC Ophthalmol 2015;15(1):3-11.
2. R N Kothari, Dipak B. Patel, Nirali Patel, Anjashi Patel, Toral Rajput. Observational comparative study to evaluate the efficacy of oral azithromycin and oral doxycycline in management of meibomian gland dysfunction. Indian Journal of Clinical and Experimental Ophthalmology 2017;3(1): 107-111.
3. Wladis EJ, Bradley EA, Bilyk JR,Yen MT, Mawn LA. Oral antibiotics for Meibomian gland-related ocular surface disease. A report by the American Academy of Ophthalmology. Ophthalmology 2016; 123:492-6.
4. Kashkouli MB, Fazel AJ, Kiavash V, Nojomi M, Ghiasian L. Oral azithromycin versus doxycycline in meibomian gland dysfunction: A randomised double-masked open-label clinical trial. Br J Ophthalmol 2015; 99:199-204.
5. Azithromycin and doxycycline Pricesp. Available from: www. costco.com 2016.
6. Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf 2004; 2:149-65.
7. Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. Eye (Lond) 2006; 20:635-44.
8. AlHity A, Lockington D. Oral azithromycin as the systemic treatment of choice in the treatment of meibomian gland disease. Clin Exp Ophthalmol. 2016; 44:199–201.
9. Tabbara KF, al-Kharashi SA, al-Mansouri SM, al-Omar OM, Cooper H, el-Asrar AM, et al. Ocular levels of azithromycin. Arch Ophthalmol. 1998; 116:1625–8.
10. Borchman D, Yappert MC, Foulks GN. Changes in human meibum lipid with meibomian gland dysfunction using principal component analysis. Exp Eye Res. 2010; 91:246–56.
11. Foulks GN, Borchman D,Yappert M, Kakar S. Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: A comparative clinical and spectroscopic pilot study. Cornea 2013; 32:44-53.
12. Sobrin L, LiuZ, Monroy DC, SolomonA, Selzer MG, Lokeshwar BL, et al. Regulation of MMP-9 activity in human tear fluid and corneal epithelial culture supernatant. Invest Ophthalmol Vis Sci 2000; 41:1703-9.
13. Siller SS, Broadie K. Matrix metalloproteinases and minocycline: Therapeutic avenues for fragile X syndrome. Neural Plast 2012; 2012:124548.
14. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol 2005;19: 258-63
15. Nelson JD, Craig JP, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II introduction. Ocul Surf 2017; 15:269-75.
16. Igami TZ, Holzchuh R, Osaki TH, Santo RM, Kara-Jose N, Hida RY. Oral azithromycin for treatment of posterior blepharitis. Cornea. 2011; 30:1145–9.
17. Bakar O, Demircay Z, Toker E, Cakir S. Ocular signs, symptoms and tear function tests of papulopustular rosacea patients receiving azithromycin. J Eur Acad Dermatol Venereol. 2009; 23:544–9.
18. Khan, A., Tidman D. M. M., Shakir, D. S., & Darmal D. I. Breast Cancer in Afghanistan: Issues, Barriers, and Incidence. Journal of Medical Research and Health Sciences, 2022;5(8), 2125–2134.
19. Dougherty J, McCulley J, Silvany R, Meyer D. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci.

Investigative ophthalmology & visual science. 1991 Oct;32(11):2970–2975.
20. Greene J, Jeng B, Fintelmann R, Margolis T. Oral azithromycin for the treatment of meibomitis. JAMA ophthalmology. 2013 Nov 10;132(1):121–122.