(e) ISSN Online: 2321-9599
(p) ISSN Print: 2348-6805

ORIGINAL ARTICLE

EVALUATION OF EFFICACY OF CYCLOSPORINE OPHTHALMIC EMULSION VERSUS VEHICLE IN PATIENTS WITH DRY EYE DISEASES IN INDIAN POPULATION: A COMPARATIVE STUDY

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ABSTRACT:

Background: Dry eye diseases are the common ocular pathologies encountered among the general population. Lubricating the ocular surfaces with artificial tears forms the traditional therapies for dry eyes. Cyclosporine has been shown to block T-cell proliferation and receptor signal transduction. Hence; we compared the efficacy of cyclosporine 0.05% ophthalmic emulsion, as compared with vehicle in Indian population with dry eye diseases. **Materials & methods:** The present study was conducted in the Department Of Ophthalmology, Shadan Institute of Medical Sciences and included assessment of 300 patients with dry eye diseases. All the patients were broadly divided into two study groups. Group 1 included patients who received cyclosporine 0.05% (1 drop, twice daily) while group 2 included patients who were administered with vehicle (1 drop, twice daily). During the first 6 months extension, patients were provided with artificial tears to be used as needed, except not within 30 minutes of cyclosporine 0.1% instillation. Within 90 days of completing the previous treatment period, patients were required to enter the second and third 6-month extensions within 90 days of completing the previous treatment period. Ocular signs and symptoms were measured at all visits, except for visual acuity, which was not evaluated at week 4.evaluation of all the patients were done at various time intervals. All the results were analyzed by SPSS software. **Results:** Number of patients included in both the groups was 180. Mean age of the patients in group 1 and group 2 were 48.2 and 49.1 respectively. No significant results were obtained while comparing the demographic details in between the various study groups. Mean change observed in group 1 patients and in group 2 patients at 14 days time was 2.99 and 2.65 respectively. However, significant results were obtained while comparing the p-value for the mean change in of the total score in between the two study groups. **Conclusion:** Cyclosporine 0.05% treatment protocol twice daily in patients with dry eyes pathologies was equally effective in comparison with the vehicle.

Key words: Cyclosporine, Dry eyes, vehicle

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This article may be cited as: Khan IA, Qamruddin M. Evaluation of efficacy of cyclosporine ophthalmic emulsion versus vehicle in patients with dry eye diseases in Indian population: A comparative study. J Adv Med Dent Scie Res 2016;4(6):199-203.

Access this article online	
Quick Response Code	Website: www.jamdsr.com
	DOI: 10.21276/jamdsr.2016.4.6.48

INTRODUCTION

Dry eyes form one of the broad spectrums of diseases encountered among general population is the Dry eyes. Dry eye syndrome (DES) is a multifactorial disease of the ocular surface with tear film abnormalities, leading to eye discomfort, visual disturbance, tear film instability, and inflammation of the ocular surface.[1] It one of the most common ocular conditions as demonstrated by its accountability for as many as 17%-25 % of visits to ophthalmology clinics. Pathogenesis of DES has advanced from the simple concepts of deficiency or impaired quality of tears, and now includes concepts of tear hyperosmolarity and ocular surface inflammation.[2] Approximately 25% of patients were affected by dry eye symptoms and sought ophthalmological consultation in Germany. In Taipei, approximately 25% of patients were affected by dry eye symptoms and sought ophthalmological consultation.[3] Traditional therapies for DES mainly focus on the lubrication of the ocular surface with artificial tears.[4] However, these treatments do not address the underlying ocular surface inflammation. Cyclosporine, an immunomodulatory agent, has been shown to block T-cell proliferation and receptor signal transduction. The cell-mediated inflammatory responses are modulated through the downregulation of IL-2 receptor expression

and gene transcription.[5] Hence; we compared the efficacy of cyclosporine 0.05% ophthalmic emulsion, as compared with vehicle in Indian population with dry eye diseases.

MATERIALS & METHODS

The present study was conducted in the department of ophthalmology of the Shadan Institute of Medical Sciences and included assessment of 300 patients with dry eye diseases from 2014 and 2016. All the patients were broadly divided into two study groups. Group 1 included patients who received cyclosporine 0.05% (1 drop, twice daily) while group 2 included patients who were administered with vehicle (1 drop, twice daily). They were diagnosed with dry eye disease based on the following criteria: symptoms of dryness, photophobia, foreign body sensation, burning, and signs of conjunctival hyperemia; a Schirmer tear test result of less than or equal to 5mm/5min without anesthesia; a tear Break-up time (BUT) of less than or equal to 5 s; and a corneal punctate fluorescein staining score of more than or equal to 1 in either eye. To be included in the study, the following criteria had to be met: Each symptom score had to be more than or equal to 2 in either eye; sum scores of dryness, photophobia, foreign body sensation, and burning had to be more than or equal to 6; and either of 2 items of Schirmer test (without anesthesia) of less than or equal to 5mm/5min, BUT of less than or equal to 5 s, and a corneal punctuate fluorescein staining score of more than or equal to 1 in either eye. The extension trial consisted of 3 consecutive 6-month periods during which all patients instilled cyclosporine 0.1% ophthalmic emulsion, 1 drop in each eye, twice daily. The baseline visit occurred on day 0
of the first 6-month extension period. Patients were provided with artificial tears (Refresh, Allergan) during the first 6-month extension to be used as needed, except not within 30 minutes of cyclosporine 0.1% instillation. Patients were required to enter the second and third 6-month extensions within 90 days of completing the previous treatment period.

Written informed consent was obtained from patients before each 6-month treatment period. Women of childbearing potential had to take a reliable measure to avoid pregnancy. To be included, subjects had to have best corrected visual acuity of 6/12 or better. Subjects were assessed at baseline and after 2, 4, and 8 weeks of therapy. All examinations were conducted by the same examiner. Ocular signs and symptoms were measured at all visits, except for visual acuity, which was not evaluated at week 4. Patients were withdrawn from the study if their clinical condition worsened or at the discretion of the researchers. All the results were analyzed by SPSS software. Chi-square test was used for the assessment of level of significance.

RESULTS

Demographic details of the patients are highlighted in **Table 1**. Number of patients included in both the groups was 180. Mean age of the patients in group 1 and group 2 were 48.2 and 49.1 respectively. Mean weight of the patients in group 1 and group 2 were 62.5 and 57.1 Kg respectively. In group 1, 31.5 percent of the patients were males while in group 2, 28.2 percent of the patients were males. **Table 1** highlights the p-value for the demographic details of the patients. No significant results were obtained while comparing the demographic details in between the various study groups. **Graph 2** shows the reduction of total score for cyclosporin 0.05% and vehicle group at 14 days, 28 days and 42 days. Mean change observed in group 1 patients and in group 2 patients at 14 days time was 2.99 and 2.65 respectively. However, significant results were obtained while comparing the p-value for the mean change in of the total score in between the two study groups (**Table 2**). **Graph 3** shows the values for various symptoms at various time intervals. Among group 1 and group 2 patients, the mean value for dryness of eyes at 14 days time was 1.95 and 2.10 respectively.

Graph 1: Demographic details of the patients

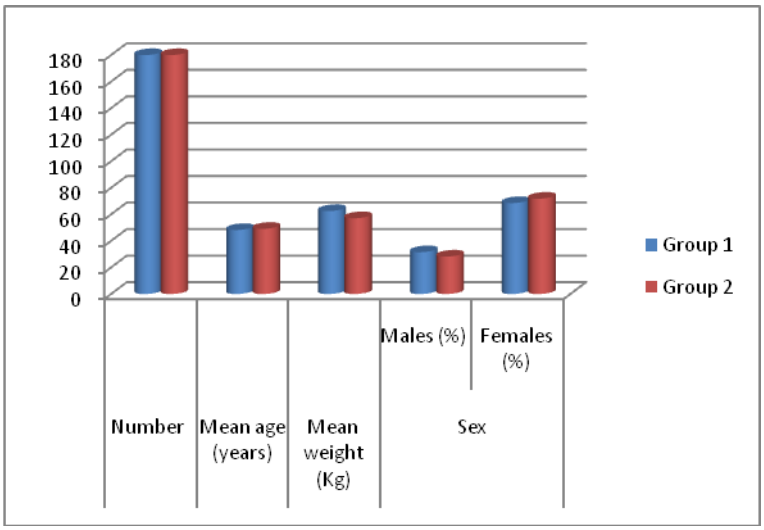

Table 1: p-value for demographic details of the patients

Parameter		Group 1	Group 2	p-value
Number		180	180	-
Mean age (years)		48.2	49.1	0.51
Mean weight (Kg)		62.5	57.1	0.67
Sex	Males (%)	31.5	28.2	0.41
	Females (%)	68.5	71.8	

Graph 2: Reduction of total score for cyclosporin 0.05% and vehicle group at 14 days, 28 days and 42 days

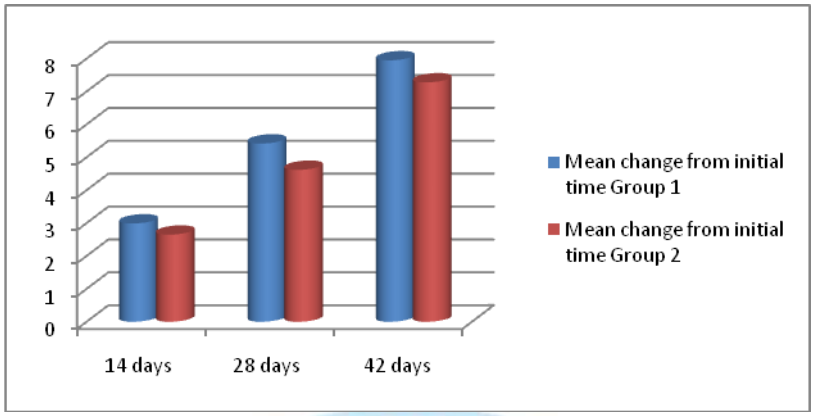

Table 2: p-value for reduction of total score for cyclosporin 0.05% and vehicle group at 14 days, 28 days and 42 days

Time	Mean change from initial time		
	Group 1	Group 2	p-value
14 days	2.99	2.65	0.02*
28 days	5.42	4.62	0.03*
42 days	7.95	7.28	0.01*

Graph 3: Values for various symptoms at various time intervals

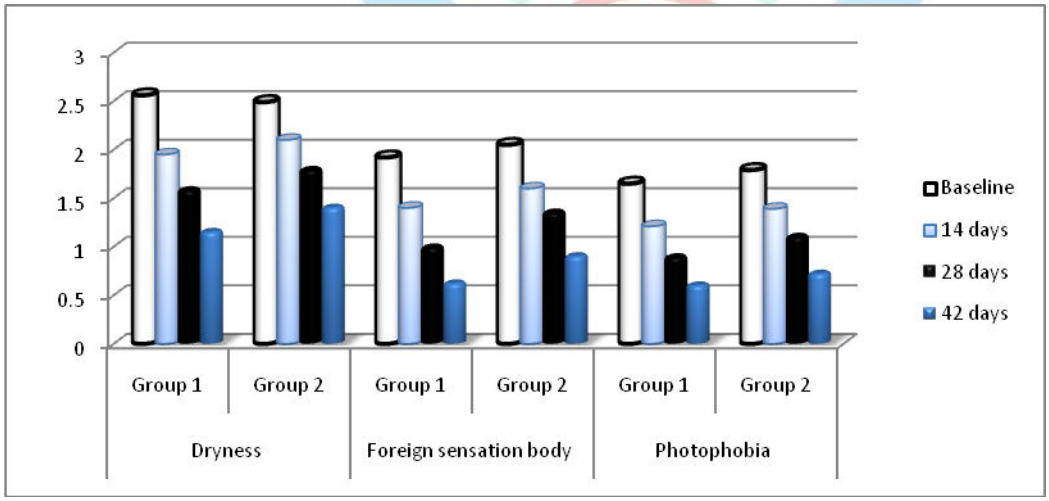

Table 3: Values of ocular symptoms at various time intervals

Parameter	Groups	Baseline	14 days	28 days	42 days
Dryness	**Group 1**	2.56	1.95	1.58	1.15
	Group 2	2.49	2.10	1.79	1.40
Foreign sensation body	**Group 1**	1.92	1.40	0.99	0.62
	Group 2	2.05	1.60	1.35	0.90
Photophobia	**Group 1**	1.65	1.21	0.89	0.60
	Group 2	1.79	1.39	1.10	0.72

DISCUSSION

A variety of signs and symptoms are presented in the dry eye disease patients which includes decreased tear production, an altered and unstable tear film, and epithelial damage evidenced by fluorescein staining of the cornea and rose bengal or lissamine green staining of the conjunctiva. Patients may complain of blurred vision, dryness, and ocular surface burning or stinging, which may be exacerbated by desiccating conditions or prolonged visual concentration. Dry eye disease can impact patients' ability to read and use a computer, in addition to the pain and suffering they experience.[6] Recent research has led to an appreciation of a complex pathology underlying the disease. In dry eye patients, elevated levels of certain cytokines and matrix metalloproteases are found in the tears, and elevated levels of T lymphocytes are present in ocular surface tissues.[7- 9] Hence; we compared the efficacy of cyclosporine 0.05% ophthalmic emulsion, as compared with vehicle in Indian population with dry eye diseases.

In the present study, we observed more effectiveness for cyclosporin 0.05% ophthalmic emulsion administered twice daily for 8 weeks. These efficacy measures were in-terms of ubjective measures, including ocular dryness, foreign body sensation, and objective measures, including corneal staining and the Schirmer tear test. From these results, it is highlighted that cyclosporine treatment is not purely palliative but also significantly affects disease severity. Our results were in correlation with the previous findings which also show significant improvements in multiple variables from baseline.[10] Stevenson et al investigated the efficacy, safety, formulation tolerability, and optimal dosing of a novel cyclosporin A oil-in-water emulsion formulation for the treatment of moderate-to-severe dry eye disease. They enrolled a total of 162 patients; cyclosporin A groups: 129 patients; vehicle group: 33 patients. In a subset of 90 patients with moderate-to-severe keratoconjunctivitis sicca, the most significant improvements with cyclosporin A treatment were in rose bengal staining, superficial punctate keratitis, sandy or gritty feeling, dryness, and itching, with improvements persisting into the posttreatment period in some treatment groups. There was also a decrease in Ocular Surface Disease Index (OSDI) scores, indicating a decrease in the effect of ocular symptoms on patients' daily lives. There was no clear dose-response relationship, but cyclosporin A 0.1% produced the most consistent improvement in objective and subjective end points and cyclosporin A 0.05% gave the most consistent improvement in patient symptoms. The vehicle also performed well, perhaps because of its long residence time on the ocular surface. There were no significant adverse effects, no microbial overgrowth, and no increased risk of ocular infection in any treatment group.

The highest cyclosporin A blood concentration detected was 0.16 ng/ml. All treatments were well tolerated by patients. From the results, they concluded that Cyclosporin A ophthalmic emulsions, 0.05%, 0.1%, 0.2%, and 0.4%, were safe and well tolerated, significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning.[10] Sall et al compared the efficacy and safety of cyclosporin A ([CsA] 0.05% and 0.1% ophthalmic emulsions) to vehicle in patients with moderate to severe dry eye disease. A total of 877 patients with defined moderate to severe dry eye disease were analyzed. Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis. Treatment with CsA, 0.05% or 0.1%, gave significantly ($P <$ or $=$ 0.05) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose-response effect. Both CsA treatments exhibited an excellent safety profile, and there were no significant topical or systemic adverse safety findings. From the results, they concluded that the novel ophthalmic formulations CsA 0.05% and 0.1% are safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both objective and subjective measures.[11]

Chen compared the efficacy and safety profile of topical cyclosporine 0.05% versus vehicle in Chinese patients with moderate to severe dry eye disease. They analyzed 233 dry eye patients who received either cyclosporine 0.05% or vehicle twice daily for 8 weeks. Changes in symptoms (ocular dryness, foreign body sensation, photophobia and burning) and signs (conjunctival hyperemia, Schirmer test, tear Break-up time (BUT), and corneal punctate fluorescein staining) at weeks 2, 4, and 8 as well as frequency of administration of concomitant artificial tears, were considered as secondary outcomes. The safety profile was evaluated by examining adverse events, changes in visual acuity, and ocular tolerance. They observed that greater improvements of the total score were seen in cyclosporine 0.05% group than in the vehicle group at all follow-up times. Improvements in ocular dryness at week 8 and foreign body sensation during weeks 4 and 8 were significantly greater with cyclosporine. The cumulative frequency of adverse events did not significantly differ between the groups, which were 11.21% and 8.55%, respectively. There were no patients who experienced reduced visual acuity. From the results, they concluded that cyclosporine 0.05% ophthalmic emulsion is an effective and safe treatment for Chinese patients with moderate to severe dry eye disease.[12]

CONCLUSION

From the results, the authors concluded that cyclosporine 0.05% treatment protocol twice daily in patients with dry eyes pathologies was equally effective in comparison with the vehicle.

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Source of support: Nil **Conflict of interest:** None declared