e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 14 (1); 114-118

Original Research Article

Pulsed Oral Azithromycin Therapy for Meibomian Gland Dysfunction: A Prospective Clinical Study

Dasari Gayatri[1*], Syam Kumar Addepalli[2], Yamalakonda Veerendra Goud[3], Chippada Tejaswi[4], Satyavaraprasad Chavali[5]

[1]Assistant Professor, Department of Ophthalmology, Gitam Institute of Medical Sciences and Research
[2]Associate Professor, Department of Pharmacology, Gitam Institute of Medical Sciences and Research
[3]Third year Post graduate, Department of Ophthalmology, Gitam Institute of Medical Sciences and Research
[4]Tutor, MSc Optometry, Department of Ophthalmology, Gitam Institute of Medical Sciences and Research
[5]Lecturer, MSc Optometry, Department of Ophthalmology, Gitam Institute of Medical Sciences and Research

Received: 18-10-2023 / Revised: 21-11-2023 / Accepted: 26-12-2023
Corresponding author: Dr. Dasari Gayatri
Conflict of interest: Nil

Abstract:

Introduction: Meibomian Gland Dysfunction (MGD) affects a substantial portion of the population, necessitating interventions beyond conservative measures. Tetracyclines, although effective, pose adverse effects. Previous trials suggest comparable outcomes for a 5-day pulsed oral azithromycin course and prolonged oral doxycycline in managing MGD. This study aims to assess the effectiveness of oral azithromycin in an Indian population.

Material and Methods: Conducted at Gitam Institute of Medical Sciences and Research from January to December 2023, this study enrolled 35 MGD patients (20 females, 15 males). Comprehensive three-month treatment regimens, including pulsed oral azithromycin (5 days), warm compresses, and lid massage and topical lubricants and azithromycin, were administered. Assessments included symptom relief, meibomian gland functionality, TBUT, lid margins, ocular staining and ocular inflammation.

Results: Post-treatment, majority experienced symptom relief, 80% with improved gland expressibility, 90% improved lid margins, with increase average TBUT and reduced ocular unflammation. Statistical analysis revealed significant improvements ($p < 0.05$) in symptoms, gland expressibility, gland pore opening, and other parameters.

Conclusion: This study validates the efficacy of short pulsed doses of oral azithromycin in alleviating MGD symptoms. This approach demonstrates potential advantages over prolonged doxycycline use, offering a short term patient-friendly and economically viable alternative. Larger studies are warranted to refine MGD management strategies in the Indian population.

Keywords: Pulsed dose oral azithromycin, Meibomian gland dusfunction.

Introduction

Meibomian gland dysfunction (MGD) is a prevalent ocular surface condition, observed in 39–50% of the population, and is a routine occurrence in the daily practice of ophthalmologists within their outpatient departments. [1] In the progression of this condition, inflammatory agents like interleukin 1, matrix metalloproteinases, collagen synthesis, nitric oxide, and stimulated B cells appear to have a significant influence. These factors contribute to the onset of hyperkeratinization in the ductal epithelium, resulting in the blockage of Meibomian Glands (MGs). The consequent build-up of meibum triggers inflammation and leads to an elevated presence of bacteria along the lid margins, characteristic of posterior blepharitis. [2] Although initial treatments typically involve conservative measures like warming, massaging the eyelids, and cleansing, along with the use of artificial tears, more assertive interventions become necessary for severe and resistant cases. [3-4] Tetracyclines, whether administered orally or topically, have demonstrated effectiveness due to their capacity to regulate the expression of inflammatory mediators

both in vivo and in vitro. This modulation contributes to a reduction in the severity of Meibomian Gland Dysfunction (MGD) signs and symptoms. The topical application of tetracyclines, often combined with local corticosteroids and other medications, is regarded as a second-line therapeutic approach, similar to oral tetracyclines. It is important to note, however, that potential adverse effects may lead to complications such as dermatologic issues, gastrointestinal problems, and hypersensitivity. [5-7]

Randomized controlled trials have demonstrated that a 5-day pulsed oral course of azithromycin yields comparable outcomes and equivalent benefits in managing Meibomian Gland Dysfunction when compared to the prolonged use of oral doxycycline. [2]

This study aims to investigate the effectiveness of oral azithromycin in the treatment of Meibomian Gland Dysfunction specifically in Indian population.

Material and Methods

This case series was carried out in the Department of Ophthalmology at Gitam Institute of Medical Sciences and Research, spanning from January 2023 to December 2023. A total of 35 patients diagnosed with Meibomian Gland Dysfunction participated in this study, comprising 20 females and 15 males. Patients presenting with symptoms such as itching and photophobia, significantly impacting their daily activities, underwent a meticulous examination to identify signs of Meibomian Gland Dysfunction (MGD). A thorough assessment of systemic history and medication usage was recorded. A comprehensive ophthalmic assessment was conducted, encompassing visual acuity testing and anterior segment examination utilizing a slit lamp.

The examination extended to the inspection of lid margins to detect indications of blepharitis, frothy secretion, and the functionality of meibomian glands was assessed by evaluating the expressibility of their secretions and identifying any blocked orifices. Ocular inflammation signs, including conjunctival congestion, were carefully observed, and ocular surface staining was identified. Quantitative measures, such as Schirmer's test and Tear Break-Up Time (TBUT), were employed to assess tear production and stability. This study included participants aged 20 years and above, who had been diagnosed with Meibomian Gland Dysfunction (MGD) and provided their informed consent for participation. Exclusion criteria involved patients with aqueous deficiency dry eye, Meibomian gland atrophy and those suffering from other ocular diseases accompanied by ocular inflammation.Patients enrolled in the study received a standardized treatment regimen designed to address Meibomian Gland Dysfunction (MGD) symptoms comprehensively. This therapeutic approach involved a combination of interventions for both eyes, including daily eyelid warm compresses and eyelid massage over a three-month period. Additionally, participants were prescribed topical lubricants four times daily for the same duration, along with nightly application of topical azithromycin ointment. In cases where ocular inflammation was present, a regimen of loteprednolone 0.5% was prescribed, with a tapering dose over a four-week period. To augment the topical treatments, all patients were administered oral azithromycin, with an initial dose of 500 mg on the first day followed by 250 mg once daily for the subsequent four days. Patients were advised to return for a follow-up assessment after three months. [8]

Following the three-month treatment period, a comprehensive ophthalmic reassessment was conducted, repeating all the previously mentioned tests and evaluations. Patients exhibiting less symptoms, improved meibomian gland secretion expressibility, opening of meibomian gland pores, absence of frothy secretion, healthy lid margins, no ocular inflammation, improved Tear Break-Up Time (TBUT), and no ocular staining were categorized as improvement.

Results

A total of 35 patients underwent examination, comprising 20 females and 15 males. Symptomatic relief, particularly in terms of itching and photophobia, was observed in the majority, with 28 out of 35 patients reporting a reduction in symptoms. Meibomian gland secretion expressibility showed improvement in 28 patients compared to the limited expressibility observed in 25 patients before treatment. Notably, opening of meibomian gland pores increased in 25 patients who initially had restricted openings in 21 cases. The presence of frothy secretion, an indicator of MGD, was completely absent post-treatment. Lid margins, deemed unhealthy in 11 patients, exhibited improvement in 32 patients. Ocular inflammation, initially present in 7 patients, was entirely absent after treatment. Tear Break-Up Time (TBUT) demonstrated a favorable increase from an average of 8 seconds to 11 seconds. Ocular staining, which serves as an indicator of surface abnormalities, was initially observed in 14 patients. 21 patients exhibited no ocular surface staining before treatment, and following the intervention, this number increased to 28 patients, signifying a notable reduction in ocular surface abnormalities post-treatment. The p value is calculated by chi-square test and t test where appropriate.

Table 1:

Ocular parameter	Pre treatment	Post treatment	p value
Symptoms (Itching, Photophobia)	35 patients	Reduced in 28 patients	<0.05
Meibomian gland secretion expressibility	Limited in 25 patients	Improved in 28 patients	<0.01
Opening of meibomian gland pores	Restricted in 21 patients	Increased in 25 patients	<0.05
Frothy secretion	Present in 18 patients	Absent in all	
Lid margins	Unhealthy in 11 patients	Improved in 32 patients	<0.001
Ocular inflammation	Present in 7 patients	Absent in all	<0.01
Tear Break Up Time (TBUT)	Average 8 seconds	Average 11 seconds	<0.05
Ocular staining	Present in 14 patients	Diminished in 28 patients	<0.01

Discussion:

Individuals diagnosed with Meibomian Gland Dysfunction (MGD) are prescribed a comprehensive treatment plan comprising a 6-week oral doxycycline course at a dosage of 200 mg once daily, in conjunction with warm compresses, topical lubricants, and topical azithromycin ointment. Doxycycline, an extended-acting derivative of tetracycline, demonstrates inhibitory effects on collagenase and possesses antichemotactic properties. The primary objective of this therapeutic approach is to stabilize the lipid layer of the tear film, consequently ameliorating symptoms associated with MGD. It is essential to note, however, that potential adverse effects, including dermatologic and gastrointestinal complications, as well as hypersensitivity, may arise with this treatment. [6,9]

Azithromycin classified as a broad-spectrum macrolide antimicrobial agent and possessing anti-inflammatory and immunomodulatory properties, represents a derivative of erythromycin. Its significantly enhanced efficacy against gram-negative bacteria, encompassing Enterobacteriaceae, and extensive coverage of gram-positive organisms contribute to its versatility as a therapeutic agent. Notably, azithromycin functions as an inhibitor of bacterial protein synthesis, exerting its antimicrobial effects through this mechanism. [10-12]

In a randomized clinical trial conducted by Kashkouli et al (2015), the efficacy and safety of oral azithromycin were compared with oral doxycycline in patients diagnosed with Meibomian Gland Dysfunction (MGD). The study's conclusion highlighted that both oral azithromycin and doxycycline demonstrated improvements in MGD symptoms. Notably, the 5-day oral azithromycin regimen was recommended due to its superior effectiveness in enhancing signs, achieving a better overall clinical response, and requiring a shorter duration of treatment. [2]

Similarly, a randomized controlled trial led by Giacomo De Benedetti et al in 2019 aimed to assess the efficacy and safety profile of oral azithromycin compared to doxycycline over a 9-month period. The conclusion of their study emphasized the effectiveness and safety of both antibiotics for persistent MGD. However, when considering the reduced dose and shorter course of therapy (5 days vs. 4 weeks), azithromycin exhibited superiority. Given the chronic nature of the disease and the observed improvement in some signs with minimal adverse effects, the study suggested that shorter therapy duration appears to be a safer and more logical alternative to longer regimens. [13]

In a systematic review and meta-analysis conducted by Tianchang Tao et al, the treatment of Meibomian Gland Dysfunction (MGD) with oral azithromycin was investigated, and the conclusion indicated that MGD can be effectively addressed through the administration of either oral or topical azithromycin. Notably, when considering the short term, topical azithromycin emerged as a superior option compared to oral azithromycin or doxycycline, particularly in enhancing the quality of the tear film. [14]

In a retrospective case note audit presented by Aws Al-Hity et al in 2016, the study encompassed an analysis of all patients who had been prescribed a 500 mg oral azithromycin regimen for a duration of 3 days. The findings of the audit suggest that azithromycin holds promise as a primary systemic treatment option for Meibomian Gland Dysfunction (MGD) in the adult population. This conclusion underscores the potential efficacy of a short-course oral azithromycin regimen in managing MGD, offering insights into its suitability as a first-line therapeutic choice for this condition. [15]

In our study, majority of patients reported symptomatic relief, specifically in terms of reduced itching and photophobia, with 28 out of 35 individuals experiencing an improvement in these symptoms. Statistical analysis revealed a significant association between the treatment and the observed reduction in symptoms ($p < 0.05$).

Furthermore, improvements in Meibomian gland functionality were evident, as reflected in the enhanced expressibility of meibomian gland secretions. A statistically significant difference was noted between pre-treatment and post-treatment

expressibility scores ($p < 0.01$). The increase in the opening of meibomian gland pores was also statistically significant ($p < 0.05$), reinforcing the positive impact of the treatment.

The absence of frothy secretion post-treatment is noteworthy, indicating a successful mitigation of this MGD-associated indicator. Lid margins, initially considered unhealthy in 11 patients, showed a statistically significant improvement in 32 patients after treatment ($p < 0.001$). Similarly, ocular inflammation, initially present in 7 patients, was entirely absent post-treatment, demonstrating a statistically significant reduction ($p < 0.01$).

Tear Break-Up Time (TBUT) demonstrated a favorable increase from an average of 8 seconds to 11 seconds post-treatment, and this improvement was statistically significant ($p < 0.05$). Additionally, the observed reduction in ocular staining, serving as an indicator of surface abnormalities, was statistically significant ($p < 0.01$).

The outcomes of this research align closely with the results obtained in previously conducted randomized clinical trials, as mentioned earlier exhibiting improvement in Meibomian Gland Dysfunction (MGD) symptoms through the administration of short pulsed doses of oral azithromycin for 5 days.

Conclusion

In conclusion, our study focused on investigating the effectiveness of oral azithromycin in treating Meibomian Gland Dysfunction (MGD) in the Indian population. The results demonstrated encouraging findings, with a majority of patients experiencing significant relief from itching and photophobia.

The improvements extended to the functionality of Meibomian glands, as evidenced by enhanced expressibility and increased opening of gland pores. Notably, the absence of frothy secretion, healthier lid margins, and the complete resolution of ocular inflammation further underscored the positive impact of the treatment. Statistical analysis revealed significant associations and differences between pre-treatment and post-treatment parameters. These findings align closely with previous randomized clinical trials, affirming the efficacy of short pulsed doses of oral azithromycin in improving MGD symptoms.

In addition, short pulsed oral azithromycin regimen not only demonstrated efficacy in managing Meibomian Gland Dysfunction (MGD) but also presents a potential advantage in avoiding the prolonged use of oral doxycycline at a dose of 200mg. This distinction is particularly significant given the well-documented adverse effects associated with prolonged doxycycline administration, including dermatologic and gastrointestinal complications, as well as hypersensitivity reactions. Importantly, this approach has potential economic benefits, as it may reduce the overall healthcare costs associated with the treatment of MGD. This regimen proves especially beneficial in developing nations where the elderly population is grappling with Meibomian Gland Dysfunction (MGD). Its advantages extend to economically disadvantaged individuals and patients preparing for cataract surgery, as it effectively minimizes the time required for them to be deemed fit for the surgical procedure.

Our study contributes valuable insights into the potential effectiveness of oral azithromycin as a therapeutic option for MGD in the Indian population. the pulsed oral azithromycin strategy contributes to a more patient-friendly and economically viable approach to managing MGD. Further research and larger-scale studies are warranted to validate and elaborate on these findings, paving the way for improved and tailored interventions in the management of MGD.

References

1. Yildiz E, Yenerel NM, Turan-Yardimci A, Erkan M, Gunes P. Comparison of the clinical efficacy of topical and systemic Systematic review and meta-analysis of treating meibomian gland dysfunction with azithromycin 1807 azithromycin treatment for posterior blepharitis. J Ocul Pharm Ther. 2018; 34:365–72.
2. 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.
3. Romero JM, Biser SA, Perry HD, Levinson DH, Doshi SJ, Terraciano A, et al. Conservative treatment of meibomian gland dysfunction. Eye Contact Lens 2004; 30:14-19.
4. Guillon M, Maissa C, Wong S. Eyelid margin modification associated with eyelid hygiene in anterior blepharitis and meibomian gland dysfunction. Eye Contact Lens. 2012; 38:319-25.
5. Foulks GN, BorchmanD,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.
6. 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.
7. 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.
8. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011; 52:2050-64.
9. Upaphong P, Tangmonkongvoragul C, Phinyo P. Pulsed Oral Azithromycin vs 6-Week Oral Doxycycline for Moderate to Severe Meibomian Gland Dysfunction: A Randomized Clinical Trial. JAMA Ophthalmol. 2023 May 1;141(5):423-429.
10. Girard AE, Girard D, English AR, Gootz TD, Cimochowski CR, Faiella JA, Haskell SL, Retsema JA. Pharmacokinetic and in vivo studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. Antimicrob Agents Chemother. 1987 Dec;31(12):1948-54
11. Retsema J, Girard A, Schelkly W, Manousos M, Anderson M, Bright G, Borovoy R, Brennan L, Mason R. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. Antimicrob Agents Chemother. 1987 Dec;31(12):1939-47.
12. Venditto VJ, Haydar D, Abdel-Latif A, Gensel JC, Anstead MI, Pitts MG, Creameans J, Kopper TJ, Peng C, Feola DJ. Immunomodulatory Effects of Azithromycin Revisited: Potential Applications to COVID-19. Front Immunol. 2021 Feb 12; 12:574425.
13. 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 Apr;67(4):464-471.
14. Tao T, Tao L. Systematic review and meta-analysis of treating meibomian gland dysfunction with azithromycin. Eye (Lond). 2020 Oct;34(10):1797-1808.
15. Al-Hity A, Lockington D. Oral azithromycin as the systemic treatment of choice in the treatment of meibomian gland disease. Clin Exp Ophthalmol. 2016 Apr;44(3):199-201.