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Original Article

The Effect of Topical Cyclosporine 0.05% on Dry Eye after Cataract Surgery

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Purpose: To evaluate the effectiveness of cyclosporine 0.05% for dry eye after cataract surgery.

Methods: Thirty-two newly diagnosed patients with dry eye syndrome 1 week after cataract surgery received a twice-daily treatment of cyclosporine 0.05% for one eye and normal saline 0.9% for the other. Disease severity was measured at 2 weeks, 1 month, 2 months, and 3 months by Schirmer test I (ST-I), tear film break-up time (tBUT), corneal temperature and dry eye symptom questionnaire (Ocular Surface Disease Index).

Results: Both groups increased in ST-I and tBUT over time. ST-I in the cyclosporine 0.05% group showed a significant increase at 3 months and tBUT in the cyclosporine 0.05% group showed an increase at 2 and 3 months. The dry eye symptom score was significantly reduced in the cyclosporine 0.05% group.

Conclusions: Cyclosporine 0.05% can also be an effective treatment for dry eye after cataract surgery.

Key Words: Cataract surgery, Cyclosporine, Dry eye syndromes

Cataract surgery is one of the most common ophthalmologic procedures and has a high rate of success. Postoperative complaints of dry eye symptoms may occur, including ocular soreness, pain, burning sensation and foreign body sensation [1-3]. Studies suggest that cataract surgery can lead to the presentation of dry eye signs and symptoms by a change in the ocular surface environment or there may be a pre-existing condition not recognized by the patient or physician [1-3].

Cyclosporine 0.05% is a topical immunomodulatory compound with inflammatory properties that have been demonstrated to have a benefit in the treatment of dry eye [4-6]. Many clinical studies revealed good results in topical cyclosporine 0.05% treatment for dry eye syndrome through the modulation of ocular surface inflammation.

However, no studies have been published regarding the use of cyclosporine 0.05% to control dry eye symptoms or to treat inflammatory ocular surface as a consequence of cataract surgery. The efficacy and safety of cyclosporine 0.05% has been demonstrated for dry eye syndrome.

In our study, we evaluated the effectiveness of the treatment of newly developed dry eye after cataract surgery by analyzing changes in Schirmer test I (ST-I), tear film break-up time (tBUT), corneal temperature, and symptom severity scores before and after cyclosporine 0.05% use (Restasis; Allergan Inc., Irvine, CA, USA).

Materials and Methods

This study was started under the permission of the institutional review board of the Catholic Medical Center Office of the Human Research Protection Program (permission no. SC08MISI0119). From April 2010 to November 2010, patients that had been recommended for bilateral cataract surgery were invited to participate in the trial after obtaining informed consent. Their medical records were analyzed prospectively. Inclusion criteria included age >50 years, diagnosis of bilateral phacoemulsification with completed implantation of posterior chamber intraocular lens, and a visual potential of 20 / 25 or better. Exclusion criteria included history of a primary condition that could cause dry eye such as a pterygium, dellen, previous refractive surgery, and systemic connective tissue disease. Exclusion

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criteria also included active ocular disease, uncontrolled systemic disease, a history of ocular allergic disease, prior refractive surgery, ocular surgery, or prior use of topical cyclosporine. We also excluded any patient who had been diagnosed with dry eye syndrome by ST-I <10 mm or tBUT <10 seconds, or those with meibomian gland disease. Based on the inclusion and exclusion criteria, we screened 88 patients.

Baseline measurements included ST-I, tBUT, and administration of a dry eye symptom questionnaire (Ocular Surface Disease Index, OSDI). Schirmer test was evaluated without corneal anesthesia (STI –I) and was performed only once. Tear film stability was assessed by placing a fluorescein-impregnated strip in the inferior fornix, instructing the patient to blink several times, and recording the time required for the tear film to break up. This test was calculated from the average time of 3 trials. The time interval between ST-I and tBUT was at least 10 minutes. Corneal temperature was measured using touch type thermometer with the tip touching the corneal center under topical anesthesia.

We quantified the intensity of dry eye symptoms from 0 to 4 as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. The frequency of dry eye symptoms was quantified as follows: 0 = none, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time. The aggravation of dry eye (when blink frequency is reduced such as while watching TV, using computer monitors, or driving) was quantified as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. The dry eye symptom score was calculated as follows: (intensity score + frequency score + aggravation score) / (number of patients responding to the question). Scores ranged from 0 to 4, with higher scores indicating more severe symptoms.

Surgical procedure

At the time of cataract surgery, a 3.0-mm-sized corneal incision was made at the temporal location. A standard phacoemulsification technique was done with topical anesthesia with proparacaine (Alcaine; Alcon-Couvreur, Puurs, Belgium). A foldable acrylic intraocular lens was implanted in the capsular bag. There was no suture at the incision site. Patients used gatifloxacin (Gatiflo; Handok, Seoul, Korea) and remexolone (Vexol; Alcon, Fort Worth, TX, USA) four times a day after surgery.

At 1 week postoperative, we performed an initial evaluation by measuring ST-I, tBUT, corneal temperature and the results of a dry eye symptom questionnaire (OSDI). Thirty-two patients were diagnosed with dry eye syndrome (ST-I <10 mm or tBUT <10 seconds) and were enrolled in our study.

Each patient was randomized to receive cyclosporine 0.05% in one eye and normal saline 0.9% as a placebo in the other eye two times a day for 3 months from the initial evaluation. We provided cyclosporine 0.05% in vials after removing the tray, and normal saline 0.9% in bottles. We explained to the patients that the difference was for preventing confusion (for example, vials for right eye and bottles for left eye). We cut and removed tips of vials which had the Restasis logo, in order to disguise the liquid.

A blinded examiner measured ST-I, tBUT, corneal temperature and administered the dry eye symptom questionnaire at 2 weeks, 1 month, 2 months and 3 months. Data were analyzed by paired *t*-test using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) with a *p*-value of <0.05 considered statistically significant.

Results

Thirty-two patients qualified and completed all study procedures. There were no protocol violations. The mean observation period was 3.4 ± 0.8 months. Table 1 shows the changes in ST-I, tBUT and dry eye symptom score (OSDI) between the preoperative state (before surgery) and the initial evaluation (postoperative 1 week). There was a significant decrease in ST-I and tBUT and a significant increase in dry eye symptoms. Table 2 reveals the patient characteristics for the eye treated with cyclosporine 0.05% and the eye treated with normal saline 0.9%. There were no significant differences in ST-I, tBUT, or symptom severity scores between the two groups. Fig. 1 demonstrates the changes of ST-I over time. Although both groups revealed significant improvement in the Schirmer test at 3 months versus the initial evaluation ($p < 0.01$, $p = 0.01$, respectively), there was significant difference at 3 months in the cyclosporine 0.05% group versus the normal saline 0.9% group ($p = 0.02$). There was significant improvement in the tear break-up time after treatment with cyclosporine 0.05% starting at 1 month and further increases were seen at 2 and 3 months ($p = 0.04$, $p < 0.01$, respectively). On the other hand, normal saline 0.9% treatment led to less improvement over time (Fig. 2). There was no difference in corneal temperature between the two groups throughout the 3 months (Fig. 3).

All OSDI scores (symptom intensity, frequency and aggravation) revealed decreasing patterns throughout the observation period in both groups except at 2 weeks in the cyclosporine 0.05% group (Fig. 4). In single analysis, the cyclosporine 0.05% group showed a significant improvement for each score at 3 months ($p < 0.01$, $p = 0.01$, $p = 0.02$, respectively). A transient and insignificant increase of the score for symptom aggravation was shown at 2 weeks ($p = 0.18$).

Table 1. Comparison of ST-I, tBUT and the dry eye symptom score (OSDI) between the preoperative state (before surgery) and the initial evaluation (postoperative 1 week)

	Preoperative state before surgery	Initial evaluation at postoperative 1 week	*p*-value
Age (yr)	68.3 ± 6 (60-84)		
ST-I (mm)	17.2 ± 6.4 (14.0-26.5)	8.0 ± 4.9 (0-17.0)	<0.01
tBUT (sec)	11.8 ± 2.2 (10.0-13.0)	7.7 ± 2.0 (5.0-11.0)	<0.01
Dry eye symptom score			
Intensity	1.2 ± 0.2 (0-2)	3.6 ± 0.5 (2-4)	<0.01
Frequency	1.5 ± 0.2 (0-2)	3.4 ± 0.4 (1-4)	0.03
Aggravation	1.2 ± 0.3 (0-2)	2.7 ± 0.4 (2-4)	<0.01

Values are presented as mean ± SD (range).
ST-I = Schirmer test I; tBUT = tear film break-up time; OSDI = Ocular Surface Disease Index.

Table 2. Patient demographics at initial evaluation (postoperative 1 week)

	Cyclosporine 0.05%	Normal saline 0.9%	*p*-value
Laterality (OD / OS)	14 / 18	18 / 14	
Schirmer test I (mm)	8.2 ± 4.4 (0-17.0)	7.8 ± 5.2 (0-16.0)	0.67
Tear film break-up time (sec)	7.7 ± 2.1 (6.0-10.5)	7.7 ± 2.0 (5.0-11.0)	0.75
Dry eye symptom score			
Intensity	3.4 ± 0.5 (1-4)	3.4 ± 0.3 (1-4)	0.93
Frequency	2.6 ± 0.4 (2-4)	2.8 ± 0.4 (2-4)	0.88
Aggravation	3.6 ± 0.6 (2-4)	3.6 ± 0.3 (2-4)	0.93

Values are presented as mean ± SD (range).

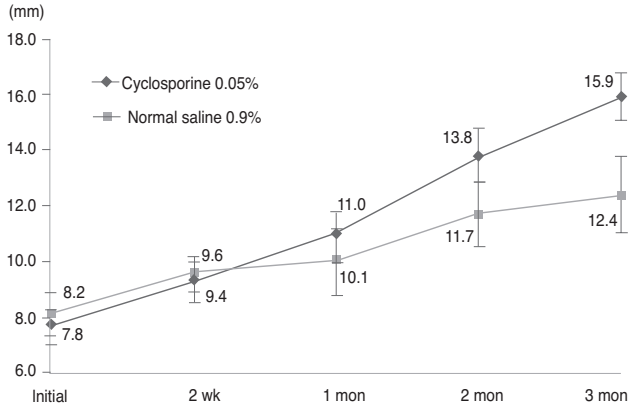

Fig. 1. Changes of Schirmer test I score over time in the cyclosporine 0.05% and normal saline 0.9% groups.

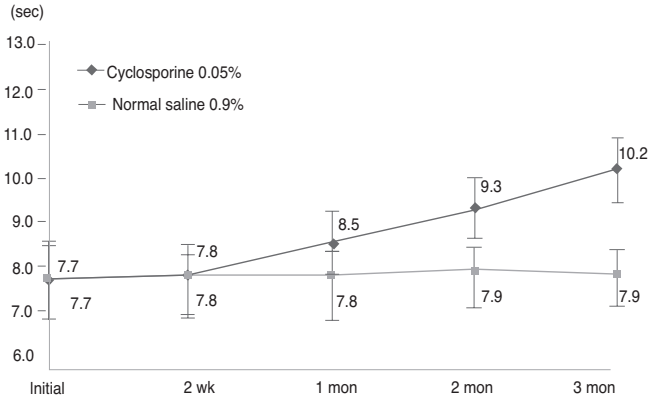

Fig. 2. Changes of tear film break-up time in the cyclosporine 0.05% and normal saline 0.9% groups over time.

Discussion

Cataract surgery is the most successful surgery for restoring visual acuity in patients with phacoemulsification. Following cataract surgery, there may be a new diagnosis of dry eye syndrome or complaints of dry eye symptoms [2,3].

Dry eye syndrome is an inflammatory disease that can interfere with patient quality of life. Inflammation alters tear film stability, and unhealthy tear film is no longer capable of providing nourishment and protection to the ocular surface [7,8]. Neural disruption between the ocular surface and the lacrimal gland can lead to abnormal tear film [9]. An unhealthy tear film can also contain inflammatory mediators [10].

Dry eye can present soon after cataract surgery. Cho and Kim evaluated dry eye after cataract surgery through tBUT, ST-I, tear meniscus height and symptoms in two different groups, previous dry eye group and non-dry eye group. Significant aggravation of dry eye symptoms was

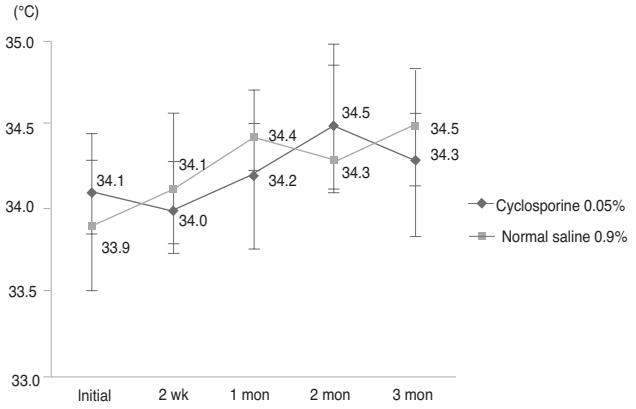

Fig. 3. Changes of corneal temperature in the two groups.

found in the non-dry eye group just 1 day after surgery [3]. Also, Li et al. [2] demonstrated that dry eye appeared 1 week postoperatively and peaked at 1 month. There are many factors that might affect ocular surface environment after cataract surgery such as benzalkonium chloride in the topical anesthetic agent [11], exposure to intense light from the operating microscope, and corneal denervation following corneal incisions [1,9]. These can act as an inflammatory trigger or disrupt the normal neuroregulatory mechanisms. Li et al. [2] carried out impression cytology in patients after cataract surgery and reported similar results to those found in keratoconjunctivitis sicca. This suggests that dry eye after cataract surgery may have a common pathology with keratoconjunctivitis sicca. Additionally, this study revealed decreased tBUT and ST-I during the postoperative period, squamous metaplasia in the conjunctival epithelium and a decreased density of goblet cells. In our study, we did not perform impression cytology but did observe an increase in ST-I, tBUT and subjective symptoms of dry eye 7 days after surgery compared with the preoperative measurements.

Cyclosporine 0.05%, topical cyclosporine A, is a well known immunomodulatory agent for dry eye syndrome [4-6]. It has been found to have an salutary effect on ocular irritation symptoms, tear production, and ocular epithelial disease in keratoconjunctivitis sicca [12]. One potential mechanism is the inhibition of cytokine production by activated T lymphocytes, a feature of keratoconjunctivitis sicca [13,14]. Strong et al. [15] compared conjunctival goblet cell numbers and epithelial turnover in experimental murine keratoconjunctivitis sicca with topical cyclosporine A and revealed a significant reduction in conjunctival goblet cell loss and epithelial apoptosis. In addition, Sahli et al. [16] reported that treatment of patients with dry eye for 6 months with topical cyclosporine A resulted in an improvement in the cytological grade of the disease. Many clinical studies have revealed good result of topical cyclosporine A treatment for dry eye [4-6]. Baiza-Duran et al.

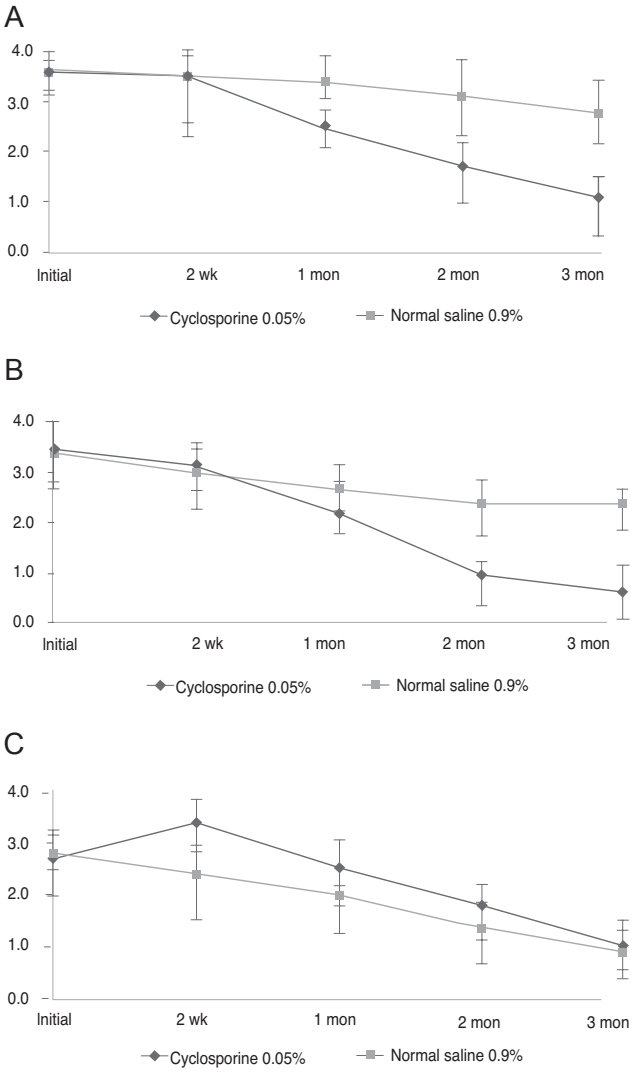

Fig. 4. Changes of symptom severity score in the two groups. (A) Intensity score, (B) frequency score, and (C) aggravation score.

[17] revealed the efficacy of cyclosporine 0.05% for the treatment of moderate to severe dry eye syndrome compared to the vehicle. They evaluated the efficacy by studying 6 symptoms (dryness, burning, photophobia, tearing, ocular fatigue, and foreign body sensation) and 6 signs (conjunctival hyperemia, tear break-up time, ocular surface condition, Rose Bengal staining, fluorescein staining, and ST-I). In single group analysis there was a significant improvement of some symptoms and signs in the vehicle group, but in inter-group analysis, significant improvement was shown only in the cyclosporine groups.

Previously, there has not been any study about topical cyclosporine treatment of dry eye after cataract surgery. In our study, we confirmed that there was significant worsening of ST-1 and tBUT after surgery and subsequent improvement in ST-I and tBUT after treatment with cyclosporine 0.05%. Dry eye symptoms were also effectively

relieved in the cyclosporine 0.05% group. Our data shows similar effects to those seen in previous studies of topical cyclosporine A treatment for keratoconjunctivitis sicca. We considered that cataract surgery induces an inflammatory condition, possibly mediated by activation of T lymphocytes on the ocular surface. Cyclosporine 0.05% may lead to relief of signs and symptoms of this condition by blocking inflammation.

Normal saline 0.9% used in the control group can be an adequate vehicle for dry eye study [18,19]. The osmolarity is 308 mOsm/L, which makes it an isotonic solution with the tears, whose osmolarity is 302 ± 6.2 mOsm/L. Therefore, normal saline 0.9% does not interfere with the ocular surface environment and acts just to lubricate the eye with a volume comparable to cyclosporine 0.05%.

In our study, the symptom aggravation score increased insignificantly at 2 weeks after starting eyedrops. In previous studies, symptom aggravation has been reported during the first few weeks of treatment with cyclosporine A [18]. This may be caused by either the pH of the emulsion or a direct effect of the cyclosporine A and is one of the causes that lead to discontinuation of cyclosporine 0.05% and thus treatment failure. Sheppard et al. [20] used a topical corticosteroid as a pretreatment for 2 to 16 months prior to application of topical cyclosporine A to overcome this discomfort and effectively reduce stinging pain. It would be a good supplemental method for comforting patients undergoing cyclosporine 0.05% treatment.

In conclusion, we observed that dry eye symptoms worsen after cataract surgery, which can be can be detected by history taking or be confirmed by performing ST-I, tBUT, and administration of dry eye symptom questionnaire such as the OSDI. Cyclosporine 0.05% is already known as a useful topical agent for keratoconjunctivitis sicca, but it can also effectively treat signs and symptoms of dry eye that occur after cataract surgery.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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