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Research Article

Efficacy of Topical Cyclosporine 0.05% Eye Drops in the Treatment of Dry Eyes

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ABSTRACT

OBJECTIVES: To determine the efficacy of cyclosporine 0.05% in the treatment of dry-eye disease.

Material and methods: This cross sectional study was conducted at Department of Ophthalmology Pak Red Crescent Medical College Lahore from March 2018 to September 2018 over the period of 6 months. Total 310 patients of dry eye were included in this study after scrutinized by inclusion criteria. All the selected patients were managed with cyclosporine 0.05% and efficacy of the drug was assessed.

RESULTS: Total 310 patients of dry eye disease were selected for this study. Mean age of the patients was 47.15 ± 3.61 years and mean duration of dry eye disease was 11.10 ± 1.75 months. Out of 310 patients, treatment was found effective in 225 (73%) patients. Efficacy of treatment was noted in 172 (96.63%) male patients in 53 (40.15%) female patients. Significantly higher rate of efficacy was noted in male patients as compared to female patients with p value 0.000.

CONCLUSION: Results of present study showed higher improvement rate of dry eye symptoms in cases of dry eye treated with cyclosporine 0.05%. Male patients were more victim of dry eye as compared to female patients and statistically significant association of efficacy with gender was observed. No association of efficacy of treatment with age group and duration of disease was observed.

KEY WORDS: Dry eye, cyclosporine, inflammation, immunomodulator agents.

INTRODUCTION

Dry eye is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners.[1] It is associated with symptoms of ocular discomfort such as burning, sense of dryness, foreign body sensation, ocular pain, and is sometimes associated with photophobia, blurred vision, visual fatigue, and sight-threatening corneal complications in severe cases.[2] Pathogenesis of Dry eye has not been completely clarified. Many clinical and pathological changes affecting tear film, lacrimal glands, and eyelids with resulting deficiency in the tear film whether caused by decreased lacrimation or excessive evaporation.[3] A wide spectrum of ocular surface cells, including epithelial, inflammatory, immune, and goblet cells, may play a role in its pathogenesis.[4]

Many studies propose new concepts of its pathogenesis, including that Dry eye seems to be caused by inflammation mediated by T-cell lymphocytes.[5] Decreased tear volume, increased osmolarity, disorder of cytokine balance, and increased matrix metalloproteinases can be seen in dry-eye disease. It has been demonstrated that inflammation and apoptosis might play a role in the development of dry eyes.[6] Currently, artificial tears are the most common initial approach used to relieve symptoms in patients with mild dry eyes.

Anti-inflammatory therapies, namely topical cyclosporine and corticosteroids, were recommended for patients with moderate to severe symptoms, mild corneal staining, conjunctival staining, followed by options such as tetracyclines and punctal plugs for severe symptoms, marked or central corneal staining, and filamentary keratitis.[7] Long-term use of topical corticosteroids may be associated with glaucoma, cataracts, and other steroid-related side effects. In contrast, topical cyclosporine, which specifically blocks T-cell activation, may be a more appropriate long-term therapy because it is not associated with either significant systemic adverse events or the common steroid-related ocular side effects.[8]

In one study by Byun et al, out of 392 patients with moderate to dry eye showed that most (72%) were satisfied with cyclosporine treatment to relieve dry-eye symptoms.[9]

The purpose of study is to decrease frequency of topical eye dropings from two hourly with other treatment modalities to 8 hourly with cyclosporin .05%, treat ocular surface disease and reduce the inflammation which is the root cause of dry eye thus reducing morbidity of disease.

OPERATIONAL DEFINITION

Efficacy: Defined as: when any 2 out of three tests was negative.

Tear break up time:

Negative: tear breakup time > 10 seconds.

Rose Bengal staining:

Negative: if there is no staining:

Schirmer's tests:

Negative: wetting of filter paper >5mm.

Dry eye:

Tear break up time(TBUT), rose Bengal staining, Schirmer's tests were performed for the assessment of dry eye. Patients were be labelled as having dry eye if at least two out of these three diagnostic tests were positive.

Tear break up time:

Tear break up time is determined by measuring the inter wall between instillation of fluorescein and appearance of first dry spots on the cornea. Measure it prior to instillation of any anesthetic eye drops. A fluorescein strip is moistened with saline and applied to the inferior fornix. After several blinks, the tear film is examined using a broad beam of slit lamp with a blue filter for the appearance of first dry spots on the cornea. Decrease tear break up time of <10 seconds is considered abnormal.

Positive: tear breakup time <10 seconds.

Rose Bengal staining:

1% liquid of rose Bengal is instilled into the eye, white light is used to assess the amount of staining in nasal conjunctiva, temporal conjunctiva and cornea.

Positive: if staining occurs in any 1 of the following:

1. nasal conjunctiva 2. Temporal conjunctiva 3. cornea

Schirmer's tests:

Schirmer test is performed by instilling a topical anesthetic and then placing a thin strip of filter paper in the inferior fornix. The corner of soft paper may be used to wick all liquid from inferior fornix by capillary attraction without any wiping or direct irritation before the paper is placed. The patients eyes are then closed for 5 minutes and the amount of wetting in the paper strip is measured. Less than 5mm of wetting is abnormal.

Positive: wetting of filter paper <5mm.

MATERIAL AND METHODS

This cross sectional study was conducted at Department of Ophthalmology Pak Red Crescent Medical College Lahore from March 2018 to September 2018 over the period of 6 months. Total 310 patients of dry eye were included in this study after scrutinized by inclusion criteria. All the selected patients were managed with cyclosporine 0.05% and efficacy of the drug was assessed.

Inclusion Criteria:

- Patients with dry eye as per operational definition.
- Both sex male and female.
- Age from 30 to 70 years.
- Patients with ocular pain, burning, and foreign body sensation

Exclusion Criteria:

- History of ocular allergic disease.
- History of pterygium, previous refractive surgery and systemic connective tissue disease.
- Active ocular disease.
- Prior use of topical cyclosporine.

DATA COLLECTION PROCEDURE

Patient's history was taken and 3 tests (tear break up time, rose Bengal staining test and Schirmer's tests) were performed on all selected patients for diagnosis of dry eye.

Cyclosporine 0.05% drops was prescribed to all the selected patients for 3 months. Efficacy (Yes/No) was measured by re-evaluating all the patients which were prescribed Cyclosporine 0.05% drops previously by applying 3 tests.

DATA ANALYSIS PROCEDURE

Data was entered on computer software SPSS version 16.

The quantitative variables of the study i.e. age, duration of symptoms were presented as Mean±SD.

The qualitative variables like gender and frequency of efficacy was presented as frequency and percentages. Pie chart was drawn for frequency of efficacy. Stratification was done for age, gender and duration of symptoms. Post stratification chi-square test was applied. P.value ≤ 0.05 was considered as significance.

RESULTS:

Total 310 patients of dry eye disease were selected for this study. Mean age of the patients was 47.15 ± 3.61 years and mean duration of dry eye disease was 11.10 ± 1.75 months. Out of 310 patients, treatment was found effective in 225 (73%) patients. (Fig. 9) Age range was 30-70 years. Patients were divided into two age groups i.e. age group 30-50 years and age group 51-70 years. In age group 30-50 years, there were 190 (61.29%) patients and in age group 51-70 years, there were 120 (38.71%) patients. Treatment was found effective in 136 (71.58%) patients of age group 30-50 years and in 89 (74.17%) patients of age group 51-70 years. There was insignificant association between efficacy of treatment and age group with p value 0.619. (Table 1)

Male patients were 178 (57.42%) and female patients were 132 (42.58%). Efficacy of treatment was noted in 172 (96.63%) male patients in 53 (40.15%) female patients. Significantly higher rate of efficacy was noted in male patients as compared to female patients with p value 0.000. (Table 2)

Duration of dry eye disease was 1-6 months. Patients were divided into two groups according to duration of disease i.e. 1-3 months and 4-6 months. Out of 151 (48.71%) patients of 1-3 months group, efficacy was found in 109 (72.19%) patients.

In 4-6 months group, treatment was found effective in 116 (72.96%) patients. Statistically insignificant association between efficacy and duration of disease was noted with p value 0.879. (Table 3)

Fig. 9: Frequency of efficacy

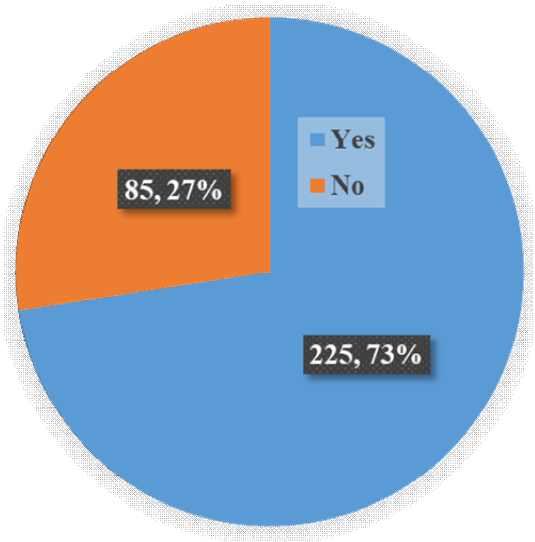

Table 1: Stratification for age

Age Group	Efficacy		Total	P value
	Yes	No		
30-50	136 (71.58%)	54 (28.42%)	190 (61.29%)	0.619
51-70	89 (74.17%)	31 (25.83%)	120 (38.71%)	
Total	225 (72.58%)	85 (27.42%)	310	

Table 2: Stratification for gender

Gender	Efficacy		Total	P value
	Yes	No		
Male	172 (96.63%)	6 (3.37%)	178 (57.42%)	0.00
Female	53 (40.15%)	79 (59.85%)	132 (42.58%)	
Total	225 (72.58%)	85 (27.42%)	310	

Table 3: Stratification for duration of disease

Duration of disease	Efficacy		Total	P value
	Yes	No		
1-3	109 (72.19%)	42 (27.81%)	151 (48.71%)	0.879
4-6	116 (72.96%)	43 (27.04%)	159 (51.29%)	
Total	225 (72.58%)	85 (27.42%)	310	

DISCUSSION:

Dry eye is a frequent disease. Among dry eye patients over the age of 65 in the US, 25% reported using artificial tears on a frequent basis and 73% visited an eye care professional during the previous year for this condition.[10] It is estimated that approximately 7.1 million people over the age of 40 in the US experience symptoms of ocular irritation due to dry eye syndrome, while more than 6% of the population over the age of 40

and more than 15% of the population over the age of 65 suffer from dry eye.[10]

The estimated global sales of artificial tears exceeded US$540 million annually in 2002, whereas the total annual healthcare cost of 1,000 dry eye syndrome sufferers managed by ophthalmologists ranged from US$0.27 million (95% CI: $0.20; US$0.38 million) in France to US$1.10 million (95% CI: US$0.70; US$1.50 million) in the UK. A large proportion of dry eye patients is either self-treated or managed by their general practitioner.[11-12]

Clinically there is a plethora of irritation symptoms associated with dry eye such as ocular burning, stinging, scratchiness, soreness, photophobia, blurred vision and foreign body sensation. Tear fi lm stability can be assessed with the fluorescein tear break-up time test, measuring the interval in seconds between a complete blink and the first appearing dry spot or discontinuity in the precorneal film. Aqueous tear production is measured more commonly with Shirmer test, calculating the length in millimeters that a folded filter paper strip placed in the lower lid wets during a 5-minute test period.[10]

The ocular surface and the lacrimal gland are considered, studied, and treated as an integrated functional unit interconnected by neural sensory/autonomic reflex arcs. Sensory afferent nerves, which enervate the ocular surface, traffic along the ophthalmic branch of the trigeminal nerve to the Pont area of the central nervous system.[13]

Total 310 patients of dry eye disease were selected for this study. Mean age of the patients was 47.15 ± 3.61 years and mean duration of dry eye disease was 11.10 ± 1.75 months. Out of 310 patients, treatment was found effective in 225 (73%) patients.

A total of 362 patients completed the study. After three months, all ocular symptom scores were significantly reduced compared to the baseline values, while the Schirmer scores were significantly increased relative to baseline ($p < 0.0001$). After three months, there were significant reductions from baseline in conjunctival staining ($p < 0.01$) and use of artificial tears ($p < 0.0001$). According to clinicians' global evaluations, most patients (>50%) experienced at least a 25% to 50% improvement in symptoms from baseline at each follow-up visit. The majority of patients (72.0%) were satisfied with the treatment results, and 57.2% reported having no or mild symptoms after treatment.[14] Results of this study are comparable with our results.

In total, 35 eyes of 20 patients diagnosed with dry-eye syndrome were included in this study. The mean age of the patients was 37.3 years (range: 26-65 years).The patients were evaluated for ocular symptoms (burning, pain, and foreign body sensation). Schirmer's paper test and BUT test were conducted for all patients. The score of ocular symptoms before the beginning of the treatment was 2.50 ± 0.46, and this score improved to 0.9 ± 0.52 after 3 months with a statistically significant difference ($P = 0.01$). Schirmer's paper test was performed before the beginning of the treatment, and showed a wetting of 1.15 ± 0.58 mm of the paper, and improved after 3 months to 5.86 ± 0.29 mm ($P = 0.001$). BUT improved from 5.57 ± 1.36 s before the treatment to 9.9 ± 0.92 s after 3 months of treatment ($P = 0.001$).[15]

Prabhasawat *et al* studied 30 cases of dry eyes defined by symptoms and signs, including the Schirmer I test, the fluorescein clearance test, and corneal staining (fluorescein and rose Bengal staining). They were treated with CsA 0.05% eye drops twice daily for 6 months. They found that 17 patients (56.67%) completed the study. Eight patients (26.67%) withdrew from the study as a result of intolerable side effects of CsA, which included pain, redness, and eyelid swelling. Five cases were lost in follow-up. All 17 cases demonstrated significant improvement in dry-eye symptoms, conjunctival injection, corneal staining, Schirmer I test, and fluorescein clearance test ($P<0.05$). Overall improvement was noted in 72.1% patients.[16]In one study thirty-five patients, most of whom were female (71.4%) and

Caucasian (62.9%) treated with cyclosporine. Authors found improvement in 80% patients.[17]

In a study, for 26 of 39 patients (52 eyes) on whom all tests were carried out for 3 months, there was a significant improvement after 3 months in the type I Schirmer test, type II Schirmer test, and tear break-up time (P=0.012, 0.009, 0.001, respectively). Only 14 patients completed the questionnaire for scoring of symptoms. After using Restasis®, foreign body sensation only improved (P=0.010).[18]

In one study by Rao et al,[19]dry eye patients received twice-daily treatment with either cyclosporine 0.05% and found improvement in 68% patients.

CONCLUSION:

Results of present study showed higher improvement rate of dry eye symptoms in cases of dry eye treated with cyclosporine 0.05%. Male patients were more victim of dry eye as compared to female patients and statistically significant association of treatment efficacy with gender was observed. No association of efficacy of treatment with age group and duration of disease was observed.

REFERENCES

1. O'Brien PD, Collum LMT. Dry eye: diagnosis and current treatment strategies. Curr Allergy Asthma Rep. 2004 Jul;4(4):314–9.
2. Zoukhri D. Effect of inflammation on lacrimal gland function. Exp Eye Res 2006;**82**:8 85–898.
3. Conrady CD, Joos ZP, Patel BCK. Review: The lacrimal gland and its role in dry eye. J Ophthalmol [Internet]. 2016 [cited 2017 Apr 15];2016. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4793137/
4. Barabino S, Chen Y, Chauhan S, Dana R. Ocular surface immunity: homeostatic mechanisms and their disruption in dry eye disease. Prog Retin Eye Res. 2012 May;31(3):271–85.
5. Bhavsar AS, Bhavsar SG, Jain SM. A review on recent advances in dry eye: pathogenesis and management. Oman J Ophthalmol. 2011;4(2):50–6.
6. Wei Y, Asbell PA. The core mechanism of dry eye disease (ded) is inflammation. Eye Contact Lens. 2014 Jul;40(4):248–56.
7. Stonecipher KG, Chia J, Onyenwenyi A, Villanueva L, Hollander DA. Health claims database study of cyclosporine ophthalmic emulsion treatment patterns in dry eye patients. Ther Clin Risk Manag. 2013;9:409–15.
8. Schultz C, Schultz C. Safety and efficacy of cyclosporine in the treatment of chronic dry eye. Ophthalmology and Eye Diseases. 2014 Jun;37.
9. Byun YS, Rho CR, Cho K, Choi JA, Na KS, Joo CK. Cyclosporine 0.05% ophthalmic emulsion for dry eye in Korea: a prospective, multicenter, open-label, surveillance study. *Korean J Ophthalmol*. 2011;25(6):369–74.
10. Kymionis GD, Bouzoukis DI, Diakonis VF, Siganos C. Treatment of chronic dry eye: focus on cyclosporine. Clinical Ophthalmology (Auckland, NZ). 2008 Dec;2(4):829.
11. Harmon D, Murphy R. Dry eye market set for robust growth. Market Scope. 2003;8:7-8.
12. Clegg JP, Guest JF, Lehman A, Smith AF. The annual cost of dry eye syndrome in France, Germany, Italy, Spain, Sweden and the United Kingdom among patients managed by ophthalmologists. Ophthalmic epidemiology. 2006 Jan 1;13(4):263-74.
13. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five–year review. Cornea. 2000 Sep 1;19(5):644-9.
14. Byun YS, Rho CR, Cho K, Choi JA, Na KS, Joo CK. Cyclosporine 0.05% ophthalmic emulsion for dry eye in Korea: a prospective, multicenter, open-label, surveillance study. Korean Journal of Ophthalmology. 2011 Dec 1;25(6):369-74.
15. Al-Nashar HY. Efficacy of topical cyclosporine 0.05% eye drops in the treatment

of dry eyes. J Egypt Ophthalmol Soc 2015;108:233-6

16. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. J Ocul Pharmacol Ther 2013; 29 :372-377.
17. Mah F, Milner M, Yiu S, Donnenfeld E, Conway TM, Hollander DA. PERSIST: Physician's Evaluation of Restasis® Satisfaction in Second Trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review. Clinical ophthalmology (Auckland, NZ). 2012;6:1971.
18. Byun YS, Jeon EJ, Chung SK. Clinical effect of cyclosporine 0.05% eye drops in dry eye syndrome patients. Journal of the Korean Ophthalmological Society. 2008 Oct 1;49(10):1583-8.
19. Rao SN. Topical cyclosporine 0.05% for the prevention of dry eye disease progression. Journal of Ocular Pharmacology and Therapeutics. 2010 Apr 1;26(2):157-64.