Check for updates

COMPARISON OF EFFICACY OF 1-WEEK ORAL AZITHROMYCIN WITH 2-WEEK TOPICAL 1% AZITHROMYCIN EYE DROPS IN THE TREATMENT OF POSTERIOR BLEPHARITIS

Adnan Ahmad✉, Mubashir Rehman

Department of Opthalmology, Qazi Hussain Ahmed Medical Complex, Nowshera - Pakistan

Address for correspondence:
Adnan Ahmad
Department of Opthalmology, Qazi Hussain Ahmed Medical Complex, Nowshera - Pakistan

E-mail:
dradnanahmad@hotmail.com

Date Received:
Jan 11th, 2022
Date Revised:
July 18th, 2022
Date Accepted:
Aug 6th, 2022

This article may be cited as
Ahmad A, Rehman M. Comparison of efficacy of 1-week oral azithromycin with 2-week topical 1% azithromycin eye drops in the treatment of Posterior Blepharitis. J Postgrad Med Inst 2022;36(3):145-9. http://doi.org/10.54079/jpmi.36.3.3041

ABSTRACT

Objective: To assess the efficacy of 1-week of oral azithromycin (AM) with 2 weeks of topical azithromycin eye drops in posterior blepharitis patients.

Methodology: In this quasi-experimental study, 80 participants were enrolled (>45 years old) with meibomian gland dysfunction (MGD) at the Department of Ophthalmology, Qazi Hussain Ahmed Medical Complex, Nowshera from January to September 2020. Patients were allocated to get either 1-week of oral azithromycin (500mg/day) or 2 weeks of continued topical azithromycin 1% once daily. A scoring system was devised which included 5 symptoms and 7 signs which were assessed at baseline and follow-ups on 1st, 2nd, and 4th-week post-therapy. The total score was documented at the end of the study by summing up the symptoms and signs score.

Results: The objective and subjective features of the disease showed improvement with either therapy, however, 2 weeks of topical azithromycin 1% once a day showed significantly more improvements (p= 0.008). We observed improvement in the symptoms of disease in both groups but that didn't achieve the level of statistical significance between the groups (0.242). Systemic side effects in the form of anorexia, nausea, and gastrointestinal upsets were negligible in topical Azithromycin as compared to its oral form.

Conclusions: Both oral and topical forms of drugs effectively ameliorated the symptoms of posterior blepharitis, however, 2 weeks of topical azithromycin 1% once a day also addressed the signs of the disease along with benefits of having better tolerance (least gastrointestinal upsets) leading to improved compliance in comparison to its oral form.

Keywords: Azithromycin; Posterior Blepharitis; Meibomian Gland Dysfunction (MGD).

INTRODUCTION

The meibomian glands (MGs) produce an oily secretion known as meibum which comprises different polar and non-polar lipids. The meibum forms the outer layer of the tear film and it mainly serves to prevent the middle aqueous layer from being evaporated in addition to that it also provides a clear refractive surface for the cornea and an important protective layer against microorganisms and debris in the external environment.[1] Posterior blepharitis is mainly due to terminal ductile blockage with altered meibum. The obstructive phenomenon is governed by certain indigenous factors, such as age, gender, and hormonal imbalances as well as by external factors such as topically applied drugs. The blockage may result in intra glandular cystic dilatation, meibomian gland degeneration, loss of glands, and reduced meibum production. Inadequate amounts of lipids may contribute toward evaporative loss with high tear film osmolality resulting in an unstable and altered tear film, enhanced microbial colonization over the lid margin, evaporative dry eyes, and ocular surface inflammatory degradation. Meibomian gland dysfunction (MGD) may lead to altered tear film composition, ocular irritation, clinically apparent inflammatory changes, and ocular surface abnormalities.[1] While standard therapeutic modalities like lid scrubbing measures and massaging along with lubricants are used as first-line therapeutic approaches but severe and resistant disease requires more stringent treatment.[2,3]

Posterior blepharitis with severe intensity and indolent nature requires therapy with both topical as well as systemic antibiotics with anti-inflammatory properties recommended and tetracyclines are the ones used for their anti-inflammatory properties along with inhibitory effects upon matrix metalloproteinases (MMP).[4-6]

Some studies have shown the effectiveness of systemic azithromycin (AM) in minimizing the inflam-

matory process in posterior blepharitis. It blocks the inflammatory cascade pathway which is responsible for the liberation of mediators like cytokines and free radicals and its antimicrobial properties include effective coverage against gram-negative bacteria. AM both topically as well as in an oral form markedly ameliorate the subjective and objective aspects of posterior blepharitis.[6-8] Studies conducted so far have convincingly shown the therapeutic effects of both AM as well as tetracyclines in their oral forms for the management of posterior blepharitis, however, there is yet any trial undertaken that compares the effectiveness of oral AM vs its topical form for the treatment of posterior blepharitis. Hence, we comparatively designed this trial to elucidate the therapeutic effects of oral AM vs its topical form in the management of posterior blepharitis, who were resistant or unresponsive to the conventional therapeutic approaches like eyelid scrubbing and massaging along with the use of lubricants.

METHODOLOGY

This quasi-experimental study was undertaken according to Good Clinical Practice Guidelines, and the tenets of the Declaration of Helsinki and was approved by the Institutional Ethical Review Board (IERB). A total of patients (48 women and 32 men) were enrolled for the study by online sample size calculator by taking consideration into the prevalence of the disease. All the subjects were diagnosed with Meibomian Gland Dysfunction (MGD) according to clinical signs and symptoms and were enrolled in the study into two equal groups of 40 patients each, between January and September 2020 at Department of Opthalmology, Qazi Hussain Ahmed Medical Complex, Nowshera. Informed consent was obtained from all participants. Participants (> 45 years.) with posterior blepharitis non-responsive to standard conventional therapies like eyelid scrubbing and massaging (5 min. 2 times/day) and lubricants (4-5 times/day) were selected for the study. While patients with structural eyelid abnormalities, inflammatory dermatological disorders, any systemic/ topical antibiotics taken within 4 weeks before the trial, those having any hepatic disorders, conceiving and lactating mothers, contact lens users, known history of allergy to the study drugs, vernal kerato-conjunctivitis and any lid surgeries undertaken were excluded. Different outcome measures were assessed including five subjective features (feeling of warmness, irritation, ocular grittiness, desiccation in eyes, and lid edema) and seven objective features (Quality of meibum, clogging of gd. openings, bulbar hyperemia, lid margin hyperemia, lid margin crusts, ocular surface erosions, and tear film breakup time (T-BUT). Symptoms were scored on a 4-point scale (0-3, shown below in table 1) according to the patient's response to questions. Signs were assessed by slit lamp examination and scored on a 4-point scale (0-3, shown below in table 1) Meibum was expressed by applying digital pressure with the index finger on the upper eyelid at its center. It was labeled as transparent, hazy, dirty, or hard consistency depending on its severity. Clogging of tarsal glands was graded as 0 (clear openings of glands in the central part of upper lid), 1 (< 1/3 of openings contained viscous/ dirty secretion), 2 (1/3 to 2/3 of the openings contained viscous/dirty secretion), 3 (> 2/3 of the openings contained viscous/dirty secretion). Hyperemia of the bulbar conjunctiva was labeled as clear, pinkish hue, faint reddish, and blood red based on increasing severity under a slit lamp. Hyperemia of the upper lid margin was also labeled as clear, pinkish hue, faint reddish, and blood red based on increasing severity under a slit lamp. Similarly, Lid margin (upper) crusting was assessed based upon no. of crusts visible under the slit lamp. T-BUT was recorded and graded as 0 (> 10 s), 1 (8–10 s), 2 (5–7 s), and 3 (less than 5s). The time for the first split was recorded and graded. The staining of the ocular surface was done after recording the T-BUT using the 4-point scale (0-3, as shown below in table 1). The patient's upper lid was lifted and the whole cornea/ocular surface was observed and assessed. The nasal and temporal inter-palpebral conjunctiva was also assessed by asking the patient to look temporally and nasally respectively. The number and pattern of dots on the cornea and conjunctiva were recorded (Table 1).

Posterior blepharitis was assigned to the patient if he/she has three subjective features and two objective features of the disease with the least severity score of two (2) for each. All pre-treatment and post-treatment observations, recordings, and evaluations were done by an observer who was blinded to the type of treatment given to that group of patients. Patients were distributed to either oral azithromycin 500mg/day (Tab. Macrobac^{R} 500 mg, Asian Continental, Pak.) regimen or topical azithromycin 1% once daily (Zithrosan 1%, Sante, Pak.) treatment regimen. Patients were also advised to carry on their conservative therapy e.g. eyelid scrubbing and massaging 2 times/day along with lubricants 4 times/day. The symptoms and signs scores were recorded before commencement of the therapy and at different time intervals during the trial i.e. 1st week, 2nd week, and 4th week (three follow-up visits). Each patient's symptoms and signs were scored from 0 to 3. The total symptom score was calculated by addition of individual symptom score (0-3) of five symptoms which resulted in a score range of 0-15, similarly, the signed score was also calculated by adding the individual score (0-3) of seven signs which resulted in score range of 0-21.

The total score of each patient was calculated by adding the symptom and sign score of that patient. The above-mentioned outcome variables were evaluated at follow-ups for each patient. The data was analyzed by using SPSS version 20.0.

RESULTS

A total of 80 patients (48 women and 32 men) were enrolled in the trial between January 2020 to September 2020. The mean age of patients in the oral azithromycin group (n=40) was 58.0 ± 16.2 (male=14, female= 26) and the mean length for the illness was 11.2 weeks. The mean age of patients in the topical azithromycin group (n=40) was 55.0 ± 14.8 (male=18, female= 22) and the mean length for the illness was 11.4 weeks.

Both the groups were almost identical in baseline characteristics. The main complaints of patients in Group A were occular grittiness (n=14, 35%), dessication in eyes (n=13, 32.5%), feeling of warmness (n=6, 15%), irritation (n=5, 12.5%), and lid edema (n=2, 5%) while the main complaints of patients in Group B were dessication in eyes (n=15, 37.5%), occular grittiness (n=12, 30%), irritation (n=8, 20%), feeling of warmness (n=4, 10%), and lid edema (n=1, 2.5%).

The symptomatic benefit was attained in both groups but statistically insignificant between the groups (p = 0.242). However statistically significant results were obtained as far as improvement in the clinical signs was concerned between the groups (p= 0.008) as shown in Table 2. Although at 1st and 2nd follow ups there wasn't any marked improvement in signs, however, significant improvement was noted in topical azithromycin 1% at the final visit. Hence, the mean total score achieved significant improvement in the topical azithromycin 1% group at the end of therapy. Systemic side effects in the form of anorexia, nausea, and gastrointestinal upsets were negligible in the topical azithromycin as compared to its oral form.

DISCUSSION

Posterior blepharitis is a chronic inflammatory disease of the lid margins most commonly caused by the meibomian gland dysfunction. Several treatment protocols exist

Table 1: Scoring of signs & symptoms in 80 patients with posterior blepharitis

Symptoms/Signs	Score 0	Score 1	Score 2	Score 3
Irritation	Negative	Positive feeling	Urge for rubbing	Frequently rubbing
Ocular grittiness	Negative	Positive feeling	Urge for rubbing	Urge to squeeze lids
Feeling of eye desiccation	Negative	Positive feeling	Use of lubricants	Using drops most of the time
Feeling of warmness in eyes	Negative	Positive feeling	Urge for rubbing	Rubbing eyes most of the time
Lid edema	Negative	Slight	Prominent	Reduced fissure height
Quality of meibum	Transparent	Hazy	Dirty	Hard secretion
Clogging of gd. openings	Clear	< 1/3rd	1/3rd -2/3rd	>2/3rd
Bulbar hyperemia	Clear	Pinkish	Faint reddish	Blood red
Eyelid margin hyperemia	Clear	Pinkish	Faint reddish	Blood red
Eyelid margin crusts	Clear	1-5	6-10	>10
T-BUT	>10sec	8-10sec	5-7 sec	<5sec
Ocular surface erosions (assessed by fluorescein stain)	Clear	Mild < 1/3	Moderate 1/3- 1/2	Severe > 1/2

Table 2: Mean symptoms/signs and total score of study participants at baseline and follow-ups.

Variables		Oral azithromycin 500mg (40)	Topical azithromycin 1% (40)	P-Value
Pre-treatment	Symptom	7.20 ± 2.11	7.08 ± 2.26	0.778
	Sign	11.04 ± 2.48	10.19 ± 2.78	0.371
	Total	18.22 ± 4.19	17.41 ± 3.51	0.596
First follow-up	Symptom	5.76 ± 1.88	5.66 ± 2.20	0.896
	Sign	8.30 ± 2.32	7.49 ± 2.81	0.294
	Total	14.11 ± 3.66	13.19 ± 3.12	0.598
Second follow-up	Symptom	5.15 ± 1.78	4.80 ± 2.14	0.512
	Sign	7.18 ± 2.10	6.36 ± 2.44	0.202
	Total	12.28 ± 3.49	11.20 ± 3.12	0.462
Third follow-up	Symptom	4.88 ± 2.10	4.02 ± 2.11	0.242
	Sign	6.30 ± 1.88	4.19 ± 2.50	0.008
	Total	11.04 ± 3.76	8.28 ± 3.19	0.035

for its management but there is no general consensus.

In the quest for better therapy we observed statistically significant improvement in the clinical signs of the disease ($p = 0.008$) with topical azithromycin 1% as compared to its oral form, however we didn't observe any significant difference ($p = 0.242$) in the improvement of symptoms between topical and oral form. Topical azithromycin was better tolerated by the patients (least gastrointestinal upsets) as compared to oral form.

In the existing research pool, there are numerous studies done that evaluated the significance of topical and oral azithromycin for the management of Posterior blepharitis.[6,9-16] The efficacy of 1.5% topical azithromycin was revealed by Balci and Gulkilik et al in the short duration treatment for MGD observing marked clinical improvement.[9] While in a study conducted by Zandian et al[11] topical azithromycin was having same response as oral antibiotics in the management of MGD showing symptomatic improvement an observation similar to our study findings. Another study was conducted by Al-Hity and Lockington et al[12] evaluating the comparative analysis of oral azithromycin and Tetracycline in MGD. However, oral azithromycin showed better efficacy (marked improvement of clinical signs of conjunctival hyperemia and corneal staining) with shorter duration of therapy, it was also observed improvement with oral azithromycin with one week therapy only. The biochemical characteristics of meibomian gland secretion and symptoms of patients with posterior blepharitis was treated with topical azithromycin and oral Tetracycline by Foulks et al[6] and they suggested that oral therapy was relatively less efficacious in relieving gritty ocular sensations and the signs of clogging of meibomian orifices and meibum quality and observed marked improvement in meibum quality with topical azithromycin therapy. The Pharmacokinetics reveals that the OD (once a day) or BID (twice a day) dosing of azithromycin is adequate.[13] The efficacy of oral azithromycin on MGD was revealed in one of the study conducted by Igami et al[4] a scoring system was devised for both signs and symptoms of the disease and were accordingly graded in all the patients. They concluded that oral azithromycin achieved statistically significant improvement in T-BUT and meibomian gland secretions pattern. However, only slight improvement was noted in the Schirmer test, OSDI score and corneal staining score. We observed symptomatic improvement with oral therapy almost similar to topical therapy, however significant improvement was observed that the clinical signs of disease with topical azithromycin are better in efficacy and their local tissue accumulation is enhanced with absorption.

Yildiz et al[17] compared topical and systemic azithromycin in the management of posterior blepharitis. It was reported that the topical therapy was efficacious than oral as far as improvement in lid margin changes were concerned. It was concluded that topical form may be associated with far better ocular tissue penetration and accumulation, hence improved anti-inflammatory and anti-bacterial efficacy as compare to oral therapy. These findings are supporting our study results showing better efficacy of topical over oral therapy in MGD. Fadlallah et al[18] evaluated the efficacy of 4 weeks therapy with 1% topical azithromycin and observed marked improvement with no significant relapse until 12th week.[18] In the similar study by Balci and Gulkilik et al[9] significant improvement in the clinical signs were observed at the end of 4th week, however these improvements lasted for only 3 months after cessation of therapy.

In our study both the groups achieved success in improving the symptoms of patients suffering from MGD as shown in table 3 above, however the topical azithromycin 1% achieved marked improvement in resolving the signs of disease ($p = 0.008$) resulting in reduction of the mean signs and total score at the end of therapy by using it for 2 weeks in once a day regimen. The reason behind the beneficial effect of topical therapy could be due to the fact that locally applied drug produced rapid accumulation in the tissues with exaggerated anti-inflammatory and anti-microbial activity, resulting in an enhanced therapeutic response at tissue and cellular level with better effects on the disease process.

CONCLUSION

It is advocated that both the topical and oral forms of azithromycin are effective in the treatment of posterior blepharitis as both exerted their beneficial effects upon the symptoms of the disease, however, the topical 1% AM in once a day regimen for 2 weeks caused more significant effects upon the signs of disease along with benefits of having better tolerance (least gastrointestinal upsets) by the patients leading to improved compliance in comparison with its oral form. Main limitation of the study was that we didn't perform long follow ups on patients after treatment so as to see for how long the therapy effect lasted in the patients and any need for repeating the doses for sustained effect.

REFERENCES

1. Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, et al. The international workshop on meibomian gland dysfunction: Executive summary. Invest Ophthalmol Vis Sci. 2011; 52(4):1922-9. DOI:10.1167/iovs.10-6997a.
2. 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(1):14-19. DOI:10.1097/01.ICL.0000095229.01957.89.
3. Guillon M, Maissa C, Wong S. Eyelid margin modification associat-

ed with eyelid hygiene in anterior blepharitis and meibomian gland dysfunction. Eye Contact Lens. 2012;38(5):319-25. DOI:10.1097/ICL.0b013e318268305a.
4. Igami TZ, Holzchuh R, Osaki TH, Santo RM, Kara-Jose N, Hida RY. Oral azithromycin for treatment of posterior blepharitis. Cornea. 2011; 30:145-9. DOI:10.1097/ICO.0b013e318207fc42.
5. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, 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(4):2050-64. DOI:10.1167/iovs.10-6997g.
6. 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. DOI:10.1097/ICO.0b013e318254205f.
7. Foulks GN, Borchman D, Yappert M, Kim SH, McKay JW. Topical azithromycin therapy for meibomian gland dysfunction: clinical response and lipid alterations. Cornea. 2010;29(7):781-8. DOI:10.1097/ICO.0b013e3181cda38f.
8. Bertino JS Jr. Impact of antibiotic resistance in the management of ocular infections: the role of current and future antibiotics. Clin Ophthalmol. 2009;3:507-21. DOI:10.2147/opth.s5778.
9. Balci O, Gulkilik G. Assessment of efficacy of topical azitromycin 1.5% ophthalmic solution for the treatment of meibomian gland dysfunction. Clin Exp Optom. 2018; 101:18-22. DOI:10.1111/cxo.12557.
10. Hosseini K, Lindstrom RL, Foulks G,. Arandomized, double masked, parallel-group, comparative study to evaluate the clinical efficacy and safety of 1% azithromycin-0.1% dexamethasone combination compared to 1% azithromycin alone, 0.1% dexamethasone alone, and vehicle in the treatment of subjects with blepharitis. Clin Ophthalmol. 2016;10:1495-1503. DOI:10.2147/OPTH.S110739.
11. Zandian M, Rahimian N, Soheilifar S. Comparison of therapeutic effects of topical azithromycin solution and systemic doxycycline on posterior blepharitis. Int J Ophthalmol. 2016; 9:1016-19. DOI:10.18240/ijo.2016.07.14.
12. Al-Hity A, Lockington D. Oral azithromycin as the systemic treatment of choice in the treatment of meibomian gland disease. Clin Exp Ophthalmol. 2016;44:199-201. DOI:10.1111/ceo.12666.
13. Friedlander MH, Protzko E. Clinical development of 1% azithromycin in DuraSite, a topical azalide anti-infective for ocular surface therapy. Clin Ophthalmol. 2007;1:3-10.
14. Luchs J. Azithromycin in DuraSite for the treatment of blepharitis. Clin Ophthalmol. 2010; 4:681-8. DOI:10.2147/opth.s6370.
15. John T, Shah AA. Use of azithromycin ophthalmic solution in the treatment of chronic mixed anterior blepharitis. Ann Ophthalmol (Skokie). 2008;40:68-74.
16. Luchs J. Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis. Adv Ther. 2008;25:858-70. DOI:10.1007/s12325-008-0096-9.
17. Yildiz E, Yenerel NM, Turan-Yardimci A, Erkan M, Gunes P. Comparison of the Clinical Efficacy of Topical and Systemic Azithromycin Treatment for Posterior Blepharitis. J Ocul Pharmacol Ther. 2018 May;34(4):365-372. DOI 10.1089/jop.2017.0095
18. Fadlallah A, Rami HE, Fahd D,. Azithromycin 1.5 % ophthalmic solution: efficacy and treatment modalities in chronic blepharitis. Arq Bras Oftalmol. 2012;75:178-182. DOI:10.1590/s0004-27492012000300006.

Author's Contribution

AA conceived the idea, designed the study, performed data analysis and wrote and edited the manuscript. MR contributed in the literature search, and collection of data performed the statistical analysis and reviewed the manuscript for final approval. 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.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.