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Ehabeldin Mohamed Magahwry Ahmed
Ophthalmology Department, Faculty of Medicine, Ain shams University, Cairo, Egypt

Corresponding Author:
Ehabeldin Mohamed Magahwry Ahmed
Ophthalmology Department, Faculty of Medicine, Ain shams University, Cairo, Egypt

Cyclosporine ophthalmic emulsion's efficacy and safety in moderate to severe dry eye patients: A randomized controlled trial

Ehabeldin Mohamed Magahwry Ahmed

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Abstract
Background: Moderate to severe dry eye disease (DED) is associated with significant pain, limitations in performing daily activities, reduced life quality, and often depression. This work aimed to evaluate the effectiveness and safety of cyclosporine A (CsA) ophthalmic emulsion in moderate to severe dry eye patients.
Methods: This controlled, randomized, double-blinded study was conducted on forty patients at least 18 years of age, both sexes, diagnosed with keratoconjunctivitis sicca, whether or not it was accompanied by Sjogren's syndrome. The patients were allocated to two equal groups: Group A: patients were treated twice daily with 0.1% cyclosporine A, and Group B: patients were treated twice daily with the vehicle in both eyes for 12 weeks.
Results: Oxford grading scale was significantly higher at 4w, 8w, 12w and 4w posttreatment in group A in comparison to group B ($p<0.05$). The Schirmer tear test was considerably higher at 4w posttreatment in group A compared to group B ($p<0.001$). The severity of superficial punctate keratitis was significantly lower at 4w, 8w, 12w and 4w posttreatment in group A than in group B. Visual analogue scale and ocular surface disease index were markedly lower at 4w, 8w, 12w and 4w posttreatment in group A in contrast to group B ($p<0.05$). Intraocular pressure, visual acuity and CsA were insignificantly different between both groups.
Conclusions: CsA 0.1% was effective as it substantially alleviated the ocular signs and symptoms of moderate-to-severe DED, it reduced the eye dryness score and reduced the disease's impact on vision-related activities. Additionally, it is well-tolerated and safe.

Keywords: Cyclosporine, ophthalmic emulsion, efficacy, safety, dry eye

Introduction

Dry eye disease (DED) is a multifactorial ocular surface disease that is characterized by a loss of tear film homeostasis and ocular symptoms. DED is caused by ocular surface inflammation and injury, neurosensory abnormalities, tear film instability, and hyperosmolarity [1, 2]. Worldwide surveys indicate that DED impacts 5%–50% of the population [3].

Moderate to severe DED is frequently accompanied by depression, considerable pain, limitations in daily activities, and a diminished quality of life. It has been demonstrated that ocular surface inflammation is a critical factor in the development of, as well as the propagation and downstream effects of DED [4, 5].

Management of DED is complicated by the self-perpetuating vicious cycle of ocular surface inflammation, hyperosmolarity, and tear film instability [6, 7]. DED can progress and worsen in severity without treatment, potentially resulting in permanent ocular injury and a greater refractoriness to treatment [8, 9].

The primary underlying pathophysiological component of chronic DED is ocular surface inflammation, which is not addressed by current treatment strategies. Nevertheless, the utilization of artificial tears to lubricate and hydrate the ocular surface is a prevalent method that offers only temporary symptomatic relief [10].

Cyclosporine A (CsA), an anti-inflammatory agent, has garnered increasing attention and investigation in recent years as a result of its substantial long-term advantages in moderate-to-severe DED [11]. Despite the fact that cyclosporine is not water-soluble, it is soluble in the water-free excipient perfluorobutylpentane (often abbreviated F4H5). This results in a transparent solution that is free of preservatives, surfactants, and lubricants. Cyclosporine is less soluble in a related compound, perfluorohexyloctane, which is already applied in the treatment of DED [12].

There are no significant adverse effects associated with CsA that are usually seen in corticosteroid-treated patients [13].
This research aims to evaluate the effectiveness and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye patients.

Patients and Methods

This randomized, controlled, double-blinded study was conducted on 40 patients (80 eyes) at least 18 years of age, both sexes, who were diagnosed with keratoconjunctivitis sicca, whether or not they also had Sjogren's syndrome, and were unable to respond to conventional treatment, admitted to Zagazig University Hospitals, Egypt. The trial was conducted from August 2023 to September 2024 following approval from the Zagazig University Hospitals. The patient's informed written permission was acquired.
Patients who were pregnant, lactating, or considering pregnancy were receiving concurrent treatment that could potentially complicate the interpretation of the study results, had any uncontrolled systemic disease or significant illness, or had any ocular disorder, including ocular injury, infection, non-dry eye ocular inflammation, trauma, or surgery within the previous six months, were excluded.

Randomization and blindness

A randomization program that is accessible online (http://www.randomizer.org) was utilized to produce random list, and the code of each patient was stored in a sealed envelope that was opaque. The patients were concurrently allocated to two equal categories in a parallel manner using a 1:1 allocation ratio: Group A: patients were treated twice daily with CsA (0.1%), and Group B: patients were treated twice daily with vehicle in both eyes for 12 weeks. Patients and investigators were blinded to the group of patients.
Initially, patients were required to undergo a two-week abstinence period during which they were halted from receiving any ongoing ophthalmic treatments. Patients used unpreserved artificial tears (AT) (saline solution, Larmabal®, Théa, Clermont-Ferrand, France) for use as frequently as required during the course of the study.

Protocol medications

The medications utilized in this investigation included unit dosage vials of unpreserved vehicle ophthalmic emulsion, refresh lubricant eye drops, and unit dose vials of unpreserved CsA 0.1%. Patients were advised to cease the use of all topical ophthalmic medications, with the exception of REFRESH, during the cessation phase. They were instructed to apply REFRESH to each eye at least four times per day, but not more than eight times. Patients who effectively completed the abstinence phase were subsequently instructed to administer their specified medication (CsA 0.1%, or emulsion vehicle) to both eyes twice daily (morning and evening) for 12 weeks. During the treatment phase, REFRESH was permissible to be administered to each eye up to eight times per day.
The efficacy measurements were determined by:

a) the variations in conjunctival staining using lissamine green dye, as per the Oxford grading scale. The total score was the sum of the score for the nasal and temporal regions, which were independently graded from 0 to 5 [12].
b) The nasal, temporal, pupil, and inferior locations of superficial punctate keratitis were assessed, and the scores were summed (each item is rated on a scale of 0 to 3, with 0 indicating no symptoms and 3 indicating severe symptoms).
c) Schirmer tear test (without anesthesia, with nasal stimulation as necessary to ascertain the patient's ability to secrete tears).
d) The dryness score was evaluated using a visual analogue scale (VAS), a patient-reported symptom index that ranges from 0 for minimal pain to 100 for maximal pain [12].
e) Ocular Surface Disease Index (OSDI) was employed to evaluate patient response to treatment. The objective of this global assessment parameter is to assess the symptoms of ocular irritation that are consistent with dry eye disease and their impact on vision-related activities. This parameter is formed by 12 questions. The inquiries encompassed three domains: environmental stimuli, ocular symptoms, and vision-related function. Each question was formulated in terms of frequency (e.g., what was the frequency with which they were aware of a symptom, how often they encountered difficulty with a specific task as a result of their symptoms, etc.) and was rated on a scale of 0 to 4 (where 0 represents "never" and 4 represents "always"). The composite OSDI score, which ranges from 0 to 100, was calculated by combining the patient responses to all responses (0 denotes the absence of disability, while 100 denotes complete disability) [14].

Whole blood was collected from all patients to assess CsA through levels at baseline, treatment weeks 4, 8, and 12, and posttreatment 4 weeks.
The safety of the treatment was evaluated through biomicroscopy, the measurement of CsA blood levels, conjunctival microbiology, intraocular pressure by applanation tonometry, and visual acuity by a 96% contrast Regan Letter Acuity Chart.
The primary outcome was VAS. The secondary outcomes were the Oxford grading scale, superficial punctate keratitis, Schirmer tear test, OSDI, biomicroscopy, Cyclosporin blood levels, conjunctival microbiology, intraocular pressure, visual acuity, and adverse events.

Sample Size Calculation

G*Power 3.1.9.2 (Universitat Kiel, Germany) was employed to calculate the sample size. We performed a pilot study (five cases in each category), and we discovered that the mean (± SD) of dryness score (VAS) at four weeks posttreatment (the primary outcome) was 32.4 ± 9.09 in group A and 39.8 ± 7.98 in group B. The following factors were taken into account when determining the sample size: a group ratio of 1:1, a 95% confidence level, a 95% power, and an effect size of 0.868. To address attrition, four eyes were added to each group. Consequently, we recruited 40 eyes in each group.

Statistical analysis

SPSS v27 (IBM©, Armonk, NY, USA) was employed to conduct statistical analysis. The Shapiro-Wilks test and histograms were employed to evaluate the normality of the data distribution. The quantitative parametric data, which were presented as mean and standard deviation (SD), were analyzed using the unpaired student t-test. The qualitative variables were presented as frequency (%), and the Chi-square test or Fisher's exact test was used to analyze them.

A two-tailed P value that was less than or equal 0.05 was considered statistically significant.

Results

In this study, 58 patients were assessed for eligibility, 11 patients did not meet the criteria, and seven patients refused to participate in the study. The remaining patients were randomly allocated into two equal groups (20 patients in each). All allocated patients were followed-up and analyzed statistically. Figure 1

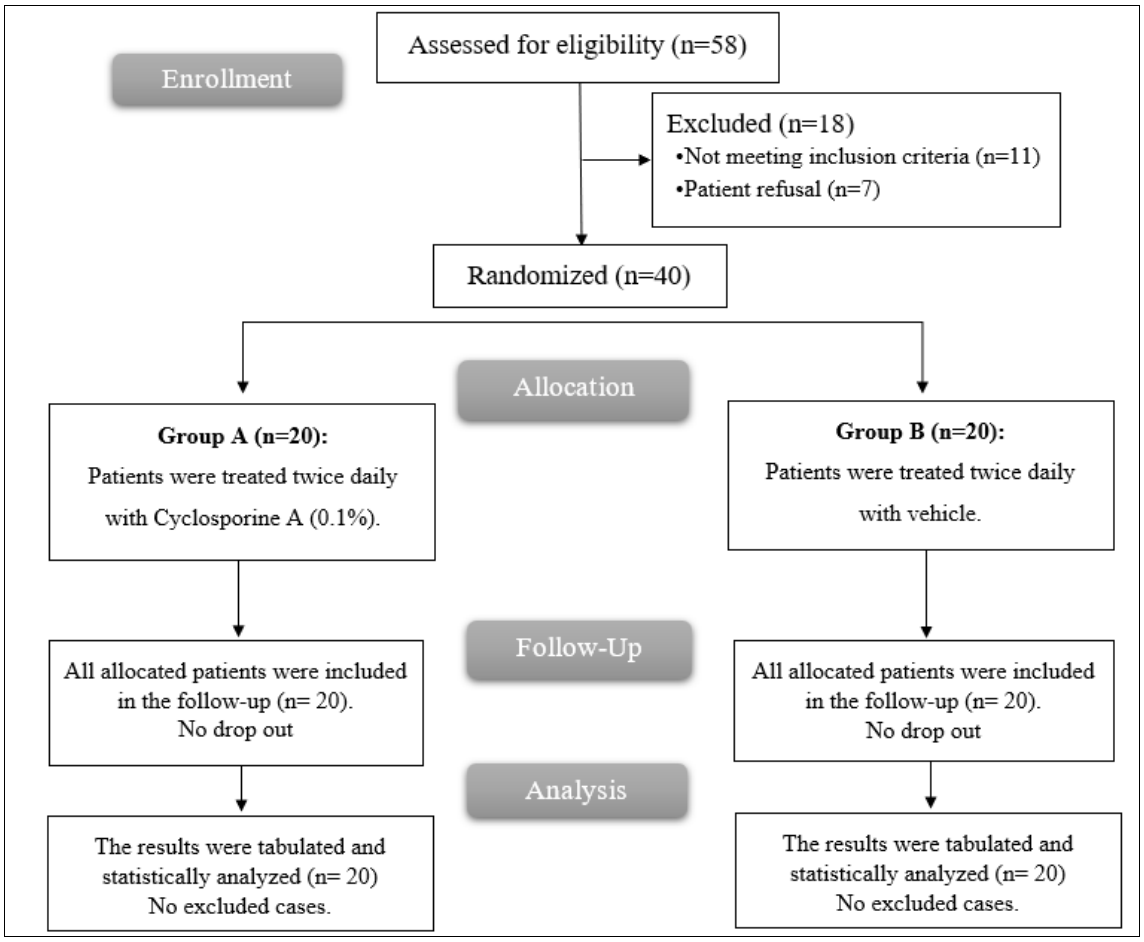

Fig 1: Consort flowchart of the enrolled patients

The two groups were comparable in terms of age, sex, Sjögren's syndrome, and the duration of disease. Table 1.

Table 1: Demographic data, Sjögren's syndrome and disease duration of the studied groups

		Group A (n=20 patients)	Group B (n=20 patients)	P value
Age (years)		48.3 ± 18.99	46.45 ± 14.82	0.733
Sex	Male	7 (35%)	9 (45%)	0.519
	Female	13 (65%)	11 (55%)	
Sjögren's syndrome		8 (40%)	7 (35%)	0.744
Disease duration (years)		9.9 ± 2.29	9.15 ± 2.13	0.291

Data was presented as mean ± SD or frequency (%).

Oxford grading scale showed no statistically significant difference between the two groups at the baselines and was significantly higher at 4w, 8w, 12w and 4w posttreatment in group A in comparison to group B (P<0.05). The Schirmer tear test was insignificantly different at baseline, 4w, 8w and 12w between both groups and was significantly higher at 4w posttreatment in group A compared to group B (P<0.001). Table 2.

Table 2: Oxford grading scale and Schirmer tear test of the studied groups

	Group A (n=40 eyes)	Group B (n=40 eyes)	P value
Oxford grading scale			
Baseline	3.9±1.32	3.75±1.35	0.617
4w	5.45±1.38	4.2±1.38	<0.001
8w	5.98±1.33	5.2±1.29	0.010
12w	6.38±1.43	5.5±1.62	0.012
4w posttreatment	7.03±1.62	5.13±1.42	<0.001
Schirmer tear test			
Baseline	2.77±0.21	2.8±0.29	0.693
4w	3.22±0.29	3.13±0.35	0.213
8w	3.46±0.4	3.39±0.32	0.425
12w	3.78±0.36	3.71±0.33	0.369
4w posttreatment	4.2±0.33	3.53±0.33	<0.001

Data was presented as mean ± SD.

Significant differences in the baseline levels of superficial punctate keratitis were not observed between the two groups. The severity of superficial punctate keratitis was significantly lower at 4w, 8w, 12w and 4w posttreatment in group A in contrast to group B (P<0.05). **Table 3**

Table 3: Superficial punctate keratitis of the studied groups

		Group A (n=40 eyes)	Group B (n=40 eyes)	P value
Baseline	None	0 (0%)	0 (0%)	0.648
	Mild	0 (0%)	0 (0%)	
	Moderate	23 (57.5%)	25 (62.5%)	
	Severe	17 (42.5%)	15 (37.5%)	
4w	None	0 (0%)	0 (0%)	0.005
	Mild	19 (47.5%)	6 (15%)	
	Moderate	17 (42.5%)	24 (60%)	
	Severe	4 (10%)	10 (25%)	
8w	None	5 (12.5%)	0 (0%)	<0.001
	Mild	22 (55%)	10 (25%)	
	Moderate	12 (30%)	23 (57.5%)	
	Severe	1 (2.5%)	7 (17.5%)	
12w	None	14 (35%)	0 (0%)	<0.001
	Mild	19 (47.5%)	14 (35%)	
	Moderate	7 (17.5%)	21 (52.5%)	
	Severe	0 (0%)	5 (12.5%)	
4w posttreatment	None	22 (55%)	2 (5%)	<0.001
	Mild	12 (30%)	15 (37.5%)	
	Moderate	6 (15%)	17 (42.5%)	
	Severe	0 (0%)	6 (15%)	

Data was presented as frequency (%).

Between the two groups, there was no statistically significant difference in terms of VAS and OSDI at the baseline and there was a substantial decrease at 4w, 8w, 12w and 4w posttreatment in group A than in group B (P <0.05). Table 4.

Table 4: VAS and OSDI of the studied groups

	Group A (n=40 eyes)	Group B (n=40 eyes)	P value
VAS			
Baseline	66.3±12.95	62.58±13.35	0.209
4w	52.03±13.38	58.33±13.46	0.039
8w	45.85±13.95	54.1±13.79	0.009
12w	39.23±13.63	48±13.74	0.005
4w posttreatment	30.43±11.78	50.15±13.58	<0.001
OSDI			
Baseline	39.3±3.78	40.35±5.17	0.303
4w	31.38±4.26	37.35±5.21	<0.001
8w	27.35±5.15	36.9±5.02	<0.001
12w	20.73±5.61	35.3±5.3	<0.001
4w posttreatment	12.5±6.01	33.53±5.58	<0.001

Data was presented as mean ± SD. VAS: Visual analogue scale. OSDI: Ocular surface disease index.

Intraocular pressure, visual acuity and CsA were insignificantly different at baseline, 4w, 8w, 12w and 4w posttreatment between both groups. Table 5.

Table 5: Intraocular pressure, visual acuity and Cyclosporin A blood level of the studied groups

	Group A (n=40 eyes)	Group B (n=40 eyes)	P value
Intraocular pressure			
Baseline	17.25±2.79	16.98±2.66	0.653
4w	17.3±2.78	17.05±2.68	0.684
8w	17.33±2.83	17.1±2.72	0.718
12w	17.4±2.84	17.15±2.81	0.693
4w posttreatment	17.45±2.94	17.2±2.87	0.701
Visual acuity			
Baseline	0.23±0.16	0.24±0.15	0.832
4w	0.23±0.16	0.24±0.15	0.777
8w	0.21±0.15	0.24±0.15	0.377
12w	0.18±0.15	0.23±0.15	0.186
4w posttreatment	0.15±0.15	0.22±0.15	0.041
Cyclosporin A blood level			
Baseline	191.68±35.02	195.65±30.94	0.592
4w	191.95±35.17	196.28±31.13	0.562
8w	192.15±35.61	195.6±31.3	0.647
12w	192.65±35.42	196.4±31.03	0.616
4w posttreatment	191.95±35.33	195.98±30.79	0.589

Data was presented as mean ± SD.

Ocular microflora was insignificantly different at baseline and at 12w between both groups. The two groups did not exhibit a statistically significant difference in the incidence of adverse events. Table 6.

Table 6: Ocular microflora and adverse events of the studied groups

		Group A (n=40 eyes)	Group B (n=40 eyes)	P value
Ocular microflora	At baseline	2 (10%)	1 (5%)	1
	At 12 w	3 (15%)	4 (20%)	1
Adverse events	Conjunctivitis	0 (0%)	1 (5%)	1
	Conjunctival hyperemia	1 (5%)	0 (0%)	1
	Burning eye	0 (0%)	1 (5%)	1
	Photophobia	0 (0%)	0 (0%)	---
	Visual disturbance	0 (0%)	1 (5%)	1
	Contact dermatitis	0 (0%)	1 (5%)	1
	Headache	1 (5%)	0 (0%)	1

Data was presented as frequency (%).

Discussion

In our study, the Oxford grading scale was significantly higher at 4w, 8w, 12w and 4w posttreatment in group A in contrast to group B. Schirmer tear test was markedly higher at 4w posttreatment in group A in comparison to group B. Superficial punctate keratitis was insignificantly different at baseline between both groups. The severity of superficial punctate keratitis was significantly lower at 4w, 8w, 12w and 4w posttreatment in group A in comparison to group B. In comparison to group B, the VAS (dryness score) was significantly reduced in group A at 4w, 8w, 12w, and 4w posttreatment.

Cyclosporine inhibits the activation of T-cells, which results in a reduction in dryness, which decreases inflammation in the tear-producing glands. This reduction in inflammation allows for increased tear production, which helps alleviate dry eye symptoms and improves the dryness score [15].

Cyclosporine helps reduce superficial punctate keratitis by decreasing inflammation on the ocular surface. It does this by inhibiting T-cell activation, which reduces immune-mediated damage to the corneal epithelial cells. This promotes healing of the corneal surface and improves symptoms associated with superficial punctate keratitis [16, 17].

This was consistent with Akpek *et al.* [12], who exhibited that the cyclosporine 0.1% group exhibited significantly greater changes in conjunctival staining from baseline than the vehicle group for the treatment of moderate to severe DED. However, there were no significant differences in the change from baseline in dryness score between the cyclosporine 0.1% and vehicle groups.

Similarly, Stevenson *et al.* [14] reported that the cyclosporine 0.1% group exhibited significantly greater alterations from baseline in superficial punctate keratitis and Schirmer tear test than the vehicle group. Moreover, Baudouin *et al.* [18] showed that the percentage of patients with ≥25% improvement in VAS was markedly more elevated with 0.1% cyclosporine than with vehicle. Furthermore, Chen *et al.* [13] demonstrated that the improvements in ocular dryness and the Schirmer test were substantially more significant with cyclosporine compared with the vehicle.

In contrast, Leonardi *et al.* [19] found that changes after 6m than baseline in the Schirmer tear test and VAS were insignificantly different between 0.1% CsA cationic emulsion and vehicle group in the management of severe DED.

In our results, OSDI was significantly lower at 4w, 8w, 12w and 4w posttreatment in group A than in group B. Intraocular pressure, visual acuity and CsA blood level were insignificantly different at baseline, 4w, 8w, 12w and 4w posttreatment between both groups.

Cyclosporine primarily targets the ocular surface to reduce inflammation and improve tear production without penetrating deeply into the eye. This localized action means it does not significantly affect visual acuity or intraocular pressure. Its mechanism is focused on the surface of the eye, leaving intraocular structures largely unaffected [20, 21].

This was agreed with Stevenson *et al.* [14], who demonstrated that OSDI could significantly reduce cyclosporine by 0.1% compared to the vehicle group. Also, they revealed that the cyclosporin group did not exhibit any significant differences in blood cyclosporin A concentrations at any visit. The comparison of the nadir whole blood CsA concentrations at the beginning and end of the treatment period demonstrated that there was no substantial accumulation of CsA after multiple ocular instillations for 12 weeks, and there was no significant change in visual acuity.

In contrast, Othman *et al.* [22] showed that visual acuity improved significantly in cyclosporine A than in the control group.

Our findings revealed that ocular microflora was insignificantly different at baseline and at 12w between both groups. The two groups did not exhibit a statistically significant difference in the incidence of adverse events.

Consistent with our results, Stevenson *et al.* [14] discovered no statistically significant difference between the vehicle and cyclosporine 0.1% groups regarding adverse events and change in ocular microflora from baseline to week 12. Also, Baudouin *et al.* [18] revealed that The cumulative incidence of adverse events did not exhibit a significant difference between the vehicle and cyclosporine 0.1% groups.

Limitations: The study was conducted in a single center, and the sample size was relatively small. Further studies are needed to compare different concentrations and doses of cyclosporine and to compare with other drugs.

Conclusions

CsA 0.1% was effective as it improved the ocular signs and symptoms of moderate-to-severe DED, the eye dehydration score was reduced, and the disease's effect on vision-related functioning decreased by CsA 0.1%, which was well tolerated and it considerably safe as it does not affect visual acuity or intraocular pressure and does not elevate cyclosporine blood level.

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