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ORIGINAL RESEARCH ARTICLE

Evaluating Role of Topical Azithromycin in Meibomian Gland Dysfunction – An Interventional Study

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ABSTRACT

Background:Meibomian gland dysfunction (MGD) is a common ocular disorder, often underdiagnosed, and is a major contributory factor causing dry eye disease and ocular discomfort due to compromised quality of tears. A variety of physical measures, lubricants and antibiotics have been tried to alleviate the condition. Topical Azithromycin has been observed to provide relief in MGD. Interest has been generated in this drug due to its anti- inflammatory properties in addition to its antibiotic effect.

Materials and Methods: The present study was undertaken to study the clinical efficacy of topical Azithromycin in MGD. 70 patients randomly detected with MGD were given Azithromycin 1% topically. In half of the patients; n=35, (Group A), the mode of administration was aqueous as 1% eye drops, twice a day for 30 days while in remaining half (Group B), it was delivered as an ointment, applied daily at night for same duration. This was combined with physical measures of lid massage and lid hygiene. Primary outcome measures of evaluation were Fluorescein tear breakup time, (FTBUT)', Tear quantification (Schirmer's test), Corneal staining score, Meibomian gland score and a subjective clinical score. Measurements were recorded prior to drug usage and at subsequent follow up visits at Day 30, 60 & 90. Statistical analysis: Considering the small sample size, the outcome measures for the two groups were statistically analysed employing the Fischer's exact test and the Mann Whitney test. P values (two sided) less than 0.05 were considered statistically significant.

Results: Azithromycin in aqueous form, showed significantly higher clinical efficacy at day 30, whereas noted efficacy of ointment was higher at day 60 and 90. The symptom score showed significant improvement among both the groups receiving azithromycin. The effect was however less significant for users of eye drops at day 90, compared to ointment. Values of Schirmer's test echoed similar results.

Conclusion: Azithromycin 1% ophthalmic solution is effective in reducing the signs and symptoms associated with meibomian gland dysfunction in both, drop and ointment form. These effects persist in ocular tissues beyond the last application. However, long term effect of azithromycin seems better when used in the ointment form.

Keywords: Meibomian gland dysfunction, azithromycin.

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INTRODUCTION

Meibomian gland dysfunction, is defined as a chronic, diffuse abnormality of meibomian glands, commonly characterized by terminal duct obstruction with qualitative & quantitative

changes in glandular secretions. These result in alteration of tear film, symptoms of ocular irritation, clinically apparent inflammation and ocular surface disease.[1,2] Even in mild forms it has a significant adverse impact on patient's quality of life. Lipids provisioned to the tear film by these glands retard evaporation of tears from the ocular surface,[3] providing a smooth refractive interface to the eye. With MGD, the meibomian gland orifices can become obstructed. Qualitative & quantitative alteration of lipids with advancing age & inflammatory processes frequently cause evaporative dry eye.[3] Eventually, all of these changes damage the ocular surface, resulting in ocular discomfort. Hence presence of MGD compromises the quality of vision, ocular comfort and indirectly affects the daily life of an average person.

MGD has remained an understated eye ailment for a long time. High prevalence of MGD among normal patients presenting for routine vision testing was documented many years ago.[3] Reports suggest that approximately 60% of Asian populations and 20% of Caucacians suffer from varying grades of MGD.[3] Variability in prevalence is also affected by age.[4] Nearly 33% of patients below 30 years and above 72% patients above 60 years are reported to suffer from MGD.[3]

The term Meibomian gland dysfunction (MGD) is often used synonymously with posterior blepharitis.[4] However, posterior blepharitis is meant to describe exclusively the inflammatory conditions of the posterior lid margin.[1,5]

The primary goal of management is to reduce or eliminate associated signs and symptoms, to improve patient comfort and to prevent sight threatening complications such as corneal scarring, resulting from infection and inflammation.[3] Conventional therapy of MGD includes mechanical options of lid massage & expression, hot compresses and improvement of lid hygiene by use of antiseptics like baby shampoo.[6,7] Medical therapy of systemic tetracycline, doxycycline and topical application of antibiotics have met with partial success. It had indirect effect on meibomian gland function by controlling the lid marginal infections that are both initiators and accompaniments of MGD. Introduction of Azithromycin, a bacteriostatic macrolide has however unfolded a paradigm shift in the management of MGD. Besides harboring antibiotic effect, Azithromycin has been reported to have anti-inflammatory properties that change the physical properties of secreted meibum.[7] Topical effect of Azithromycin as drops in the concentration of 1% & 1.5% administered on a twice daily basis have been incompletely studied & understood. The efficacy in ointment form is even more poorly explored.

Hence this study has been devised to venture into the quantum of the problem of MGD prevalence and measure the clinical efficacy of topical Azithromycin.

MATERIALS & METHODS

The present study was carried out in a multi centric manner at two tertiary eye care centres at Rohilkhand Medical College, Bareilly and Government Doon Medical College, Dehradun. It was designed as a prospective, double blinded, interventional study. Patients attending the Ophthalmology OPD at the two hospitals and detected with MGD, fulfilling the inclusion criteria were included following clearance from respective ethical committees. Relevant history and demographic data was noted on the study proforma that included an Informed consent. Detailed ocular examination was done employing Slit lamp biomicroscopy for anterior segment evaluation. A total of 70 patients were enrolled. Half of these patients were given topical Azithromycin as 1% eye drops in aqueous mode with the drug regime of twice daily application for 30 days. The remaining half received 1% Azithromycin in the ointment form that was applied at bed time for 30 consecutive days.

Inclusion criteria: Patients attending eye OPD, and detected with Meibomian gland dysfunction.

Exclusion criteria: Patients with any other existing ocular inflammation or lid disorders, patients with history of ocular trauma, intraocular inflammation or ocular surgery within the previous year, patients allergic to Azithromycin and patients with existing ocular surface disorder.

The ocular surface indices were assessed on the basis of Schirmers test, Fluorescein Tear film breakup time (FTBUT) and Corneal staining.

Schirmers testing was performed without anaesthesia for 5 minutes with the patient's eyes closed. It was performed on the patient's initial visit to obtain baseline data and subsequently at all the follow up visits. Both the reflex and basal secretions were measured. FTBUT was measured using sterile sodium fluorescein strips, which were placed in each eye and the patient was asked to blink several times to ensure the even distribution of fluorescein over the cornea. While looking straight ahead, the tear film was evaluated using cobalt blue filter on a Slit lamp bio-microscope. The FTBUT was defined as the interval between the last complete blink and the first appearance of a dry spot or disruption in the tear film. Corneal fluorescein staining was conducted five minutes after the FTBUT measurements. Five areas of the cornea; the centre, nasal, temporal, superior and inferior regions, were evaluated. The type of staining was graded using following scale: No staining (–) normal, mild- superficial stippling or micro-punctate staining (+), moderate- macro punctate staining (++), severe- numerous coalescent macro punctate areas or patches (+++).

Meibomian gland grading was performed using the standardized scale [Table 1].

Table 1: Meibomian Gland grading Scale

Meibomian gland score	Description of secretions	Digital pressure to express
0	Clear	Easily expressed
1	Cloudy fluid	Easily expressed
2	Cloudy fluid	Mild pressure
3	Cloudy, particulate matter	Moderate pressure
4	Thick, tooth paste like secretion	Hard pressure

Patient's ocular comfort & subjective symptoms were evaluated on a clinical score ranging from 0 to 3. The symptoms enquired included itching, lacrimation & foreign body sensation [Table 2].

Table 2: Patients subjective symptoms

Symptom score	Description of score
0	None
1	Mild
2	Moderate
3	Severe

Observations were taken at the time of initiation of treatment (Day 0) and subsequently at the end of the treatment (Day 30) and the follow up period (Day 60) and (Day 90).

RESULTS

70 patients with MGD were included in the study, randomly assorted into 2 groups; the eye drops group – A and the Ointment group -B. There were 37 female patients (52.86% per

cent). Patient's age varied from 40 to 80 years with a mean age of 62.91 ± 7.82 in Group A and 61.66 ± 8.43 in Group B. The prevalence of MGD in the total OPD was noted as 66%.

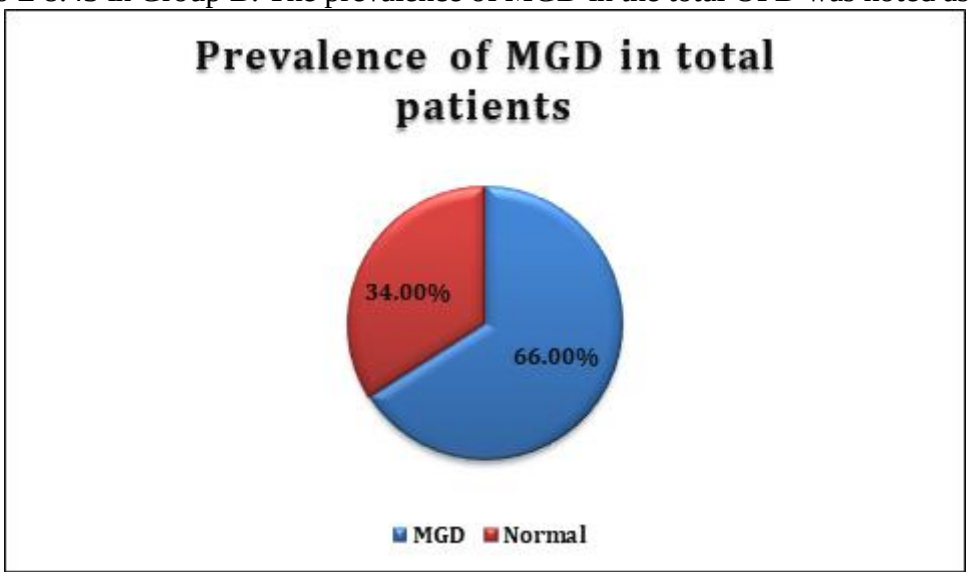

Figure 1: Prevalence of MGD in total patients.

Table 3: Comparison of age in years between groups drop and ointment.

Age in years	Drop (n=35)	Ointment (n=35)	Total (n = 70)	P value	Test performed
41-50	2 (5.71%)	3 (8.57%)	5 (7.14%)	0.934	Fisher's Exact test
51-60	13 (37.14%)	14 (40%)	27 (38.57%)		
61-70	13 (37.14%)	13 (37.14%)	26 (37.14%)		
71-80	7 (20%)	5 (14.29%)	12 (17.14%)		
Total	35 (100%)	35 (100%)	70 (100%)		
Mean ± S D	62.91 ± 7.82	61.66 ± 8.43	62.29 ± 8.1	0.733	Mann Whitney test; 583.5
Median(IQR)	62(58-68)	64(55-67)	62(56-67)		
Range	48-79	41-77	41-79		

Table 4: Comparison of corneal staining between group drop and ointment.

Corneal staining	Drop (n=35)	Ointment (n=35)	Total	P value	Test performed
Pre treatment					
-	34 (97.14%)	32 (91.43%)	66 (94.29%)	0.614	Fisher Exact test
++	1 (2.86%)	3 (8.57%)	4 (5.71%)		
Day 30					
-	34 (97.14%)	32 (91.43%)	66 (94.29%)	0.743	Fisher's Exact test
+	1 (2.86%)	1 (2.86%)	2 (2.86%)		
++	0 (0%)	2 (5.71%)	2 (2.86%)		
Day 60					
-	34 (97.14%)	33 (94.29%)	67 (95.71%)	1.000	Fisher Exact test
+	1 (2.86%)	2 (5.71%)	3 (4.29%)		
Day 90					
-	34 (97.14%)	33 (94.29%)	67 (95.71%)	1.000	Fisher Exact test
+	1 (2.86%)	2 (5.71%)	3 (4.29%)		

Table 5: Comparison of FTBUT (in seconds) between group drop and ointment

FTBUT (in seconds)	Drop (n=70)	Ointment (n=70)	Total	P value	Test performed
Pre treatment					
Mean ± S D	8.4 ± 2.57	7.9 ± 2.62	8.15 ± 2.6	0.199	Mann Whitney test;2145
Median (IQR)	8 (6-10)	7 (6-10)	8 (6-10)		
Range	4-14	4-15	4-15		
Day 30					
Mean ± S D	17.54 ± 3.52	15.94 ± 2.86	16.74 ± 3.29	0.002	Mann Whitney test;1719
Median (IQR)	18(15-20)	15(14-18)	16 (14-20)		
Range	9-25	10-22	9-25		
Day 60					
Mean ± S D	18.47 ± 3.96	18.57 ± 2.85	18.52 ± 3.44	0.887	Mann Whitney test;2416.5
Median(IQR)	18(15-22)	19(16-20.25)	18 (16-22)		
Range	9-25	15-25	9-25		
Day 90					
Mean ± S D	18.67 ± 4.3	19.94 ± 3.5	19.31 ± 3.96	0.034	Mann Whitney test;1947.5
Median(IQR)	18(15-22)	20(16-22)	20 (16-22)		
Range	9-30	15-26	9-30		

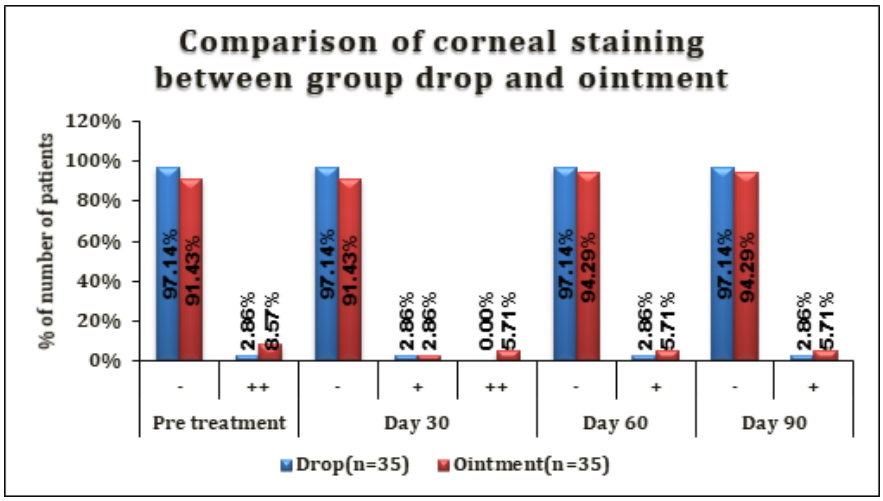

Figure - 2

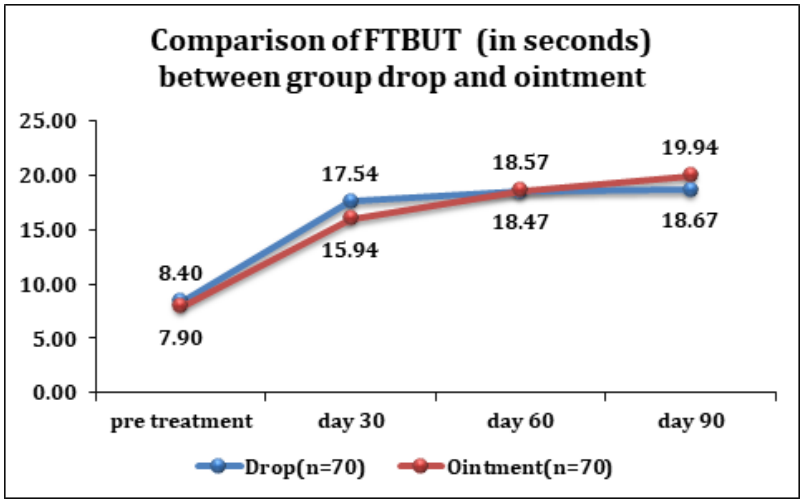

Figure - 3

Table 6: Comparison of Schirmer's test (mm) between group drop and ointment

Schirmers test(mm)	Drop (n=35)	Ointment (n=35)	Total (n = 70)	P value	Test performed
Pre treatment					
Mean ± S D	5.7 ± 1.33	5.34 ± 1.57	5.52 ± 1.46	0.058	Mann Whitney test;2011.5
Median(IQR)	5 (5-6.75)	5 (4-6)	5 (5-6)		
Range	3-8	2-9	2-9		
Day 30					
Mean ± S D	15.37 ± 3.54	13.37 ± 3.74	14.37 ± 3.76	0.001	Mann Whitney test;1675
Median(IQR)	15(13-18)	14(11-15)	15(12-16)		
Range	9-24	7-24	7-24		
Day 60					
Mean ± S D	16.44 ± 3.78	16.17 ± 2.47	16.31 ± 3.18	0.578	Mann Whitney test;2320
Median(IQR)	16(14-20)	15(15-18)	15(15-18)		
Range	9-25	12-24	9-25		
Day 90					
Mean ± S D	16.63 ± 4.21	17.4 ± 2.37	17.01 ± 3.42	0.064	Mann Whitney test;2012.5
Median(IQR)	16(14-20)	17.5(15.75-18)	16(15-20)		
Range	9-30	14-24	9-30		

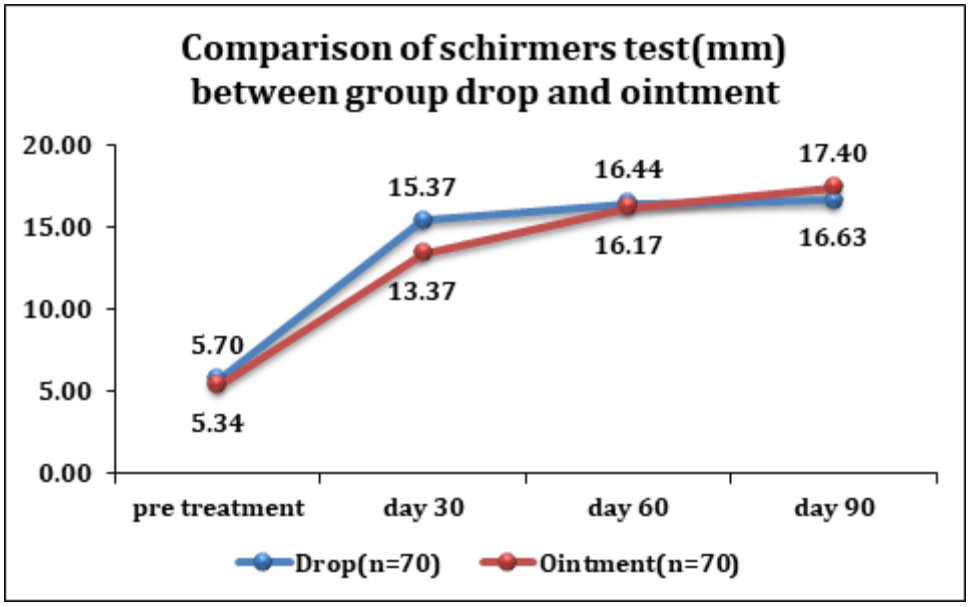

Figure - 4

Table 7: Comparison of meibomian gland score between group drop and ointment

Meibomian gland score	Drop (n=35)	Ointment (n=35)	Total (n = 70)	P value	Test performed
Pre treatment					
Mean ± S D	2.54 ± 0.65	2.71 ± 0.74	2.63 ± 0.7	0.1	Mann Whitney test;2092
Median(IQR)	3 (2-3)	3 (2-3)	3 (2-3)		
Range	1-4	1-4	1-4		
Day 30					
Mean ± S D	1.34 ± 0.63	1.71 ± 0.78	1.53 ± 0.73	0.004	Mann Whitney test;1828
Median(IQR)	1(1-2)	2(1-2)	1(1-2)		
Range	0-3	0-3	0-3		
Day 60					
Mean ± S D	0.74 ± 0.7	0.91 ± 0.61	0.83 ± 0.66	0.094	Mann Whitney test;2090
Median(IQR)	1(0-1)	1(1-1)	1(0-1)		
Range	0-2	0-2	0-2		
Day 90					
Mean ± S D	0.63 ± 0.73	0.57 ± 0.6	0.6 ± 0.67	0.845	Mann Whitney test;2408
Median(IQR)	0(0-1)	1(0-1)	0.5(0-1)		
Range	0-2	0-2	0-2		

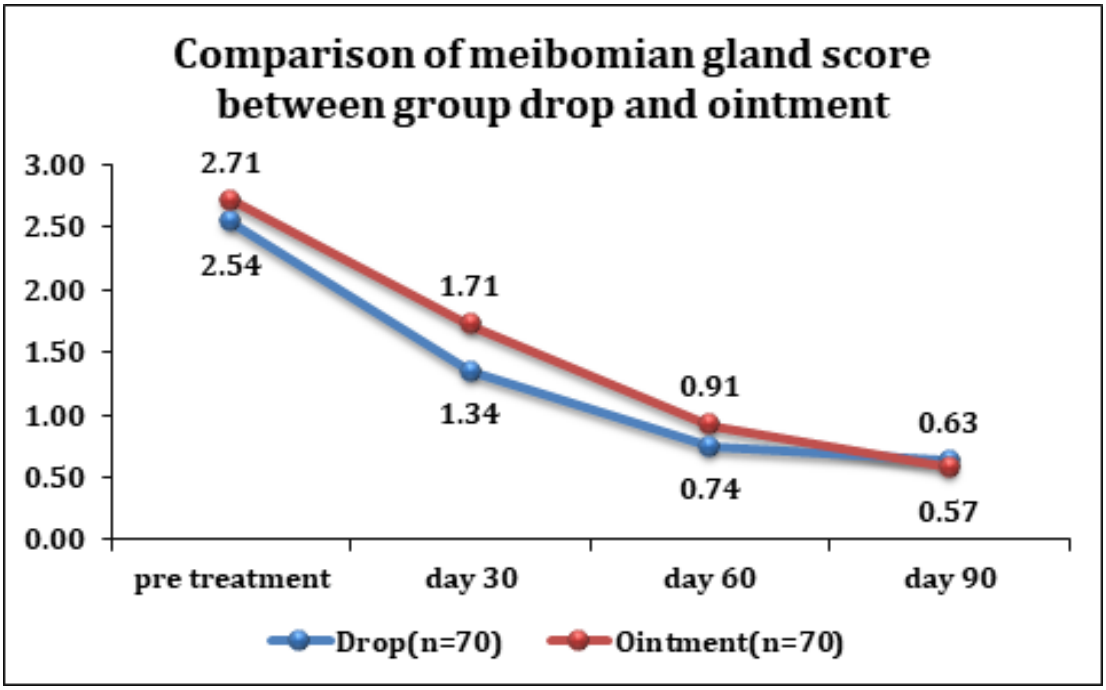

Figure - 5

Table 8: Comparison of clinical score between group drop and ointment

Clinical score	Drop (n=70)	Ointment (n=70)	Total	P value	Test performed
Pre treatment					
Mean ± S D	8.13 ± 2.01	8.44 ± 1.95	8.29 ± 1.98	0.359	Mann Whitney test;2233.5
Median(IQR)	8 (7-10)	8 (7-10)	8 (7-10)		
Range	5-12	4-12	4-12		
Day 30					
Mean ± S D	4.01 ± 1.39	4.79 ± 1.76	4.4 ± 1.63	0.056	Mann Whitney test;2003.5
Median(IQR)	4(4-5)	4(3-6)	4(3-5)		
Range	0-7	2-8	0-8		
Day 60					
Mean ± S D	2.66 ± 1.39	2.84 ± 1.67	2.75 ± 1.54	0.639	Mann Whitney test;2340.5
Median(IQR)	3(2-3)	3(2-5)	3(2-4)		
Range	0-6	0-5	0-6		
Day 90					
Mean ± S D	2.51 ± 1.5	1.83 ± 1.54	2.17 ± 1.55	0.008	Mann Whitney test;1831
Median(IQR)	3(1-3)	1(1-3)	2(1-3)		
Range	0-6	0-5	0-6		

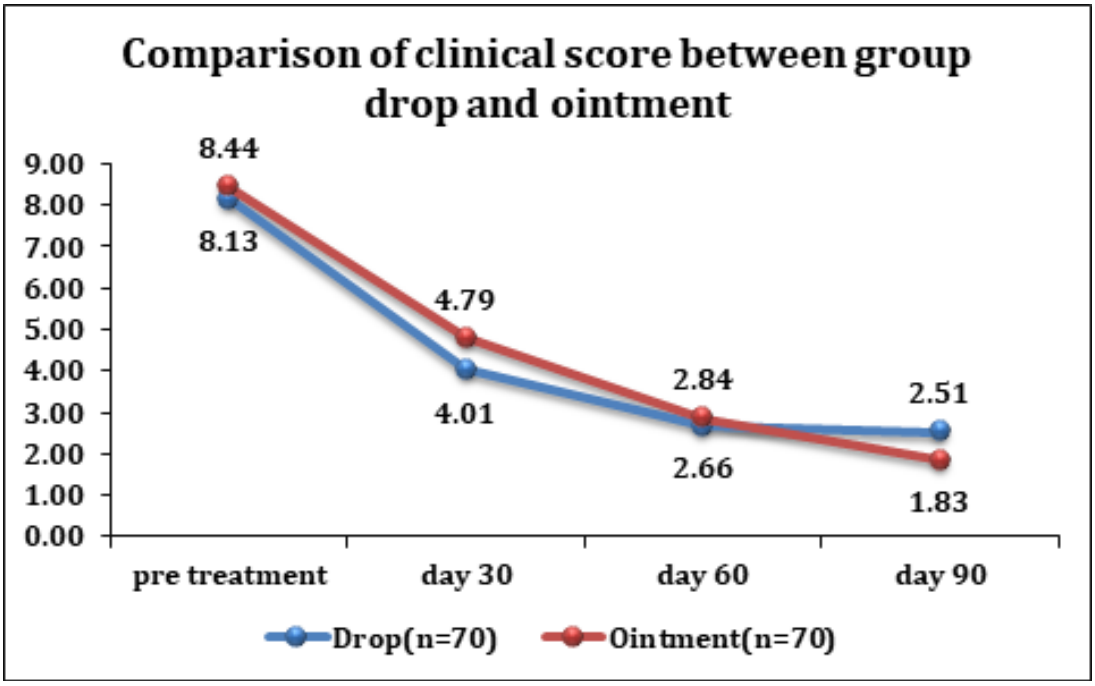

Figure - 6

Table 9: Comparison of symptom score between group drop and ointment

Symptom score	Drop (n=70)	Ointment (n=70)	Total	P value	Test performed
Pre treatment					
Mean ± S D	5.31 ± 1.15	5.6 ± 1.37	5.46 ± 1.27	0.201	Mann Whitney test;2152
Median(IQR)	5 (5-6)	6 (5-7)	5.5(5-6)		
Range	3-7	3-8	3-8		
Day 30					
Mean ± S D	2.37 ± 0.76	2.91 ± 1.14	2.64 ± 1	0.004	Mann Whitney test;1812
Median(IQR)	2(2-3)	3(2-4)	2.5(2-3)		
Range	0-4	1-5	0-5		
Day 60					
Mean ± Stdev	1.49 ± 0.78	1.51 ± 0.88	1.5 ± 0.83	0.927	Mann Whitney test;2430
Median(IQR)	1(1-2)	1(1-2)	1(1-2)		
Range	0-3	0-3	0-3		
Day 90					
Mean ± S D	1.46 ± 0.77	0.97 ± 0.78	1.21 ± 0.81	0.0005	Mann Whitney test;1682
Median(IQR)	1(1-2)	1(0-1)	1(1-2)		
Range	0-3	0-3	0-3		

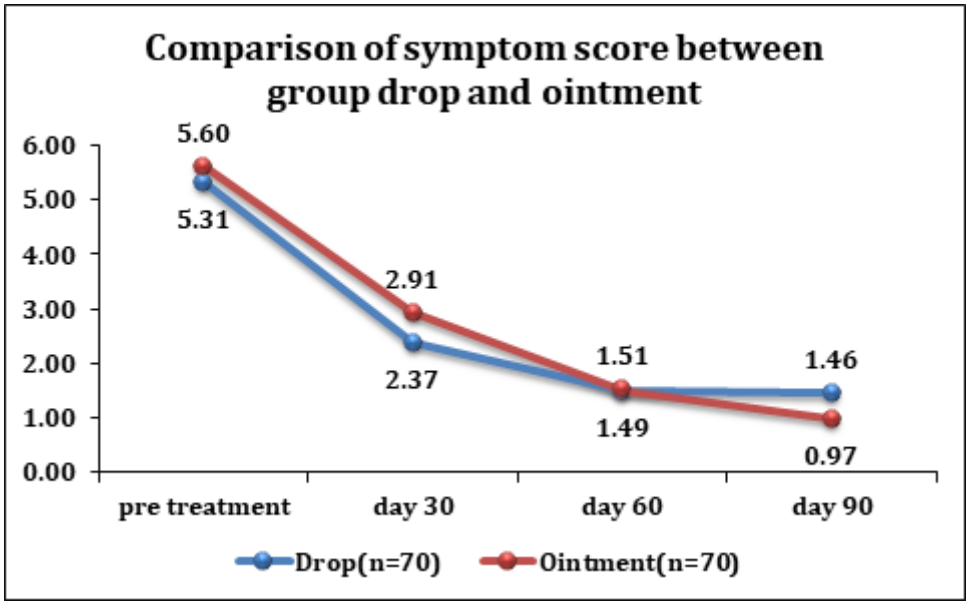

Figure - 7

DISCUSSION

The present study analysed the subjective and objective parameters of MGD by using, tear quantification, ocular surface (FTBUT, corneal staining) and meibomian and clinical scores. Drug intervention sought to assess the alleviation of symptoms, enhancement of ocular surface parameters and overall improvement in eye comfort. Also a novel attempt was made to compare the impact of Azithromycin in MGD treatment when used in different physical forms.

While corneal staining seemed unchanged in both the study groups (p value>.05), the FTBUT values showed significant increase at day 30 ($p<0.05$). This correlates well with previous studies.[3-6] Most studies however report marked decrease in corneal staining at day 30. In comparison between Azithromycin eye drop and ointment group, significant difference was seen in increase in FTBUT at day 30 ($p<0.05$) with higher mean values for drops group; 10 secs (8-10.75) being significantly higher as compared to eye ointment 8 secs (7-9.75). The difference in FTBUT values was higher in Ointment group at day 60 & 90 as compared to the drops group.

Significant increase was seen in Schirmer's values at day 30 (p value<.05) for both groups which was in accordance with previous studies.[7,8] Shirmer's values were significantly higher for drops group at day 30; 10 mm(8-11.75) as compared to eye ointment 9mm(6-10). The trend was reversed in favour of ointment group at day 60 & 90.

Significant decrease was seen in meibomian gland score at day 30(p value<.05) which correlates well with studies by Opitz, D et al.[8] Comparison of decrease in meibomian gland score between the two groups in the present study showed significant decrease in score at day 30 as compared to pre-treatment for both groups (p value <.05). The difference in group eye drop was significantly higher than eye ointment at day 30 & 60. This trend of improvement in Meibomian score continued for both groups in a sustained manner. However a significant improvement of the score was noted in favour of subjects in the ointment group at Day 90 in comparison with those being administered the eye drops (p value <.05).

In our study statistically significant improvements from baseline in Clinical score was seen at day 30 and persisted for 60 days (p value<.05). Most of the studies did not conduct a longer follow up, however Haque et al,[15] showed improvement in clinical score, at day 29 that persisted for 45 days.

While evaluating clinical score of the two groups (eye drop and ointment), a significant difference was seen for both groups at day 30. Significant differences were also noted at day 60 & 90 for each group.

Median (IQR) decrease in clinical score at day 60 as compared to day 30 with ointment administration was 2, day 90 as compared to day 60 was 1 respectively. This was significantly higher compared to alterations in clinical score in the eye drop group at day 60 & 90 which was 1& 0 respectively.

Decrease in symptom score at day 30 was higher among the patients receiving eye drops as compared to eye ointment. Significant decrease in symptom score was also seen among the patients receiving eye ointment compared to eye drop at day 60 and day 90 of follow up (p value <.05) Median (IQR) decrease in symptom score at day 60 and day 90 among the patients receiving eye ointment was 1(1-2) and 1(0-1) which was significantly higher than the patients receiving eye drops which was 1(1-1), 0(0-0) at day 60 and day 90 respectively.

In the current study Azithromycin in both forms showed significant improvement in MGD in most of the parameters. However, the effect of eye drop was more significant at day 30, while a sustained effect was seen in the ointment group for longer follow up periods (Day 60 & 90). We hypothesize that this may be due to the fact that eye drops has an aqueous base which may have better anti-microbial effect and therefore provide early relief whereas ointment with a paraffin base has prolonged action which may prove beneficial in long run.

CONCLUSION

Azithromycin 1% was found effective in reducing the signs and symptoms associated with meibomian gland dysfunction when used topically in both, drop and ointment forms. Also the effect persisted in ocular tissues beyond the last application. However, long term effect of azithromycin was better in the ointment form. Since azithromycin has dual action i.e. anti-bacterial and anti-inflammatory hence both the actions appear to work synergistically to suppress inflammation, improve the meibomian gland secretions and tear film quality.

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