RESEARCH ARTICLE

Comparative study evaluating the efficacy of topical azithromycin versus oral doxycycline in the treatment of meibomian gland dysfunction

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Abstract

Objective: To assess the efficacy of topical azithromycin drops versus oral doxycycline therapy in meibomian gland dysfunction.

Method: The prospective randomised trial was conducted from December 2019 to June 2020 at the Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan, and comprised patients of either gender aged 26-42 years having long-standing posterior blepharitis / meibomian gland dysfunction. The subjects were randomised into two equal groups. Both the groups were advised to do warm compresses and lid massage three times a day for 5 min. each for 4 weeks. In addition, group A received azithromycin 1% drops 2 times/day for 1 week, followed by once a day for 3 weeks, while group B received oral doxycycline 100mg once a day for 4 weeks. Baseline, midstream at 2 weeks and post-intervention status, including subjective symptoms, were compared.

Results: Of the 60 subjects enrolled, there were 30(50%) in each of the two groups; 32(53.3%) males and 28(46.4%) females. While all 30(100%) the participants in group A completed the trial without any adverse reaction to medication, 8(26.7%) in group B quit midstream owing to anorexia/nausea and gastrointestinal discomfort. Compared to baseline, reduction in both subjective and objective features of the disease in both groups were noted regardless of gender (p=0.08). No significant difference was evident in symptoms healing rate and improvement in foreign body sensation between the groups (p>0.05). Group A treatment improved eye redness, while group B proved better in respect of meibomian glands obstruction healing and corneal staining p<0.05).

Conclusion: Both topical azithromycin and oral doxycycline were effective and had their own edge as far as symptomatic improvement was concerned in the treatment of meibomian gland dysfunction.

Key Words: Meibomian gland dysfunction, Topical azithromycin, Oral doxycycline, Efficacy.

(JPMA 73: 995; 2023) **DOI: 10.47391/JPMA.6732**

Submission completion: 08-04-2022 **— Acceptance** 23-01-2023

Introduction

Meibomian gland dysfunction (MGD), or posterior blepharitis, is a commonly encountered ocular disease mostly affecting the elderly and is seen frequently in ophthalmic practice, but mostly remains undertreated or maltreated due to non-uniform treatment protocol globally. MGD presents with ocular signs, such as lid erythema, thickening of lid margins, altered structure and function of meibomian glands (MGs) with deposition of oily secretions at the lid margins.[1-4] MGD, as defined by the International Workshop on MGD, is a chronic, diffuse abnormality of the MGs, commonly characterised by terminal duct obstruction and qualitative/quantitative alterations in the secretions. It may cause an abnormal tear film, ocular irritation, eyelid telangiectasias, and punctate epithelial erosions[4]. The American Academy of Ophthalmology (AAO) has divided this condition into two groups; anterior and posterior blepharitis. The former mainly affects the area anterior to MG orifices, while the latter primarily affects the MG orifices[5]. Medical treatment of MGD is targeted towards relief of symptoms and reduction of inflammation. Management for both anterior and posterior blepharitis involves daily lid scrubbing along with warm compresses and ocular lubricants. Flare-up or resistant nature of the disease requires therapy with topical steroids, topical antibiotics, combination therapy, topical calcineurin inhibitors or oral antibiotics.[6] No uniform and definite treatment protocol has yet been devised, but usage of oral antibiotics and topical antibiotic/steroid combinations has given promising results in the management of MGD[7].

Doxycycline, a long-acting semi-synthetic tetracycline, is quite effective in ameliorating both subjective and objective features of MGD when given in a low dose for a few weeks in chronic blepharitis[3]. Other conditions in which it is efficacious include acne rosacea with ocular involvement[8]. Tetracyclines are quite unique in their properties as they not only have an antibacterial activity, but produces an anti-inflammatory effect by decreasing

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the activity of phospholipase A2 with reduced production of inflammatory mediators like interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α) in ocular tissues.[9,10] In high doses, tetracyclines block the release of inflammatory mediators from styphylococcal epidermidis/aureous liberated exotoxins present in the lid flora[11]. Doxycycline is more effective in relieving the obstruction by its enzymatic action on lipases, but its efficacy is almost similar to topical azithromycin (AM) in symptomatic improvement. The only concern in its prolonged use is its gastrointestinal (GI) side-effects.[12,13]

Systemic AM in some studies has proven to be effective in improving the features of MGD[1,14]. A meta-analysis and systemic review has shown that MGD improved with oral and topical AM in terms of symptomatic and clinical improvement with stabilised tear composition.[14] Topical AM 1.5% is safe and efficacious in improving the subjective and objective features of MGD in the short term.[15] AMs, like tetracyclines, also exerts anti-inflammatory properties by reducing the production of different inflammatory mediators, and also possesses effective coverage against gram-negative bacteria[16]. Numerous trials have unveiled the effectiveness of topical AM in improving the signs and symptoms of MGD in chronic and therapy-resistant cases.[17-19]

The current study was planned to assess the efficacy of topical AM drops versus oral doxycycline therapy in MGD.

Patients and Methods

The prospective randomised trial was conducted from December 2019 to June 2020 at the Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan. After approval from the institutional ethics review board, the sample size was calculated in line with literature.[20] The trial was registered with the Iranian registry of clinical trials IRCT20220607055097N3 www.irct.ir

The sample was raised using convenience sampling technique. Those included were patients of either gender aged 26-42 years having long-standing posterior blepharitis secondary to MGD, and those with MGD who were non-responsive to conventional therapy, such as lid massage, warm compresses and lid scrubbing. Those excluded were patients with blepharitis other than posterior, patients with other inflammatory lid conditions, like atopic blepharoconjunctivitis, patients with traumatic eyelid injuries, patients with neoplastic lid disorders, pregnant and lactating women, those with history of any allergy to the study drugs, and patients treated with oral or topical medications other than study drugs for posterior blepharitis within the preceding 3 months.

After taking informed consent from all the subjects, they were randomised into two equal groups, using table of random numbers for group allocation.

All the participants were advised to apply warm compresses and massaging of lids 2 times per day for 5 min. each for 4 weeks. In addition, group A received AM 1% drop 2 times per day for 1 week and then once daily for further 3 weeks (Zithrosan 1%, Sante, Pakistan). Group B received oral doxycycline 100mg (Cap. Contimycin, Asia Continental, Pakistan) once daily for 4 week. Participant's assessment was conducted at baseline, at 2nd week and at the 4th week. At baseline and follow-ups, the patients were assessed under slit lamp for peripheral conjunctival hyperaemia and corneal staining. Each of these ocular signs were graded by a scoring system depending upon the area of involvement. For corneal staining, the cornea was divided into 5 regions and was assigned a score of 1 for peripheral staining and 4 for staining of central cornea, implying more severe involvement by the disease (Figure 1). Similarly, bulbar conjunctival area was divided into six regions and scoring from 0 to 4 was done depending upon the number of involved regions (Figure 2). Subjective symptoms, including itchy eyes, grittiness, MG plugging, foreign body (FB) sensation, and watering were recorded using a convenient self-devised checklist as 0 =

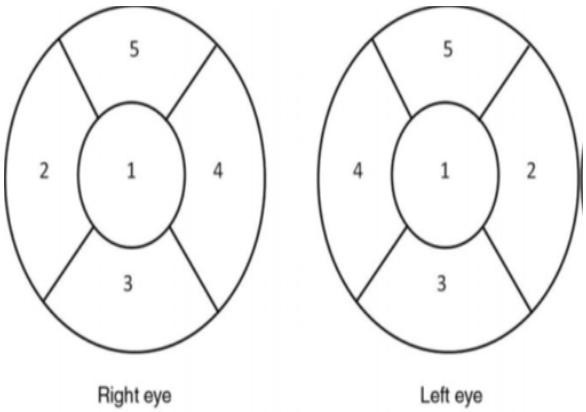

Figure-1: Illustrated map of the 5 regions assessed for corneal staining.

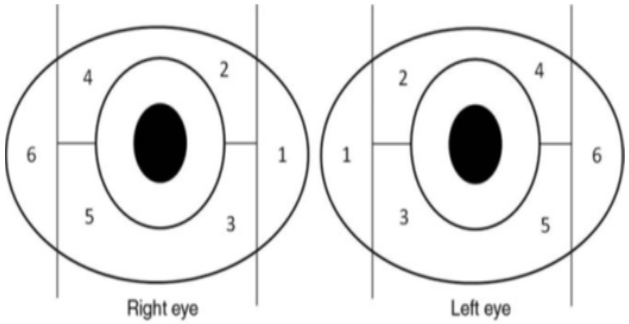

Figure-2: Illustrated map depicting 6 regions for conjunctival staining.

asymptomatic and 2 = severe symptoms. In addition, Schemers I test (5min test without anaesthesia) was performed in all the participants, and >10mm wetting was considered normal.

Data was analysed using SPSS 25. Therapeutic agents were taken as independent variables, while their outcomes were taken as dependent variables. Categorical variables were presented as frequencies and percentages, while quantitative variables were presented as mean and standard deviations. Comparison between categorical variables was done through chi-square test, while for numerical/quantitative variables, one-way analysis of variance (ANOVA) was used. Mann Whitney test was applied for intergroup analysis between different signs and symptoms of the disease as the data was not normally distributed. The confidence interval (CI) was set at 95%. *P*<0.05 was considered statistically significant.

Results

Of the 60 subjects enrolled, there were 30(50%) in each of the two groups, meaning a total of 120 eyes. There were 32(53.3%) males and 28(46.4%) females. While all 30(100%) the participants in group A completed the trial without any adverse reaction to medication, 8(26.7%) in group B quit midstream owing to anorexia/nausea and GI discomfort (Figure 3).

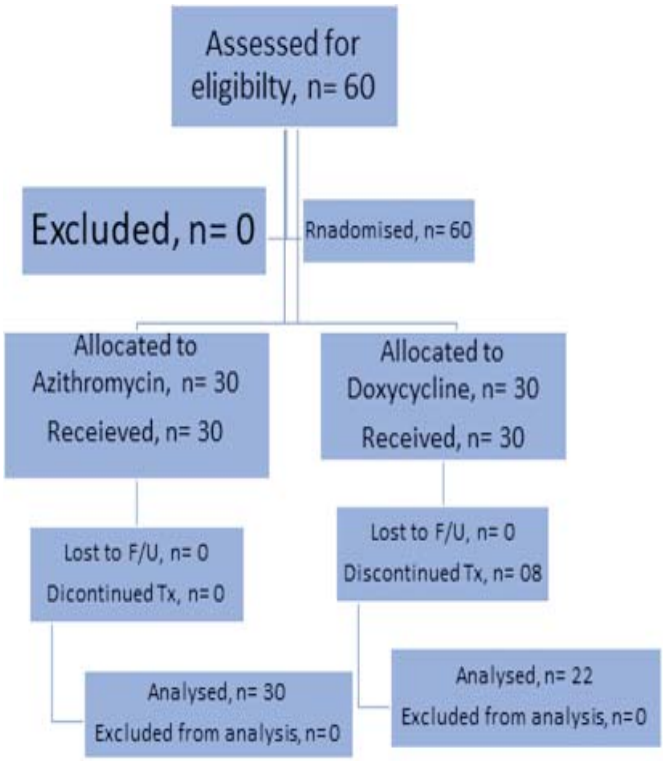

Figure-3: Study flowchart

Table-1: Mean value of Schirmers 1 test between the groups.

Visit	Top. Azithromycin (N= 30)	Oral Doxycycline (N= 22)	p- value b/w groups
Baseline (Mean ± SD)	6.56 ± 5.64	8.86 ± 5.43	0.438
2nd week (Mean ± SD)	7.82 ± 6.36	9.44 ± 6.11	0.278
4th week (Mean ± SD)	8.44 ± 6.58	11.13 ± 6.35	0.252

SD: Standard deviaton

Differences between the groups at different follow-ups were not significant (Table 1).

Symptoms, including itchy eyes, grittiness, watering and FB sensation, decreased significantly during therapy in both groups (p<0.05), but no significant difference was noted in the improvement of FB sensation between the groups (p>0.05) (Tables 2-3).

Table-2: Mean scoring of symptoms in the groups.

	Baseline	2nd week	4th week	P(Chi-square)	1st to last visit difference	P (Mann-Whitney)
Azithromycin (N= 30)	1.12	0.71	0.31	<0.01	0.81	0.688
Doxycycline (N= 22)	1.04	0.64	0.29	<0.01	0.75	

Table-3: Mean foreign body (FB) sensation represented in percentage in the groups. scoring of symptoms in the groups.

	Baseline	2nd week	4th week	P(Chi-square)	1st to last visit difference	P (Mann-Whitney)
Azithromycin (N= 30)	55%	42%	28%	0.013	27%	0.832
Doxycycline (N= 22)	51%	40%	26%	0.022	25%	

Table-4: Mean peripheral conjunctival hyperaemia scores in the two groups..

	Baseline	2nd week	4th week	P(Chi-square)	1st to last visit difference	P (Mann-Whitney)
Azithromycin (N= 30)	1.69	1.14	0.39	<0.01	1.30	0.040
Doxycycline (N= 22)	1.62	1.25	0.42	0.001	1.20	

The mean score of peripheral conjuntival hyperaemia reduced significantly in both groups, but it was significant only in group A (Table 4).

The mean corneal staining score reduced markedly in both groups, but it was significant only in group B (Table 5).

Table-5: Mean corneal staining scores in the two groups..

	Baseline	2nd week	4th week	P(Chi-square)	1st to last visit difference	P (Mann-Whitney)
Azithromycin (N= 30)	1.34	1.11	0.88	0.004	0.46	0.020
Doxycycline (N= 22)	1.56	1.24	0.40	0.021	1.16	

Table-6: Mean meibomian gland clogging percentage in the two groups..

	Baseline	2nd week	4th week	P(Chi-square)	1st to last visit difference	P (Mann-Whitney)
Azithromycin (N= 30)	94%	66%	36%	<0.01	58%	0.036
Doxycycline (N= 22)	95%	68%	15%	<0.01	80%	

Mean score of MG plugging reduced in both groups, but it was significant only in group B (Table 6).

Discussion

There was improvement in the symptoms and signs of posterior blepharitis / MGD except for Schirmers 1 test in both the therapeutic arms of the current trial, but there was non-significant difference in improvement and healing of the subjective features of the disease between the groups. Topical AM 1% was more effective in resolving peripheral conjunctival hyperaemia, while doxycycline showed promising results in ameliorating MG clogging and corneal staining.

One study revealed that the signs and symptoms of the disease achieved significant improvement after therapy, except lid swelling[19,21]. The current findings matched those of Igami et al[22].

The current study used topical AM instead of oral form to avoid the systemic adverse effects associated with the latter. Furthermore, the oral form of administration could lead to the development of bacterial resistance[23].

Another study conducted on patients with long-standing MGD showed marked resolution in subjective and objective aspects of the disease similar to the findings of the current study, and further reported that doxycycline reduces the level of matrix metallopeptidase 9 (MMP-9) activity and enhances the anti-lipase level in tears[24]. One study found that oral doxycycline was relatively inferior in resolving FB sensation and MG plugging along with meibum quality[11]. Contrasting results were noted in the current study. This difference in the outcome might be attributed to the large sample size in the current study along with different treatment regimen and duration of treatment.

Prolonged duration of action and convenient dosage regimen of once-a-day with reduced course of therapy makes AM both in topical and oral forms superior to doxycycline[25]. Similar to the current study, a comparative study of systemic azithromycin versus oral doxycycline revealed that both the drugs were therapeutically responsive in relieving the signs and symptoms of MGD, but AM had an edge over doxycycline in terms of decreased duration of therapy and reduced dosage.[26]

The only disadvantage of using topical AM 1% is due to its shortage of availability in Pakistan, as only one pharmaceutical company is manufacturing it in smaller quantities that are insufficient for large number of patients suffering from this common condition along with lack of awareness among the ophthalmologist fraternity about this new but effective treatment modality. On the other hand, doxycycline is widely available and is an inexpensive drug which has been in use for quite a long time and most of the ophthalmic community is familiar with it.

The current study has its limitations, like a small sample size drawn from a single centre and studied over a relatively short period of time. Also, there was no control group or blinding during the trial.

Conclusion

Both topical AM and oral doxycycline had almost similar efficacy as far as symptomatic improvement was concerned in the treatment of MGD. But oral doxycycline was more effective in improving signs, such as corneal staining and MG obstruction, compared to topical AM.

Acknowledgement: We are grateful to Mr Samiullah for statistical assistance, and to Mr. Nouman for data-keeping and liaison with the patients.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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