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COMPARISION OF EFFECTIVENESS OF TOPICAL AZITHROMYCIN AND SYSTEMIC DOXYCYCLINE IN TREATMENT OF MEIBOMIAN GLAND DYSFUNCTION

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KEYWORDS :

INTRODUCTION:

Meibomian glands, also known as glandulae tarsales, are large sebaceous glands found within the eyelids. They produce lipids that constitute the outermost layer of the tear film, serving to prevent the evaporation of the aqueous phase. The detailed description of these glands was originally provided by the German physician Heinrich Meibom (1638-1700), and they bear his name[1] . Korb and Henriquez introduced the term Meibomian Gland Dysfunction (MGD) when investigating contact lens intolerance and the blockage of Meibomian gland openings by shedding epithelial cells [2]. According to the International Workshop on MGD, this condition is described as "a persistent, widespread anomaly of the meibomian glands, typically marked by blockage in the terminal ducts and/or variations in the quality or quantity of glandular secretions. It can lead to changes in the tear film, sensations of eye discomfort, observable inflammation, and disorders of the eye's surface"[3].

CLASSIFICATION:

The 2011 International Workshop on Meibomian Gland Dysfunction (MGD) introduced a new classification system [4]. MGD is categorized based on its ultimate impact on Dry Eye Diseases (DED) and can be divided into low delivery and high delivery groups based on the status of glandular secretion. The most common cause of hyposecretion is the obstruction of Meibomian glands, stemming from ductal epithelium hypertrophy, keratinization linked to aging, decreased androgen receptor expression, or medication usage. Obstructive MGD can be further divided into cicatricial and noncicatricial forms. Hypersecretory MGD arises from an excessive release of lipids. Overall, MGD leads to changes in the tear film, eye discomfort, ocular surface disorders like dry eye, and clinically observable inflammation.
Doxycycline is a commonly used treatment for Meibomian Gland Dysfunction (MGD). It's a derivative of tetracycline and is chosen for its ability to regulate lipid anti-inflammatory, and antimicrobial characteristics. Doxycycline also inhibits matrix metalloproteinases, which play a role in connective tissue degradation. It has proven effective in managing ocular rosacea by relieving irritation symptoms and improving tear film stability. Moreover, it has been employed to treat corneal erosions [5].

Clinical trials have identified topical azithromycin as a potentially well-tolerated and effective treatment for MGD and lid margin conditions. Azithromycin, a macrolide antibiotic, boasts broad-spectrum antimicrobial properties, anti-inflammatory effects, and the ability to regulate lipids. When applied topically, it achieves concentrations that inhibit bacterial growth on the lid margin, making it a promising option [6].

This work aimed compare topical azithromycin eye drops versus oral doxycycline effectiveness in meibomian glands dysfunction.

MATERIALS AND METHODS:

This comparative prospective cohort study involved 60 patients of both genders and ages who presented with symptomatic MGD. The study was conducted in the Ophthalmology Department of Mathuradas Mathur Hospital from October 2022 to august 2023.

Prior to participating in the study, informed written consent was obtained from either the patient or their relatives.

Inclusion Criteria:

- Individuals within age group of 18-60 years.
- Individuals with a confirmed diagnosis of meibomian glands dysfunction.
- Individuals who will adhere with scheduled follow up sessions.

Exclusion Criteria:

- Individuals who have a recent history of any ocular surgery or ocular injury.
- Individuals with hypersensitivity to drugs involved in study azithromycin or doxycycline.
- Individuals who have any active pathology involving anterior or posterior segment of eye.
- Individuals on any active medication be it ocular or systemic (oral antibiotics, topical or oral steroids, ocular NSAIDs, topical cyclosporine topical antihistamines).

All patients underwent a comprehensive assessment, which included gathering their personal medical history and conducting a thorough eye examination, which included measuring visual acuity, refraction and conducting slit lamp examination.

Patients with Meibomian Gland Dysfunction (MGD) were randomly divided into two groups using a computer-assisted program. Group 1 received treatment with topical azithromycin (1%) eye drops 4 times daily for 4 weeks, while group 2 was administered oral doxycycline 100 mg BD for the same duration.

Both groups continued conservative management, which included eyelid massage, cleaning with a gentle eye-friendly soap (Baby Johnson Shampoo, Johnson & Johnson) at bedtime, warm compresses twice daily, and the use of artificial tears four times daily.

Data were collected at three time points: upon 1st OPD visit (Day 0), 14th day (first follow-up), and 28th day (second follow-up). Subsequently, the collected parameters were compared between the two groups.

- The pain evaluation was performed employing the Wong and Baker Face Pain Scale, which features a range of facial expressions. In our research, we classified the scale into 3 groups: severe pain (scores 7–10), moderate pain (scores 4–6), and mild pain (scores 1–3).

- Regarding the lid margin telangiectasia scale, the grading system relies on specific criteria. Abnormal vascularity observations at the lid margin are determined by two main components: the presence of telangiectasia crossing meibomian gland orifices and the degree of redness at the lid margin.
  - Grade 0: No or slight redness in the lid margin conjunctiva and no telangiectasia crossing meibomian gland orifices.
  - Grade 1: Redness in the lid margin conjunctiva but no telangiectasia crossing meibomian gland orifices.
  - Grade 2: Redness in the lid margin conjunctiva and telangiectasia crossing meibomian gland orifices covering less than half of the full length of the lid.
  - Grade 3: Redness in the lid margin conjunctiva and telangiectasia crossing meibomian gland orifices covering half or more of the full length of the lid.

We also assessed the presence or absence (positive or negative) of conjunctivitis, frothy discharge, and tear film meniscus floaters.

The Break-up Time Test is a clinical examination used to diagnose evaporative dry eye disease. In this test, fluorescein is instilled into the patient's tear film to measure the Tear Break-Up Time (TBUT). The tear film is observed under broad cobalt blue Illumination. After a certain time-interval, lines or black spots appear in the fluorescein-stained film, indicating the presence of dry patches. The time elapsed between the last blink and the appearance of the first dry spot is referred to as the TBUT. A TBUT of less than ten seconds is considered abnormal.

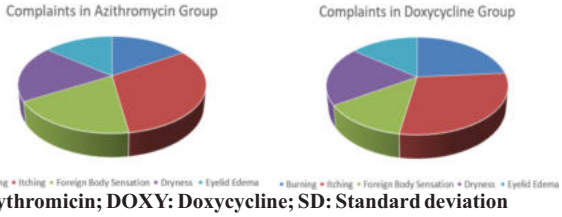
Statistical Analysis:

For statistical analysis, we employed SPSS. Quantitative variables were presented as the mean and standard deviation (SD) and were compared between the two groups using an unpaired Student's t-test. Qualitative data were expressed as frequency and percentage (%), and their analysis was conducted using the chi-square test or Fisher's exact test when appropriate. The significance level for all tests was set at $P < 0.05$.

RESULTS:

There was an insignificant difference between both groups in terms of age and gender. Burning, itching, foreign body sensation, Dryness, eyelid edema in the first visit were insignificant different between both groups (Table 1).

Table 1 Demographics And Main Complaints Of Patient Groups, According To Drug Administration



Azythromicin; DOXY: Doxycycline; SD: Standard deviation

Demographics	AZT	DOXY	
Male/female	16/14	18/12	0.75
Mean age (years) (SD)	50 (15.9)	51 (15.3)	0.65
Mean duration of disease (weeks) (SD)	15 (8.2)	13 (7.4)	0.37
Main complaints			
Burning	10%	18%	0.92
Itching	20%	22%	0.71
Foreign body sensation	12%	10%	0.69
Dryness	12%	15%	0.62
Eyelid edema	09%	11%	0.78

In the first visit, there were no significant differences observed between both groups in terms of pain and discomfort, lid margin telangiectasia, conjunctivitis, frothy discharge, meniscus floaters, and break-up time tests (as shown in Table 2).

Table 2 Pain and discomfort, lid margin telangiectasia, conjunctivitis, frothy discharge, meniscus floaters and break-up time test in 1st visit between studied groups.

		Topical azithromycin ($n = 30$)	Systemic doxycycline ($n = 30$)	*P* value
Pain and discomfort	Mild	7 (23.34%)	8 (26.67%)	
	Moderate	12 (40%)	15 (50.00%)	0.267
	Severe	11 (36.67%)	7 (23.34%)	
Lid margin telangiectasia	0 & 1	2 (6.67%)	4 (13.34%)	
	2	11 (36.67%)	16 (53.34%)	0.671
	3	17 (56.67%)	10 (33.34%)	
Conjunctivitis	+ve	17 (56.67%)	13 (43.34%)	0.427
	−ve	13 (43.34%)	17 (56.67%)	
Frothy Discharge	+ve	25 (83.34%)	23 (76.67%)	0.285
	−ve	5 (16.67%)	7 (23.34%)	
Meniscus floaters	+ve	20 (66.67%)	21 (70%)	0.751
	−ve (no or minimal floaters)	10 (33.34%)	9 (30%)	
Break-up time test (seconds)		7.42±1.96 2–9	6.84±2.11 3–9	0.590
Data are presented as mean ± SD				

In the initial follow-up, we observed a notable difference between the groups under investigation concerning the degree of pain and discomfort, with a P-value of 0.047 indicating statistical significance. Notably, patients experiencing mild pain were notably more prevalent in the topical azithromycin group (P-value = 0.049), while patients reporting severe pain were notably more common in the systemic doxycycline group (P-value = 0.031). The variation in moderate pain levels and lid margin telangiectasia between the studied groups was not statistically significant.

Furthermore, when examining conjunctivitis and meniscus floaters, topical azithromycin group exhibited significantly lower occurrences compared to the systemic doxycycline group, as indicated by P-values of 0.019 and 0.048, respectively. Additionally, break-up time tests showed a significant difference, with higher values in the topical azithromycin group compared to the systemic doxycycline group (P-value = 0.045). Similarly, patients with negative frothy discharge were notably more prevalent in the topical azithromycin group compared to the systemic doxycycline group, with a statistically significant P-value of 0.036 (Table 3).

Table 3 Pain And Discomfort, Lid Margin Telangiectasia, Conjunctivitis, Frothy Discharge, Meniscus Floaters And Break-up Time Test In 1st Follow Up Between Studied Groups.

		Topical azithromycin ($n = 30$)	Systemic doxycycline ($n = 30$)	*P* value
Pain and discomfort	Mild	15 (50%)	8 (26.67%)	0.049
	Moderate	10 (33.34%)	9 (30%)	0.612
	Severe	5 (16.67%)	13 (43.34%)	0.031
Lid Margin telangiectasia	0 & 1	7 (23.34%)	5 (16.67%)	0.422
	2	14 (46.67%)	12 (40%)	
	3	9 (30%)	13 (43.34%)	
Conjunctivitis	+ve	10 (33.34%)	16(53.34%)	0.019
	−ve	20 (66.67%)	14 (46.67%)	
Frothy discharge	+ve	11 (36.67%)	18 (60%)	0.036
	−ve	19 (63.34%)	12 (40%)	
Meniscus Floaters	+ve	11 (36.67%)	20 (66.67%)	0.048
	−ve (no or minimal floaters)	19 (63.34%)	10 (33.34%)	
Break-up Time Test (seconds)		8.17±2.05 5-13	6.92 ±2.39 3-11	0.045

During the second follow-up, there were no significant differences observed between the groups in terms of pain and discomfort, lid margin telangiectasia, conjunctivitis, or frothy discharge. However, it's worth noting that in the second follow-up, meniscus floaters were significantly less prevalent in the topical azithromycin group compared to the systemic doxycycline group, as indicated by a (P-value of 0.039). Additionally, the break-up time test yielded significantly higher results in the topical azithromycin group, with a (P-value of 0.020) (Table 4).

Table 4 Pain And Discomfort, Lid Margin Telangiectasia, Conjunctivitis, Frothy Discharge, Meniscus Floaters And Break-up Time Test In 2nd Follow Up Between Studied Groups.

		Topical azithromycin ($n = 30$)	Systemic doxycycline ($n = 30$)	*P* value
Pain and discomfort	Mild	17 (56.66%)	15 (50%)	0.805
	Moderate	7 (23.34%)	8 (26.67%)	
	Severe	6 (20%)	7 (23.34%)	
Lid Margin telangiectasia	0 & 1	12 (40%)	10 (33.34%)	0.417
	2	12 (40%)	13 (43.34%)	
	3	6 (20%)	7 (23.34%)	
Conjunctivitis	+ve	7 (23.34%)	12 (40%)	0.061
	−ve	23 (76.67%)	18 (60%)	
Frothy discharge	+ve	5 (16.67%)	7 (23.34%)	0.598
	−ve	25 (83.3%)	23 (76.67%)	
Meniscus Floaters	+ve	08 (26.67%)	14 (46.67%)	0.039
	−ve(no or minimal floaters)	22 (73.34%)	16 (53.34%)	
Break-up Time Test (seconds)		9.11±2.14 7-13	7.71 ±2.01 5-10	0.020

Concerning side effects observed in both groups, there was a notable

increase in the occurrence of a burning sensation in the tropical azithromycin group (P = 0.026), while gastrointestinal upset was markedly more prevalent in the systemic doxycycline group (P < 0.001). In contrast, the absence of side effects, as well as experiences such as stinging sensation, sticky eyelids, photosensitivity, and allergic reactions, showed no significant differences between the two groups.

DISCUSSION:

Obstructive MGD is most prevalent cause of EDE. The increased viscosity of meibum or the excessive keratinization of Meibomian gland ducts can obstruct them, resulting in reduced meibum secretion. This reduction affects the stability of the tear film, potentially leading to dry eyes.

The primary objective in treating Meibomian Gland Dysfunction (MGD) is to enhance the quality and quantity of meibomian gland secretions, alleviating discomfort. Numerous studies have demonstrated the effectiveness of certain clinical management approaches. These include maintaining good eyelid hygiene, employing warm compresses or heat therapy. This can be achieved through gentle eyelid massage, applying heat using methods such as warm, damp towels or specialized devices like the LipiFlow Thermal Pulsation System, MiBo Thermaflow, BlephEx, Intense Pulse Tx, KCL1100, which aid in liquefying meibum and preventing excessive tear evaporation [7] [8] [9] [10]. Additionally, the use of topical or systemic antibiotics can be considered to manage infections and facilitate the restoration of meibomian gland function.Antibiotics like azithromycin can effectively alleviate dry eye symptoms due to anti-inflammatory properties. There dual action involves modifying or diminishing eyelid flora and the microbiome that contributes to meibomian gland dysfunction, thereby mitigating ocular surface inflammation through direct anti-inflammatory effects.

The two primary categories of antibiotics used for this purpose are tetracyclines and macrolides. Oral doxycycline, minocycline, or lymecycline have demonstrated success in improving both symptoms and signs of meibomian gland dysfunction, albeit with some potential gastrointestinal side effects. There is also concern regarding their impact on the gut microbiome. For example, the long-term effects of doxycycline or lymecycline on altering gut flora and how this might modulate the body's immune system remain somewhat unclear. As an alternative, azithromycin can be used either topically, orally, or a combination of both. [11][12]

Our study aimed to compare the effectiveness of topical azithromycin with systemic doxycycline for treating meibomian gland dysfunction. In our findings during the initial visit, we observed no significant differences in terms of pain and discomfort, lid margin telangiectasia, or conjunctivitis between the two groups under study.

Regarding pain and discomfort, our results align with a randomized study conducted by Marwa Aly Zaki who checked efficacy between topical azithromycin and oral doxycycline their study also found no significant difference in pain levels between the doxycycline and azithromycin groups during the initial visit also a long-term randomized study conducted by De Benedetti and Vaiano [13] ,which compared doxycycline (4 g for 30 days) and oral azithromycin (1.25 g for 5 days) in MGD patients over 9 months. Their study also found no significant difference in pain levels between the doxycycline and azithromycin groups during the initial visit. Additionally, they reported no significant variance in conjunctivitis between these groups.

Concerning lid margin telangiectasia, our findings mirror those of Foulks et al.[14], who demonstrated that there was no significant distinction between the doxycycline and azithromycin groups in terms of lid margin telangiectasia. Furthermore, our present findings indicate that there were no significant differences observed between the groups receiving azithromycin and doxycycline during the initial visit, specifically concerning frothy discharge and the presence of meniscus floaters. These results align with the study conducted by Hamed et al. [15], who conducted a comparative analysis to assess the effectiveness of topical azithromycin and doxycycline in improving the signs and symptoms of posterior blepharitis leading to Meibomian gland dysfunction (MGD).

Our study included a total of 120 eyes from sixty patients of both genders, all aged 18 and above, diagnosed with posterior blepharitis contributing to dry eye disease. During the first visit, our findings revealed that there was no significant difference in the occurrence of frothy discharge between the two treatment groups.

Additionally, when examining the results from the first visit, the break-up time test showed no significant difference between the two groups. These outcomes are consistent with the findings of Foulks et al.[14], who reported that the tear film break-up time for patients with MGD did not show statistically significant differences between those treated with azithromycin and those treated with doxycycline at the time of admission. Our findings revealed a noteworthy distinction during the initial follow-up when it came to the levels of pain and discomfort between the groups under investigation. Notably, a significantly higher number of patients in the topical azithromycin group reported mild pain, whereas the systemic doxycycline group had a significantly higher number of patients experiencing severe pain. However, we observed no significant difference in the occurrence of moderate pain between these groups. This observation is in line with the results of Kashkouli et al.[22], who noted improvements in signs and symptoms in both treatment groups after a 60-day period. Remarkably, the azithromycin group exhibited a more substantial reduction in overall symptoms, pain severity, and signs, with these symptoms diminishing to mild levels compared to the doxycycline group.

Furthermore, our study found no significant difference in the presence of lid margin telangiectasia during the initial follow-up between the groups under examination. This outcome contrasts with the findings of Kashkouli et al. [16] , who reported a significant reduction in lid margin telangiectasia in the azithromycin group compared to the doxycycline group during the first follow-up of patients. It's worth noting that the limited sample size in our study may account for this difference.

Additionally, our collected data revealed a significant difference during the first follow-up.

Notably, the topical azithromycin group had a significantly higher number of patients with no frothy discharge compared to the systemic doxycycline group. This finding contradicts the results of Hamed et al. [15], who reported that the signs during the first follow-up, one week after treatment, did not show a significant difference between the azithromycin and doxycycline groups in terms of frothy discharge.

Furthermore, our results indicated that conjunctivitis during the first follow-up, two weeks after treatment, was significantly less prevalent in the topical azithromycin group (33.34%) compared to the systemic doxycycline group (53.34%). These results are consistent with the findings reported by Foulks et al.[14] Additionally, our study found that meniscus floaters during the first follow-up were significantly less common in the topical azithromycin group compared to the systemic doxycycline group.

Furthermore, our results revealed that during the first follow-up, the break-up time test showed a significant improvement in the topical azithromycin group. These findings are consistent with the study conducted by Marwa Zaky et al. [17], where they observed a significant increase in tear break-up time among patients treated with azithromycin compared to the doxycycline group during the first follow-up.

Additionally, our research indicated that during the second follow-up, there were no significant differences between the studied groups in terms of pain and discomfort, lid margin telangiectasia, and conjunctivitis. These results align with the findings of Satitpitakul et al.[18], who conducted a prospective randomized trial evaluating the efficacy of azithromycin 1.5% eye drops in individuals with moderate to severe Meibomian gland dysfunction (MGD) compared to oral doxycycline. Their results showed no significant differences in MGD-related symptoms, including discomfort, between the azithromycin and doxycycline groups after 4 weeks of follow- up. Similarly, De Benedetti and Vaiano[13] reported no statistically significant difference between both groups concerning conjunctivitis during the second follow-up. Foulks et al. [14] also found that all signs of eyelid margin disease, including telangiectasia, improved after 4 weeks of follow- up in both groups without a statistically significant difference.

Moreover, our findings indicated that during the second follow-up, the break-up time test was significantly higher in the topical azithromycin group. These results were consistent with those reported by Foulks et al.[14], who demonstrated improved tear break-up time in azithromycin-treated patients after 4 weeks of follow-up and in doxycycline-treated

patients after 8 weeks.

Furthermore, these findings align with the results of a study conducted by Fadlallah and colleagues [19]. Their research aimed to assess the effectiveness of topical 1.5% azithromycin in treating moderate-to-severe chronic blepharitis and to compare two different treatment approaches. Patients were randomly divided into two groups: Group I received topical 1.5% azithromycin twice daily for three days, while Group II received the same treatment for three days and then continued with bedtime treatment for the rest of the month. Another noteworthy observation during the second follow-up was that frothy discharge did not significantly differ between the investigated groups. This insignificant improvement in frothy discharge may be attributed to the challenge of azithromycin reaching therapeutic levels in the Meibomian glands to stabilize the tear film.

CONCLUSION:

The effective treatment of Meibomian gland dysfunction (MGD) can be achieved through the use of oral doxycycline and topical azithromycin, leading to improvements in symptoms, clinical signs, and the stability of the tear film. However, it's important to note that doxycycline, while effective, can sometimes result in gastrointestinal side effects. In contrast, the topical treatment group appears to have advantages over the oral group in the short term, as it offers a more favourable balance between effectiveness, fewer side effects, improved patient compliance, and better tolerance.

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Conflict Of Interest**:** *NIL*

Limitations:

This study had noteworthy limitations. First, the sample size was relatively small. Second, the follow-up period was comparatively brief. Additionally, we did not incorporate various visual function tests, including contrast sensitivity and colour vision assessments.

Furthermore, a comprehensive evaluation of Meibomian gland secretion and plugging was not performed.

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