Randomised Controlled Trial

ANNALS OF MEDICINE & SURGERY

OPEN

Evaluation of cyclosporine 0.05% and artificial tears for the management of dry eye disease following cataract surgery: a randomized controlled trial

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Purpose: To compare the effects of cyclosporine 0.05% and artificial tears on dry eye disease following cataract surgery.
Methods: This prospective, double-masked, randomized clinical trial enroled 60 eyes of 60 eligible cataract patients who completed the study. Patients were randomized to receive either cyclosporine 0.05% or artificial tear four times daily for 1 month following cataract surgery. Clinical assessments included refraction, corrected distance visual acuity, tear break-up time (TBUT), Schirmer's test, and the visual analogue scale (VAS). An independent sample *t*-test was used to compare the means of the variables between the two groups.
Results: Mean patient age was 64.15 ± 9.17 (range, 45–90), of which 53% ($n = 32$) were female. There was no significant difference in mean age ($P = 0.308$) between the two groups. One month postoperatively, the cyclosporine 0.05% group had a significantly higher TBUT value ($P = 0.004$). Schirmer's result ($P = 0.095$) and the VAS questionnaire scores ($P = 0.374$) did not show a statistically significant difference between the two groups. There was no significant difference in the visual outcomes ($P > 0.05$).
Conclusion: Cyclosporine 0.05% was superior to artificial tears in improving tear stability after cataract surgery in the management of immediate postoperative dry eye. It may provide a more effective therapeutic option for the management of dry eye symptoms in the clinical setting.

Keywords: artificial tears, cataract surgery, cyclosporine, dry eye disease

Introduction

Dry eye disease (DED) is a complex ocular surface disorder that involves tear film imbalance, inflammation, neurosensory abnormalities, and ocular symptoms[1]. This disease can be as a secondary to medical and surgical procedures, such as systemic or topical medications, contact lens usage, and ocular surgeries, including refractive surgery or cataract surgery[2,3]. On the other hand, cataract is one of the main causes of preventable blindness worldwide[4], and cataract surgery is one of the most common ophthalmic procedures with a high success rate[5,6]. It can affect nerve responses, reduce lacrimation, and disrupt the natural tear film, which is crucial for maintaining a healthy ocular surface[7]. While cataracts are more prevalent in individuals over 65 years of age[8], the incidence of DED following cataract surgery remains unclear[9]. Evaluation of ocular parameters at the first month postoperatively is more important in predicting persistent DE symptoms after cataract surgery[10].

Even patients without pre-existing dry eye symptoms may develop DED within the first month after surgery[3]. Therefore, optimizing the ocular surface before and after cataract surgery is essential.

There are different options for managing dry eye, such as tear supplements, anti-inflammatory drugs, corticosteroids, dietary supplements (omega-3 fatty acids), and vitamin A[11]. Moreover, several topical medications have been used to treat dry eye. Topical cyclosporine 0.05% is a useful adjunct for the prevention

HIGHLIGHTS

- Cyclosporine 0.05% demonstrated superior efficacy in enhancing tear stability after cataract surgery compared to artificial tears.
- The potential efficacy of cyclosporine 0.05% in the management of immediate postoperative dry eye symptoms is suggested.
- Cyclosporine 0.05% appears to be a more effective therapeutic choice for the management of dry eye symptoms following cataract surgery.
- The study opens avenues for further research and exploration of cyclosporine 0.05% as a preferred treatment in the broader context of dry eye disease.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:1983–1988

Received 14 September 2023; Accepted 23 January 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 9 February 2024

http://dx.doi.org/10.1097/MS9.0000000000001795

and treatment of dry eye symptoms associated with cataract surgery[12]. Limited research suggests that cyclosporine 0.05% therapy may slow or prevent disease progression in patients with severe dry eye[13,14], without any inhibition of wound healing, causing any adverse changes in the lens, and any systemic adverse effects[15].

Although its effectiveness in treating different types of DED is unclear[16]. Artificial tears are other supplements recommended to relieve symptoms after cataract surgery[17,18]. These products maintain ocular surface lubrication and hydration. Artificial tears are typically considered the first-line medication for DED[19]. However, in cases that do not improve with artificial tear supplements, antibiotics, and anti-inflammatory medications may be considered as alternatives[20].

Topical cyclosporine acts as an immunomodulatory and anti-inflammatory drug by interacting with T cells and inhibiting lymphocyte proliferation[21]. Studies have confirmed increased goblet cell numbers in patients treated with topical cyclosporine[22]. Although goblet cell protection with cyclosporine may provide a healthy ocular surface, cyclosporine has been shown to improve dry eye symptoms by restoring tear film balance in dry eye patients[23].

Previous studies have determined different management strategies for dry eyes using cyclosporine 0.05% or artificial tears. However, direct comparisons of the clinical efficacy of cyclosporine in enhancing tear secretion and artificial tears in increasing tear volume for the treatment of dry eye after cataract surgery have rarely been reported. The purpose of this study was to compare the therapeutic effects of cyclosporine 0.05% and artificial tears in relieving dry eye symptoms after cataract surgery.

Methods

This prospective double-masked clinical trial adhered to the CONSORT statement (CONSORT 2010 Checklist, Supplemental Digital Content 1, http://links.lww.com/MS9/A373), and was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1400.10443). The study protocol followed the guideline of the Declaration of Helsinki and registered at Iran Registry of Clinical Trials (http://www.irct.ir) with IRCT20211227053548N1 registration number All participants provided written informed consent prior to enrolment by an examiner blinded to the drug type.

Participants

The study was conducted at the Bu-Ali Sina Hospital, Sari, Iran between June 2020 and May 2021. Based on eligible criteria, 60 cataract surgery candidates completed the trial and were assigned to 2 intervention arms. The target sample size of 30 participants per arm was calculated based on 80% power at a two-tailed significance level of 0.05.

Patients aged more than 45 years who were diagnosed with cataract by an ophthalmologist were included in the study. Patients with a history of dry eye or ocular allergies, any ocular disease, connective tissue disorders, uncontrolled systemic diseases, specific drugs that may cause DED, such as anti-glaucoma drugs, and pregnancy were excluded. Also, patients who had complications during or after cataract surgery such as endophthalmitis, intraocular lens displacement, keratopathy, macular oedema, and retinal detachment were excluded from the study.

Randomization

All patients were randomly assigned to two intervention arms based on a random list with an independent examiner (M.J.). A 1:1 allocation ratio was used to randomize participants to 1 of the 2 arms. A drop of topical cyclosporine 0.05% (Lacrosporin, Sina Darou Co.) was instilled in the first group, and patients in the second group received one drop of artificial tear with 0.3 g hydroxypropyl methylcellulose and 0.1 g of dextran (TearLose, Sina Darou Co.) in the operated eyes. A unique randomization code (from 01 to 060) was used for drug labelling. Eligible patients were enroled sequentially by a masked research optometrist (Z.H.) who dispensed the investigational product labelled with the appropriate code. Examiners and patients were blinded to the choice of medication.

Examinations and surgical method

Routine ophthalmic examinations including Slit-lamp biomicroscopy, fundoscopy, manifest refraction, corrected distance visual acuity (CDVA), and uncorrected distance visual acuity (UCDVA) measurement using the Snellen E chart, were performed for all participants. All cataract procedures were performed by the same surgeon (H.A.) and involved topical anaesthesia and a 2.75 mm clear corneal incision. The anterior chamber was filled with a dispersive viscoelastic substance (specifically, hydroxypropyl methylcellulose from Easy Visc). Following a continuous curvilinear capsulorhexis, hydro dissection, and hydro delineation were carried out and a side-port entrance was made. The nucleus was removed using the "stop and chop" technique (Sovereign Compact, Phacoemulsification System, AMO), and the cortex was aspirated with coaxial irrigation/aspiration. The capsular bag was then filled with a cohesive viscoelastic substance (Sodium Hyaluronate 1.6, Easyluron), and a foldable monofocal posterior chamber intraocular lens (IOL) (Acriva, VSY) was implanted into the capsular bag using an injector system. The viscoelastic material was fully aspirated and the entrances were closed using stromal hydration[24].

Postoperative protocol

The fixed regimen in both groups included steroid eye drops (0.1% betamethasone as a tapering dose from 8 times a day for 4 weeks) and antibiotic eye drops (chloramphenicol 6 times a day for 10 days). One group received cyclosporine 0.05% drops four times daily for four weeks, while the other group used artificial tear drops four times daily for the same duration. All patients were examined 1 month after surgery and CDVA, UCDVA, and spherical equivalent were measured. A visual analogue scale (VAS) was used to assess the degree of ocular discomforts such as tearing, foreign body sensation, blurred vision, and photophobia. It is a reliable technique for the quantitative assessment of dry eye symptoms[25]. Patients responded to this standard questionnaire in the first month after surgery. Based on their answers, they were given a score from zero (no discomfort) to 10 (most discomfort). The scores were given subjectively by an experienced examiner, and both the patient and the examiner were masked to the choice of medication administered. In addition, the tear break-up time (TBUT) test was performed using fluorescein stain corneal paper to measure the duration of the appearance of the dry spots. A duration of more than 10 s was considered normal, whereas a duration of less than 5 s indicated DED. The Schirmer test was

Table 1

Comparison of the frequency (percentage) of cataract types in studied groups

Cataract types	Artificial tear ($n=30$), n (%)	Cyclosporine 0.05% ($n=30$), n (%)	P
NS + 2	7 (63.6)	4 (36.4)	0.100
NS + 3	7 (35.0)	13 (65.0)	
NS + 4	4 (36.4)	7 (63.6)	
PSC + 2	2 (40)	3 (60)	
PSC + 3	6 (75.0)	2 (25.0)	
CC + 2	0	1 (100)	
MATURE	4 (100)	0	

CC, cortical cataract; NS, nuclear sclerotic cataract; PSC, posterior subcapsular cataracts.

also used to assess DED in both groups. A Schirmer strip (OptiTech Co.) was placed in the outer 1/3 of the palpebral conjunctiva for 5 min, and the length of the absorbed moisture was measured. A length of more than 15 mm was considered normal, whereas a length of less than 10 mm indicated DED.

Statistical analysis

The data were analyzed using SPSS software version 23. Descriptive statistics, such as the mean and standard deviation, were used to describe the characteristics of the study population. The Kolmogorov–Smirnov test was used to assess the normality of the continuous variables. An independent samples t-test was used to compare the means of the continuous variables between the two groups. The Mann–Whitney test was used to compare the means of variables that did not meet the criteria for normal distribution. The $\chi 2$ test was used to compare categorical variables. A P value less than 0.05 was considered statistically significant.

Results

Participants

Of 78 potential participants screened for eligibility, 66 met the eligibility criteria and enroled in the clinical trial; 60 completed the study. Of the 6 participants who did not complete the study, 3 were from the cyclosporine group; 1 discontinued after 5 days because of keratopathy, and 2 participants were lost to follow-up for up to day 30. One participant in the artificial tear group withdrew from the study on day 3 due to postoperative endophthalmitis, and 2 participants were lost to follow-up for up to 30 days (Figure S1, Supplemental Digital Content 2, http://links.lww.com/MS9/A374).

Primary outcomes

Data from 60 patients (60 eyes) with a mean age of 64.15 ± 9.17 (range, 45–90) years, of whom 53% ($n=32$) were female, were analyzed. There was no significant difference between the two groups in terms of mean age ($P=0.308$). The different types of cataract at baseline are presented in Table 1.

The means of clinical tear test results are shown in Table 2. The mean value of TBUT was significantly higher in the cyclosporine 0.05% group than in the artificial tear group ($P=0.004$). However, the mean Schirmer's value was not significantly different between the two groups ($P=0.095$). The assessments with subjective VAS questionnaire determined no difference between the two groups ($P=0.374$). The results of the clinical trial of cyclosporine 0.05% and the artificial tear are shown in Figure 1. The analysis was performed with adjustments based on the type of cataract, age, and sex, and no significant difference was observed in clinical tear test between the cyclosporine 0.05% and artificial tear groups ($P>0.05$).

Table 2

Clinical test results in studied groups 4 weeks after cataract surgery

	Artificial tear ($n=30$)	Cyclosporine 0.05% ($n=30$)	P
Primary outcome measures			
TBUT (s)	9.50 ± 4.25	13.56 ± 6.0	0.004*
Schirmer (mm)	8.26 ± 3.37	7.12 ± 3.16	0.095
Visual analogue score	0.83 ± 0.874	1.13 ± 1.61	0.374
Secondary outcome measures			
UCDVA (LogMAR)	0.13 ± 0.19	0.18 ± 0.25	0.215
CDVA (LogMAR)	0.05 ± 0.13	0.10 ± 0.14	0.425
SE (Dioptres)	− 0.36 ± 0.68	− 0.39 ± 0.76	0.603

Data are reported as mean ± standard error of the mean.
CDVA, corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; SE, spherical equivalent; TBUT, Tear break-up time; UCDVA, uncorrected visual acuity.
*P values <0.05 represent a statistically significant difference.

Secondary outcomes

There were no statistically significant differences in mean CDVA, and UCDVA between eyes randomized to receive cyclosporine 0.05% and eyes randomized to receive artificial tears before and after surgery (all $P>0.05$). The mean spherical equivalent (SE) before ($P=0.734$) and after ($P=0.603$) cataract surgery was not different between the two groups.

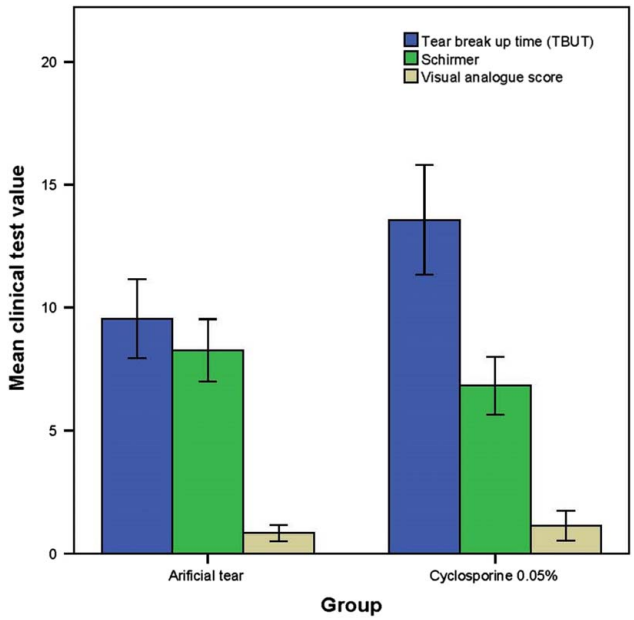

Figure 1. Mean clinical test values 4 weeks after cataract surgery in the two study groups (error bars indicate 95% CIs).

Discussion

Dry eye is a common complication of cataract surgery, and the outcomes of the surgery can be improved by reducing the symptoms of dryness[26]. However, the treatment of dry eye remains challenging because of the weak correlation between symptoms and its condition[27]. One month after cataract surgery, more eyes with ocular surface damage and dry eye appeared at a peak in more patients[28].

In this study, an investigation of the clinical parameters at 1 month postoperatively showed that tear film quality improved after cyclosporine 0.05% therapy. In dry eye disease, the immune system plays a role in the chronic inflammation of the ocular surface. Cyclosporine suppresses the activation of T cells involved in the inflammatory response[4]. Specifically, it inhibits the production of pro-inflammatory cytokines and helps to maintain a more stable tear film. This anti-inflammatory effect contributes to a reduction in symptoms associated with dry eye and supports the function of the lacrimal glands, helping to improve tear production and the overall health of the ocular surface. In addition, some studies have reported that cyclosporine 0.05%, by reducing ocular aberrations[29] and increasing contrast sensitivity[30], leads to better visual acuity during long-term follow-up. However, in the present study, the visual quality showed no significant difference between the two groups at 1-month follow-up. These differences may be related to the length of follow-up and the samples analyzed. In the current study, the longer TBUT in eyes that were treated with cyclosporine 0.05% suggests that topical cyclosporine 0.05% has better effects in reducing dry eye after cataract surgery than artificial tears. In line with our results, Kang *et al.*[31] found a significant improvement in the TBUT score in subjects who received treatment with cyclosporine 0.05% compared with the group treated with 0.5% carboxymethylcellulose. Furthermore, in patients treated with topical lubricants and cyclosporine 0.05%, Ganesh *et al.*[7] showed an improvement in tear osmolarity, TBUT, and Schirmer test results after 3 months of follow-up. In addition, Chung *et al.*[4] reported an increase in TBUT in the cyclosporine 0.05% group compared to the 0.9% sodium chloride group at 2 and 3 months after cataract surgery. In contrast, Park *et al.*[32] reported that Schirmer test scores in the 0.15% sodium hyaluronate artificial tear group had a significant improvement compared with the cyclosporine 0.05% group after 12 weeks of treatment in patients with dry eye ($P < 0.05$). The artificial tear with sodium hyaluronate in a previous study differed from the artificial tear with hydroxypropyl methylcellulose (TearLose) in our study, which may have affected the results. Another study found that both TBUT and Schirmer tests showed significant improvement in the cyclosporine 0.05% group[4]. On the other hand, Kudyar *et al.*[17] found that combined treatment with both cyclosporine 0.1% and artificial tears 0.5% was more effective than artificial tears alone in dry eye after cataract surgery. In this study, we did not evaluate combination therapy for the treatment of dry eye conditions.

In the present study, the Schirmer test results in the artificial tear group were not significantly different from those in the cyclosporine 0.05% group. The Schirmer test measures the tear volume and function of the main lacrimal gland[33], and more patients had the same tear quantity after surgery. Similarly, Kim *et al.*[34] found no significant changes in the Schirmer test scores. In contrast, a study reported that the Schirmer test had a higher value in the cyclosporine 0.05% group compared to the normal saline 0.9% at 3 months[4]. However, another study showed a significant improvement in Schirmer scores in both the cyclosporine 0.05% and antioxidant groups compared with the artificial tear control group[35]. This difference may be due to the difference in the time of tear measurement, the patients' follow-up duration, or the disease severity.

In the current study, the mean VAS scores were similar in both groups after cataract surgery. Ganesh *et al.*[7] reported the mean subjective questionnaire score was reported to be better in eyes receiving combined cyclosporine 0.05% and lubricant had a better score ($P = 0.031$), whereas it did not differ in the lubricant group. Other studies found that the ocular surface disease index (OSDI) questionnaire showed no significant difference between cyclosporine 0.05% and normal saline 9% ($P = 0.93$)[4] and also between cyclosporine 0.05% and carboxymethylcellulose ($P = 0.17$)[12]. These different results may be related to the use of different questionnaires in different populations.

Although some studies reported that artificial tear carboxymethylcellulose (CMC) 0.5% may have better function than steroids and NSAIDs for decreasing the DED symptoms[36], and ocular surface may be protected with an antioxidant lubricant[37], another study found that diquafosol may be more effective than cyclosporine 0.05% in increasing tear secretion with higher TBUT values at 1 and 3 months[29]. Cyclosporine 0.05% eye drops in combination with 0.3% sodium hyaluronate eye drops may also optimize ocular symptoms in patients with dry eye after cataract surgery[38]. The use of cyclosporine in the postoperative regimen is beneficial. The anti-inflammatory effects may help to reduce postoperative dryness and lead to ocular comfort.

The limitations of this study are related to the short follow-up period and the small sample size. However, the study followed the guidelines of the CONSORT statement, which minimized the main potential sources of bias and increased the internal validity of the study.

Conclusion

This study demonstrates the beneficial effect of cyclosporine in reducing dry eye symptoms after cataract surgery due to its anti-inflammatory properties and improvement in tear secretion. Our findings suggest that cyclosporine may have additional benefits over artificial tears, particularly an improvement in TBUT and its potential to improve tear film stability. Further investigation of the therapeutic potential of cyclosporine and artificial tears for the treatment of DED is warranted with a larger multicenter clinical trial over a longer treatment period to confirm its long-term efficacy.

Ethical approval

The Ethics Committee of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.REC.1400.10443).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contribution

H.A: conceptualization, methodology, clinical studies, supervision, and project administration; S.T: clinical studies, experimental studies, data acquisition, and draft preparation; M.J and A.A: literature search, clinical studies, and writing original draft preparation; Z.H: Design, methodology, literature search, clinical studies, statistical analysis, manuscript editing, review, and supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

The study registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with IRCT20211227053548N1 registration number.

Guarantor

The corresponding author (Z.H.) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Data availability statement

The data are available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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