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The Clinical Efficacy of Topical and Systemic Azithromycin Treatment for Posterior Blepharitis

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Abstract

Background: Meibomian gland dysfunction (MGD) is a chronic, diffuse disorder of the Meibomian glands, usually characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretions, which may result in abnormality of the tear film. Meibomian gland dysfunction (MGD) is classified into two major classes based on Meibomian gland secretion: low-delivery state and high- delivery state. Low-delivery state is further classified into hypo-secretory or obstructive, with cicatricial and non-cicatricial sub-categories. **Aim:** To evaluate the various options in management of meibomian gland dysfunction. **Methods:** This is a prospective, randomized, open-label study. Forty five patients with a diagnosis of posterior blepharitis were enrolled in the study and were divided into three groups of patients each have 15 patients received azithromycin. A group received topical, a group received systemic and another group received both topical and systemic azithromycin treatment. **Results:** All symptoms, signs and special tests improved in all of the three groups with statistically significant difference with P value < 0.05. Both topical and oral azithromycin had beneficial effects in patients with meibomian gland dysfunction (MGD). Topical azithromycin group and combination group were proven to have better effect regarding symptoms and special tests (TBUT and Schirmer). However, systemic group and combination group were found to be more effective in improving Hyperemia and debris. **Conclusion:** Meibomian gland dysfunction (MGD) could be treated effectively with oral or topical azithromycin by improving symptoms, clinical signs, and stabilization of tear film. However, topical group and combination group seemed to be superior over oral azithromycin in improving the quality of tear film in the short term.

Keywords: Azithromycin, Meibomian gland dysfunction Posterior Blepharitis.

1. Introduction

Meibomian glands (MGs) are modified sebaceous glands that are arranged vertically in tarsal plate which secretes lipids and protein that are delivered at upper and lower eyelid [1]. Meibomian gland dysfunction(MGD) is a prevelant disease which may involve inflammation, hyper secretion and abnormal excreta of the gland [2]. It may result in alteration of tear film and leading to evaporative dry eye [3].

MGD is classified into two major classes based on Meibomian gland secretion: high delivery and low delivery. This is further classified into hypo secretion and obstructive, with cicatricial and non cicatricial sub categories [4]. The leading cause of MGD is obstruction of MG with secondary hyper keratinization of the duct epithelium and accumulation of meibum, resulting in inflammation and possibly an increased bacterial colonization of the lid margins [5]. MGD may be asymptomatic, only detectable by gland expression, or, more often, presents with dry eye symptoms [6].

Common symptoms are foreign body and itching, red eye, lacrimation and photophobia [7]. Common signs are loss of clarity and heaviness of expressed meibum, pouting or plugging of Meibomian gland openings, meibomian gland drop out detected by meibography, increased eyelid margin thickness and vascularity, eyelash loss, trichiasis and vascular invasion [8].

Most cases usually require conservative treatment including warm compresses to provide appropriate meibum secretion, mechanical eyelid massage and cleansing with shampoo and cotton buds to remove excess debris, and lubricants to continuously lubricate the ocular surface [8][9]. In severe and refractory cases, however, antibiotics (topical and systemic) with anti-inflammatory properties are proposed [10]. Steroid topically, cyclosporine and oral omega 3 fatty acid may be used. Surgical solutions are generally limited in treatment [11].

The prevalence of dry eye disease is big worldwide and poses a considerale burden on patients' daily lives. Accurate diagnosis of the disease is crucial, and it requires application of various methods. Hyperosmolarity is believed to be the disease marker & thus measuring it provides useful data, along with other diagnostic tests (Ocular Surface Disease Index questionnaire, Tear film break-up time, Ocular Protection Index, Ocular Surface Staining, Schirmer I test). Tear film hyperosmolarity is assumed to be an etiological factor in dry eye disease (DED), hence the measurement of tear osmolarity has been considered important for diagnostic purposes. Several measurement methods have been used previously, with the Clifton and vapor pressure osmometers being the most commonly used methods. Despite high accuracy, sensitivity, and specificity, these methods are not obtainable for use at the point-of-care and require special setups that would need a considerable amount of time [12].

The aim of this study was to evaluate the efficacy of topical azithromycin ophthalmic solution, oral azithromycin and both (topical & systemic) azithromycin for the treatment of posterior blepharitis. The comprehensive evaluation included the changes in the ocular symptoms, eyelid margin signs, environmental triggers as measured by Ocular Surface Disease Index (OSDI), and traditional dry eye diagnostic tests.

2. Patients and methods

This is a prospective, randomized, open-label study. Forty five patients with a diagnosis of posterior blepharitis were enrolled in the study. A total of 45 subjects were

included in the study. Three groups of patients each have 15 patients received azithromycin. A group received topical, a group received systemic and another group received both topical and systemic azithromycin treatment. Written informed consent was obtained from each subject.

Patients with any of the following will be excluded from the study: Younger than 18 years of age, history of posterior blepharitis treatment, including topical antibiotic ointments or drops, topical anti-inflammatory drops, oral antibiotics within the previous 6 months, history of ocular surgery within the previous 6 months, history of ocular allergy, presence of ocular inflammation, glaucoma and history of the use of systemic antibiotics for any reason within the previous 6 months.

Complete ophthalmological evaluation was done for all patients including detailed history taking, clinical examination, special tests (TBUT, Shirmer, ocular surface staining with fluorescein) and ocular surface disease index (OSDI) administration and scoring.

After the baseline evaluation, patients were randomly assigned to treatment groups: Group I: topical azithromycin group, azithromycin 1% ophthalmic solution was used twice a day for 3 days and then once a day until the treatment completed a month[13]. Group II: systemic treatment group, patients were instructed to use oral 5-day azithromycin (500 mg on day 1 and then 250 mg/day)[14]. Group III: both treatments group both regimens were used[13][14]. Warm compress, once a day, was recommended to all study subjects.

For the follow up, all tests were repeated 1 week after discontinuation of treatment and 4 weeks after the second visit (5 weeks after the end of treatment).

Statistical dissection

Data were collected, revised, coded and entered to the Statistical Package for Social Science (SPSS) version 20 and the following were done: Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data were done by using Chi-square test. The comparison between more than two groups with parametric distribution were done by using One Way Analysis of Variance (ANOVA). The confidence interval was set to 95% and the margin of error accepted was set to 5%.

3. Results

The present study included 45 patients were divided into three groups of patients each have 15 patients. Demographic and anthropometric data in all studied groups in Table (1).

Table (1): Demographic data in all studied groups.

		No. = 45
Age	Mean±SD	42.78 ± 14.18
	Range	19.00 – 63.00
Sex	Female	21 (46.7%)
	Male	24 (53.3%)

Table (2): Treatment groups

Treatment	**No.**	**%**
Topical group	15	33.3%
Systemic group	15	33.3%
Combination group	15	33.3%
Total	***45***	***100.0%***

Table (3): Break up time (BUT).

Break up time (BUT)		**No. = 45**
Baseline	Mean ± SD	9.07 ± 2.25
	Range	4 – 12
After 1 week	Mean ± SD	10.22 ± 1.88
	Range	5 – 13
After 5 weeks	Mean ± SD	11.11 ± 1.67
	Range	6 – 14

Table (4): Schirmer test.

Schirmer test		**No. = 45**
Baseline	Mean ± SD	13.18 ± 4.05
	Range	5 – 18
After 1 week	Mean ± SD	14.20 ± 3.49
	Range	5 – 19
After 5 weeks	Mean ± SD	15.00 ± 3.52
	Range	7 – 20

Table (5): Itching.

Itching		**No. = 45**
Baseline	Median(IQR)	1 (1 – 2)
	Range	0 – 3
After 1 week	Median(IQR)	1 (1 – 2)
	Range	0 – 3
After 5 weeks	Median(IQR)	0 (0 – 1)
	Range	0 – 3

Table (6): Hyperemia.

Hyperemia		No. = 45
Baseline	Median(IQR)	1 (1 – 2)
	Range	0 – 3
After 1 week	Median(IQR)	1 (0 – 1)
	Range	0 – 3
After 5 weeks	Median(IQR)	0 (0 – 1)
	Range	0 – 3

Table (7): Debris.

Debris		No. = 45
Baseline	Median(IQR)	1 (0 – 2)
	Range	0 – 3
After 1 week	Median(IQR)	1 (0 – 1)
	Range	0 – 3
After 5 weeks	Median(IQR)	0 (0 – 1)
	Range	0 – 2

Table (8): Ocular Surface Disease Index.

OSDI		No. = 45
Baseline	Mean ± SD	29.01 ± 9.25
	Range	14.2 – 53.5
After 1 week	Mean ± SD	25.28 ± 8.88
	Range	10.7 – 46.4
After 5 weeks	Mean ± SD	19.73 ± 8.70
	Range	7.1 – 42.8

Table (9): Demographic values in treatment groups.

		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Age	Mean±SD	36.73 ± 14.61	48.73 ± 10.46	42.87 ± 15.21	2.923•	0.065	NS
	Range	19.00 – 60.00	29.00 – 62.00	19.00 – 63.00			
Sex	Female	8 (53.3%)	7 (46.7%)	6 (40.0%)	0.536*	0.765	NS
	Male	7 (46.7%)	8 (53.3%)	9 (60.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: Chi-square test; •: One Way ANOVA test

Table (10): Break up time (BUT) values in treatment groups.

Break up time (BUT)		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Mean ± SD	8.87 ± 2.45	9.20 ± 1.82	9.13 ± 2.56	0.088	0.916	NS
	Range	5 – 12	6 – 12	4 – 12			
After 1 week	Mean ± SD	10.53 ± 1.68	9.60 ± 1.76	10.53 ± 2.13	1.244	0.299	NS
	Range	8 – 13	7 – 12	5 – 13			
After 5 weeks	Mean ± SD	11.80 ± 1.37	10.53 ± 1.30	11.00 ± 2.07	2.347	0.108	NS
	Range	9 – 14	8 – 12	6 – 13			
Repeated Measure ANOVA test		**26.426**	**10.558**	**24.234**			
P-value		**0.000**	**0.002**	**0.000**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: One Way ANOVA test

Break up time (BUT) values in treatment groups at baseline and follow up visits.

Break up time (BUT)	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.004	0.162	0.002
Baseline Vs 5week	0.000	0.007	0.000
1 week Vs 5 week	0.000	0.031	0.041

Table (11): Schirmer test values in treatment groups.

Schirmer test		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Mean ± SD	13.67 ± 4.20	12.27 ± 3.51	13.60 ± 4.50	0.558	0.576	NS
	Range	7 – 18	7 – 18	5 – 18			
After 1 week	Mean ± SD	14.60 ± 3.52	13.80 ± 3.12	14.20 ± 3.97	0.190	0.828	NS
	Range	8 – 18	9 – 18	5 – 19			
After 5 weeks	Mean ± SD	15.33 ± 3.44	14.73 ± 3.15	14.93 ± 4.13	0.108	0.898	NS
	Range	8 – 20	9 – 20	7 – 20			
Repeated Measure ANOVA test		**10.319**	**11.336**	**8.797**			
P-value		**0.001**	**0.001**	**0.002**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: One Way ANOVA test

Schirmer test values in treatment groups at baseline and follow up visits.

Schirmer test	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.051	0.019	0.323
Baseline Vs 5week	0.003	0.005	0.004
1 week Vs 5 week	0.179	0.159	0.047

Table (12): Itching values in treatment groups.

Itching		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Median(IQR)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	0.279	0.870	NS
	Range	1 – 3	0 – 3	0 – 3			
After 1 week	Median(IQR)	1 (1 – 2)	1 (1 – 1)	1 (0 – 2)	0.768	0.681	NS
	Range	0 – 2	0 – 3	0 – 2			
After 5 weeks	Median(IQR)	1 (0 – 1)	1 (0 – 1)	0 (0 – 1)	2.307	0.316	NS
	Range	0 – 2	0 – 3	0 – 2			
Friedman test		**16.158**	**10.692**	**17.756**			
P-value		**0.000**	**0.005**	**0.000**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

‡: Kruskal Wallis test

Itching values in treatment groups at baseline and follow up visits.

Itching	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.014	0.014	0.034
Baseline Vs 5week	0.002	0.014	0.001
1 week Vs 5 week	0.021	0.180	0.007

Table (13): Hyperemia values in treatment groups.

Hyperemia		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Median(IQR)	1 (0 – 2)	1 (1 – 2)	1 (1 – 2)	1.143	0.565	NS
	Range	0 – 3	0 – 3	0 – 3			
After 1 week	Median(IQR)	1 (0 – 2)	1 (0 – 1)	1 (1 – 1)	0.734	0.693	NS
	Range	0 – 3	0 – 3	0 – 3			
After 5 weeks	Median(IQR)	1 (1 – 2)	0 (0 – 1)	0 (0 – 1)	0.530	0.767	NS
	Range	0 – 3	0 – 2	0 – 3			
Friedman test		**7.600**	**19.158**	**13.040**			
P-value		**0.022**	**0.000**	**0.001**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

‡: Kruskal Wallis test

Hyperemia values in treatment groups at baseline and follow up visits.

Hyperemia	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.083	0.014	0.083
Baseline Vs 5week	0.025	0.001	0.007
1 week Vs 5 week	0.157	0.005	0.014

Table (14): Debris values in treatment groups.

Debris		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Median(IQR)	0 (0 – 1)	1 (0 – 2)	1 (1 – 2)	3.518	0.172	NS
	Range	0 – 3	0 – 3	0 – 2			
After 1 week	Median(IQR)	0 (0 – 1)	1 (0 – 1)	1 (0 – 1)	2.886	0.236	NS
	Range	0 – 2	0 – 3	0 – 2			
After 5 weeks	Median(IQR)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0.337	0.845	NS
	Range	0 – 2	0 – 1	0 – 1			
Friedman test		**8.400**	**15.200**	**20.000**			
P-value		**0.015**	**0.001**	**0.000**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

‡: Kruskal Wallis test

Debris values in treatment groups at baseline and follow up visits.

Debris	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.046	0.025	0.008
Baseline Vs 5week	0.025	0.006	0.000
1 week Vs 5 week	0.317	0.014	0.000

Table (15): Ocular Surface Disease Index values in treatment groups.

OSDI		Topical group No. = 15	Systemic group No. = 15	Combination group No. = 15	Test value	P-value	Sig.
Baseline	Mean ± SD	28.53 ± 7.99	31.15 ± 11.08	27.36 ± 8.61	0.649	0.528	NS
	Range	17.8 – 42.8	14.2 – 53.5	14.2 – 46.4			
After 1 week	Mean ± SD	22.83 ± 6.60	28.07 ± 11.12	24.96 ± 8.10	1.342	0.272	NS
	Range	10.7 – 35.7	10.7 – 46.4	14.2 – 42.8			
After 5 weeks	Mean ± SD	17.59 ± 8.26	23.54 ± 9.23	18.07 ± 7.81	2.297	0.113	NS
	Range	7.1 – 35.7	10.7 – 42.8	10.7 – 35.7			
Repeated Measure ANOVA test		**33.346**	**17.949**	**34.604**			
P-value		**0.000**	**0.000**	**0.000**			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

•: One Way ANOVA test

Ocular Surface Disease Index values in treatment groups at baseline and follow up visits.

OSDI	Topical group	Systemic group	Combination group
Baseline Vs 1week	0.000	0.001	0.058
Baseline Vs 5week	0.000	0.001	0.008
1 week Vs 5 week	0.003	0.019	0.000

4. Discussion

Meibomian gland dysfunction (MGD) is one of the most common diseases encountered in ophthalmology clinic [15] that impact of MGD on patients can be severe with negative effect on their quality of life that may lead to a loss of productivity. [15]

The study included (45) patients presented to the outpatient clinic of Cairo Fatemic Hospital suffering from MGD in period from October 2019 to June 2020.

These patients divided into three groups each have 15 patients received azithromycin. 1st group receives topical, 2nd group receives systemic and 3rd group receives both topical and systemic azithromycin treatment. In the topical

group, azithromycin 1% ophthalmic solution was used twice a day for 3 days and then once a day until the treatment completed a month. In the systemic treatment group, patients were instructed to use oral 5-day azithromycin (500 mg on day 1 and then 250 mg/day). In the both treatments group both regimens were used.

In our study the age of the patients ranged from (19-60y) with mean ±SD 36.73 ± 14.61 in topical group, from (29.00 – 62.00y) with mean ±SD 48.73 ± 10.46 in systemic group, and from (19.00 – 63.00y) with mean ±SD 42.87 ± 15.21 in combination group. In the year 2011, Nien *et al.* [16] studied the effects of age on human Meibomian glands. They recruited 86 participants with MGD with a mean age of 72 years ranging from 18 to 95 years. Their study revealed a significant positive correlation between age and Meibomian glands expression grade, as older participants displayed significantly higher grades of meibomian gland dysfunction (MGD) [16]. Hykin and Bron reported in cross sectional study on 80 subjects between (5-87) years of age without ocular disease , that an increase in eyelid margin vascularity, keratinization, telangiectasia and opacification of Meibomian gland secretion was observed with age[17]. A detailed study of Meibomian gland morphology assessment in 37 human eyes (age range, 10–79 years) showed that with an increase in age, there is significant reduction in the Meibomian gland duct length along with an increase in gland dropout of the upper and lower eyelids[18].

Sex distribution, in the current study, group I had 46.7% males and 53.3% females, group II had 53.3% males and 46.7% females and group III had 60% males and 40% females. A study done by Kwan *et al.*[19] published in the year 2014 demonstrated the association between sex and Meibomian gland dysfunction. Who took a sample from 122 participants (75 females and 47 males) older than 18 years (mean age: 45.7±16.3 years) and classified them as having MGD dry eye or aqueous-deficient dry eye based on the accepted tests and Ocular Surface Disease Index. Females were found to have significantly higher frequency and intensity of dryness and vision disturbances than males[19].

A randomised double-masked open-label clinical trial by Kashkouli MB, Fazel AJ, Kiavash V, *et al.[14]* to assess the efficacy and safety of oral azithromycin compared with oral doxycycline in patients with meibomian gland dysfunction, their study included 110 patients (>12 years old) with MGD who were randomly assigned to receive either oral 5-day azithromycin (500 mg on day 1 and then 250 mg/day) or 1-month doxycycline (200 mg/day). They also continued eyelid warming/ cleaning and artificial tears. Symptoms and signs improved significantly in both groups (p=0.001). While improvement of symptoms was not different between the groups, bulbar conjunctival redness (p=0.004) and ocular surface staining (p=0.01) were significantly better in the azithromycin group. The azithromycin group showed a significantly better overall clinical response (p=0.01) [14].

All of the groups studied in this work showed marked improvement in many symptoms and signs (itching, eyelid debris and eyelid hyperemia). At the first follow-up visit, patients of group I and II reported significant lower rates of itching than group III. At the second follow-up visit, patients of group I and group III had better improvement in itching than group II. In addition, eyelid hyperemia and eyelid debris showed more improvement in group II and group III than in group I patients.

Regarding the special tests used, including TBUT, Schirmer 1 test, they did not differ significantly between the three groups. However, the ocular surface staining showed better results in group I and group III than in group II (at all the follow-up visits). This agrees with the results of Elvin Yildiz *et al.* [13] who compared the clinical efficacy of topical and oral azithromycin treatments for posterior blepharitis. Their study included 30 patients older than 18 years with MGD who were randomly assigned to receive topical azithromycin twice a day for 3 days and then once a day until the treatment completes a month or oral 5-days azithromycin. The improvement of the symptoms was nearly equal in both groups with no significant difference between them [13]. Although, both treatment methods were found to be effective, the results of topical treatment group showed some superiority over those of systemic treatment group. In addition, a systematic review and meta-analysis of treating meibomian gland dysfunction with azithromycin by Tianchang Tao et al.[20], reported that the overall pooled symptom scores were significantly reduced after administering both topical azithromycin and oral azithromycin [$P < 0.0001$; SMD = 1.54 (95% CI: 1.15-1.92)]. Similarly, the overall combined eyelid signs, plugging of the meibomian gland, meibum quality, and tear secretion were also distinctly improved. However, significant improvements for tear break-up time (TBUT) was achieved by topical azithromycin (TBUT: $P = 0.02$; CS: $P = 0.02$) but not by oral azithromycin (TBUT: $P = 0.08$; CS: $P = 0.14$)[20].

5. Conclusion

Both topical and oral azithromycin had beneficial effects in patients with meibomian gland dysfunction (MGD). Topical group and combination group seemed to be superior over oral azithromycin in improving the quality of tear film in the short term.

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