Topical Cyclosporine A 0.05% for the Treatment of Dry Eye Disease
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Abstract: Dry eye disease (DED) is a common clinical condition that challenges ophthalmologists. Topical Cyclosporine A is an anti-inflammatory therapy being approved by the Food and Drug Administration (FDA) for the therapy for DED. This study aimed to evaluate the efficacy and patient tolerability of topical Cyclosporine A 0.05% for the treatment of DED. A total of 87 patients diagnosed with DED were included in this study. Dry eye symptoms (foreign body sensation, burning, and pain) were scored. As a baseline measurement, the tear break-up time test (TBUT) and the Schirmer’s test were performed for all the patients. Cyclosporine A 0.05% was given topically twice daily to all the patients for four months. They were followed up every month for a period of four months. The clinical signs (Schirmer’s test, the TBUT), and the symptoms scores, were recorded for each visit. The mean age of the patients was 57.25±9.70 years (Range 32 - 80 years); 25 males (28.7%) and 62 females (71.3%). Out of them, 23 (26.4%) cases had Sjögren’s syndrome, and 12 (13.7%) cases had previous LASIK (laser in-situ keratomileusis). The symptoms score of the cases improved from (4.95±1.73) pretreatment to (0.40±.70) four months after treatment (P <0.001). The Schirmer’s test results improved from (4.10 ±1.089) pretreatment to (10.80±2.40) four months post-treatment (P <0.0001), and the TBUT test results improved from (5.54±1.77 s) pre-treatment to (12.95±3.12 s) four months post-treatment (P <0.0001). Only seven patients (8%) developed ocular side effects in the form of redness, pain, and systemic side effects in the form of headache. In conclusion, Cyclosporine A 0.05% eye drops is an effective treatment for DED, improving both signs and symptoms of DED with few ocular side effects.

Keywords: Cyclosporine A, Dry Eye Disease (DED), Anti-inflammatory

INTRODUCTION

Dry eye disease (DED) is a common clinical condition challenging ophthalmologists and affecting 14% to 33% of the population (Brewitt & Sistani, 2001; Pei-Yu et al., 2003; Schaumberg et al., 2003; Schein et al., 1997). The 2007 International Dry Eye Workshop (DEWS) updated the definition of dry eye disease to incorporate inflammation as an association with DED (Definition, 2007). The definition of dry eye disease was revised by (Craig et al., 2017) as follows:

“Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.” (P. 278)

DED was classified pathophysiologically into two overlapping groups; evaporative dry eye and aqueous deficient dry eye (Lemp et al., 2012). In DED, the tears variations initiate positive feedback of ocular surface inflammatory response, damaging the surface in

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which T-cell lymphocytes play a role (Definition, 2007; Javadi & Feizi, 2011). To interrupt the inflammatory cascade in the management of DED, the usual trend of using tear replacement therapy, punctal occlusion, and environmental control is now changing toward anti-inflammatory therapy like corticosteroids, tetracyclines, and cyclosporine (Javadi & Feizi, 2011; Kymionis et al., 2008). Cyclosporine is an anti-T-cell immunosuppressive drug used systematically to prevent rejection after organ transplantation (Barbarino et al., 2013). It has been reported that the anti-inflammatory effect of Cyclosporine improves Schirmer’s test results, increases the goblet cell number, with therapeutic benefits being achieved in about a month (Behrens et al., 2006; Phogat et al., 2019). Cyclosporine could be a better alternative to corticosteroids because of lacking steroid-related ocular side effects such as glaucoma and cataract (Phogat et al., 2019; Strong et al., 2005). Cyclosporine A (Restasis®) is approved by the Food and Drug Administration (FDA) for the therapy of DED (De Paiva et al., 2019).

This study aimed to assess the efficacy and patient tolerability of topical cyclosporine A 0.05% for the treatment of moderate to severe dry eye disease (DED).

MATERIALS AND METHODS

A prospective study was conducted at the Ophthalmology outpatient department in Benghazi/ Libya during a one-year period from January to December 2019; patients with dry eye disease of both genders were included. Written informed consent was obtained from the patients before their enrolment in the current study, which adhered to the tenets of the Declaration of Helsinki for research in human subjects.

Inclusion criteria: Patients aged ≥ 21 years presented to the outpatient department complaining of dry eye-related symptoms; burning, pain, or foreign body sensation were evaluated, including patients having DED associated with Sjögren’s syndrome or previous LASIK (laser in-situ keratomileusis), and those with a tear film break-up time ≤10 s, and Schirmer tear test with anesthesia ≤5 mm in 5 minutes were included. Schirmer’s test was done under topical anesthetic eye drops, by inserting the Schirmer strip into the lower conjunctival sac at the junction of the middle and outer third of the lower eyelid without touching the cornea, then informing the patient to keep the eyes gently closed. After 5 minutes, the strip was removed and the amount of wetting from the fold was measured (Li et al., 2012). For the tear break-up time test (TBUT); fluorescein strips were introduced into the conjunctival sac with minimal stimulation, the patient was asked to blink several times, then the tear film over the cornea was examined with a cobalt-blue filter. The time between the last blink and the appearance of a random dry spot was recorded in seconds as the tear film breakup time (Isreb et al., 2003). Grading the severity of the symptoms of burning, pain and a foreign body sensation was done for each symptom as follows: 0 (none), 1 for mild (occasional symptoms), 2 for moderate (frequent symptoms), and 3 for severe (constant symptoms), consequently, the total ocular symptoms were given a score from 0 to 9. The complete evaluation was based on both eyes’ examination. All patients were instructed to stop all topical eye drops for two weeks. Cyclosporine 0.05% (Restasis) eye drops were prescribed as monotherapy twice daily for four months, and the patients were instructed to keep in contact any time they feel any problem. The patients were followed up after the first, second, third, and fourth months. They were examined and scored for ocular symptoms, amount of wetting on Schirmer paper, and for the TBUT at each visit. Additionally, they were examined for any ocular side effects of the drug.

Exclusion criteria: Patients who were not willing to give consent, or unable to buy the drug due to its cost were excluded. In addi-
tion to patients with ocular surgery/trauma within the previous six months, patients with active lid margin inflammation, blepharitis, Meibomian gland disease, or ocular allergy, and any structural abnormalities on external eye examination e.g., entropion, trichiasis, lid scarring and many more, any systemic or topical medication other than artificial tears. Pregnant or lactating mothers and patients with a history of hypersensitivity to cyclosporine were also excluded.

**Statistical analysis:** Data were presented as frequencies and mean ±SD. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 23.0. The data were analyzed statistically for the treated eye or the mean data for both eyes (if the patient was given treatment for both eyes). A nonparametric paired-samples test (Wilcoxon signed-ranks) was used to statistically analyze the changes in the results of Schirmer’s test, TBUT tests, and the symptoms’ score after treatment with Cyclosporine A 0.05 %. *P*-values of 0.05 or less were considered statistically significant.

**RESULTS**

A total of 87 patients diagnosed with dry-eye syndrome were included in this study with a mean age of 57.25±9.70 (Range 32-80 years). There were 62 female cases (71.3%) and 25 males (28.7%). (tab.1)

| Age group (years) | No. of Females (% | No. of Males (% |
|------------------|------------------|------------------|
| 30-40            | 4 (4.6%)         | 0 (0%)          |
| 41-50            | 17 (19.5%)       | 3 (3.4%)        |
| 51-60            | 19 (21.8%)       | 9 (10.3%)       |
| 61-70            | 17 (19.5%)       | 9 (10.3%)       |
| 71-80            | 5 (5.7%)         | 4 (4.6%)        |
| Total            | 62 (71.3%)       | 25 (28.7%)      |

Table: (1). Showing demographic data of the patients included in the current study.

Out of the 87 patients, 52 (59.8%) patients only had dry eye with no other associations. 23 (26.4%) patients had DED associated with Sjögren’s syndrome, and 12 (13.7%) patients had previous LASIK.

There was a statistically significant difference (*Z* = -8.122, *p* < 0.0001) between Schirmer’s test results pretreatment compared to Schirmer’s test results four months after the initiation of the therapy.

Similarly, the TBUT test showed a statistically significant difference (*Z* = -8.110, *p* < 0.0001) of pretreatment results compared to the results 4 months after the initiation of the therapy.

The symptoms’ score showed a significant improvement (*Z* = -8.134, *p* < 0.0001) 4 months after the initiation of the therapy compared to the pretreatment score. The improvement in Schirmer’s test, TBUT test, and symptoms’ score results over four months of treatment are shown in table 2.

Only seven patients (8%) had ocular side effects in the form of redness, pain, and systemic side effect in the form of headache. Two of them discontinued the study.

**DISCUSSION**

The symptoms of DED affect the patient’s daily activities, so patients should be treated appropriately. The advancement in the understanding of the pathophysiology of DED and the inflammatory role in the reduction of tear film production led to the emergence of new therapeutic drugs (Definition, 2007; Stern et al., 1998).

Cyclosporine A is an immunomodulatory drug having anti-inflammatory properties (Barbarino et al., 2013; Matsuda & Koyasu, 2000). It improves tear production as measured by the Schirmer’s test, decreases elevated tear osmolarity (Sullivan et al., 2012), decreases the numbers of activated lymphocytes within the conjunctiva (Kunert et al., 2000), in addition to an increase in goblet cell density in the conjunctiva of subjects with DED.
The benefits of topical Cyclosporine A eye drops on DED are noticed both; subjectively by the improvement of symptoms and objectively as measured by Fluorescein staining tests, TBUT, and Schirmer's tests (Tuan et al., 2020).

Table: Showing pre-treatment and post-treatment (one, two, three and four months), Schirmer’s, TBUT, and symptoms’ score with respective P-values.

| Test parameter | Pre-treatment | One-month | Two-months | Three-months | Four-months | P-value |
|----------------|--------------|-----------|------------|-------------|-------------|---------|
| Schirmer’s test (mm) | 4.10±1.08 | 7.01±2.28 | 8.43±2.65 | 9.71±2.57 | 10.80±2.40 | < 0.0001 |
| TBUT (s) | 5.54±1.77 | 6.76±2.23 | 8.99±2.54 | 11.22±2.84 | 12.95±3.12 | < 0.0001 |
| Symptoms score | 4.95±1.73 | 2.49±1.75 | 1.74±1.12 | .83±.89 | 0.40±.70 | < 0.0001 |

P-values based on Wilcoxon signed-ranks test. TBUT (s) = Tear break up time test (seconds); SD = standard deviation

In the present study, the Schirmer’s test results improved from (4.10 ±1.089) pretreatment to (10.80±2.40) four months after the initiation of Cyclosporine A treatment (P<0.0001). The TBUT test results improved from (5.54±1.77s) pretreatment to (12.95±3.12s) four months post-treatment (P<0.0001). These results are comparable to the results of a study conducted by AL-Nashar (2015) on 35 eyes of 20 patients of DED, in which the Schirmer’s test results improved significantly (P = 0.001) from (1.15 ± 0.58) pretreatment to (5.86 ± 0.29 mm) 3months after treatment and the TBUT increased from (5.57 ± 1.36 s) before treatment to (9.9 ± 0.92 s) after 3 months of treatment (P = 0.001).

Another study was done by (Othman et al., 2018), who evaluated 32 cases of DED and yielded significant improvement in all the evaluated indices including TBUT and Schirmer’s test (P<0.0001), which were also similar to the present study.

Similarly, the significant improvement in the objective clinical signs in the present study was associated with a parallel improvement in the symptoms’ score of the patients, which changed from (4.95±1.73) pretreatment to (0.40±.70) four months after treatment (P<0.001). This is similar to a study done by Byun et al. on a large number of patients; (362 patients) with DED who were studied prospectively and treated with Cyclosporine A 0.05% for three months, they showed a significant reduction in all ocular symptoms scores from baseline values (Byun et al., 2011).

There is no detectable systemic absorption associated with the topical application of Cyclosporine A due to its low concentration and low solubility in water, resulting in less penetration into the bloodstream and no systemic side effects (Baudouin et al., 2017; Leonardi et al., 2016; Yavuz et al., 2012). However, few ocular side effects are reported. In the current study, only seven patients (8%) had ocular side effects, which are similar to the previous reports by (Al-Nashar, 2015; Phogat et al., 2019), but less than what was reported by other studies (Mah et al., 2012; Prabhasawat et al., 2013).

The present study shows the capability of Cyclosporine A in improving the signs and symptoms of DED with different etiology, supporting the hypothesis of the role of inflammation in the process of DED irrespective of the cause (Byun et al., 2011; Definition, 2007).

One of this study’s difficulties was that Cyclosporine A topical eye drops were not always...
available in pharmacies, in addition to its high cost, making its prescription to the patients occasionally limited.

CONCLUSION

Cyclosporine A eye drops improve both subjective symptoms and objective clinical parameters of DED. They are effective in the treatment of DED regardless of the etiology, with few ocular side effects.

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سيكلوسربورين آ الموضعي 0.05% لعلاج أمراض العين الجافة (DED)

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الملخص: مرض العين الجافة (DED) هو حالة سريرية شائعة تحدث لأطباء العيون. السيكلوسربورين آ الموضعي هو علاج مضاد للالتهابات ومراقبة ضعيفة للداء، وتحديداً للداء الجاف. تمت دراسة هذه الدراسة إلى تقييم فعالية السيكلوسربورين آ الموضعي 0.05% لعلاج داء DED. تم تضمين مجموعة من 87 مريضًا تم ترشيحهم بمرض DED في هذه الدراسة، وتم تسجيل أعراض جاف العين (الحساس بجسم غريب، والحرق، والألم) كقياس خط أساسي، تم إجراء اختبار وقت تفكك الدموع (TBUT)، وتحديد شكل العين. لمتم تقديم مستخدم وفيما بعد، وحقن عيني شهريًا لمدة أربعة أشهر. في كل زيارة تتم قياس الدراسات السريرية [اختبار شيرمر و (TBUT)]، وتسجيل درجات الأعراض. كان متوسط عمر المرضى 37.2 ± 9.2 سنة (المنحة 32-80 سنة) 25 ذكرًا (28.7%) و 62 أنثى (71.3%). كان هناك عدد 23 (26.4%) من الحالات مصابة بمرض أو SJögren’s Syndrome، و12 (13.7%) حالة لديها سابقة لزيت (التنفس القريبة بالليزر في الموقع). تحسنت درجة أعراض الحالات من (4.93 ± 4.73) قبل المعالجة إلى (4.0 ± 7.7) بعد 4 أشهر من العلاج (P < 0.001)، وتحسن نتائج اختبار شيرمر من (4.10 ± 0.89) إلى (5.84 ± 1.77) ثانية قبل المعالجة إلى (2.40 ± 1.08) ثانية بعد 4 أشهر من العلاج (P = 0.001). وتبينت نتائج اختبار TBUT تحسناً كبيراً جدًا بعد المعالجة إلى (2.71 ± 0.8) ثانية. أما عدد الحالات المحتملة، فإنها تمت كل من الأعراض، والعلامات السريرية الموضعية لـ DED، فهي تحسنت كل من الأعراض، والعلامات السريرية الموضعية 0.05% فعالة لعلاج DED، وتشمل كل من الأعراض، والعلامات السريرية الموضعية لـ DED، مع القليل من الأعراض الجانبية.

الكلمات المفتاحية: السيكلوسربورين آ، مرض جاف العين، مضاد الالتهاب.

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