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A STUDY OF EFFICACY OF 0.05% CYCLOSPORINE EYE DROPS IN CHRONIC DRY EYE DISEASE

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy of Cyclosporine ophthalmic emulsion in patients with chronic dry eye disease. **Methods**: This was a single centred, open label, 3 months prospective study. Patients with unilateral or bilateral dry eye disease and an ocular surface disease index score >12, atleast one eye with schirmer score <5mm and TBUT <10 s were enrolled in the study. Cyclosporine A 0.03% eye ointment was instilled twice daily for three months in the affected eye. The primary efficacy outcome was Schirmer score after 3 months. The secondary outcomes were TBUT, OSDI score and adverse drug reactions. **Results:** A total of 27 patients with the mean age of 52.39 ± 8.10 were enrolled and 23 patients completed the study. After 3 months significant improvement was seen in schirmer tear test, 52.17 % patients showed ≥ 5 mm improvement and 21.8% patients showed ≥ 10 mm improvement in Schirmer score. Mean tear film breakup time also showed significant improvement after 3 months ($p < 0.0001$). Patients also reported significant improvement in ocular discomfort and dry eye symptoms suggested by decrease in OSDI score ($p < 0.001$). No patients discontinued treatment because of minor ocular adverse reactions. **Conclusion**: Dry eye patients demonstrated improvement in schirmer score, TBUT and OSDI score in patients of Chronic dry eye disease after 3 months of treatment with Cyclosporine A 0.05% ophthalmic emulsion.

KEYWORDS: Cyclosporine ophthalmic solution,Schirmer score,TBUT,OSDI Score.

INTRODUCTION

Dry eye is a prevalent, chronic, multifactorial disease of the tears and ocular surface.[1,2] Instability of the tear film accompanied by T-cell-mediated ocular surface inflammation plays a major role in disease development and progression.[3,4] Dry eye symptoms are a key complaint of patients with dry eye. Patients with dry eye suffer from symptoms of ocular discomfort, dryness, and visual disturbances, which may be episodic and also vary during the day.[5–7] It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1,2] The diagnosis of dry eye disease is usually based on the presence of symptoms, but various tests are available for diagnosis in certain cases.[8] For example, Schirmer's test measures the amount of tears wetting the precorneal surface, tear film breakup time measures the stability of tear film, ocular surface staining assesses the damage to the ocular surface as a result of dryness.

Dry eye disease can seriously impair the affected individual's quality of life.[9,10,11] In addition to the negative effects of ocular pain, DES can also have adverse effects on mental health, such as depression and anxiety.[12] Miljanovic et al.[13] reported in a study of 690 participants that dry eye disease affected the ability to perform common daily activities, such as driving, television viewing, and computer work.

Although the reported prevalence of dry eye disease varies among populations, dry eye disease affects millions of individuals worldwide. In American men, Schaumberg et al.[14] found prevalence rates ranging from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older. In American women, the prevalence also increased with age, from 5.7% among women younger than 50 years to 9.8% among women aged 75 years or older.[15] Other studies have found dry eye disease in 14% of individuals aged 65–85 years.[16] Prevalence rates in Asian populations appear to be even higher.[16,17] However, at least some of the variation between studies relates to differences in the definition of disease used.[16]

Treatment for DES depends on the severity of the condition. Environmental conditions that increase tear evaporation and factors that may decrease tear

production should be minimized or eliminated.[18] Artificial tears or ocular lubricants (preservative free) are often successful in ameliorating symptoms, especially in mild cases.[19] Nutritional supplementation with omega-3 fatty acids may be useful, but research in this area is limited and the results somewhat inconclusive to date.[20] Based on the concept that inflammation is a key component of the pathogenesis of dry eye, a number of anti-inflammatory agents have been used, including corticosteroids, tetracyclines, and cyclosporine.[16,21] Other treatments may include intraductal meibomian gland probing, application of simultaneous heat and pressure to the eyelid to affect the meibomian glands, and N-acetyl-cysteine.[22] Severe or prolonged dry-eye cases may require surgical procedures, such as lid surgery, tarsorrhaphy, or mucus membrane, salivary gland, or amniotic membrane transplantation.[16]

Among the plethora of available treatment options, cyclosporine A (Restasis, Allergan, Irvine, CA) is the only prescription drug approved by the US Food and Drug Administration (FDA) specifically for patients with dry eye disease and seems to be the most widely used current therapy for dry eye disease.[23,24] The aim of the present manuscript is to evaluate the efficacy and safety of cyclosporine A in the treatment of dry eye disease.

MATERIAL AND METHODS

The present study was randomized, prospective, interventional study carried out on patients who were diagnosed as case of dry eye disease, attending outpatient department at Regional Institute of Ophthalmology (M.D. Eye Hospital), Allahabad during the year 2016-2017, after taking permission from ethical committee of M.L.N. Medical College, Allahabad.

Out of the patients who attended outpatient department, adult patients of either sex were screened on the basis of inclusion criteria and those fulfilling the criteria were included in the study.

Inclusion criteria

- Patients included men and women aged ≥ 18 years.
- Have symptoms of dry eye disease for ≥ 6 months in any or both the eyes supported by a previous clinical diagnosis.
- Must be able to understand and follow study related advice.
- Patients reporting no improvement in subjective symptoms in response to artificial tear therapy.
- OSDI score ≥ 12 at screening.
- Following signs at screening and baseline visits in atleast one eye :
- Tear film break up time ≤ 10 s.
- Schirmers tear test without anesthesia ≤ 5 mm in 5 minutes.

Exclusion Criteria

- Not willing to give consent.
- Active blepharitis, meibomian gland disease, lid margin inflammation or ocular allergy.
- Any structural abnormalities on external eye examination for ex: entropion, trichiasis, lid scarring, etc
- Any inflammation or active structural changes in the iris or anterior chamber.
- Single functioning eye.
- Glaucoma.
- Previous eye surgery or punctual occlusion 6 months before study entry.
- Any systemic or topical medication other than artificial tears.
- Any systemic or topical antibacterial or antiinflammatory drug treatment 30 days before study entry.
- Immunosuppressive systemic therapy 90 days before the study entry.
- Contact lens wearer.
- Presence of any corneal infection or any corneal disease (marginal ulcer, opacity, scar, bullous keratopaty, symblepharon or tumor)

Commercially available standard pharmaceutical preparation of the same batch, available in our set up was used in our study. The study consisted of 5 visits conducted during 2 sequential phases (i) the screening/eligibility phase, which included a screening visit, and (ii) the treatment phase, which included next 4 visits conducted at day 1, 1 month, 2 months, and 3 months. At screening, patients discontinued use of all pre study medications, and the eligibility visit was scheduled after a predetermined washout period according to patient's pre study medication. One eye from each patient was chosen as the study eye, and only the study eye was used in the efficacy analysis. If only 1 eye of a patient was treated, that eye was selected as the study eye. If both eyes were treated, the worse evaluable eye was selected as the study eye. The worse eye was defined as the eye with the lower Schirmer score across the eligibility visit, if the score in both the eyes were equal the right eye was selected for analysis.

All patients were required not to use any other topical ophthalmic medications, other than given medication during the study period. Patients were instructed to visit after 1 month, 2 months, and 3 months after starting treatment for the subsequent study visits, which was scheduled for each patient. At each study visit, an interval medical history was obtained and any side effects were assessed, an ophthalmic examination including slit lamp biomicroscopy of the anterior eye segment, Schirmer test, tear film breakup time (TBUT), was performed and the OSDI questionnaire was completed. In each study visit, TBUT was evaluated first, followed by Schirmer tear test. The need for at least a 3-month trial period to fully gauge the effectiveness of this therapy was stressed to each patient. All patients were advised to contact us and return at any time should problems arise and in 3 months for a follow-up examination after their initial evaluations. Patients were

also advised that mild burning or irritation on application of cyclosporine A is common.

Efficacy was evaluated primarily with an objective measure and secondarily with objective and subjective measures. There was one primary objective outcome which is Schirmer score at each study visit. Secondary objective outcome was TBUT at each follow- up visit and secondary subjective outcome was ocular surface disease index (OSDI) questionnaire for the grading of the symptoms score. The OSDI composite scores before initiation of treatment i.e baseline and post treatment after completion of treatment i.e, after 3 months was used in the analysis. The safety outcome was measured as the incidence of adverse reactions and the nature of adverse reactions, determined at various visits by means of physical signs and symptoms, external eye examination, slit-lamp microscopy, visual acuity, intraocular pressure, and funduscopy. All patients were also questioned regarding any ocular symptoms related to the study medications by phone calls as well as at all follow up visits.

Data were expressed as means ± SD. In all analysis, $P < 0.05$ was taken to indicate statistical significance for each time interval of 1 month, 2 months, and 3 months. All data were summarized using frequency distributions and/or descriptive summary statistics (mean and standard deviation [SD]). The efficacy analysis population included all patients who completed the study. The safety analysis population included all patients who were enrolled in the study. All statistical analyses included data for the selected eye. Paired Student's *t* test was used to assess the statistical significance. Chi square test ($\chi 2$) was used to analyse the categorical variables. All tests were two tailed, with a significance level of 0.05.

OBSERVATION AND RESULTS

A total of 27 patients were enrolled in the study out of which 23 patients completed the study. The study covered wide range of age (40-75 years). The mean standard derivation (SD) age was 52.39 ± 8.10 yrs, 7 were females and 16 were males.

Efficacy

Schirmer Score

Schirmer's tear test was done in all patients. Baseline mean ± SD schirmer's score was 2.67 ±1.16 (mm) and at 1 month, 2 months and 3 months were 5.33 ± 1.99 (mm), 6.98 ± 2.19 (mm), and 9.26 ± 2.90 (mm).

We also observed the responder rate in terms of number of patients who achieved atleast 5 mm and 10 mm improvement in Schirmer score after completion of treatment i.e, 3 months. 12 patients (52.17 %) showed 5 mm improvement and 5 patients (21.8%) showed 10 mm improvement in Schirmer's score at 3 months.

Table 1: Mean (SD) Schirmer Score (in mm) at baseline and follow-up visits.

Point of time	Mean Schirmer score(mm)	SD
Baseline	2.67	1.16
1 month	5.33	1.99
2 months	6.98	2.19
3 months	9.26	2.90

Tear film breakup time (TBUT)

Secondary efficacy outcome was objectively measured in terms of changes in TBUT (seconds) at baseline, 1 month, 2 months and 3 months visit to evaluate quality of tear films. Baseline mean ± SD TBUT (secs) was 5.83 ± 1.74 (secs) and at 1 month, 2 months and 3 months were 7.74 ± 2.09 (secs), 9.30 ± 1.99 (secs) and 10.61 ± 1.94 (secs), respectively.

Table 2: Mean (SD) TBUT (in secs) at baseline and follow-up visits.

Point of time	Mean TBUT	SD	P value
Baseline	5.83	1.74	
1 month	7.74	2.09	0.0001
2 months	9.30	1.99	0.0001
3 months	10.61	1.94	0.0001

OSDI Score

OSDI scores was also calculated before initiation of treatment (baseline) and after completion of treatment (3 months) for evaluating dry eye symptoms. Baseline mean ± SD OSDI score was 43.25 ± 11.09 and at 3 months 33.07 ±11.10, reduction in OSDI score was statistically significant showing remarkable reduction in ocular and visual symptoms.

Table 3: Mean OSDI (SD) before treatment and after 3 months.

Point of time	Mean OSDI	SD	P value
Baseline	43.25	11.09	
3 months	33.07	11.10	0.0001

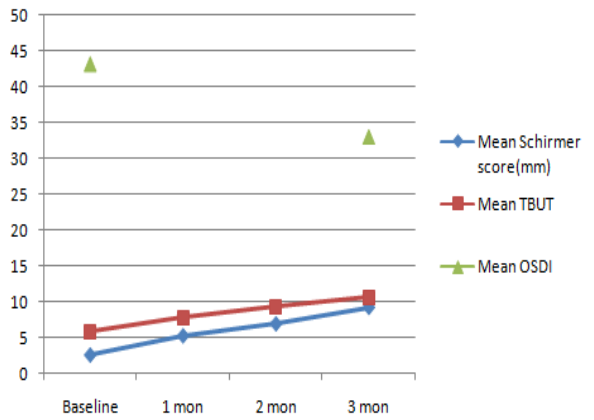

Fig 1: Improvement after treatment with cyclosporine A.

Safety

Incidences of non-serious adverse effects were also reported in our study. No ocular infection was reported during the treatment period. No serious adverse effects warranting the discontinuation of treatment was reported. The most common treatment related ocular adverse event was ocular burning (18/23) followed by conjunctival hyperemia (4/23).

DISCUSSION

Dry eye is underdiagnosed and potentially undertreated.[25] The ocular discomfort and visual disturbances associated with untreated dry eye have a negative impact on the quality of life of affected individuals.

Topical cyclosporine has been used successfully in the treatment of a number of ocular surface diseases in addition to dry eye.[26] The improvement in tear film stability provided by topical cyclosporine and its anti-inflammatory effects on meibomian glands have been shown to be beneficial in patients with meibomian gland dysfunction.[27,28] Topical cyclosporine has also been shown to be an effective anti-inflammatory treatment for vernal and atopic keratoconjunctivitis.[26,29,30] Studies have demonstrated that topical cyclosporine reduces contact lens intolerance in contact lens wearers with dry eye[31] and improves signs and symptoms in patients with ocular rosacea[32] as well as superior limbic keratoconjunctivitis.[33] Most recent studies of cyclosporine treatment in ocular surface disease other than dry eye have used topical cyclosporine (0.5%–2%) or cyclosporine ophthalmic emulsion 0.05% (Restasis®) off-label. Restasis® is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.[34]

Consistent with the approved indication for cyclosporine ophthalmic emulsion for the increase in tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, patients demonstrated clinically significant improvements in quantity of tears as suggested by increase in Schirmer score after 3 months of treatment. A similar magnitude of improvement was seen in tear film stability and OSDI score. Patient-reported outcomes of ocular discomfort and other symptoms of dry eye also were significantly improved. Patients reported excellent compliance with the dosing schedule, and treatment was well tolerated. Notably, no patient discontinued the use of cyclosporine because of stinging upon instillation.

The beneficial effects of cyclosporine ophthalmic emulsion treatment on the signs and symptoms of dry eye in this study are consistent with the previously reported effects of cyclosporine treatment in controlled clinical trials. The improvement in tear production was similar to the significant increase from 3.93±1.21 mm at baseline to 7.30±1.79 mm after 3 months of cyclosporine ophthalmic emulsion 0.05% treatment that was reported in a study by Kim et al.[35] In a study by Demiryay et al,[36] the increase in mean Schirmer scores from baseline after 4 months was 3.33 mm greater in patients treated with cyclosporine ophthalmic emulsion 0.05% than in patients treated with vehicle. Deveci and Kobak[37] investigated the efficacy of 0.05% topical cyclosporine A in 26 patients with keratoconjunctivitis sicca because of primary or secondary Sjögren's syndrome compared to 22 control patients treated with saline solution. All subjective symptoms and objective signs (Schirmer's test, tear break-up time, and redness) were significantly improved after one-week and one-month follow-up examinations in patients receiving cyclosporine A compared with controls ($P = 0.0001$).

A limitation of this study was the lack of a control group and small sample size. The study was open label to allow the evaluation of efficacy of cyclosporine ophthalmic emulsion 0.05% in patients with dry eye. Data are already available from controlled clinical trials evaluating treatment versus no treatment.

CONCLUSION

The results of this study confirm the clinical benefit of cyclosporine ophthalmic emulsion 0.05% treatment for patients with dry eye. Cyclosporine 0.05% emulsion treatment reduced the signs and symptoms of dry eye and improved the performance of patients on common vision-related tasks as suggested by changes in OSDI score. Patients reported very good compliance with treatment. No patient discontinued the use of cyclosporine because of ocular intolerability.

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