Original Article

Effects of mitomycin-C on tear film function following photorefractive keratectomy for mild-to-moderate myopia

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ABSTRACT

Background: Mitomycin C (MMC) is used to prevent corneal opacity after photorefractive keratectomy (PRK). This study sought to determine the effect of MMC on tear film function after PRK in eyes with mild-to-moderate myopia.

Methods: This prospective, contralateral eye comparison was conducted on 30 eyes of 15 patients with low-to-moderate myopia referred to Alzahra Eye Hospital, Zahedan, Iran. The eyes of the control group underwent PRK with a balanced salt solution, while the fellow eyes in the intervention group underwent PRK with 0.02% MMC for 25 s. The tear breakup time test (TBUT) and basic Schirmer test results of eyes in the control and intervention groups were compared at baseline and 1, 3, and 6 months postoperatively. Tear osmolarity was recorded and compared at baseline and 3 months postoperatively.

Results: The mean ± standard deviation (SD) age of participants was 27.53 ± 7.04 years. No statistically significant differences were observed in the means ± SDs for tear osmolarity, TBUT, and basic Schirmer test values (all $P > 0.05$) between MMC-treated eyes and untreated fellow eyes at baseline and during postoperative follow-up. The means ± SDs for tear osmolarity, TBUT, and basic Schirmer test results were comparable in both groups between the baseline and postoperative follow-ups (all $P > 0.05$).

Conclusions: Single application of a standard dose of MMC (0.02%) for 25 s in PRK did not change tear stability, tear production, or variation in tear dynamics up to 6 months postoperatively in eyes with low-to-moderate myopia. Future longitudinal studies with a longer follow-up and a larger sample size are warranted to confirm our findings.

KEY WORDS

photorefractive keratectomy, mitomycin-C, tear, osmolarity, tear breakup time test, Schirmer test, myopia

INTRODUCTION

Refractive errors are the fourth most common cause of blindness worldwide [1] and are listed as the highest of five priorities of the 2020 Vision Program of the World Health Organization [2]. Photorefractive keratectomy (PRK) is a safe and effective procedure for correcting refractive errors [3]. Following corneal epithelium removal in PRK, the anterior stromal tissue is ablated using excimer laser to change the corneal refractive power. This

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alters the natural structure of the extracellular matrix, as the number and shape of the cells change, a variable level of extracellular matrix is disorganized, myofibroblasts are formed, and corneal sub-epithelial opacities may be produced, which are clinically significant in some patients [4]. The degree of opacity is correlated with the level of refractive error correction [5, 6].

Intraoperative topical administration of mitomycin-C (MMC) reduces corneal opacity after PRK [7, 8]. Prophylactic use of 0.02% MMC reduces corneal opacity, improves uncorrected visual acuity, and yields better visual results after keratorefractive surgery [8-10]. The application of 0.02% MMC solution for 12 to 120 s is variably recommended for corrections of ≥ 4.00 diopters (D) or an estimated ablation depth of > 60 μm [11, 12].

Nonetheless, the notable toxic effects of MMC have raised concerns [13, 14]. The appropriate concentration and ideal duration of administration for MMC to reduce postoperative opacity and minimize adverse effects on corneal cells are yet to be determined [12]. Various durations ranging from 5 s to 2 min with concentrations ranging from 0.01% to 0.4% have been utilized [12, 15].

Reduced tear production after PRK has also been reported [14]. Dry eye can be detected using the tear breakup time (TBUT) test, measuring tear mucus, counting goblet cells, and measuring lysozyme and lactoferrin concentrations in the tear. The tear hyper-osmolarity test is used to diagnose dry eye disease (DED); however, difficulties in measurement have restricted its application. The most commonly used method is the measurement of tear osmolarity [16], which has the highest predictive value of all tests for diagnosing DED.

Few studies have investigated the effect of PRK with and without prophylactic MMC on tear film function test results, such as tear osmolarity, TBUT, and the Schirmer test [17-19], and conflicting results have been reported. Considering the widespread prophylactic use of MMC, the present study aimed to investigate the postoperative effects of PRK with MMC on tear film function test results in eyes with mild-to-moderate myopia.

METHODS

The protocol for this prospective, contralateral eye comparison study was approved by the Zahedan University of Medical Sciences Institutional Review Board (thesis number: 6007), and the study adhered to the tenets of the Declaration of Helsinki. Candidates for PRK for myopic corrections of < - 3.00 D were recruited from the Alzahra Ophthalmology Clinic, Zahedan, Iran; all procedures and possible complications of the PRK surgery were explained, informed consent was obtained, and fulfillment of inclusion criteria was verified.

Inclusion criteria were age > 18 years, spherical myopia between - 0.50 and - 3.00 D, no contact lens use for at least 2 weeks before baseline examination, best-corrected distance visual acuity (BCDVA) of 20/25 or better (≥ 0.1 logarithm of the minimum angle of resolution [logMAR]), stable refraction for at least 1 year, and central corneal thickness (CCT) of more than 500 μm. The exclusion criteria were contraindications or relative contraindications to refractive surgery, such as dry eye, blepharitis, corneal ulcer or scar, history of herpetic keratitis, keratoconus or unstable keratometry readings with irregularly shaped mires, corneal dystrophy or degeneration, cataract, glaucoma, and retinal disease; ocular or collagen vascular diseases affecting tear production or wound healing, such as Sjogren's syndrome; contact lens use; use of ocular or systemic medications; immunodeficiency; previous intraocular or corneal surgery; and a predicted residual stromal bed thickness of < 400 μm. Eyes with keratoconus and subclinical keratoconus were excluded using the Pentacam Ambrosio-Belin module (Oculus Optikgeräte, Wetzlar, Germany).

The following baseline clinical information of participants was collected using a specifically designed form: uncorrected distance visual acuity (UCDVA) and BCDVA using the Snellen chart at a distance of 6 m, converting Snellen fractions to logMAR units; manifest and cycloplegic refractions with objective autorefraction using Topcon KR 8900 (Topcon Corp., Tokyo, Japan); detailed anterior segment and dilated fundus examinations using a slit lamp (Haag-Streit, Mason, OH, USA); intraocular pressure measurement using Goldmann applanation tonometry (Model AT 900 C/M; Haag-Streit, Bern, Switzerland); and Scheimpflug camera–Placido disk topography imaging (Pentacam HR, Oculus Optikgeräte) by a single ophthalmologist (K. S.) who conducted repeated postoperative follow-up examinations.

The patients were administered no medications within 24 h before the operation. Patients received contralateral treatments of PRK with 0.02% MMC for 25 s in 1 eye and PRK with a balanced salt solution (BSS) for 25 s in the fellow eye using a different set of sterile instrument. All PRK operations were performed by a fellowship-trained corneal surgeon (M. A. N.) using a Nidek 193-nm excimer laser with a 40-Hz pulse repetition rate using the same technique. All surgeries were non-monovision treatments to achieve emmetropia and were performed under topical anesthesia with 0.5% tetracaine eye drops (Anestocaine, Sina Darou Co., Tehran, Iran). The corneal epithelium was removed with 20% alcohol for 1 min as an 8.0-mm diameter circle, followed by copious irrigation with a BSS. Excimer photoablation was then performed. The ablation zone diameter matched

that of the mesopic pupil. For the eye in the intervention group, MMC 0.02% was applied for 25 s, and for the fellow eye, BSS was applied for 25 s, to the ablated stroma, followed by copious irrigation with BSS. Finally, a therapeutic disposable contact lens (Purevision; Bausch & Lomb, Rochester, NY, USA) was inserted.

Postoperatively, we administered 0.5% chloramphenicol eye drops (Chlobiotic; Sina Darou Co.) and 0.1% betamethasone eye drops (Betasonate; Sina Darou Co.) every 6 h, as well as preservative-free artificial tears (Sinalone; Sina Darou Co.) every 3 h for 1 week. Once the corneal epithelium healed (ranging from 3 to 5 days postoperatively), the contact lens was removed, and betamethasone was replaced with 0.1% fluorometholone eye drops (Flucort; Sina Darou Co.) every 6 h, which was then slowly tapered over 2 months. Artificial tear drops were continued for up to 2 months. Postoperative examinations were scheduled at 1 week, 1 month, 3 months, and 6 months.

The osmolarity test was performed before surgery and at 3 months postoperatively. The basic Schirmer test and TBUT were performed before surgery and at 1 month, 3 months, and 6 months postoperatively. A trained optometrist performed all tear function tests.

The tear osmolarity test was conducted using the TearLab Osmolarity System (TearLab Corp., San Diego, CA, USA), as suggested by the manufacturer. The disposable test card was installed in the system pen. The pen was lowered sufficiently for its tip to reach the wet line above the eyelid margin. The pen's beeping sound and green light signal indicated that sufficient tear volumes were collected. The pen was then placed into the reader, and the tear osmolarity result appeared on the display screen within a few seconds [20] and was recorded on the data collection sheet. This process was repeated for the fellow eye.

To conduct TBUT, sterile fluorescein paper (Tus Negah, Mashhad, Iran) moistened with distilled water was placed in the lower conjunctival fornix. After several eye blinks, the corneal tear film was examined using blue cobalt light from a slit lamp. The time interval between the last blink and the appearance of the first dry spot on the corneal tear film was measured; this process was repeated three times, and the mean value was recorded for each eye [21]. A TBUT < 10 s was considered abnormal.

A basic Schirmer test was conducted following topical anesthesia with 0.5% tetracaine (Anestocaine; Sina Darou Co.) and drying. A Schirmer filter paper strip (Biotech Vision Care Pvt. Ltd., Gujarat, India) was folded at the pre-specified area and placed in the lateral one-third of the palpebral fissure in the lower fornix. The patient then closed the eyes gently, and after 5 min, the length of the paper wetted by each eye was measured in millimeters and recorded [22].

Statistical analyses were performed using SPSS version 22 for Windows (IBM Inc., Chicago, Illinois, USA). For intragroup comparisons, the variable scores at each postoperative follow-up were compared with the preoperative baseline values. For intergroup comparison, variables of the MMC and control eyes were compared at the different time points. Normal distribution of the data was assessed using the Kolmogorov–Smirnov test. Results are expressed as the mean ± standard deviation (SD). The Student's *t*-test, Wilcoxon signed-rank test, or Mann–Whitney U test were used to analyze data. Statistical significance was set at $P < 0.05$.

RESULTS

Thirty eyes of 15 patients with mean age of 27.53 ± 7.04 (range: 18–40) years were followed for 6 months postoperatively. No intraoperative or postoperative complications or corneal opacity were observed during the study period. Because this was a contralateral eye study, the age and sex distributions of the MMC and control groups were similar. The mean preoperative UCDVA and BCDVA, mesopic pupil diameter, CCT, and spherical equivalent were comparable between the groups (all $P > 0.05$) (Table 1).

Between the MMC and control groups, the mean preoperative (305.73 ± 8.72 mOsms/L and 301.33 ± 9.55 mOsms/L, respectively) and 3-month postoperative (308.40 ± 16.46 mOsms/L and 299.73 ± 10.35 mOsms/L, respectively) tear osmolarities were comparable (both $P > 0.05$). The mean tear osmolarity in either group, at baseline and at the 3-month postoperative follow-up, was not significantly different (both $P > 0.05$) (Table 2).

Between the MMC and control groups, the mean preoperative (13.53 ± 3.44 s and 14.20 ± 4.03 s, respectively) and 1-month (13.60 ± 4.05 s and 13.80 ± 3.09 s, respectively), 3-month (14.33 ± 2.61 s and 14.20 ± 2.78 s, respectively), and 6-month (13.47 ± 2.99 s and 14.20 ± 3.50 s, respectively) postoperative TBUT scores were comparable (all $P > 0.05$). The mean TBUT scores in either group, at baseline and at the 1-, 3-, and 6-month postoperative follow-ups, were not significantly different (all $P > 0.05$) (Table 2).

Between the MMC and control groups, the mean preoperative (19.93 ± 6.71 mm and 20.20 ± 5.57 mm, respectively) and 1-month (20.00 ± 8.95 mm and 17.80 ± 3.61 mm, respectively), 3-month (20.27 ± 6.26 mm and 17.00 ± 4.70 mm, respectively), and 6-month (18.27 ± 4.65 mm and 18.33 ± 4.35 mm, respectively) postoperative basic Schirmer test results were comparable (all $P > 0.05$). The mean basic Schirmer test results in either group, at baseline and at the 1-, 3-, and 6-month postoperative follow-ups, were not significantly different (all $P > 0.05$) (Table 2).

Table 1. Comparison of preoperative characteristics of MMC in treated versus fellow control eyes

Variable	Intervention Group (n = 15 eyes)	Control Group (n = 15 eyes)	*P*-value
Sex, Male / Female, n (%)	8 (53.3) / 7 (46.7)	8 (53.3) / 7 (46.7)	*
Preoperative UCDVA in logMAR, Mean ± SD	1.23 ± 0.31	1.05 ± 0.12	*P* = 0.568
Preoperative BCDVA in logMAR, Mean ± SD	0.00 ± 0.03	0.00 ± 0.05	*P* = 0.253
Age (y), Mean ± SD	27.53 ± 7.04	27.53 ± 7.04	*
Mesopic pupil diameter (mm), Mean ± SD	6.57 ± 1.25	6.62 ± 1.22	*P* = 0.563
CCT (μm), Mean ± SD	543 ± 12.55	539 ± 11.76	*P* = 0.675
SE (D), Mean ± SD	- 2.51 ± 0.69	-2.51 ± 0.55	*P* = 0.887

Abbreviations: n, number; %, percentage; UCDVA, uncorrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; BCDVA, best-corrected distance visual acuity; y, years; mm, millimeter; CCT, central corneal thickness; μm, micrometer; SE, spherical equivalent; D, diopters. Note: Intervention group received intraoperative mitomycin-C 0.02% for 25 seconds, whereas control group received balanced salt solution for 25 seconds. *Because this was a contralateral eye study, age and sex distribution of the intervention and control groups were similar.

Table 2. Baseline and post-photorefractive keratectomy tear film characteristics in MMC-treated versus fellow control eyes

Time Point	Variable	Intervention Group (n = 15 eyes)	Control Group (n = 15 eyes)	*P*-value
Baseline, Mean ± SD	**Tear osmolarity test (mOsms/L)**	305.73 ± 8.72	301.33 ± 9.55	*P* = 0.199
	TBUT (s)	13.53 ± 3.44	14.20 ± 4.03	*P* = 0.639
	Basic Schirmer test (mm)	19.93 ± 6.71	20.20 ± 5.57	*P* = 0.907
1-month post-op, Mean ± SD	**TBUT (s)**	13.60 ± 4.05	13.80 ± 3.09	*P* = 0.974
	Intragroup *P*-value	*P* = 0.661	*P* = 0.661	
	Basic Schirmer test (mm)	20.00 ± 8.95	17.80 ± 3.61	*P* = 0.153
	Intragroup *P*-value	*P* = 0.365	*P* = 0.365	
3-month post-op, Mean ± SD	**Tear osmolarity test (mOsms/L)**	308.40 ± 16.46	299.73 ± 10.35	*P* = 0.771
	Intragroup *P*-value	*P* = 0.101	*P* = 0.101	
	TBUT (s)	14.33 ± 2.61	14.20 ± 2.78	*P* = 0.856
	Intragroup *P*-value	*P* = 0.545	*P* = 0.545	
	Basic Schirmer test (mm)	20.27 ± 6.26	17.00 ± 4.70	*P* = 0.853
	Intragroup *P*-value	*P* = 0.522	*P* = 0.522	
6-month post-op, Mean ± SD	**TBUT (s)**	13.47 ± 2.99	14.20 ± 3.50	*P* = 0.956
	Intragroup *P*-value	*P* = 0.633	*P* = 0.633	
	Basic Schirmer test (mm)	18.27 ± 4.65	18.33 ± 4.35	*P* = 0.944
	Intragroup *P*-value	*P* = 0.463	*P* = 0.463	

Abbreviations: n, number; SD, standard deviation; TBUT, tear film break-up time; s, seconds; mm, millimeter; post-op, postoperatively. Note: Intervention group received intraoperative mitomycin-C 0.02% for 25 s, whereas control group received balanced salt solution for 25 s.

DISCUSSION

We found no statistically significant differences in mean tear osmolarity, TBUT, and basic Schirmer test results between MMC-treated eyes and untreated fellow eyes, or in either group at baseline and over 6 months' postoperative follow-up.

Various studies have shown that PRK may cause postoperative dry eye syndrome [23-26]. As the Schirmer test result is less reproducible, the present research studied tear osmolarity, which is a more conclusive test for studying DED [16]. The possible effects of MMC on tear tests were also investigated. Although the mean tear osmolarity increased slightly in the MMC group, this increase was not statistically significant.

Beheshtnejad et al. [17] evaluated 50 myopic eyes (spherical equivalent between - 2.00 and - 6.00 D) of 25 patients ranging in age from 22 to 45 years. Dry eye function tests (Schirmer test, TBUT, and tear osmolarity) were abnormal at 2 months' follow-up. In contrast, we found no significant differences in mean tear osmolarity, TBUT, and basic Schirmer test values between MMC-treated eyes and untreated fellow eyes, or in either group.

However, Beheshtnejad et al. [17] found that tear function test results returned to preoperative values 4 months postoperatively. Likewise, a single application of MMC 0.02% for 25 s in our study did not change tear stability or tear production up to six months postoperatively, versus untreated eyes, with spherical myopia between - 0.50 and - 3.00 D.

Our results are consistent with those of Farahi et al. and Mohammadi et al. [27, 28]. Farahi et al. studied the effect of MMC on the Schirmer test, TBUT, and rose bengal and fluoresceine staining and found no significant difference between the MMC-treated and -untreated groups postoperatively. Although the TBUT results deteriorated at the first and fifth postoperative months, they improved afterward [27]. Mohammadi et al. [28] found no significant postoperative difference between MMC-treated and -untreated groups. The average tear index based on the scores assigned to the Schirmer test, TBUT, and subjective symptoms of patients declined in both groups within the first month but increased thereafter [27, 28].

Bower et al. [29] found no significant association between chronic dry eye and intraoperative prophylactic application of 0.01% MMC for 30 s in eyes with myopia or myopic astigmatism (manifest spherical equivalent - 3.83 ± 1.96 D) at 12 months post-PRK. However, correlation analysis revealed that eyes with lower preoperative Schirmer scores and lower TBUT tended to develop chronic dry eye postoperatively. They concluded that preoperative ocular surface and tear film abnormalities could influence chronic DED progression after surgery [29]. Likewise, we found that a single application of a prophylactic dose of 0.02% MMC for 25 s in PRK did not change tear stability or tear production up to 6 months postoperatively in eyes with low-to-moderate myopia. However, we did not investigate other parameters, such as those of Bower et al. [29]. A possible justification for the lack of MMC effect on tear function tests in this context might be its local application on the cornea in PRK and because it is washed out immediately with copious irrigation.

The absence of direct contact of MMC with the main and accessory lacrimal glands or other ocular structures might justify the lack of significant changes on tear production, stability, and dynamics. Tear osmolarity was not affected in this study. Considering that tear osmolarity is a reliable indicator of ocular surface health and tear stability, and that its variations signify the core of a complex etiopathogenic mechanism in dry eye [20], the stability of postoperative tear osmolarity in our study clarifies the ineffectiveness of prophylactic single short-duration intraoperative application of 0.02% MMC on postoperative dry eye syndrome following PRK. However, these rationalizations must be validated in future studies.

We found no significant change in tear stability or tear production 6 months after PRK in MMC-treated versus -untreated contralateral eyes. These results indicate that a single application of a standard dose of MMC for 25 s in PRK could be safe in eyes with low-to-moderate myopia. The study was limited by the small number of patients, recruitment of only patients with low-to-moderate myopia, and measurement of tear osmolarity only once postoperatively. Future studies with longer follow-up periods are necessary to confirm our hypothesis. Moreover, using a contralateral eye study design could prevent the influence of potential confounding factors, which should be considered in future studies. Although not investigated in this study, a subjective assessment using dry eye questionnaires should be conducted.

CONCLUSIONS

A single application of a standard dose of MMC (0.02%) for 25 s in PRK did not change tear stability, tear production, or variation in tear dynamics up to 6 months postoperatively in eyes with low-to-moderate myopia.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the Zahedan University of Medical Sciences Institutional Review Board (thesis number: 6007), and the study adhered to the tenets of the Declaration of Helsinki. Patients were enrolled after all procedures and possible complications of the PRK surgery were explained, informed consent was obtained, and fulfillment of inclusion criteria was verified.
Conflict of interests: None

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