Efficacy of Using Topical Cyclosporine A (0˙05%) Eye Drops for the Treatment of Mild to Severe Dry Eye Disease

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Abstract

Introduction: Dry eye is a multifactorial disease of the tears and ocular surface, is highly prevalent and has a significant impact on quality of life. Long term use of Cyclosporine has demonstrated that this drug halt progression of chronic dry eye disease and is associated with a cure of signs and symptoms of Dry Eye disease. The aim of our study is to evaluate the efficacy of topical Cyclosporine A (0˙05%) for the treatment of mild, moderate and severe dry eye disease.

Methods: This prospective study was conducted in the ophthalmology department of Combined Military Hospital, Jashore from January 2019 to December 2019 among selected 20 patients aged 20-26 years with a confirmed diagnosis of dry eye syndrome refractory to conventional management. All the patients were treated with Cyclosporine A twice daily and were evaluated at month 1,2,3,4,5 and 6 for changes from base line in tear film break up time, schirmer test, fluorescein staining, tear meniscus height, symptoms of ocular discomfort and visual acuity.

Result: Mean age of 20 cases was 48.7 years among them 14(70%) female and 6(30%) male. Mean TBUT improved from 4.4 second to 8.7 second (p=0.001) after 6 months of treatment. SCHIRMER'S paper test was performed before the beginning of the treatment and showed improvement of wetting from mean 3.5mm to 8.2mm (p=0.001) after 6 month. Mean lower tear meniscus height improved from 0.2 mm to 0.63 mm (p=0.002) after 6 months of treatment. Fluorescein staining was significantly lowered from mean 2.8 to 1.8 (p=0.001) with significant reduction of ocular symptoms and improvement of visual acuity after 6 months of treatment.

Conclusion: Topical Cyclosporine A (0˙05%) has been demonstrated to be effective in all categories of dry eye disease. It reduces symptoms and signs of dry eye disease with the greatest improvement of signs in patients with severe dry eye disease.

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Introduction

Dry eye disease or keratoconjunctivitis sicca is a common, multifactorial symptomatic disease of the ocular surface involving the tear film and the reflex control of tear homeostasis that is associated with increased osmolarity of the tear film and ocular surface inflammation.[1]

Women are particularly affected after menopause because of hormonal status modification.[2] DED is associated with symptoms of ocular discomfort such as burning sensation, sense of dryness, foreign body sensation, ocular pain, photophobia, blurred vision, visual fatigue and sight threatening corneal complications in severe cases.[3]

Keratoconjunctivitis Sicca, is the most severe presentation of DED. Despite being common condition, dry eye syndrome is underdiagnosed. Clinically DES has been classified into two

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separate, overlapping categories; evaporative loss and aqueous deficiency.[4]

Pathogenesis of KCS has not been completely understood. Many clinical and pathological changes affecting the lacrimal glands and eyelids with resulting deficiency in the tear film whether caused by decreased lacrimation or excessive evaporation.[5]

Several factors have been identified in DED.Inflammation plays a major role with an increased expression of inflammatory markers, namely HLA-DR, intracellular adhesion molecules, inflammatory cytokines (IL-1, IL-6,IL-8), tumour necrosis factor and increased activity of metalloproteinases in the tear fluid.[6]

It has been demonstrated that not only inflammation but also apoptosis might play a role in the development of dry eye.[7]

Not only has inflammation been linked aqueous deficiency dry eye disease but also to that of evaporative loss. Accumulation of meibum within the meibomian gland can lead to inflammation of the gland and bacterial colonization. This colonizing bacteria produce free fatty acids and triglycerides, that alter the normal composition of the meibum. Most of the treatment modalities of DES depend on tear substitutes or tear preservatives.[8] Currently artificial tears are the most common initial approach used to relieve symptoms in patients with mild dry eyes. Unlike artificial tears, topical cyclosporine A (0.05%) works to restore the ocular surface, allowing increased production of tears presumably due to ocular inflammation that causes reduced tear production.[9]

In the normal situation, T-cell receptor activation leads to the influx of calcium (Ca^{+}) into the cytoplasm. Intracellular calcium binds the cytosolic protein calmodulin, which in turn binds and activates calcinuerin.

This calmodulin/calcineurin complex then dephosphorylates the transcription factor, nuclear factor of activated T cells (NFATc), which translocates into the nucleus and increases the activity of genes coding for IL-2 and other inflammatory cytokines. CsA exerts its action after it enters the cytoplasm of T cells and binds to cyclophilin. The CsA/cyclophilin complex affects T-cell activity by blocking the action of calcinuerin and preventing NFATc dephosphorylation. The subsequent reduction in IL-2 levels also reduces the function of effector T cells. CsA can also affect mitochondrial activity in some cells. In human conjunctival epithelial cells, the inflammatory mediators TNF-α and IFN-γ induce mitochondrial permeability transition pore (MPTP) opening upregulare Fas/FasL and caspase, and increase cell apoptosis. tCsA prevents epithelial cell death by blocking MPTP opening, Fas/FasL and caspase activation.[10]

In our randomized, prospective, clinical trials, topical cyclosporine (0˙05%) was shown to improve schirmer values and TBUT, reduced corneal staining, improve subjective symptoms and dependence on artificial tears.[11] The purpose of this study is to assess the effectiveness of cyclosporine eye drops (0.05%) in the treatment of patients with all varieties of dry eye.

Materials and Methods:

This prospective study was done at CMH, Jashore Cantonment from January 2019 to December 2019. Total 35 eyes of 20 patients with DED having age more than 20 years and visual acuity more than 6/9 were included in this study. Exclusion criteria were the presence of uncontrolled systemic disease, active ocular inflammation, known allergy or sensitivity to the study medications, pregnancy, previous

photorefractive surgery, abnormal lid position and contact lens wear. TBUT test was conducted by instilling a fluorescein drop in the eye. The patient was asked to blink several times, after which the tear film was examined with a broad beam cobalt-blue filter in slit lamp. After an interval of time, black spots or lines appeared in the fluorescein-stained film indicating formation of dry areas. The TBUT is the interval (s) between the last blink and the appearance of the first dry spot.

Schirmer's test was performed after the installation of local anesthetic agent (Schirmer-1). Then the filter paper was folded 5 mm from one end and inserted at the junction of middle and outer-third of the lower eyelid; the patient was asked to keep the eyes gently closed, and then after 5 min the filter paper was removed and the amount of wetting from the fold was measured in millimeters.

Corneal fluorescein staining was performed using a slit-lamp cobalt blue filter 1 minute after fluorescein was added to the tear film.

Detailed history was taken from all patients, including age, sex, previous medical and ocular diseases, and duration of symptoms. For all patients, routine ophthalmic examination was carried out. Slit-lamp biomicroscopy, Schirmer's test, and tear film break-up time (TBUT) test were conducted. Before the beginning of the treatment the patients were examined for ocular symptoms of dry eye. Data were collected using a specific data collection sheet and coded using Microsoft Excel 2013. The analysis was done using SPSS.

Result:

Total 35 eyes of 20 patients diagnosed with dry eye syndrome were included in this study.

Table -I: Distribution of patents by age and sex (n=20)

Age (years)	Frequency	Percentage
10-20	01	05
21-30	01	05
31-40	02	10
41-50	04	20
51-60	08	40
61-70	04	20
Sex		
Male	14	70
Female	06	30

The mean age of the patients was 48˙7 years (range 20-66 years). This study include 14 female (70%) and 6 male (30%) (Table–I).

Table-II: Systemic Disease of the study patients with severity (n=20)

Characteristic	Mild	Moderate	Severe
RA	0	0	9(45%)
DM	0	4(20%)	0
MGD	0	0	3(15%)
TAD	0	0	1(5%)
HZO	0	2(10%)	0
SJS	0	1(5%)	0

In our study we found 9 patients (18 eyes) had dry eyes due to systemic rheumatoid arthritis, 4 patients (8 eyes) had dry eyes due to diabetes mellitus, 3 patients (3 eyes) had dry eyes due to meibomian gland dysfunction, 2 patients (2 eyes) had dry eye due to herpes zoster ophthalmicus, 1 patient (2 eyes) had dry eye due to thyroid associated eye disease and 1 patient (2 eyes) had dry eye due to stevens johnson syndrome (Table-II).

Table-III: Pretreatment and post treatment data

Test	Before treatment	After treatment (6month)
TBUT (seconds)	4.4	8.7 (p=0.001)
Schirmer paper test (mm)	3.5	8.2 (p=0.001)
Lower tear meniscus height(mm)	0.2	0.6 (p=0.002)
Fluorescein staining score	2.8	1.8 (p=0.001)

The mean TBUT score was detected before the beginning of the treatment as 4.4 second and improved after 6 month of treatment to 8.7 second. The mean wetting of schirmer's paper tests score before the beginning of the treatment was 3.5 mm of the paper and improved after 6 month of treatment to 8.2. The mean lower tear meniscus height was detected before the beginning of the treatment as 0.2 mm and improved after 6 month of treatment to 0.6 mm. The fluorescein staining score was significantly lowered from mean 2.8 to 1.8 (Table-III).

Discussion

DES is a common disorder that is on the rise and is responsible for a significant impact on quality of life even in people with good vision and considered as a public health problem.[12,13] It is more prevalent in women and in patient with advancing age that correlates with the study done by Ozdemir M *et al.*[14]

The management of KCS involves two main approaches. The non-pharmacological approach includes eyelid hygiene, avoidance of exacerbating factors and punctal plugs in selected cases. The pharmacological approach includes artificial tears, oral antibiotics in selected cases, topical corticosteroids and tCsA. Several studies suggest that decrease in inflammation by blocking T-cell activation and improvements in ocular epithelial surface may result in better stimulation of the nerve endings in the cornea and conjunctiva by blinking.[15-16] Through its ability to modulate inflammation and improve the ocular epithelium, CsA may play a role normalizing neural signals to the lacrimal gland, in turn improving the quantity and quality of tear production.[17] Many studies reported a positive effect of CsA on the symptoms and signs of dry eye in patients with moderate to severe dry eye disease.[18-19]

It is difficult to directly compare these studies as many used different inclusion criteria in their definition of dry eye and different primary outcome measures. In a survey study completed with 5884 patients, one third of patients reported decreased symptoms severity by 1 week and two thirds by 3 weeks after treatment with cyclosporine.[20] Other factors that have found to improve with CsA treatment are goblet cell density, corneal sensitivity and tear meniscus height and volume.[21-23] The diagnosis of the dry eye begins with the patient history. Some diagnostic questionnaires are provided for the evaluation of the symptoms objectively and support the diagnosis of DES.

In our study 3 patients (15%) presented associated meibomitis and showed a good clinical improvement with tCsA. In a study by Rubin *et al*.[23] reported that tCsA should have a positive impact on meibomitis. With an improvement of the viscosity of the meibomian gland secretion, TBUT and schirmer score. In our study 4 patients (20%) presented associated with DM and all the cases showed a good clinical improvement with tCsA application with controlled blood sugar.

Moon *et al.*[24] treated 36 patients with moderate to severe dry eye with CsA four times a day for 6-8 weeks. After treatment, TBUT was significantly prolonged with greater increase in TBUT (p=0.02).This result is comparable to the present study, where TBUT increased from mean 4.4 second before treatment to mean 8.7 second after 6 months of treatment (p=0.001).

Haitham Y. Al-nashar *et al.*[25] treated 20 patients with dry eye disease with CsA two times a day for 3 months. After treatment schirmer paper test score was improved from 1.15±0.58 (mm) to 5.80±0.29 (mm) with p value 0.001. This result is comparable to the present study where mean schirmer value increased from 3.5 mm before

treatment to 8.2 mm after 6 months of treatment (p=0.001).

Wang J *et al*.[26] treated 14 patients with dry eye disease with CsA for 2 months. Tear meniscus height measurements were made by slit lamp biomicroscope. He found tear meniscus height significantly improved from baseline (p=0.003).This result is comparable to the present study where LTM height was improved significantly (p=0.002) compared with the baseline. In our study, the mean fluorescein staining scores at baseline was 2.8, which was significantly lowered to mean 1.8 (p=0.001) after 6 months of treatment. This result is comparable to Perry HD *et al.*[27] where they found beneficial effects in all categories of dry eye disease after treatment with tCsA.

Prabhasawat P *et al.*[28] studied 30 cases of Steven Johnson Syndrome patients who developed dry eyes. They were treated CsA (0.05%) eye drops twice daily for 6 months. They demonstrated significant improvement in dry eye symptoms, conjunctival injection, corneal staining, schirmer test and fluorescein clearance test ($p< 0.05$).

Overall in our series tCsA was well tolerated with few patients presenting few side effects. Interestingly this occurred only in a later period. This could be related to recovery of corneal sensation after tCsA treatment. I acknowledge few limitations to this study. First of all, the small size of the sample and the retrospective design of the study undertaken in one centre are real weakness. Secondly, a potential confounding factor is the common use of systemic treatments such as immunosuppressive drugs and hypoglycaemic drugs. Our aim was to assess the efficacy of tCsA treatment in improving ocular symptoms as well as ocular surface condition.

Conclusion

Dry eye is an important public health problem given its prevalence, morbidity and cost implications. Inflammation has been shown to play a role in dry eye, resulting in a reduced tear production. Several studies suggest that decreased inflammation and an improved epithelial surface may result in improved quantity and quality of tear production through normalization of the reflex control of tear homeostasis. Cyclosporine A (0˙05%) is the definitive treatment that targets an underlying pathological mechanism of chronic dry eye, immune mediated inflammation. tCsA treatment decrease the objective clinical signs of KCS and is associated in a long term perspective with an improvement of symptoms on everyday activities and a reduction of artificial tear use.

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