·Clinical Research·

Comparison of therapeutic effects of topical azithromycin solution and systemic doxycycline on posterior blepharitis

Mehdi Zandian[1], Neda Rahimian[2], Sanaz Soheilifar[3]

[1]Department of Ophthalmology, Faculty of Medicine, Hamadan University of Medical sciences, Hamadan 6516836595, Iran
[2]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran 193954763, Iran
[3]Department of Orthodontics, Faculty of Dentistry, Hamadan University of Medical Sciences, Hamadan 6516836595, Iran
Correspondence to: Sanaz Soheilifar. Tavoos Alley, Andalib Avenue, Hamadan 6516836595, Iran. sanaz_soheilifar@yahoo.com
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Abstract

• **AIM: To compare the effect of azithromycin drop and doxycycline capsule on treatment of posterior blepharitis.**

• **METHODS: Fifty patients (100 eyes) with moderate posterior blepharitis, randomly divided into two therapeutic groups; all the patients got warm eyelid compress and massage three times a day for 3wk. In addition the first group got azithromycin 1% drop, twice daily for 1wk and then one drop daily for 2wk. The second group got oral doxycycline 100 mg daily for 3wk. At the end of the research, patients´ signs and symptoms were compared together. ANOVA, Chi-square and Mann-Whitney tests were used for statistical analysis.**

• **RESULTS: Topical therapy with azithromycin and oral therapy with doxycycline relieved signs and symptoms after 3wk. There were no significant differences between symptoms healing rate and foreign body sensation healing in these two groups (P>0.05). However, azithromycin drop was more effective in reduction of eye redness and doxycycline was more effective in meibomian glands plugging healing and reducing the corneal staining.**

• **CONCLUSION: Topical azithromycin could have similar effects as oral doxycycline on posterior blepharitis in improving subjective symptoms. However, doxycycline can reduce objective signs such as ocular surface staining and meibomian gland plugging more than azithromycin.**

• **KEYWORDS:** blepharitis; azithromycin; doxycycline

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INTRODUCTION

Blepharitis or eyelid margin inflammation is one of the most common ocular diseases encountered by eye care professionals and is often characterized by erythematous, thickened eyelid margins with dysfunctional meibomian glands and accumulation of debris along the eyelid margin[1-4]. Common signs of chronic blepharitis are conjunctival hyperemia, mucous secretion, meibomian gland dysfunction, and superficial punctuate keratitis [3]. Patients with blepharitis usually complain of itching, foreign body sensation, burning, dryness, and tearing[3]. American Academy of Ophthalmology classified the disease as anterior or posterior blepharitis, according to whether it primarily affects the lash-bearing region of the eyelids or meibomian gland orifices, respectively [5]. However, it is clear that these classifications are not mutually exclusive and are often observed together because of the proximity of the areas involved[5].

Management of blepharitis may include daily eyelid cleansing methods and the use of therapeutic agents that reduce infection and inflammation [6-7]. There are no established guidelines regarding therapeutic regimens but antibiotics and topical corticosteroids can produce significant improvement in signs and symptoms of blepharitis. In most cases subjective symptoms may persist even when signs have been improved[7].

Systemic therapy with low-dose doxycycline, a long-acting semi-synthetic tetracycline, has become the treatment of choice for patients whose symptoms and signs are not adequately controlled [3]. It has been used to treat ocular rosacea, improving irritation symptoms and increasing tear film stability [8-9]. It has also been used to treat corneal erosions [10-11]. Other than their antibacterial activity, tetracyclines have anti-inflammatory and antiangiogenic properties.

In fact, these compounds decrease the activity of phospholipase A2 and reduce the production of interleukin IL-1α and tumor necrosis factor (TNF)-α in corneal

epithelium [12-14]. At high concentrations, tetracyclines inhibit staphylococcal exotoxin-induced cytokines and chemokines[15]. Gastro-intestinal effects including nausea, vomiting and diarrhea are the side effects of tetracyclines and are common especially with high doses and most of them could be attributed to iritation of the mucosa [16]. Doxycycline is one of the most common causes of drug induced esophageal ulcers[17]. Oral azithromycin therapy improves the signs and symptoms associated with dry eyes [1,18]. It is believed that systemic azithromycin penetrates into the ocular surface and remains at therapeutic levels days after the cessation of the medication [19]. Azithromycin is anti-inflammatory, inhibiting proinflammatory cytokines, and is potent against Gram-negative microorganisms [20]. Clinical trials have identified topical azithromycin as a potentially effective treatment for lid margin disease and meibomian gland dysfunction[21-23].

The aim of the present study was to compare the therapeutic effects of topical azithromycin and oral doxycycline on improving the signs and symptoms of posterior blepharitis.

SUBJECTS AND METHODS

Fifty patients (26 men, 24 women) with chronic blepharitis, 25-40 years old with the mean age of 33.88 ±9.03y were included in this study and randomly divided into two groups. These two groups were matched by sex and age. All of the patients instructed to use warm eyelid compress and massage three times 1d for 3wk. In addition the first group received azithromycin 1% drop (Azithromax, Sinadarou, Tehran, Iran), twice daily for 1wk and then one drop daily for 2wk. The second group received oral doxycycline 100 mg (Doxycycline, Mahbandarou, Tehran, Iran) once daily for 3wk. All the experiments were approved by the Ethics Committee in the Research Center of Hamadan University of Medical Sciences and a written informed consent was obtained from every participant in the study.

The patients were visited three times (at the beginning of the study, 2 and 3wk after initiation of the treatment). On each visit, conjunctival peripheral injection and corneal staining were examined with slit lamp. Each of these features was graded based on area involved from 1+ to 4+. For corneal staining, cornea divided into four imaginary concentric cycles and staining of most peripheral band recorded as 1+ and central cycle as 4+. Furthermore bulbar conjunctiva imaginary divided into four equal quadrants and grading was done based on the number of involved quadrants. Subjective symptoms including itching, irritation and lacrimation were recorded in a check list as 0 for no symptom and 2+ for severe symptoms. In addition Schirmer I test (2min test without anesthesia) performed in all of the patients, while considering more than 10 mm tear production as normal [24]. The presence of foreign body sensation and meibomian glands plugging were also determined for all of the patients in every visit.

Table 1 Schirmer test mean in azithromycin group, results of ANOVA

Visits	Mean	SD	*P*
1st	6.12	5.89	
2nd	7.12	6.51	0.287
3rd	8.16	6.84	

Table 2 Schirmer test mean in doxycycline group, results of ANOVA

Visits	Mean	SD	*P*
1st	9	5.64	
2nd	9.9	6.07	0.246
3rd	11.04	6.48	

Statistical Analysis Analysis was performed using the statistical package SPSS 16. ANOVA was used for comparing the results of Schirmer test and Chi-square test was used to compare signs and symptoms at different time intervals within each group. Mann-Whitney test was used for comparing sign and symptoms between the groups. The level of significance for all tests was set at $P<0.05$.

RESULTS

All patients in the azithromycin group completed the study and none of them experienced side effects; however 6 out of 25 patients in doxycycline group (24%) left the study. In the doxycycline group 6 out of 19 patients (31.5%) reported nausea and 2 patients (10.5%) complained of vomiting and diarrhea. The results of this study showed that the reduction of the signs and symptoms in the two groups was not affected by sex ($P>0.05$).

The results of ANOVA test showed that Schirmer I test score did not change significantly at different intervals in the two groups (Tables 1, 2).

The scores of subjective symptoms including itching, irritation, lacrimation and the frequency of foreign body sensation decreased significantly during the treatment time ($P<0.05$, Tables 3, 4). However no significant difference was found in the reduction of subjective symptoms score and frequency of foreign body sensation from the 1st to the 3rd visit between the groups ($P>0.05$, Tables 3, 4).

The mean score of peripheral injection was improved significantly from the 1st to the 3rd visit in the two groups. Furthermore the reduction of the peripheral injection score in the azithromycin group was significantly more than the doxycycline group ($P<0.05$, Table 5).

The mean score of corneal staining was improved significantly from the 1st to the 3rd visit in the two groups. Furthermore the reduction of corneal staining score in the doxycycline group was significantly more than the azithromycin group ($P<0.05$, Table 6).

The frequency of meibomian glands plugging reduced significantly from the 1st to the 3rd visit in the two groups. Furthermore the reduction of the meibomian glands plugging

Table 3 Subjective symptoms scores in the groups at different visits

Groups	1st visit	2nd visit	3rd visit	*P* (Chi-square)	1st to 3rd visit difference	*P* (Mann-Whitney)
Azitromycin	1.2	0.64	0.24	<0.01	0.96	0.701
Doxycycline	0.96	0.58	0.32	<0.01	0.64	

Table 4 Frequency of foreign body sensation in the groups at different visits

Groups	1st visit	2nd visit	3rd visit	*P* (Chi-square)	1st to 3rd visit difference	*P* (Mann-Whitney)
Azithromycin	58%	44%	26%	0.016	28%	0.881
Doxycycline	54%	46%	28%	0.027	26%	

Table 5 Peripheral injection scores in the two groups

Groups	1st visit	2nd visit	3rd visit	*P* (Chi-square)	1st to 3rd visit difference	*P* (Mann-Whitney)
Azithromycin	1.76	1.16	0.36	<0.01	1.4	0.041
Doxycycline	1.54	1.24	0.26	0.001	1.28	

Table 6 Corneal staining scores in the two groups

Groups	1st visit	2nd visit	3rd visit	*P* (Chi-square)	1st to 3rd visit difference	*P* (Mann-Whitney)
Azitromycin	1.24	1.09	0.9	0.004	0.34	0.022
Doxycycline	1.66	1.26	0.36	<0.01	1.3	

Table 7 Meibomian glands plugging frequency in the two group

Groups	1st visit	2nd visit	3rd visit	*P* (Chi-square)	1st to 3rd visit difference	*P* (Mann-Whitney)
Azitromycin	96%	68%	32%	<0.01	64%	0.039
Doxycycline	96%	70%	14%	<0.01	82%	

frequency in the doxycycline group was significantly more than the azithromycin group (P<0.05, Table 7).

DISCUSSION

In the present clinical trial it was found that topical therapy with azithromycin and systemic treatment with doxycycline relieved signs and symptoms of posterior blepharitis except for Schirmer I test score. On the other hand, no significant differences was demonstrated in improvment and healing of the subjective symptoms, including foreign body sensation, itching, irritation and lacrimation between patients treated with azithromycin ophthalmic solution and patients treated with doxycycline capsule. However azithromycin ophthalmic solution led to more improvement in peripheral injection than doxycycline capsule and doxycycline caused more improvement in meibomian glands plugging and corneal staining than azithromycin.

Igami *et al* [25] in their clinical trial evaluated the effects of oral azithromycin on posterior blepharitis. They graded the subjective clinical outcomes and also performed tear break-up time, Schirmer I test, corneal fluorescein staining score and rose bengal staining score in all of the patients. They observed that all clinical outcome scores showed statistically significant improvement after treatment with oral azithromycin, except for eyelid swelling. On the other hand they found no statistically significant improvement on average values of Schirmer I test, corneal fluorescein staining score, and rose bengal staining score [25]. In the present study, azithromycin ophthalmic solution improved subjective symptoms and no significant improvement was found in Schirmer I test, similar to Igami *et al*'s[25] study.

In our study topical azithromycin instead of systemic azithromycin was used in order to prevent potential systemic side effects associated with oral administration. In addition consuming oral azithromycin could result in microbial resistance to this antibiotic, especially for staphylococous species[26].

Iovieno *et al* [27] in their study on patients with chronic blepharitis concluded that 4wk treatment with doxycycline significantly improved symptoms and signs, similar to our study. Furthermore they found that this drug decreases matrix metalloproteinase-9 activity and increase anti-lipase level in tear film[27].

Foulks *et al* [15] compared biochemical features of meibomian gland secretions and subjective symptoms of patients with meibomian gland dysfunction who were treated with topical azithromycin and oral doxycycline. They resulted that oral doxycycline treatment was slightly less effective in improving foreign body sensation and the signs of plugging and secretion and found more biochemical lipid quality improvement with azithromycin treatment[15]. However, in the present study, oral doxycycline had slightly better effect on meibomian glands plugging than topical azithromycin and no significant difference was found in foreign body sensation in the two groups. This may be justified with larger number of our cases and different treatment schedule and duration of treatment compared to Foulks *et al*'s[15] study.

Long half life and low frequency of usage are advantages of using azithromycin [26], but azithromycin solution is not available as a generic drug in our country, while doxycycline is readily available and it may be considered a disadvantage of using azithromycine solution.

From economic point of view, the cost of using topical azithromycin 1% (www.drugs.com/price-guide/azasite) for 14d (Azasite, Inspire Pharmaceuticals, Whitehouse station, USA) is approximately four times more than using doxycycline capsule 100 mg (Doxycycline Monohydrate, Lupin Pharmaceuticals, Baltimore, Maryland, USA) for 28d of treatment in US market[28].

Topical azithromycin could have similar effects as oral doxycycline on posterior blepharitis in improving subjective symptoms, however doxycycline can reduce objective signs such as ocular surface staining and meibomian gland plugging more than azithromycin. Regarding the gastrointestinal complaints of the patients treated with systemic doxycycline, azithromycin solution can be a comparable choice with less systemic side effects in treatment of posterior blepharitis.

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