EFFICACY OF CYCLOSPORINE EYE DROPS IN TREATMENT OF MEIBOMIAN GLAND DISEASE

Fatima Khan, Summaya Khan, Amjad Akram, Imran Basit, Sadia Humayun, Shafaq Rabbani

Armed Forces Institute of Ophthalmology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To assess the efficacy of topical cyclosporine ophthalmic solution in patients with Meibomian Gland Disease.

Study Design: Quasi-experimental study.

Place and Duration of Study: Armed Forces Institute of Ophthalmology (AFIO), from March to May 2019.

Methodology: Adult patients of 20-40 years of age, diagnosed for Meibomian Gland Dysfunction, were enrolled and divided into two groups (group A was assigned cyclosporine and group B was assigned polyvinyl alcohol povidone eye solution). Patients were instructed to administer one drop of the assigned treatment in each eye, twice daily, for 3-months. Two follow-up visits were planned for this study, first follow-up was conducted after thirty days of starting the assigned treatment while second follow-up was done at the end of three months.

Results: There were total 80 patients enrolled, forty in each group. Patients were assessed for ocular signs and symptoms for Meibomian Gland Disease after one, two and three months of starting the treatment and were compared to control group. Patients belonging to cyclosporine group were found to show greater improvements in signs/symptoms of Meibomian Gland Disease including tear break up time (p 0.001 vs 0.540), Schrimer I test (p 0.001 vs 0.290), fluoresceine staining (0.007 vs 0.041), lid margin/conjunctival inflammation (0.001 vs 0.06) and Meibomian Gland expressibility (0.01 vs 0.311).

***Conclusion*:** Topical cyclosporine ophthalmic solution was found to be significantly better in resolving ocular signs and symptoms among Meibomian Gland Disease patients as compared to polyvinyl alcohol povidone.

Keywords: Meibomian gland disease (MGD), Posterior blepharitis, Topical cyclosporine, Tear break-up time.

INTRODUCTION

Meibomian glands are located on both upper and lower eyelids. These are sebaceous glands which provide lipids for tear film and contributes to clear and smooth optical surface, reduce tear evaporation, act as a barrier to germs entering the tear film, prevent tears from falling off the lid margin and firmly seal the lid margins during sleep[1]. Any abnormality in the functioning of Meibomian gland can lead to eye irritation, inflammation and ocular surface diseases, and the condition is termed as Meibomian Gland Dysfunction, characterized either by obstruction of gland ducts or changes in glandular secretions[2,3].

Meibomian Gland Disease MGD is a prevalent disease condition specially among Asian population, with prevalence ranging from 46% to 70% and is said to be the leading cause of dry & itchy eyes and blurred vision[4]. It is multifactorial and chronic in nature and the patients usually present with swelling of eyelids, thickening of gland secretions, deformed gland orifices, and foamy tears[5]. A wide-range of mechanical interventions, including lifestyle changes, thermal compression, eyelid hygiene, dietary supplements and Pharmaceuticals interventions like artificial lubricants, topical antibiotics, anti-inflammatory drugs and steroids and available for treatment of meibomian-gland disorders. Individualized treatment regimen is recommended for patients, and the choice of management/ treatment options depends both on symptoms and severity of the disease with a purpose of alleviating the symptoms and thus enhancing quality of life[6].

The current treatment options are reported not to be fully effective as none of them act on the

Correspondence: Dr Fatima Khan, Department of Ophthalmology, AFIO Rawalpindi Pakistan

Received: 25 Feb 2020; revised received: 28 Mar 2020; accepted: 19 Jun 2020

core mechanism of Meibomian gland disorder, and studies are being conducted to explore other treatment options for managing Meibomian gland disorders. Recent literature suggests effectiveness of cyclosporine A on the disease management of Meibomian gland, but there are controversial views about it[7]. Cyclosporine A belongs to class of immunosuppressant drugs, which modulates T-cells and decreases the release of inflammatory cytokines responsible for causing inflammation. Although inflammation is not the sole cause of Meibomian gland disorders, but it is evident that it plays a vital role in pathogenesis of the disease and is more associated with gland as compared to duct obstruction or atrophy of ducts[8]. Long-term use of steroids is not recommended, therefore keeping in mind the safety profile of cyclosporine, it can be a more efficient choice to tackle inflammation in MGD patients and improve their disease condition[9].

In this study, we aimed to test the effectiveness of cyclosporine topical solution in patients reporting to our institution with MGD in comparison toroutinely-used artificial tears. The main objective of the study was to assess the improvement in mean tear breakup time (TBUT) among two groups of patients, and to compare lid margin and conjunctival inflammation, MG expressibility, SchrimerI test and fluoreceine staining scores among two groups of patients.

METHODOLOGY

This quasi-experimental study was conducted at Armed Forces Institute of Ophthalmology from March to May 2019. The study was approved by Institutional Ethics & Review Board (IERB No. 217) and informed consent was sought from all the participants prior to their enrollment. Adult patients of 20 to 40 years of age, diagnosed for MGD, using the diagnostic criteria reported by Geerling *et al*[6] which is based on presenting complaints, physical examination, fluorescein tear break-up time, ocular surface staining, lid margin inflammation, Meibomian gland expression and schrimer test, were enrolled in the study. Patients with severe ocular surface abnormalities, past ocular surgeries, glaucoma, regular contact lens wear, keratitis, immunocompromised status, hypersensitivity to cyclosporine, pregnancy, lactation and previous use of cyclosporine eye drops were excluded from the study. Patients were divided into two groups, group A was assigned to cyclosporine eye solution (0.05% cyclosporine, Atco) while group B was assigned to polyvinyl alcohol, Allergan. Patients were instructed to administer one drop of the assigned treatment in each eye, twice daily, for 3-months. Two follow-up visits were planned for this study, first follow-up was conducted after thirty days of starting the assigned treatment while second follow-up was done at the end of three months.

Sample size of 80 patients (40 in each group) was calculated by considering alpha of 5%, power 80%, effect size 4.0, standard deviation 5.9 and 10% compensation for drop outs[10]. Patient's baseline data was collected at the start of the study, while data on effect of the treatment on signs/symptoms of the disease was collected at two follow-up visits.

Outcome measures comprised of objective signs examined via slit-lamp examination of the eye lid margin and Meibomian glands, tear break-up time, gland expressibility, corneal and conjutival dye staining and tear volume measured via schirmer test. Lid margin and conjunctival inflammation was scored as 0 for no inflammation, 1 for mild, 2 for moderate and 3 for severe inflammation; Meibomian gland expressibility was scored as 0 for no fluid expression, 1 for clear, 2 for cloudy and 3 for inssipisated fluid expression; tear break-up time was noted in seconds; fluorescein staining was scored from 0 to 15 in accordance with the guidelines provided by National Eye Institute system[11]; and tear volume was measured in millimeters.

Data was entered and analyzed using data management software SPSS-23. Descriptive statistics for continuous variables were presented via mean and standard deviation while for categorical variable frequencies and percentages were

calculated. Normality of data was checked visually by fitted-histogram and statistically via shapirowilk test. Normal data was compared by independent samples t-test while skewed data was compared by Man Whitney U test. Outcome data was compared for control and intervention group for first and second follow-up using paired-samples t-test or Wilcoxon signed rank test depending on normality of data. Categorical data was compared by chi-square test with a significance value of ≤0.05.

RESULTS

Eighty patients were enrolled in the study, divided into two groups of forty each, group A was administered topical cyclosporine while group B was administered artificial eye lubricant control. Overall there were 44 males (55.0%) and 36 (45%) females in the study group with mean age of 48.79 ± 13.0 years (range 19-70). In ROPSOL group A, there were 24 males (60%) while 16 females (40.0%) with mean age of 50.08 ± 13.1 years; where as in group B, there were 20 (50%) males and female each with mean age of 47.5 ± 12.9 years. The baseline characteristics were comparable among two groups, as shown in table-I. Age, tear breakup time, severity of lid margin inflammation, MG expressibility grade, schirmer's test and fluoreceine staining score were not significantly different in two groups at the start of the study.

At baseline, mean value of tear break-up time (TBUT) was 5.53 ± 1.48 and 4.97 ± 2.32 (p 0.211) for group A and B respectively. At first follow up of thirty days, mean TBUT value increased to 8.98 ± 1.18 from baseline of 5.53 ± 1.48 (p<0.001) and at second follow up of three months TBUT increased to 11.45 ± 1.35 (p<0.001) for group A; whereas at first follow up of group B patients, there was an insignificant increase in the mean TBUT i.e. 5.13 ± 3.20 from 4.97 ± 2.32 (p 0.504) and at second follow-up TBUT significantly increased to 6.23 ± 3.9 (p 0.01). Inter-group comparison among group A and B revealed significant differences at both one and three months follow-up visits i.e. 8.98 ± 1.18 vs 5.13 ± 3.20 (p<0.001) and 11.45 ± 1.35 vs 6.23 ± 3.9 respectively.

Lid margin and conjunctival inflammation significantly improved among group A while insignificantly changed in group B at one and three months follow-up (p=0.001 vs p=0.06 respectively). At first follow-up none of the patient belonging to group A had severe inflammation, 6 (15.0%) and 21 (52.5%) had moderate and mild inflammation respectively, while 13 (32.5%) had no inflammation at all. At first follow-up of group B, 1 patient (2.5%) still had severe inflammation, while 18 (45.0%) and 21 (52.5%) had moderate and mild inflammation respectively. On second follow-up, 33 (82.5%) patients belonging to group A had no inflammation, and only 7 (17.5%) had mild inflammation; whereas 16 (40%), 21 (52.5%) and 3 (7.5%) had mild, mode-

Table-I: Summary of baseline clinical characteristics among study groups.

Clinical Characteristics	Study Groups		p-value
	Group A (n=40)	Group B (n=40)	
Gender (n%)			
Male	24 (60)	20 (50)	0.369
Female	16 (40)	20 (50)	
Age (Mean ± SD) years	50.08 ± 13.1	47.5 ± 12.9	0.381
TBUT (Mean ± SD) seconds	5.53 ± 1.48	4.97 ± 2.32	0.211
Lid Margin + Conjunctival Inflammation (n%)			
Nil	-	-	0.713
Mild	10 (25)	7 (17.5)	
Moderate	17 (42.5)	19 (47.5)	
Severe	13 (32.5)	14 (35)	
Meibomian-Gland (MG) Expressibility (n%)			
No	-	-	0.667
Clear	4 (10)	2 (5)	
Cloudy	23 (57.5)	23 (57.5)	
Inssipisated fluid	13 (32.5)	15 (37.5)	
Schrimer-I test (Mean ± SD) mm	6.23 ± 1.02	6.03 ± 1.44	0.477
Fluoreceine staining (Mean ± SD) score	9.75 ± 3.01	9.32 ± 2.63	0.504

TBUT: Tear break-up time

rate and severe inflammation respectively as shown in table-II.

Meibomian-gland expressibility significantly improved from baseline to first follow-up for patients belonging to group A as compared to group B (p=0.02 vs 0.11 respectively). Similarly, Meibomian-glandexpressibility further improved significantly for group A as compared to group B up on second follow-up (0.01 vs 0.31 respectively) as shown in table-II.

Fluorescein staining score was not significantly different at first follow-up for group B, while significantly decreased on second follow-up time (p 0.007 vs 0.001 respectively). For intervention group A, the fluorescein staining score significantly reduced on both first and second follow-up (p 0.04 vs p 0.02 respectively (table-II).

Tear volume was measured by schrimer test, value of which improved significantly for group A at both first and second follow-up visit (p=0.001 & 0.008 respectively), while for group B it significantly improved on first follow-up while insignificant improved was observed on second follow-up (p=0.001 and 0.29 respectively) compared to baseline.

Table-II: Comparison of outcome variables among study groups at follow-up visits.

Outcomes	Group A			Group B		p-value
	1 month follow-up	3 months follow-up	p-value	1 month follow-up	3 months follow-up	
Tear Break-Up Time (TBUT) in seconds						
Mean ± SD	8.98 ± 1.18	11.45 ± 1.35	0.001	5.13 ± 3.20	6.23 ± 3.90	0.540
Schrimer I Test in mm						
Mean ± SD	9.73 ± 0.96	13.20 ± 2.26	0.001	6.95 ± 2.05	6.78 ± 2.44	0.290
Fluoreceine Staining Score						
Mean ± SD	5.00 ± 2.66	1.48 ± 1.86	0.007	8.93 ± 2.68	7.90 ± 2.48	0.041
Lid margin + conjunctival inflammation (n%)						
Nil	13 (32.5)	33 (82.5)	0.001	-	-	0.06
Mild	21 (52.5)	7 (17.5)		21 (52.5)	16 (40)	
Moderate	6 (15)	-		18 (45)	21 (52.5)	
Severe	-	-		1 (2.5)	3 (7.5)	
Meibomian-gland (MG) expressibility (n%)						
No	-	-	0.01	-	-	0.311
Clear	28 (70)	33 (82.5)		9 (22.5)	12 (30)	
Cloudy	12 (30)	7 (17.5)		29 (72.5)	28 (70)	
Inssipisated fluid	-	-		2 (5.0)	-	

DISCUSSION

Cyclosporine A is a specific immunosuppressant agent, which targets T-lymphocytes and decreases release of inflammatory cytokines. In comparison to steroids, cyclosporine has a relatively better safety profile as it does not effects wound healing, phagocytic system and lens changes. Topical cyclosporine ophthalmic solution in different concentrations, has a wide variety of indications specially associated to immune based inflammatory response, ranging from keratoplasty graft, blepharitis, dry-eye syndrome, ocular rosacea, steroid induced glaucoma, keratitis, contact-lens intolerance and atopic keratoconjuctivitis[12,13]. In addition to that, topical cyclosporine solution has been shown to be effective for resolving ocular signs and symptoms of Meibomian Gland Disease as well, but a mixed view exists[13].

In this study, two groups were formed, one was administered cyclosporine ophthalmic solution while other was administered artificial eye lubricant. The demographic and baseline clinical characteristics were comparable among two groups with no significant differences. Both the groups were evaluated for primary and secondary outcomes on two follow-up groups.

On the first follow-up of thirty days, the primary outcome measure i.e. mean tear break-up time, was evaluated by tear scope for all patients of group A and B. The results show a significant improved in patients belonging to cyclosporine group A compared to baseline value (8.98 ± 1.18 vs 11.45 ± 1.35 seconds, *p* 0.001) where as in control group there was not significant improvement in mean tear break-up time on the first follow up visit (5.13 ± 3.20 vs 6.23 ± 3.90, *p* 0.540). These results of our study werein-line with results reported by Prabhasawat *et al*[11] where a randomized controlled double blind

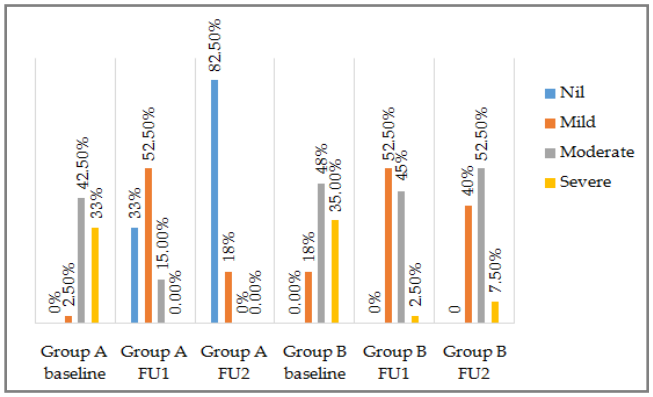

Figure: Comparison of inflammation among two study groups at baseline, first and second follow-up visit.

study was conducted on seventy patients with ninety days of follow-up. Prabhasawat *et al* reports that tear break-up time in terms of NIBUT and FBUT improved significantly assessed ninety days after starting the intervention (*p*<0.001). Similarly, in another study conducted by Kim *et al*[13] where retrospective analysis was done on 106 eyes to compare effects of cyclosporine and hyaluronate eye drops, reports that the mean tear break-up time significantly improved in cyclosporine group as compared to control (5.64 ± 1.42 vs 7.85 ± 1.58, *p*<0.001) at three months follow up. Perry *et al*[14] conducted a double blinded study in which he randomly assigned thirty-three patients with Meibomian Gland Disease to cyclosporine intervention or placebo group and reported significant improvements in mean tear break up times for patients belonging to intervention group up on three months follow up. Similarly, another study conducted by same author Perry in 2006[16], reported significant improvement in mean tear break up time for patients administered with cyclosporine as compared to placebo at three months follow up (*p* 0.001).

The secondary outcome measures of our study including lid margin and conjunctival inflammation significantly improved among both intervention and control groups (*p* 0.001 vs *p* 0.06 respectively), but comparing the frequencies of patients suffering from severe and moderate inflammation were relatively less in intervention group as compared to control group. At first follow up only 6 (15.0%) patients from group A had moderate inflammation while one had severe inflammation as compared to 18 (45%) patients from group B with moderate and 1 (2.5%) patient with severe inflammation. Similarly, on second follow up 7 (17.5%) patients from group A had mild inflammation while none had moderate or severe inflammation as compared to 21 (52.5%) and 3 (7.5%) patients from group B has moderate and severe inflammation. Similar sort of findings had been reported by various studies where cyclosporine has been reported to significantly improve the symptoms of Meibomian Gland Disease including lid margin and conjunctival inflammation[15-17]. MG expressibility is another outcome measure used to assess the efficacy of treatment on Meibomian Gland Disease. In our study, MG expressibility significantly improved from baseline to first and second follow ups for group A as compared to group B (*p* 0.02 vs 0.11 and 0.01 vs 0.31 respectively). Studies have similarly reported improved expressibility of gland secretions in terms of quantity and quality among cyclosporine study group[11,16,17].

Our study also reports that ophthalmic cyclosporine solution might improve tear film stability and tear volume as assessed by Schrimer I test. At first and second follow up the values for Schrimer I test increased to 9.73 ± 0.96 and 13.20 ± 2.26 (*p* 0.001) as compared to control group where Schrimer I test value did not increase significantly i.e. 6.95 ± 2.05 and 6.78 ± 2.44 (0.290). Prabha-

sawat *et al*[11] Kim *et al*[14], and Perry *et al*[15] reported same results where cyclosporine A has been reported to increase the tear volumes as compared to artificial eye lubricant control group. A study conducted by Rubin and Rao[18] reported cyclosporine to reduce the viscocity and increase volume of Meibomian gland secretions as well as Schrimer test score. In this study mean fluoreceine staining score significantly decreased in both cyclosporine and lubricant group (p 0.007 and p 0.041), but the intervention group has relatively lower fluoreceine staining value at two follow up visits as compared to lubricant group (5.00 ± 2.66 vs 8.93 ± 2.68, and 1.48 ± 1.86 vs 7.90 ± 2.48, respectively). Most of the studies assessing efficacy of different concentrations of cyclosporine A ophthalmic solution had reported decreased fluoreceine staining values in patients on three to six months of follow up as compared to other treatments and artificial lubricants[11-16].

In the end, it is concluded from this study that topical cyclosporine ophthalmic solution was found to be significantly efficacious in treatment of Meibomian Gland Disease. Multiple objective clinical findings were better in the topical cyclosporine treatment group as compared to artificial lubricant control group after three months follow up in terms of tear break-up time, lid margin/ conjunctival inflammation, gland expressibility and tear volume.

First limitation of study is that the treatment assignment was not randomized, that could have imposed bias in results, secondly the patients and consultant were not blinded to treatment assignment. It is recommended to carry out a randomized controlled trial with sufficient sample size to access short term and long term efficacy of cyclosporine in treating Meibomian Gland Disease.

CONCLUSION

Topical cyclosporine ophthalmic solution was found to be significantly better in resolving ocular signs and symptoms among Meibomian Gland Disease patients as compared to polyvinyl alcohol povidone.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Turgut B, Çatak O, Demir T. Meibomian gland dysfunction: an overlooked eyelid disease. Adv Ophthalmol Vis Sys 2018; 8(3): 168-72.
2. Chhadva P, Goldhardt R, Galor A. Meibomian gland disease: the role of gland dysfunction in dry eye disease. Ophthalmol 2017; 124(11): S20-06.
3. Sullivan BD, Evans JE, Dana MR, Sullivan DA. Influence of aging on the polar and neutral lipid profiles in human meibo-mian gland secretions. Arch Ophthalmol 2006; 124(9): 1286-92.
4. Baudouin C, Messmer EM, Aragona P, Geerling G, Akova YA, Benítez-del-Castillo J et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. Br J Ophthalmol 2016; 100(3): 300-06.
5. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The interna-tional workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Investigative Ophthalmol Visual Sci 2011; 52(4): 1938-78.
6. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Investigative Ophthalmol Visual Sci 2011; 52(4): 2050-64.
7. Qiao J, Yan X. Emerging treatment options for meibomian gland dysfunction. Clini Ophthalmol 2013; 7(4): 1797–803.
8. Opitz DL, Harthan JS, Fromstein SR, Hauswirth S. Diagnosis and management of meibomian gland dysfunction: optome-trists' perspective. Clini Optometry 2015; 7(1): 59–69.
9. Thode AR, Latkany RA. Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction (MGD). Drugs 2015; 75(11): 1177-85.
10. Lemp A. Report of the National Eye Institute/Industry work-shop on clinical trials in dry eyes. Eye Contact Lens 1995; 21(4): 221-32.
11. Prabhasawat P. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibo-mian gland dysfunction. Cornea 2012; 31(12): 1386-93.
12. Donnenfeld E. Topical ophthalmic cyclosporine: pharmacology and clinical uses. Survey Ophthalmol 2009; 54(3): 321-38.
13. Perry HD. Report: Topical Cyclosporine Use in Meibomian Gland Dysfunction. US Sensory Dis 2006; 19(4): 17-19.
14. Kim HY, Lee JE, Oh HN, Song JW, Han SY, Lee JS. Clinical efficacy of combined topical 0.05% cyclosporine a and 0.1% sodium hyaluronate in the dry eyes with meibomian gland dysfunction. Intl J Ophthalmol 2018; 11(4): 593-96.
15. Perry HD, Doshi S, Donnenfeld ED, Biser SA, Bloom AH. Double masked randomized controlled study evaluating topical 0.05% cyclosporine A in the treatment of meibomian gland dysfunction (posterior blepharitis). Investigative Ophthalmol Visual Sci 2003; 44(13): 1395-99.
16. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea 2006; 25(2): 171-5.
17. Khoo P, Ooi KG, Watson S. Effectiveness of pharmaceutical interventions for meibomian gland dysfunction: An evidence based review of clinical trials. Clini Experimental Ophthalmol 2019; 47(5): 658-68.
18. Rubin M, Rao SN. Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. J Ocular Pharma Therapeutics 2006; 22(1): 47-53.