ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(2); 531-538

Original Research Article

Open Label, Prospective Study to Assess the Efficacy of Topical Cyclosporine and Osmoprotective Lubricating Eye Drops in Treating Dry Eye Disease and Inflammation

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Received: 02-11-2021 / Revised: 20-12-2021 / Accepted: 14-02-2022
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Conflict of interest: Nil

Abstract

Aim: Efficacy of topical cyclosporine 0.05% and osmoprotective lubricating eye drops in treating dry eye disease and inflammation.

Methods: This drug interventional, open label, prospective study conducted in the Department of Ophthalmology, Nalanda medical College and Hospital Patna, Bihar, India, for 12 months. A total of 100 eyes of 50 patients were included in the study. All patients underwent detailed slit‑lamp examination, noncontact tonometry, and dilated fundus examination in addition to dry eye evaluation as part of the routine clinical examination. Patients with mild to moderate aqueous deficiency and evaporative dry eye with two or more of the following criteria were included in the study: Ocular Surface Disease Index (OSDI) >12, tear break up time (TBUT) between 6 and 10 s; Schirmer's test I result 8–10 mm/5 min and ocular surface staining. Severity of DED was graded as per the Dry Eye Workshop Study classification.

Results: 36 eyes (36%) had minimal punctate epithelial erosions (PEEs) inferiorly scored as 1, while 64 eyes (64%) did not show any PEEs and were scored as 0. Patients with MMP‑9 positivity were associated with higher OSDI score with a mean OSDI score among these patients being 28.7 ± 7.1, P = 0.0057. MMP‑9 positivity was also significantly associated with decreased Schirmer's test values, P = 0.0011. The average Schirmer's level in this group of patients was 9.41 ± 4.61 mm. Patients with lower TBUT were found to have higher OSDI and more MMP9 positivity. P =0.07 Dendritic cell density is measure on the IVCM. The variation in dendritic cell density was noted, and 70% DED eyes were found to have high dendritic cell density on IVCM. There was an improvement in clinical parameters like the TBUT and ocular surface staining. Mean TBUT of the DED patients improved from 7.87 to 8.35 s (P = 0.07), and the percentage of eyes with corneal staining reduced from 35% (35 eyes) to 19% (19 eyes). There was no statistically significant change in Schirmer's test values (P = 0.15). Out of 70 eyes that tested MMP‑9 positive, 70eyes (70%) showed a negative test after treatment (P = 2.5), while the remaining 30 eyes (30%) showed no change in the MMP‑9 status post-treatment. There was also a reduction in dendritic cell density observed on

IVCM. There was a significant improvement in the mean OSDI scores of patients on treatment (14.2 ± 7.4 after 6 months compared to 24.7 ± 10.8 at baseline, $P < 0.001$.
Conclusion: The treatment of DED can be extremely challenging due to the varied subjective symptoms and objective signs with which the patient presents.
Keywords: cyclosporine, osmoprotective, dry eyes

Introduction

Dry-eye disease or kerato conjunctivitis sicca (KCS) is a common, multifactorial, symptomatic disease that is associated with increased osmolarity of the tear film and ocular surface inflammation.[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 KCS 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 KCS 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] Topical cyclosporine ophthalmic emulsion 0.05% is a topical anti-inflammatory drug that has been approved by the United States Food and Drug Administration for the treatment of moderate to severe dry eyes. It is indicated to increase tear production in patients with reduced tear production presumably due to ocular inflammation.[9] Cyclosporine A (CsA) is a fungal-derived peptide that inhibits T-cell activation and consequently inhibits the inflammatory cytokine production (selective inhibition of interleukin-1). In addition, CsA inhibits apoptosis and increases the density of conjunctival goblet cells.[10] In two multicenter, randomized, prospective, phase III clinical trials, topical cyclosporine 0.05% was shown to improve categorized Schirmer values, reduce corneal staining, and improve subjective measures, including blurred vision and dependence on artificial tears relative to vehicle. Burning and stinging upon instillation were the most common treatment-related side effects.[11] This study evaluates the effect of a combination

of lubricant osmoprotectant eye drops with cyclosporine A 0.05% eye drops in the treatment of DED and associated inflammation.

Material and methods

This drug interventional, open label, prospective study conducted in the Department of Ophthalmology, Nalanda medical College and Hospital Patna, Bihar, India, for 12 months.

Methodology

A total of 100 eyes of 50 patients were included in the study. All patients underwent detailed slit-lamp examination, noncontact tonometry, and dilated fundus examination in addition to dry eye evaluation as part of the routine clinical examination. Patients with mild to moderate aqueous deficiency and evaporative dry eye with two or more of the following criteria were included in the study: Ocular Surface Disease Index (OSDI) >12, tear break up time (TBUT) between 6 and 10 s; Schirmer's test I result 8–10 mm/5 min and ocular surface staining. Severity of DED was graded as per the Dry Eye Workshop Study classification.[12]

Patients with severe aqueous deficiency dry eye, meibomian gland dysfunction requiring treatment, cicatrizing causes of ocular surface inflammation (e.g. Stevens Johnson syndrome, ocular cicatricial pemphigoid), active or past history of uveitis, use of chronic topical medications, ocular infections, previous ocular surgery, those already on medications, and use of contact lens were excluded from the study. Patients who did not come for follow‑up at the scheduled visit or stopped medications prematurely were excluded from the study. Dry eye examinations were performed in the following sequence: OSDI questionnaire, Inflamma Dry test, Schimers test, TBUT, and ocular surface staining with fluorescein and *in vivo* confocal microscopy (IVCM) by Heidelberg Retinal Tomograph 2 Rostock cornea module (Heidelberg engineering, GmBH, Dossenheim, Germany). OSDI is a globally accepted DED assessment tool consisting of 12 questions. The OSDI score ranges from 0 to 100, with higher grading scores implying more severe disease (0–12 is normal, 13–22 mild, 23–32 moderate, and 33–100 severe disease). TBUT assessment was done using a fluorescein dye strip and TBUT was measured on the slit‑lamp under cobalt‑blue light. The time interval between the patient's blink and the break in the stained tear film is noted as the TBUT. Schirmer's test 1 was done by placing standardized strips in the lateral one‑third of the lower eyelid without anesthesia. After 5 min, the length of the wetting of the strips noted. Schirmer's test with anesthesia was performed by instilling topical anesthetic proparacaine 0.5% eye drops in the eye and repeating the same test with the Schirmer's strip after dabbing off the excess fluid from the lid margin. The cornea staining score was graded as per the Sjogren's International Collaborative Clinical Alliance registry ocular examination protocol.[13]

The MMP‑9 assessment was done using the Inflamma Dry assay, which is a visual, qualitative clinic‑based test. The sample is collected from the tear meniscus at multiple locations on the lower lid. It is then transferred to the cartridge for testing. The test kit is placed on the horizontal surface and read after 10 min. A positive test has a blue and red line in the test window. A test result without a blue line is invalid. [7] IVCM was done before and after using the medications to identify dendritic cell density in the cornea, which is also a marker of inflammation.[14]

All patients were advised to use osmoprotective eye drops (Osmodrops, Cipla Ltd) four times a day and topical preservative free cyclosporine ophthalmic

emulsion 0.05% (Imudrops, Cipla Ltd), one drop twice a day in each eye, approximately 12 h apart, as per the international recommendations for the use of cyclosporine in the management of DED.[15] After 6 months, the treatment response was evaluated by repeating the same tests done before starting medications and comparing the values to pretreatment levels.

Statistical analysis

All statistical analysis was performed using the GraphPad 6.0 (GraphPad Software, Inc., La Jolla, CA, USA). The mean value of the individual groups was reported as mean ± SD. A *P* value of < 0.05 was considered statistically significant.

Results

A total of 100 eyes of 50 DED patients were included in the study. The mean age was 31.67 ± 10.24 years (range: 20–45 years). There were 25 females and 25 males included. These patients were followed up for a period of 6 months and underwent a repeat clinical assessment of their dry eye status at 6 months. Mean Schirmer's test value was 10.41 ± 4.32 at 5 min (range 6–30) in DED patients. Mean TBUT of the DED patients was 7.87 ± 3.35 s (range 5–10). Mean OSDI score was 24.7 ± 10.8.

36 eyes (36%) had minimal punctate epithelial erosions (PEEs) inferiorly scored as 1, while 64 eyes (64%) did not show any PEEs and were scored as 0 [table 1].

Table 1. Pre-treatment Punctate epithelial erosions (PEEs) score

	Number of eyes	%
Punctate epithelial erosions (PEEs) scored as 1	36	36
Punctate epithelial erosions (PEEs) scored as 0	64	64

Of the 100 eyes in the 50 DED patients, 50% (50 eyes) tested positive for MMP‑9 at presentation. Patients with MMP‑9 positivity were associated with higher OSDI score with a mean OSDI score among these patients being 28.7 ± 7.1, *P* = 0.0057. MMP‑9 positivity was also significantly associated with decreased Schirmer's test values, *P* = 0.0011. The average Schirmer's level in this group of patients was 9.41 ± 4.61 mm. Patients with lower TBUT were found to have higher OSDI and more MMP9 positivity. *P* =0.07 Dendritic cell density is measure on the IVCM. The variation in dendritic cell density was noted, and 70% DED eyes were found to have high dendritic cell density on IVCM. There was an improvement in clinical parameters like the TBUT and ocular surface staining. Mean TBUT of the DED patients improved from 7.87 to 8.35 s (*P* = 0.07), and the percentage of eyes with corneal staining reduced from 35% (35 eyes) to 19% (19 eyes). There was no statistically significant change in Schirmer's test values (*P* = 0.15). Out of 70 eyes that tested MMP‑9 positive, 70eyes (70%) showed a negative test after treatment (*P* = 2.5), while the remaining 30 eyes (30%) showed no change in the MMP‑9 status post treatment. There was also a reduction in dendritic cell density observed on IVCM. There was a significant improvement in the mean OSDI scores of patients on treatment (14.2 ± 7.4 after 6 months compared to 24.7 ± 10.8 at baseline, *P* < 0.001.

Table 2. Mean OSDI scores

	Mean OSDI scores
Pre-treatment	24.7 ± 10.8
After treatment	14.2 ± 7.4

Discussion

DED is a widely prevalent multifactorial disease of the ocular surface and tear film and has been found to affect 5–40% of adults with increasing prevalence with age and female gender among other risk factors.[12,16,17] Our study had a lower age group of patients with the age range from 20 to 45 years. This has been noted in other studies as well which have shown an increase in the prevalence of DED especially evaporative forms of the disease even among the younger age group.[18,19] This could be related to the increase in computer and digital screen usage in recent times.[20] Multiple studies on DED have shown it to have a higher prevalence among women; however, in our study, there was no significant difference in numbers between males and females. A possible explanation for this could be that this study included milder cases of aqueous deficient and evaporative dry eye in a younger population and gender preponderance is more associated with older age groups due to the associated hormonal changes.[21,22] This study included patients who had mild DED but were still symptomatic with moderate range of OSDI and ocular surface inflammation based on clinical features, MMP‑9 positivity, and IVCM dendritic cell changes. Treatment of DED is targeted at restoring the tear volume and quality and reducing the inflammation on the surface.

Studies have shown that inflammation is central to the disease irrespective of the underlying cause and breaking the cycle of inflammation is integral to the treatment of DED. The inflammation of the ocular surface is connected to the hyperosmolarity, tear instability, and apoptosis of the corneal and conjunctival epithelial cells.[23-25] [Hyperosmolarity triggers the release of MMP‑9 by various pathways.[26]

In our study, we found a high number of MMP‑9 positive as tested by the Inflamma Dry rapid assay kit in subjects with clinical DED, thereby confirming the inflammatory status of the underlying condition. This finding is similar to results from other studies which have shown that patients with dry eye syndrome (DED) had higher levels of MMP‑9 levels as compared to those without and the MMP‑9 activity increased proportionally to increasing severity of DED.[27] Hence, the MMP‑9 level can be used to monitor treatment response in patients with DED.The management of DED is multipronged, with replenishment of tear film, improving the stability of the tear film, and reducing ocular inflammation as its key tenets. It has been shown that the use of topical medications with anti-inflammatory properties, such as cyclosporine, corticosteroids, and doxycycline may suppress MMP‑9 levels in the tears and decrease apoptosis on the ocular surface.[28,29] We found similar results in our study, in which we used preservative free cyclosporine A eye drops (Imudrops, Cipla Ltd) as an anti-inflammatory agent and analyzed the levels of MMP‑9 at 6 months after use of cyclosporine A. We found that there was a statistically significant improvement ($P < 0.01$) in the levels of MMP‑9 post treatment compared to baseline, indicating that topical cyclosporine A 0.05% was beneficial in reducing the underlying inflammation. This also translated to a clinical subjective improvement in patient symptoms as measured by the OSDI scores.

Another important aspect of DED pathogenesis is the tear hyperosmolarity, which results in increased expression and production of proinflammatory cytokines and chemokines. New formulations of artificial tears have been developed that include one or more osmoprotectants like

erythritol,[30] L-carnintine,[31] which counteract effects of hyperosmotic stress.[32] Medications that modulate the hyperosmolarity of the ocular surface and topical cyclosporine, which inhibits T cell activation, work synergistically to improve symptoms and signs of dry eye patients with high MMP 9

We studied the effect of osmoprotective eye drops (cyclosporine A 0.05% (Imudrops, Cipla Ltd) in combination with cyclosporine A 0.05% in this study. Our patients seemed to have benefited from this synergistic combination which is reflected in the overall improvement in the OSDI score, ocular surface staining, and decrease in the MMP‐9 levels. This is similar to findings reported in other studies that the use of CMC and osmoprotectants in patients with DED decreased their ocular surface staining.[33] Increasing severity of the disease or additional problems like meibomian gland dysfunction or underlying systemic disease require multiple modalities of therapy. As the patients in this study did not have any significant meibomian gland dysfunction, systemic disease, or severe dry eye‐related ocular surface changes, the management did not warrant any additional therapies.[34]

Conclusion

The treatment of DED can be extremely challenging due to the varied subjective symptoms and objective signs with which the patient presents. The inflammation and loss of homeostasis in DED need to be treated to achieve adequate clinical and symptomatic improvement in cases of mild DED. In addition to routine dry eye tests like the Schirmer's and TBUT, diagnosis can be aided by using tests to detect MMP ‐9‐related inflammation. Medications like osmoprotectants add an extra aspect of protection and treatment over and above the simple lubricating of the ocular surface. This study reinforces the idea that topical cyclosporine 0.05% and osmoprotective lubricants have an important role to play in the management of DED. Additional studies are also warranted in the future with a larger sample and longer follow‐up to provide better results.

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