Original Article

Comparison of Pterygium Recurrence with and without Using Postsurgical Topical Cyclosporin A 0.05%: A Randomized Clinical Trial

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Abstract

Purpose: To evaluate the efficacy of 3-month administration of topical cyclosporin A (CsA) 0.05% on postoperative recurrence after pterygium surgery.

Methods: In this randomized clinical trial, 78 patients undergoing pterygium surgery (using the rotational conjunctival flap technique with mitomycin C [MMC]) were enrolled and randomly allocated into the control ($n = 39$) and case (CsA) ($n = 39$) groups in a single-blind method. The patients were examined on postoperative days 1, 3, and 7 and months 1, 3, and 6, and their best-corrected visual acuity, intraocular pressure, clinical inflammation, postoperative complications, and recurrence were compared.

Results: The mean age of patients was 53.22 ± 9.99 years; most (57.7%) of them were men. The two groups were not different in terms of demographics, pterygium size, or pterygium grade. The clinical inflammation at the first and third postoperative months was not different between the groups ($P = 0.108$ and 0.780, respectively). No serious complications were detected; complication rates were not different between the groups ($P = 0.99$). The recurrence rate was 5.1% in the case group and 7.7%% in the control group ($P = 0.99$).

Conclusion: The present study showed no priority for 3-month administration of CsA 0.05% drops on postoperative outcomes, including prevention of pterygium recurrence, complications, and inflammation after the rotational conjunctival autograft technique with MMC.

Keywords: Cyclosporin A, Inflammation, Pterygium, Recurrence

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Introduction

Pterygium is a common ocular surface disease that is a fibrovascular growth from the conjunctiva onto the cornea.[1] Ultraviolet light, which is believed to cause pterygium, may induce chronic inflammatory cells in the conjunctiva or damage limbal stem cells. Chronic inflammatory cells were shown to be present in pterygium samples; thus, chronic inflammation may contribute to pterygium occurrence.[2-4] One of the important concerns of pterygium surgery is the high risk of recurrence, the severity of which may vary according to patients' characteristics and surgical methods and control of postsurgical inflammation.[5-8] Furthermore, pterygium grade and size, as well as vascularity index, have also been identified as determinants of recurrence after pterygium surgery.[9-11] Accordingly, adjunctive therapies, such as mitomycin C (MMC), 5-fluorouracil, and beta-irradiation, have been suggested to be used after surgery; however, their efficacy on reduction of recurrence is uncertain, and they are associated with adverse effects.[12] Because of the role of inflammation

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in pterygium formation and association of inflammatory biomarkers with a higher risk of recurrence, special attention has been paid to anti-inflammatory agents.[13]

Calcineurin inhibitors such as cyclosporin A (CsA) are an anti-inflammatory agent that suppresses T-helper cells selectively, controls interleukin synthesis, and inhibits vascular endothelial growth factor.[14] CsA can also suppress the change from fibroblast to myofibroblast via the inhibition of myofibroblast markers induced by transforming growth factor-beta 2.[15] A meta-analysis comparing recurrence rate after different surgical techniques showed conjunctival autograft and CsA 0.05% eye drop as the most efficient method.[16] However, the results of the studies are controversial in this regard, and some have suggested no significant effect for CsA on recurrence rate.[17-20] We aimed to evaluate the efficacy of 3-month administration of topical CsA 0.05% on postoperative recurrence after pterygium surgery. Accordingly, in the present study, we selected pterygium cases undergoing the rotational conjunctival autograft technique plus MMC and compared the efficacy of adjunctive therapy with CsA on the postoperative outcomes, including prevention of pterygium recurrence, inflammation, and complications compared with the control group.

Methods

In this randomized clinical trial, all patients who were referred to Amiralmomenin Hospital, Rasht, Iran, from March 2019 to September 2020 and who were diagnosed with primary pterygium and indicated for surgery were enrolled. The diagnosis of primary pterygium was made by an expert cornea surgeon (M.A.), and the patients with pterygia extending more than 3 mm on the cornea on slit-lamp examination were indicated for surgery. The study protocol was approved by the Ethics Committee of the Guilan University of Medical Sciences (IR.GUMS.REC.1398.248) and registered in the Iranian Registry of Clinical Trials by the code: IRCT 20160919029871N4. The patients signed written informed consent.

The sample size was calculated at 39 in each group with a 1:1 ratio, considering a confidence interval of 95%, study power of 80%, and the clinical difference of 22%, suggested by Özülken *et al*.[18] The researcher selected the participants according to the inclusion criteria (patients with primary pterygium >3 mm on a horizontal axis of the cornea), explained the research purpose and possible outcomes to the eligible patients, and asked them to read and sign the written informed consent form. Those who were willing to participate in the study were enrolled in the study by the census method. The patients with a history of pterygium recurrence and pseudopterygium, systemic diseases such as diabetes mellitus and heart disease, eye diseases such as keratitis and conjunctivitis and severe dry eye, a history of eye surgery in the past 6 months, and hypersensitivity reaction to CsA, as well as pregnant and lactating mothers were excluded. The participants were randomly assigned to two groups: the control group and case (CsA) group. The randomization was performed using Random Allocation Software version 1.0 using the equal size in the setting of blocks. The statistical analysis performed the randomization, and the study was single-blind, which means the patients were blind to the study groups.

Complete ophthalmic examination with a slit-lamp was performed for all patients. All pre- and postoperative examinations were done by a single examiner. The demographic and preoperative data of the participants, including age, sex, smoking, and the side of the diseased eye, were recorded, and the preoperative best-corrected visual acuity (BCVA) and intraocular pressure (IOP) were measured. The slit-lamp examination was performed for the measurement of pterygium size and grading. Pterygium size was considered as the distance from the corneal limbus to the head of the pterygium. Pterygium was graded according to the classification proposed by Tan *et al*.[21]

All patients underwent pterygium surgery using the rotational conjunctival autograft technique with MMC. All surgeries were performed by a single anterior segment attending (M.A.). The surgical procedure was performed under local anesthesia. Topical tetracaine 0.5% (Anestocaine, Sina Darou, Iran) eye drops were initially instilled. An eye speculum was inserted, and 0.5 mL of local anesthetic lidocaine hydrochloride 20 mg/mL was infiltrated under the pterygium body with a 27-gauge needle. The pterygium body was grasped and dissected with the Tenon's capsule. Hemostasis was performed with thermal cautery. A sterile cotton tip applicator, soaked in MMC 0.02% (MMC Kyowa; Kyowa Hakko Kirin, Seoul, Korea), was applied to the scleral bed for 90 s. Copious irrigation with 200 mL of normal saline solution was performed. A conjunctival flap was thinly dissected from the superior bulbar conjunctiva, near the limbus, while avoiding the Tenon's capsule. The flap was carefully rotated onto the pterygium excision site with its base at the supranasal region. The limbal portions of the flap were sutured with 10-0 nylon to the episclera in the superior and lower limbal area. The remaining free sides of the flap were secured to the adjacent conjunctiva and sutured with a 10-0 nylon suture. Topical antibiotic ointment (Tetracycline 1%, Sina Darou, Iran) was applied, and the eye was patched for 1 day.

All patients, including control and treatment groups, received antibiotic eye drops (0.5% Chloramphenicol; Sina Darou, Iran) and steroid eye drops (0.1% Betamethasone; Sina Darou, Iran) four times a day for the 1st week. Topical antibiotics were discontinued after complete corneal epithelium healing. Topical steroids were tapered the following weeks and discontinued over the course of 2 months. The patients also received preservative-free artificial tear drops (Artipic, Sina Darou, Iran). In addition to these drugs, patients in the treatment group received topical CsA eye drops (Lacrosporin 0.05%, Sina Darou, Iran) four times a day for 3 months.

Postoperatively, the patients were examined on days 1, 3, and 7 and months 1, 3, and 6. Sutures were removed in all

patients on the 1 month after operation. Slit-lamp examination was performed on each visit, and the data regarding clinical inflammation at the surgical site, the horizontal dimension of the corneal epithelial defect, possible complications of pterygium surgery, IOP, and recurrence were recorded.

Clinical grading for postoperative inflammation was based on objective hyperemia of the surgical site,[22] examined 1 and 3 months after the surgery, graded as no inflammation (0), mild (1), moderate (2), and severe inflammation (3). Recurrence was classified using the G0-G3 classification, provided by Prabhasawat *et al*.[23] Grades 2 and 3 were regarded as recurrence in our study, evaluated 6 months after the surgery. The postoperative complications were recorded. All cases with postoperative complication were closely followed until complete resolution and healing were observed. The primary outcomes of the present study included the pterygium recurrence rate, and the secondary outcomes were inflammation and postoperative complications rate.

Statistical analysis

All statistical analyses were performed using the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. Armonk, NY, USA). The normal distribution was tested by the Kolmogorov–Smirnov test, according to the result of which mean ± standard deviation or median and interquartile range was used for the description of variables with and without normal distribution, respectively. The frequency (percentage) was used for the categorical variables. Comparisons between the two study groups were made using the Student's *t*-test for numeric variables with normal distribution and the Mann–Whitney *U*-test for those without. For comparison of categorical variables, the Chi-square or Fisher's exact test was used, based on the number of samples. Wilcoxon signed-rank test or paired sample *t*-test was used for comparing before–after differences in each study group, for variables with and without normal distribution, respectively. The Partial Eta Coefficient was calculated for the effect of the treatment on IOP. The Partial Eta Coefficient varies between zero and one, and values near one have high effective rates. In all tests, $P < 0.05$ was considered statistically significant.

Results

Thirty-nine patients in each group completed the study [Figure 1]. The distribution of age categories, sex, smoking, and the side of the diseased eye, as well as mean age, were not different between the two study groups [$P > 0.05$; Table 1]. As stated in Table 1, the median pterygium size (4.0 vs. 3.50, respectively; $P = 0.175$) and distribution of preoperative pterygium Tan grading ($P = 0.402$) were not different between the case and control groups.

Complete epithelial healing occurred 1–4 days after the surgery without difference between the two study groups ($P = 0.110$); there were no cases of delayed corneal healing or infection in this study. The distribution of inflammation grades was not different between the study groups, 1 and 3 months after the surgery [$P = 0.108$ and 0.780, respectively; Table 2]. According to Table 2, no inflammation was observed in the case and control groups after 1 (20.5% and 15.4%) and 3 months (82.1% and 79.5%), respectively. As shown in Table 2, the results of the intragroup comparison showed a significant decrease in the degrees of inflammation from 1 to 3 months in both the groups ($P < 0.001$). In terms of BCVA, the median logMAR of the two study groups was not different before ($P = 0.697$) or after the surgery ($P = 0.722$); the rate of change in BCVA (after vs. before surgery) was not statistically different between the two groups [$P = 0.881$; Table 2]. A significant decrease was observed in mean logMAR BCVA after the surgery versus before the surgery in each group and in all participants [$P < 0.05$; Table 2].

There was no statistically significant difference between the two groups in terms of IOP at any intervals. However, in both treatment groups, pterygium surgery elicited a slight increase in IOP levels from preoperation to 6 months postoperation follow-up measurements [$P < 0.001$ and 0.006 in case and control groups, respectively; Table 3]. The interaction between time and groups was not statistically significant ($P = 0.918$). This means that the increasing trend of IOP during the measurement times was generally parallel in both the groups. The effect of CsA based on the Partial Eta Coefficient was very small (Eta = 0.033).

No serious complications were detected in any of the participants. The frequency of postoperative complications and recurrence rates are shown in Table 3. There was no statistically significant difference between the two groups in terms of complication and recurrence rates (both $P = 0.999$). Recurrence was observed in 5.1% (two women) of the case group and 7.7% (three patients; two men and one woman) of the control group. The recurrence rate was not different according to patients' sex in case and control groups ($P = 0.184$ and 0.999, respectively), nor according to the age categories of the patients and preoperative pterygium size [$P > 0.05$; Table 4].

Discussion

The present study investigated the effect of adjunctive therapy with CsA 0.05% for 3 months on postoperative outcomes of patients with primary pterygium, compared with the control group with similar demographic and presurgical characteristics, and the results showed no difference in terms of time to complete corneal epithelial healing, postoperative inflammation, BCVA, IOP, complications, and recurrence rates between the case and control groups. These results suggest that CsA could not significantly reduce the recurrence of pterygium after surgery with a conjunctival autograft and MMC. It has to be mentioned that the surgical technique selected in the present study has been recommended as one of

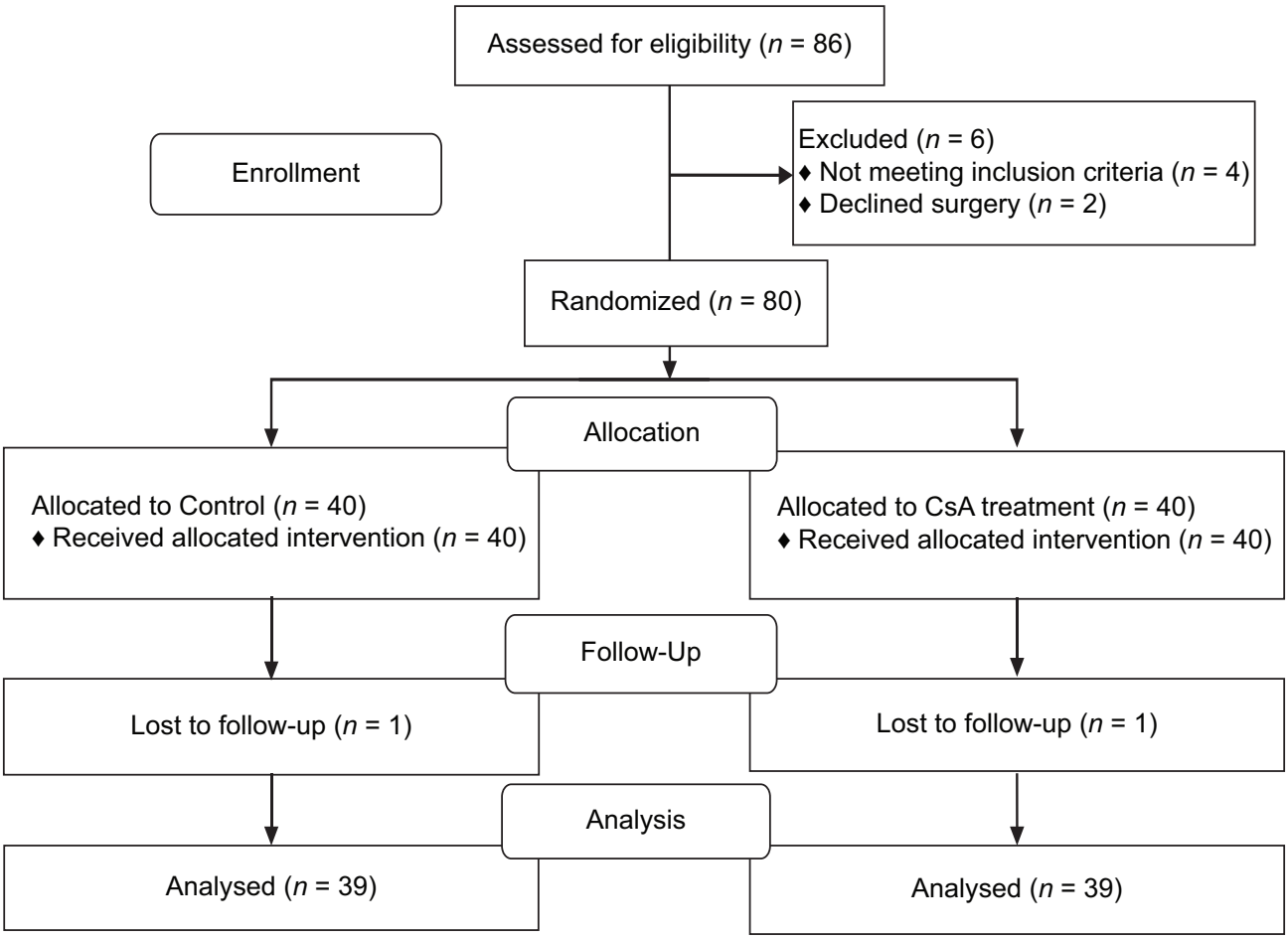

Figure 1: The flow diagram of patients' enrollment into the study

the two pterygium surgical methods with the utmost favorable postoperative outcomes;[8] the low recurrence rate in the study population (6.41%), no severe complications, and reduction in inflammation in the total sample also confirmed the appropriateness of rotational autograft technique. Furthermore, previous studies have suggested promising results for applying of MMC in conjunctival autograft pterygium surgery.[24,25] Therefore, we used a combination of these two methods, which were the main keys for the low recurrence rate in the present study.

Considering the effect of CsA on postoperative outcomes, definite conclusions cannot be drawn about recurrence because of the few patients with recurrence in each group (two in the case and three in the control group), although the sample size was according to the calculated value and close to similar studies. In another study on 56 patients, Özülken *et al*. showed that 6-month administration of CsA did not result in a significant reduction of recurrence rate after rotational autograft technique: two in the case group (7.7%) and six in the control group (20%).[18] The overall recurrence rate in their study (14.2%) was higher than that of ours, which could be because of the effect of additional treatments in the present study, like MMC. Meneghim *et al*. also showed that administration of CsA 0.05% 10 days before and 10 days after rotational conjunctival flap technique plus 5-fluorouracil showed no difference between the 6-month recurrence rate of the control and case groups (61% vs. 40%, respectively).[17] Although these results are consistent with the general conclusion of the present study, they used 5-fluorouracil instead of MMC, and the duration of CsA administration was different from that in the present study, which might be the reason for the higher recurrence rate in their study. Dhar *et al*. also showed no effect for CsA 0.05%, administered 4 weeks before and after surgery, on the recurrence rate (6% in the case and 8% in the control group).[19] However, the surgical technique (conjunctival limbal autograft with fibrin glue) and definition of the recurrence (any encroachment of conjunctiva >1 mm inside the limbus) were different in the study by Dhar from that in the present study, which could be another source of different rates reported. Other researchers reporting no effect for CsA have also used different inclusion criteria, such as bilateral pterygium with >2 mm corneal invasion.[18] On the other hand, the studies, reporting significantly lower recurrence rate by CsA 0.05%; Yalcin Tok *et al.* and Ahmed *et al.* showed recurrence rates of 12.9 versus 45.2% and 7.5 versus 43.4% in the CsA versus control groups,

Table 1: Comparison of demographic and preoperative characteristics of the study groups

Demographic parameters	Cyclosporin A (*n*=39), *n* (%)	Control (*n*=39), *n* (%)	Total (*n*=78), *n* (%)	*P*
Age (years)				
<40	5 (12.82)	3 (7.69)	8 (10.26)	0.622*
40-49	7 (17.95)	10 (25.64)	17 (21.79)	
50-59	18 (46.15)	14 (35.90)	32 (41.03)	
>59	9 (23.08)	12 (30.77)	21 (26.92)	
Mean±SD	52.77±10.25	53.67±9.85	53.22±9.99	0.694†
Minimum-maximum	31.0-78.0	31.0-71.0	31.0-78.0	
Sex				
Male	22 (56.41)	23 (58.97)	45 (57.69)	0.819‡
Female	17 (43.59)	16 (41.03)	33 (42.31)	
Smoker				
Yes	8 (20.51)	10 (25.64)	18 (23.08)	0.591‡
No	31 (79.49)	29 (74.36)	60 (76.92)	
Eye side				
Right	19 (48.72)	18 (46.15)	37 (47.44)	0.821‡
Left	20 (51.28)	21 (53.85)	41 (52.56)	
Mean±SD	3.88±0.71	3.66±0.59	3.77±0.66	0.175§
Horizontal pterygium size (mm)				
Median (IQR)	4.0 (1.3)	3.50 (1.0)	3.6 (0.9)	
Minimum-maximum	3.00-5.50	3.00-5.50	3.00-5.50	
Pterygium Tan grade				
I	1 (2.56)	4 (10.26)	5 (6.41)	0.402*
II	17 (43.59)	14 (35.90)	31 (39.74)	
III	21 (53.85)	21 (53.85)	42 (53.85)	

*Fisher's exact test, †Independent *t*-test, ‡Chi-square test, §Mann-Whitney *U*-test. SD: Standard deviation, IQR: Interquartile range

respectively.[26,27] These two studies indicated statistically lower recurrence rates in the CsA 0.05%-treated group. This difference may be due to the dose of cyclosporin used and the duration of follow-up. Therefore, differences among the studies hinder the appropriate comparison of the results. The results of the meta-analysis of 408 patients (from seven studies) also confirmed adjuvant use of CsA significantly reduces recurrence compared to bare sclera technique alone. However, this meta-analysis stated that there was no difference in the recurrence rate of pterygium between "pterygium excision + limbal conjunctival autograft or rotational conjunctival flap technique" with and without CsA,[28] which is consistent with the results of the present study.

Considering the complications, no severe complications were observed in any patients in the present study, and the frequency of minor complications (observed in nine patients; 11.5% of the total study population) was also not different between the groups. The study by Özülken *et al*. reported significantly lower overall complication rates and severe complications (pyogenic granuloma and sclera thinning) in the case group receiving CsA.[18] Furthermore, the meta-analysis of 408 patients showed a significantly lower frequency of total complications and conjunctival granulomas in CsA group.[28] Although the recurrence and complication rates were not different between the two study groups in the present study. Subgroup analysis in our study showed that the recurrence rate was not associated with patients' age, sex, and pterygium size before the surgery. Consistent with these results, Han *et al*. have also reported no role for patients' sex or age on 1-year recurrence after pterygium excision with limbal-conjunctival autograft.[11] The study by Anguria *et al*. also reported that the effect of age on recurrence lost its significance in multivariate analysis,[29] which is consistent with our results. However, they reported disease extent (Grade ≥3) as a significant predictor.[29] Other studies have also suggested greater pterygium size or grade before surgery as an important predictor of postsurgical recurrence.[30,31] The difference in the predictors of pterygium recurrence reported in the studies can be attributed to the different surgical techniques used. We believe that the low recurrence in our study is because of the simultaneous use of MMC with the rotational conjunctival autograft, and the small number of samples limited the statistical significance of the difference between the groups and associated factors.

Our study had some limitations. The limited number of samples, 6-month follow-up, and selection of samples from one center were among the factors that limit the generalizability of the results to the whole population. Furthermore, the factors that can have an influence on the study outcomes, such as patients' occupation and ultraviolet exposure, which were not evaluated in the present study, could act as a confounder. In addition, the observer was not blind to the group allocations and the study was single blind.

Table 2: The results of comparing the postoperative parameters between the two study groups

Parameters	Group		Total ($n=78$), n (%)	P
	Case group ($n=39$), n (%)	Control ($n=39$), n (%)		
Time to complete corneal epithelial healing (days)				
Mean±SD	2.56±0.71	2.82±0.75	2.69±0.74	0.110*
Median	2.0	3.0	3.0	
Clinical inflammation after 1 month				
None	8 (20.5)	6 (15.4)	14 (17.95)	0.108†
Mild	13 (33.3)	15 (38.6)	28 (35.90)	
Moderate	11 (39.3)	17 (43.6)	28 (35.90)	
Severe	7 (17.9)	1 (12.6)	8 (10.26)	
Clinical inflammation after 3 months				
None	30 (76.9)	32 (82.1)	62 (79.49)	0.780†
Mild	8 (20.5)	7 (17.9)	15 (19.23)	
Moderate	1 (2.6)	0	1 (1.28)	
Severe	0	0	0	
Change in clinical inflammation (3 vs. 1 month[s])	−66.7%	−56.4%	-	<0.001‡
P	<0.001‡	<0.001‡		
Preoperative BCVA				
Mean±SD	0.28±0.22	0.27±0.23	0.28±0.22	0.697*
Median	0.22	0.22	0.22	
Minimum-maximum	0-1.0	0-1.0	0-1.0	
Postoperative BCVA				
Mean±SD	0.26±0.22	0.25±0.22	0.25±0.22	0.722*
Median	0.22	0.22	0.22	
Minimum-maximum	0-1.0	0-1.0	0-1.0	
Change in BCVA				
Mean±SD	0.02±0.07	0.02±0.05	0.02±0.06	0.881§
Median	0.00	0.00	0.00	
Minimum-maximum	−0.07-0.30	−0.05-0.18	-0.07-0.30	
Intragoup comparison				
P	0.016	0.046	0.003	

*Mann-Whitney *U*-test, †Fisher's exact test, ‡Wilcoxon signed-rank test, §Paired sample *t*-test. BCVA: Best-corrected visual acuity, SD: Standard deviation

Table 3: The comparison of intraocular pressure values at different intervals between the two study groups

IOP (mmHg)	Statistics	Groups			P^*
		Control	Cyclosporin A	Total	
Preoperative value	Mean±SD	15.62±2.20	14.87±1.85	15.24±2.05	0.110
	Median	16.00	15.00	15.50	
Seven days after surgery	Mean±SD	15.87±1.92	15.19±1.92	15.53±1.92	0.124
	Median	16.00	15.00	16.00	
One month after surgery	Mean±SD	16.05±2.47	15.54±1.82	15.79±2.17	0.300
	Median	16.00	16.00	16.00	
Three months after surgery	Mean±SD	16.72±2.81	15.92±1.80	16.32±2.38	0.142
	Median	16.00	16.00	16.00	
Three months after surgery	Mean±SD	16.15±2.17	15.59±1.65	15.87±1.94	0.200
	Median	16.00	16.00	16.00	
Preoperation to 6 months	*P*	0.006†	<0.001†		
Postoperation measurments					
Partial eta squared			0.033		

*Independent *t*-test, †Paired sample *t*-test. SD: Standard deviation, IOP: Intraocular pressure

In conclusion, the results of the present study showed that the pterygium surgery with rotational conjunctival autograft and the use of MMC and nonabsorbable sutures is a successful surgical procedure for the treatment of primary pterygium, resulting in low recurrence and complication rates 6 months after surgery. However, the main hypothesis

Table 4: Comparison of the postoperative complication and recurrence rates between the two study groups

Parameters	Group		Total (*n*=78), *n* (%)	*P*
	Case group (*n*=39), *n* (%)	Control (*n*=39), *n* (%)		
Complications				
None	34 (87.2)	35 (89.7)	69 (88.5)	0.999*
Dellen	2 (5.1)	1 (2.6)	3 (3.8)	
Flap necrosis	1 (2.6)	2 (5.1)	3 (3.8)	
Granulation tissue	2 (5.1)	1 (2.6)	3 (3.8)	
Recurrence grades				
G0	23 (59.0)	20 (51.3)	43 (55.1)	0.524*
G1	14 (35.9)	16 (41.0)	30 (38.5)	
G2	1 (2.6)	3 (7.7)	4 (5.1)	
G3	1 (2.6)	0	1 (1.3)	
Recurrence according to age categories (years) (*n*)				
<40	0	0	-	-
40-49	1	1	-	-
50-59	0	1	-	-
>59	1	1	-	-
*P**	0.999	0.283		
Preoperative pterygium size				
Median	3.10	3.33	-	0.400†
Mean±SD	3.10±0.14	3.50±0.29	-	

*Fisher's exact test, †Mann-Whitney *U*-test. SD: Standard deviation

of the present study was rejected, and the addition of CsA 0.05%, administered for 3 months postoperation, could not reduce the risk of postoperative pterygium recurrence. Lack of significance in adverse outcomes could be because of the small number of patients with the measured outcome. Therefore, more studies with a larger sample size and longer follow-up periods are required for definite conclusions about the effect of adjunctive CsA on the reduction of postoperative adverse outcomes after this specific type of procedure.

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Conflicts of interest

There are no conflicts of interest.

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