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Topical Tea Tree Oil versus Systemic Azithromycin in the Treatment of Posterior Marginal Blepharitis

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Abstract:

Purpose: To compare between the effectiveness of systemic azithromycin and topical tea tree oil in treating posterior marginal blepharitis. Design: prospective comparative research. Participants: sixty cases suffering from posterior marginal blepharitis, assigned into 2 groups, each one comprised thirty cases. **Methods:** Group I applied TTO once daily at bedtime. Group II administered oral azithromycin once daily before breakfast for six days and all patients applied topical lubricant eye drops five times daily. The tear film break-up time, ocular symptoms, Schirmer's test and eyelid margin signs have been assessed at baseline and five weeks later. **Results:** Each group was sub-divided into (severe) and (mild to moderate) sub-groups, then we compared the baseline data of (severe) sub-groups and (mild to moderate) sub-groups. Insignificant variance was observed in results regarding symptoms, signs, Schirmer's test and TBUT. Five weeks after receiving treatment, we collected patients' data same as first visit. We compared the data in first and second visits in each sub group and significant variance was observed in both groups. We compared results in severe sub-groups, significant variance was observed regarding symptoms ($p< 0.001$), signs ($p< 0.001$), TBUT test ($p< 0.001$) and Schirmer's test ($p< 0.001$). We compared results in mild to moderate sub-groups and significant variance was observed according to symptoms ($p< 0.001$), signs ($p< 0.001$), TBUT test ($p< 0.001$) and Schirmer's test ($p< 0.001$). **Conclusions:** Both TTO and oral azithromycin are effective in treating posterior marginal blepharitis with higher efficacy of TTO.

Keywords: posterior marginal blepharitis; tea tree oil; azithromycin; dry eye.

Introduction

Posterior marginal blepharitis is one of the most frequent illnesses in ophthalmology which can badly affect the cases' quality of life and reduce their productivity[1].

Chronic posterior marginal blepharitis is a complicated disease that we see frequently in outpatient clinics. The International Dry Eye Workshop describes it as abnormal secretion and eyelid inflammation or Meibomian gland obstruction that leads to evaporative dry eye or lipid tear deficiency[2.]

Posterior blepharitis is an illness may be caused by many pathogens, such as commensal bacteria, infective bacteria or their toxins. The infective bacteria that can cause posterior blepharitis are like *Staph aureus, Staph epidermidis*, *Propionibacterium acnes*, *Corynebacterium* and *Moraxella*. Demodex mite is a common cause as well. It infests the lashes follicles resulting in posterior blepharits[3].

Chronic posterior marginal blepharitis is generally presented by photophobia, burning, irritation, dry eye, foreign body sensation and lacrimation. The disorder is mainly related to Meibomian secretion stasis caused by atrophy of the Meibomian gland, inflammation, or obstruction which results in evaporative dry eye and tear instability. This may result in significant visual impairment and severe ocular discomfort[2].

The Demodex mite, which is a commensal member of the skin's bacterial flora, doesn't typically cause signs, however, its presence in certain eyelid tissues might lead to an inflammatory response and play a role in posterior marginal blepharitis [4].

Chronic marginal blepharitis is treated conservatively using warm compresses to enhance adequate meibum secretion, massaging of the eyelid, cleaning the lid margin with shampoo and remove any debris and regular use of lubricants. In resistant cases, topical and systemic antibiotics with anti-inflammatory activities are prescribed[5].

Tea tree oil (TTO) is a fragrant essential oil containing terpinen-4-ol (T4O). This component effectively kills Demodex mites, eggs and larvae. TTO similarly works as an antifungal and antibacterial agent as it shows efficacy against Staph. aureus, Escherichia coli, Candida albicans and Pseudomonas aeruginosa. Moreover, TTO has an anti-inflammatory effect as terpinen-4-ol can reduce the production of Interleukin-1β, Interleukin -8, Interleukin -10, prostaglandin E2 and TNF-α by lipopolysaccharide-activated monocytes [4].

Oral azithromycin has been reported to develop the symptoms and signs of posterior blepharitis and meibomian gland dysfunction. It has anti-microbial effect against Gram-negative microorganisms, as well as anti-inflammatory action by inhibiting pro-inflammatory cytokines.5

Azithromycin is a broad-spectrum antibiotic which belongs to the macrolides family. It has a strong anti-bacterial effect against a large number of bacteria, such as *H. influenza*, *Staph aureus*, and *Strept pneumonia*. It also has anti-inflammatory properties[6] .

In this research we are aiming to compare the effectiveness of oral azithromycin and topical tea tree oil in cases with posterior marginal Blepharitis.

Patients and Methods

This prospective comparative research was held in Benha University Hospitals between January 2023 and March 2023. Upon receiving authorization from the Department of Ophthalmology and the research ethics committee of the Benha Faculty of Medicine, the work was initiated. Informed consent was gained from all participants in the research following they were provided the information regarding the nature of the investigations, medications and the potential outcomes of the study. The ethical committee of the Faculty of Medicine, Benha University Hospitals granted approval for this investigation. Parents provided informed written consent.

The ethical approval code number is {M.S.39.3.2023}.

Participants inclusion and exclusion criteria

One hundred and twenty eyes of sixty cases (27 females and 33 males) with posterior marginal blepharitis have been included in this research regarding the following criteria: cases with any signs or symptoms of posterior marginal blepharitis, cases who need to use lubricants frequently and cases with history of unsuccessful blepharitis therapy such as eye drops, ophthalmic ointment, or oral medication.

On the other hand, we excluded cases on topical or systemic antibiotics or anti-inflammatory drugs in a period of 3 months before the beginning of our study, cases who had eye surgery or punctal occlusion, cases on topical or systemic drugs that affects the ocular surface such as antiglaucoma and antihistamine medications, or cases who wore contact lenses within 3 months before the study. Cases with any eyelid structural abnormalities, cases who had any inflammation in the iris or anterior chamber, glaucoma cases, cases with hypersensitivity to azithromycin and pregnant females were also excluded.

Data collection

Patient demographic data (age, gender, occupation, and residence) were collected. Dry eye symptoms (dryness, irritation, burning sensation, lacrimation) were quantified using the validated Arabic version of the Ocular Surface Disease Index (OSDI) questionnaire which is a questionnaire consisting of 12 items, which include 5 levels of symptoms. Score of each symptom was recorded as following: zero (none of the time), one (some of the time), two (half of the time), three (most of the time), and four (all of the time) [7].

A thorough examination with a slit lamp was performed looking for signs such as capping of meibomian gland orifices with oil globules, hyperemia of the posterior lid margin, froth on the eyelid margin, and expression of meibomian fluid that may be muddy or toothpaste-like when the lid margin is pressed on. Plaque, recession, or clogging of meibomian gland orifices, cystic dilatation of meibomian ducts, dandruff-like scales around the base of eyelashes, papillary conjunctivitis, and corneal punctate epithelial erosions [6].

A grading scale from 0 to 3 was used to grade symptoms as following: grade 0 (no telangiectasia \ Marx line (Fluorescein Staining Line on the Inner Lid) [ML] doesn't touch meibomian orifice(MO) at all \ no Irregularity, plugging or foaming \ clear meibum easily expressed\ clear meibomian gland dropout). Grade 1 (mild telangiectasia \ parts of ML touch MOs \ mild Irregularity, plugging, foaming \ cloudy meibum expressed with mild pressure \ small number of meibomian gland dropout). Grade 2 (moderate telangiectasia \ ML courses through MOs \ severe Irregularity, plugging, foaming \ large number of meibomian gland dropout \ cloudy meibum expressed with more than moderate pressure). Grade 3 (severe telangiectasia or redness \ Marx line courses along the eyelid margin beside meibomian orifices \ meibum could not be expressed not even with strong pressure) [8].

Tear film break-up time test (TBUT): We used a fluorescein-impregnated strip that has been moistened with a saline solution that has not been conserved. After the dye had been spread through blinking, the patient was instructed to look ahead without blinking and to maintain a straight gaze. With the cobalt blue light of the slit lamp, the tear film has been examined, and the amount of time elapsed between the 1st appearance of a dry patch or hole in the tear film and the last time case blinked and was calculated. Following the administration of fluorescein, the tear film breakup time has been estimated 3 times in a row, and mean value was selected as the baseline for further analysis [6].

Schirmer's test: After drying, a paper strip has been placed into the lateral third

of the lower fornix, and then we measure the area of the strip that had been moistened after five minutes had passed. The Schirmer test was carried out without the use of anesthetic, and as a result, it measured both fundamental and reflex tears [2].

The score of symptoms and signs as well as the values of TBUT and Schirmer test were recorded at baseline and five weeks after receiving treatment.

Treatment protocol

All cases were prescribed topical lubricant; sodium hyaluronate eye drops [Hyfresh ® eye drops / Jamjoom Pharma] five times per day. The cases have been classified into 2 groups, with every group including thirty cases, and the assignment was done randomly. One application of topical tea tree oil (blefaritto ® eye gel/ Jeomed Pharma) was made by the first group on a daily basis before going to bed for 5 weeks. In the second group, oral azithromycin (Epizithro ® 500mg caps/ Eipico Pharma) was administered once daily, prior to breakfast, for a period of six days. During the initial appointment, as well as five weeks later, evaluation took place. For statistical purposes, the two groups of cases were further subdivided according to the pre-treatment OSDI score and signs score into: A- severe subgroup (with OSDI score of 20 and more and total signs score of 10 and more) and B- mild to moderate subgroup (with OSDI score less than 20 and total signs score less than 10).

Statistical analysis

All data have been tabulated, collected, and examined statistically by the usage of SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA). The quantitative data have been represented by utilizing range (minimum and maximum), mean, standard deviation and median. and the qualitative data have been represented by utilizing percents and numbers. All statistical comparisons have been 2-tailed with significance Level of p-value less than 0.001 represents highly significant variance while, $P > 0.05$ represents Non-significant variance and P-value ≤ 0.05 represents significant.

The tests we used were:

- Chi-square (X^2) test of significance: which we utilized in comparing proportions among qualitative variables.
- Independent T-test: which we used in comparing among two independent groups with parametric quantitative data.

Results

Patient Demographics

Sixty cases with posterior marginal blepharitis have been enrolled in this research and assigned into 2 groups. Group I had a mean age of 58.1 ± 8.67 years, consisting of 13 males and 17 females, with 15 cases having mild to moderate disease and 15 having severe disease. Group II had a mean age of 56.33 ± 10.08 years, with 10 females and 20 males, including 14 patients with mild to moderate disease and 16 with severe disease. Table 1 provides a summary of the demographic and baseline clinical characteristics of the two groups.

Pre-treatment and Post-treatment Comparisons

Significant improvements were observed in all assessment parameters post-treatment for both groups, as shown in Table 1. In Group I, the mean before treatment OSDI score of 19.97 ± 4.58 significantly improved to 4.4 ± 2.33 after treatment ($p < 0.001$). Similarly, Group II demonstrated a development in the mean OSDI score from 18.67 ± 4.41 pre-treatment to 9.03 ± 3.24 post-treatment ($p < 0.001$). For signs scores, Group I demonstrated a significant enhancement from a mean score of 8.5 ± 2.29 before treatment to 2.47 ± 1.17 after treatment (p-value less than 0.001), while Group II enhanced from 9.07 ± 2.39 to 5.43 ± 2.19 (p-value less than 0.001). Tear film break-up time (TBUT) values also improved significantly, with Group I showing an increase from 4.47 ± 1.41 before treatment to 11.11 ± 1.88 after treatment (p-value

less than 0.001), and Group II improving from 4.07 ± 1.34 to 8.19 ± 1.48 (p-value less than 0.001). Schirmer's test values in Group I improved from 6.83 ± 2.1 before treatment to 14.4 ± 2.19 after treatment (p-value less than 0.001), and in Group II, from 6.77 ± 2.01 to 10.67 ± 2.6 ($p < 0.001$).

Comparative Analysis Between Groups

When comparing results of the two groups, the OSDI scores demonstrated no significant difference pre-treatment between Group I (19.97 ± 4.58) and Group II (18.67 ± 4.41) (p-value = 0.267). Nevertheless, after treatment OSDI scores indicated a significant variance, with Group I at 4.4 ± 2.33 and Group II at 9.03 ± 3.24 (p-value less than 0.001). Also, the signs scores demonstrated insignificant variance pre-treatment between Group I (8.5 ± 2.29) and Group II (9.07 ± 2.39) ($p = 0.352$), while post-treatment scores were significantly different, with Group I at 2.47 ± 1.17 and Group II at 5.43 ± 2.19 ($p < 0.001$). TBUT values pre-treatment were not significantly different between Group I (4.47 ± 1.41) and Group II (4.07 ± 1.34) ($p = 0.263$), but post-treatment values were significantly different, with Group I at 11.11 ± 1.88 and Group II at 8.19 ± 1.48 ($p < 0.001$). Schirmer's test values also demonstrated no significant difference pre-treatment between Group I (6.83 ± 2.1) and Group II (6.77 ± 2.01) ($p = 0.901$), but post-treatment values were significantly different, with Group I at 14.4 ± 2.19 and Group II at 10.67 ± 2.6 ($p < 0.001$). Table 1 and Figure 1 demonstrate these comparisons.

Sub-group Analysis

Further analysis was conducted within sub-groups of severe and mild to moderate cases. For severe cases (sub-groups I-A and II-A), the mean OSDI score for sub-group I-A improved from 23.6 ± 3.02 pre-treatment to 5.13 ± 2.75 post-treatment ($p < 0.001$), while sub-group II-A improved from 22.57 ± 1.45 to 11.29 ± 2.87 ($p < 0.001$). Signs scores for sub-group I-A improved from 10.47 ± 1.14 to 3.13 ± 0.99 ($p < 0.001$), and sub-group II-A from 11.29 ± 1.14 to 7.07 ± 1.77 ($p < 0.001$). TBUT values for sub-group I-A improved from 3.19 ± 0.59 to 9.59 ± 1.2 ($p < 0.001$), and for sub-group II-A from 2.88 ± 0.42 to 7.09 ± 1.16 ($p < 0.001$). Schirmer's test values for sub-group I-A improved from 4.93 ± 0.88 to 12.53 ± 0.99 ($p < 0.001$), and for sub-group II-A from 4.93 ± 0.92 to 8.29 ± 0.83 ($p < 0.001$). Table 2 and Figure 2 demonstrate these comparisons.

For mild to moderate cases (sub-groups I-B and II-B), the mean OSDI score for sub-group I-B improved from 16.33 ± 2.44 before treatment to 3.67 ± 1.59 after treatment (p-value less than 0.001), while sub-group II-B improved from 15.25 ± 3.02 to 7.06 ± 2.08 ($p < 0.001$). Signs scores for sub-group I-B improved from 6.53 ± 1.13 to 1.8 ± 0.94 ($p < 0.001$), and sub-group II-B from 7.13 ± 1.15 to 4.0 ± 1.37 ($p < 0.001$). TBUT values for sub-group I-B improved from 5.76 ± 0.51 to 12.63 ± 0.96 ($p < 0.001$), and for sub-group II-B from 5.18 ± 0.82 to 9.14 ± 1.0 ($p < 0.001$). Schirmer's test values for sub-group I-B improved from 8.73 ± 0.8 to 16.27 ± 1.22 ($p < 0.001$), and for sub-group II-B from 8.38 ± 1.09 to 12.75 ± 1.61 ($p < 0.001$). Table 2 and Figure 3 demonstrate these comparisons.

Correlational Analysis

Correlational analyses between TBUT, OSDI score and Schirmer's test after and before treatment were conducted in each group. Before treatment, Group I demonstrated a significant positive association among TBUT and Schirmer's test (r -value = 0.843), a significant negative association among OSDI score and Schirmer's test (r -value = -0.853), and a negative association among TBUT and OSDI scores (r -value= -0.755). Similarly, Group II demonstrated a significant positive association among TBUT and Schirmer's test (r -value = 0.764), a significant negative association among OSDI score and Schirmer's test (r -value= -0.873), and a negative association

among TBUT and OSDI scores (r -value= -0.705). Table 3 summarizes these correlations before treatment.

After treatment, Group I demonstrated a significant positive association among TBUT and Schirmer's test (r -value= 0.873), a significant negative association among OSDI score and Schirmer's test (r -value = -0.686), and a negative association among TBUT and OSDI scores (r -value = -0.505). Group II similarly demonstrated a significant positive association among TBUT and Schirmer's test (r -value = 0.788), a significant negative association among Schirmer's test and OSDI score (r -value = -0.687), and a negative association among TBUT and OSDI scores (r -value= -0.546). Table 3 summarizes these correlations after treatment.

Sub-group Correlational Analysis

Further correlational analyses were conducted within sub-groups. Before treatment, sub-group I-A demonstrated non-significant correlations between Schirmer's test and either OSDI score or TBUT (r = 0.083 and 0.424, respectively), and non-significant correlations between OSDI score and TBUT (r = -0.112). Similarly, sub-group II-A demonstrated non-significant correlations between Schirmer's test and either OSDI score or TBUT (r = -0.363 and 0.422, respectively), and non-significant correlations between OSDI score and TBUT (r = -0.016). Table 3 summarizes these correlations before treatment for sub-groups II-A and I-A.

After treatment, sub-group I-A demonstrated non-significant associations among Schirmer's test and either OSDI score or TBUT (r -value = -0.385 and 0.388, respectively), but demonstrated a significant positive association with Schirmer's test and TBUT (r= 0.735) and demonstrated non-significant association among TBUT and OSDI score (r -value = -0.146). Subgroup II-A demonstrated insignificant association among Schirmer's test and OSDI score (r= -0.073), and insignificant association among TBUT and OSDI score (r -value =0.174). Table 3 summarizes these correlations after treatment for sub-groups I-A and II-A.

As regards to sub-groups I-B and II-B, before treatment, subgroup I-B demonstrated significant negative association among OSDI score and Schirmer's test (r -value = -0.805), but demonstrated non-significant association among TBUT and Schirmer (r -value =0.233), and demonstrated non-significant association among TBUT and OSDI score (r -value = 0.149). Subgroup II-B demonstrated non-significant association among Schirmer's test and either OSDI score or TBUT (r= -0.26 and -0.233 respectively), and non-significant correlation between OSDI score and TBUT (r = 0.415). Table 3 summarizes these correlations before treatment for sub-groups I-B and II-B.

After treatment, subgroup I-B demonstrated significant positive association among TBUT and Schirmer's test (r -value =0.739), but demonstrated insignificant association among OSDI score and Schirmer (r -value =-0.272), and demonstrated insignificant association among TBUT and OSDI score (r -value = -0.071). Subgroup II-B demonstrated non-significant correlation between Schirmer's test and either OSDI score or TBUT (r -value = -0.132 and 0.361 respectively), and non-significant correlation between OSDI score and TBUT (r -value = -0.097). Table 3 summarizes these correlations after treatment for sub-groups I-B and II-B.

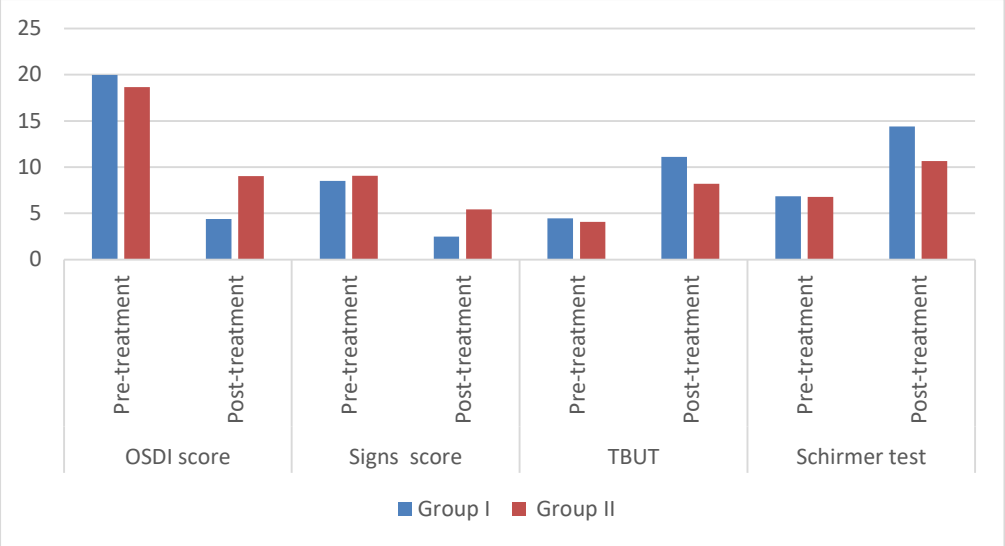

Figure (1) Multiple bar chart showing comparison between the studied groups (Group I and Group II) regarding OSDI score, signs scores, TBUT and Schimer test values

Table 1: Comparison between the studied groups (group I and group II) regarding demographic, baseline clinical characteristics, total OSDI score, signs score, TBUT, and Schirmer test values.

	Group I **N=30(%)**	Group II **N=30(%)**	χ^2	p
Gender:				
Female	17 (56.7%)	10 (33.3%)	3.3	0.069
Male	13 (43.3%)	20 (66.7%)		
Severity:				
Mild/moderate	15 (50%)	14 (46.7%)	0.067	0.796
Severe	15 (50%)	16 (53.3%)		
	Mean ± SD	**Mean ± SD**	t	p
Age (year)	58.1 ± 8.67	56.33 ± 10.08	0.724	0.47
	Mean ± SD	**Mean ± SD**	t	P
OSDI score				
Pre-treatment	19.97 ± 4.58	18.67 ± 4.41	1.12	0.267
Post-treatment	4.4 ± 2.33	9.03 ± 3.24	-6.357	<0.001**
pt	<0.001**	<0.001**		
Signs score				
Pre-treatment	8.5 ± 2.29	9.07 ± 2.39	-0.938	0.352
Post-treatment	2.47 ± 1.17	5.43 ± 2.19	-6.543	<0.001**
pt	<0.001**	<0.001**		
TBUT				
Pre-treatment	4.47 ± 1.41	4.07 ± 1.34	1.13	0.263
Post-treatment	11.11 ± 1.88	8.19 ± 1.48	6.689	<0.001**
pt	<0.001**	<0.001**		
Schirmer test				
Pre-treatment	6.83 ± 2.1	6.77 ± 2.01	0.125	0.901
Post-treatment	14.4 ± 2.19	10.67 ± 2.6	6.009	<0.001**
pt	<0.001**	<0.001**		

χ^2Chi square test t independent sample t test **p≤0.001 is statistically highly significant pt paired sample t test

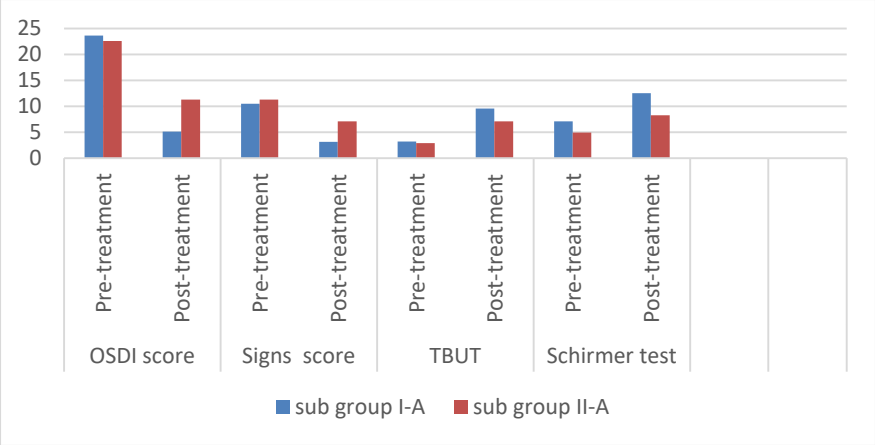

Figure (2) Multiple bar chart showing comparison between sub-group I-A and sub-group II-A regarding OSDI score, signs score, TBUT and Schirmer test values

Table 2: Comparison between sub-group I-A and sub-group II-A, and between sub-group I-B and sub-group II-B, regarding OSDI score, signs score, TBUT, and Schirmer test values.

	Sub-group I-A (n=15) **Mean ± SD**	Sub-group II-A (n=14) **Mean ± SD**	t	P
OSDI score				
Pre-treatment	23.6 ± 3.02	22.57 ± 1.45	1.115	0.258
Post-treatment	5.13 ± 2.75	11.29 ± 2.87	-5.9	<0.001**
pt	<0.001**	<0.001**		
Signs score				
Pre-treatment	10.47 ± 1.14	11.29 ± 1.14	-1.947	0.062
Post-treatment	3.13 ± 0.99	7.07 ± 1.77	-7.309	<0.001**
pt	<0.001**	<0.001**		
TBUT				
Pre-treatment	3.19 ± 0.59	2.88 ± 0.42	1.623	0.116
Post-treatment	9.59 ± 1.2	7.09 ± 1.16	5.692	<0.001**
pt	<0.001**	<0.001**		
Schirmer test				
Pre-treatment	4.93 ± 0.88	4.93 ± 0.92	0.014	0.989
Post-treatment	12.53 ± 0.99	8.29 ± 0.83	12.496	<0.001**
pt	<0.001**	<0.001**		
	Sub-group I-B (n=15) Mean ± SD	**Sub-group II-B (n=16) Mean ± SD**	**t**	**p**
OSDI score				
Pre-treatment	16.33 ± 2.44	15.25 ± 3.02	1.094	0.283
Post-treatment	3.67 ± 1.59	7.06 ± 2.08	-5.801	<0.001**
pt	<0.001**	<0.001**		
Signs score				
Pre-treatment	6.53 ± 1.13	7.13 ± 1.15	-1.448	0.158
Post-treatment	1.8 ± 0.94	4.0 ± 1.37	-5.186	<0.001**
pt	<0.001**	<0.001**		
TBUT				
Pre-treatment	5.76 ± 0.51	5.18 ± 0.82	2.311	0.028*
Post-treatment	12.63 ± 0.96	9.14 ± 1.0	9.9	<0.001**
pt	<0.001**	<0.001**		
Schirmer test				
Pre-treatment	8.73 ± 0.8	8.38 ± 1.09	1.039	0.307
Post-treatment	16.27 ± 1.22	12.75 ± 1.61	6.806	<0.001**
pt	<0.001**	<0.001**		

t independent sample t test **p≤0.001 is statistically highly significant within patients with mild/moderate disease

Table 3: Correlation between Schirmer's test, TBUT, and OSDI score before and after treatment in group I, group II, subgroup I-A, subgroup II-A, subgroup I-B, and subgroup II-B.

	Group I		**Group II**	
	r	**p**	**r**	**p**
OSDI score	-0.853	<0.001**	-0.873	<0.001**
TBUT	0.843	<0.001**	0.764	<0.001**
Correlation between OSDI score and TBUT				
TBUT	-0.755	<0.001**	-0.705	<0.001**
	Group I		**Group II**	
	r	**p**	**r**	**P**
OSDI score	-0.686	<0.001**	-0.687	<0.001**
TBUT	0.873	<0.001**	0.788	<0.001**
Correlation between OSDI score and TBUT				
TBUT	-0.505	0.004*	-0.546	0.002*
	subgroup I-A		**subgroup II-A**	
	r	**p**	**r**	**P**
OSDI score	0.083	0.768	-0.363	0.201
TBUT	0.424	0.115	0.422	0.133
Correlation between OSDI score and TBUT				
TBUT	-0.112	0.692	-0.016	0.956
	subgroup I-A		**subgroupII-A**	
	r	**p**	**r**	**p**
OSDI score	-0.385	0.165	-0.073	0.804
TBUT	0.388	0.153	0.735	0.003*
Correlation between OSDI score and TBUT				
TBUT	-0.146	0.603	0.174	0.551
	subgroup I-B		**subgroup II-B**	
	r	**p**	**r**	**p**
OSDI score	-0.805	<0.001**	-0.26	0.33
TBUT	0.233	0.404	-0.233	0.241
Correlation between OSDI score and TBUT				
TBUT	0.149	0.596	0.415	0.124
	subgroup I-B		**subgroup II-B**	
	r	**p**	**r**	**p**
OSDI score	-0.272	0.327	-0.132	0.626
TBUT	0.739	0.002*	0.361	0.169
Correlation between OSDI score and TBUT				
TBUT	-0.071	0.8	-0.097	0.722

r Spearman rank correlation coefficient **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

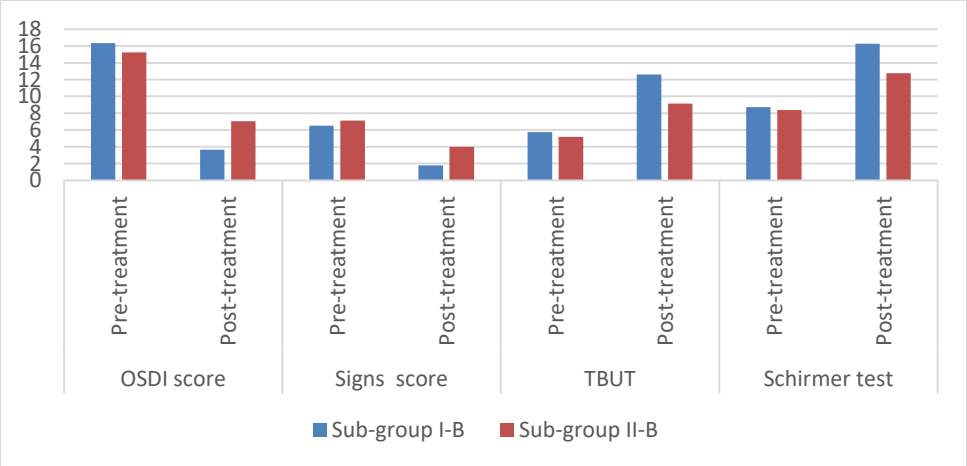

Figure (3) Multiple bar chart showing comparison between sub-group I-B and sub-group II-B regarding OSDI score, signs score, TBUT and Schirmer test values

Discussion

Posterior marginal blepharitis is a chronic inflammation of lid margin and Meibomian glands which can be caused by multiple factors and contributes to tear film alteration and irritative dry eye disease [3].

There is significant evidence that highly colonized ocular flora, for example Staph. aureus, Propionibacterium acnes and Staphylococcus epidermidis play critical roles in the development of illness. The microorganisms which have colonized the eye produce lipolytic exoenzymes, which in turn produce extremely cholesterol and irritating fatty acids. This leads to instability in the tear film, inflammation, and an increase in the rate at which tears evaporate [6].

In most cases, the therapy for chronic marginal blepharitis includes a routine of rigorous eyelid cleanliness that consists of continual washing of the eyelids to eliminate debris and the application of warm compresses in order to provide adequate meibum secretion. Antibiotics having anti-inflammatory effects, both topically applied and taken internally, should be considered for severe or resistant instances [2].

Tea tree oil is natural oil extracted from the leaves of Melaleuca alternifolia plant. It has antifungal, anti-bacterial, antiprotozoal, anti-inflammatory and antiviral effects. It demonstrated high efficacy against Pseudomonas aeruginosa, Escherichia coli, Candida albicans and Staph. aureus, besides it's highly potent against Demodex mites [3].

Azithromycin, a semisynthetic macrolide antibiotic, has a long half-life and a good intracellular penetration. It has a great effect in treating posterior blepharitis via its anti-inflammatory and immunomodulatory activities. It inhibits the synthesis of metalloproteinases (MMP-1, MMP-3 and MMP-9) and chemokines and pro-inflammatory mediators such as cytokines (TNFα, IL-1β) [5].

In our research all cases in the two groups demonstrated enhancement in OSDI score, signs score and special tests (TBUT and Schirmer's test) five weeks after receiving treatment. However, cases who received tea tree oil demonstrated better relief of signs and symptoms as well as better enhancement of TBUT and Schirmer's test more than cases who received oral azithromycin.

In accordance with our outcomes who made research on forty cases. Half of them (eleven men and nine women) received lid scrubbing with a formula of tea tree oil (Naviblef™) and the other half has been managed by eyelid cleansing and massage. The impact on tear film stability, lid signs, and ocular surface symptoms was assessed. All cases in tea tree oil group reported improvement in symptoms particularly grittiness, light sensitivity, soreness, discomfort during night driving or reading, and whereas utilizing visual display units. This research stated that cases in TTO group demonstrated significant development in OSDI score from (47.83 ± 8.37) in baseline visit to (8.71 ± 3.99) post-treatment and improvement of TBUT from (6.68 ± 0.84 s) in baseline visit to(14.47 ± 1.78 s) post-treatment [3.]

In research done by, 106 cases with ocular demodecosis (Demodex positive) completed 1 month of receiving eyelid scrubs with TTO. Cases involved seventy females and thirty-six men, with an average age of 53.7 ± 10.3 yr (range, 23-85 yr). In these cases, the OSDI score and the average number of Demodex were significantly reduced. Count of Demodex has been reduced from 4.0 ± 2.5 to 3.2 ± 2.3 (P-value = 0.001), and the OSDI score similarly reduced from 34.5 ± 10.7 to 24.1 ± 11.9 (P-value = 0.004) [9].

This is in agreement with the outcomes of who made research on 11 cases with ocular demodecosis and MGD treated with TTO 50% for weekly office lid scrub, facial hygiene and TT shampoo for daily home lid scrub. After treatment, nine of

eleven cases experienced fifty percent to one hundred percent development in symptoms. Signs like conjunctival injection, misdirected lashes, impaired visual acuity and discomfort were significantly improved, which agrees with our results. However, the study reported that six cases experienced moderate irritation and three cases experienced mild irritation following receiving treatment, which disagrees with our results as no patient in our study experienced such side effect. This could be due to the TT shampoo or the mineral oil used to dilute TTO used in the study [10].

In agreement with our results, Karakurt and Zeytun did a study on 135 cases with Demodex blepharitis and examined the effectiveness of a 7.5 % tea tree oil eyelid wash. Eyelid shampoo has been utilized on all the cases, some with tea tree oil and some without tea tree oil. Cases managed with tea tree oil demonstrated a statistically significant decrease in Demodex mite by 36% (p-value less than 0:001), with an average count decreased from 6.33/cilia to 0. In those not managed with tea tree oil, nevertheless, the mean reduced from 12.46/lash to 4.15/lash (p-value less than 0:001). Final outcomes demonstrated that tea tree oil eyelid shampoo was 3 times more effective in achieving reduction of total Demodex and improving ocular discomfort [11].

In compared the efficiency of 2 tea tree oil -based washing ointments in forty-nine cases with chronic blepharitis that have been classified into 2 groups. Group 1 (twenty-five subjects) obtained a basic gel with three percent tea tree oil, while group 2 (twenty-four participants) obtained an improved gel with three percent tea tree oil plus vitamins and essential oils. The tear break up time (TBUT), ocular surface disease index (OSDI), Schirmer's test, ocular surface staining pattern, impression cytology, TNF-, IL-6, and IL-1 levels , and Demodex presence have been calculated at the initial visit and following one month of therapy. The two groups demonstrated development in the mean OSDI score which reduced in both groups (p1:0.001, p2:0.001), Tear film break-up time test that elevated in the two groups (p1:0.002, p2:0.004). Count of Demodex similarly reduced from 42% to 27.8%in group 1 and from 54.2% to 20.6%; in group 2 (p1:0.302, p2:0.004). IL-6 and IL-1β reduced in group-2 (p1:0.002, p2:0.050). TNF-α reduced in the two groups (p1:0.001, p2:0.001). All variables have been enhanced in the two groups with better decrease of Demodex counts and cytokines in group 2 [12].

Also, made research on forty-five cases classified into three groups. Group I: received topical azithromycin (azithromycin one percent ophthalmic solution) 2 times a day for three days and then 1 time a for a month. Group II received systemic azithromycin (oral five times day azithromycin five hundred milligram on day one and then two hundred and fifty milligram per day). Group III: both regimens have been utilized. All cases were recommended to do warm compress one time a day. All groups demonstrated significant development in many signs and symptoms (itching, eyelid debris and hyperemia)., Cases at the 1st follow-up visit stated significant lesser rates of itching in topical an oral azithromycin groups than the combination group .At the 2nd follow-up visit, although itching was better in topical and combination groups than in oral azithromycin group, eyelid hyperemia and debris were better in oral azithromycin group and combination group than in topical group [1].

Our results also agree with that comparing the clinical effectiveness of oral and topical azithromycin therapies for posterior blepharitis. Their research involved thirty cases with meibomian gland dysfunction that have been randomly classed to give topical azithromycin 2 times a day for three days and then one time a day for a month or oral five times days azithromycin. following therapy,

symptoms like foreign body sensation and itching, and signs such as meibomian gland secretion, eyelid hyperemia, and eyelid debris were significantly enhanced in the two groups. Nevertheless, the outcomes of topical treatment group demonstrated some superiority over those of systemic therapy group [6].

Additionally, a meta-analysis and systematic review of treating meibomian gland dysfunction with azithromycin by stated that the overall pooled symptom scores were significantly decreased following administering both oral azithromycin and topical azithromycin [P-value less than 0.0001; SMD = 1.54 (95% CI: 1.15-1.92)]. Also, the overall combined eyelid signs, meibum quality, tear secretion and plugging of the meibomian gland were also significantly enhanced and this is in agreement with our research. Nevertheless, significant developments for tear break-up time has been 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) which disagrees with our research as we recorded significant improvement in TBUT in all cases who received oral azithromycin in our research. This might be due to not using artificial tears in some of the studies reviewed by or may be due to using different concentration of oral azithromycin than we used [13].

A randomized controlled trial with a cross-over design research by comparing oral azithromycin and oral doxycycline in cases with meibomian gland dysfunction (MGD) revealed that azithromycin demonstrated better results throughout the research, showing a significant improvement in most cases (65%) especially in VA, conjunctival redness, and corneal staining. It demonstrated quick and maintained improvement throughout the research. On the other hand, cases treated with doxycycline had similar results only in a relatively small percentage of cases (10%) which indicates that azithromycin may be preferable to doxycycline in treatment of MGD 14.

In agreement with our results, did a randomized double-masked open-label clinical trial to assess the efficacy and safety of oral azithromycin compared with oral doxycycline in cases with meibomian gland dysfunction, 110 cases (>12 years old) with MGD were enrolled into the research and were randomly assigned to two groups. One group received oral 5-day azithromycin (500 mg on day 1 and then 250 mg/day) and the other group received 1-month doxycycline (200 mg/day). The two groups used artificial tears and followed a routine of warm compresses and eyelid cleansing. Signs and symptoms enhanced significantly in the two groups (p-value =0.001). While enhancement of symptoms was not variant among the groups, the last follow-up mean score of all clinical signs was better in the azithromycin group and in a statistically significant variance was only found for conjunctival redness and ocular surface staining. The azithromycin group demonstrated a significantly better clinical enhancement [5].

Limitations of the study

The major limitations in our study were the few numbers of participants, the follow-up time was short, and not including a control untreated group.

Conclusion and recommendations

Both topical tea tree oil and oral azithromycin are effective in treating cases with posterior marginal blepharitis. They both managed to significantly improve symptoms and signs, as all cases demonstrated markedly lower OSDI scores and lower signs scores after treatment, in addition to special tests (Schirmer's test and TBUT) which were significantly enhanced with markedly larger values after treatment in all cases. However, results demonstrated higher efficacy of topical TTO over systemic azithromycin at all parameters, as TTO cases demonstrated

better OSDI and signs scores, as well as better TBUT an schirmer test values.

However, further investigations including a large number of cases over longer duration are recommended to clarify the role of TTO in treatment of posterior blepharitis and ocular surface disease, and to evaluate different doses and time intervals of oral azithromycin and TTO courses of treatment, and to compare topical azithromycin with TTO.

Conflict of interest

None of the contributors declared any conflict of interest

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