

Photorefractive Keratectomy With Mitomycin-C for High Myopia: Three Year Follow-Up Results

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Abstract- Photorefractive keratectomy (PRK) is a safe and effective surgical keratorefractive technique which is done with the application of mitomycin-C (MMC) in cases of high myopia to prevent the formation of corneal haze. This study was conducted to evaluate 3-year visual acuity and quality outcomes of PRK-MMC in high myopia. This before-after study was conducted on 20 individuals (40 eyes) with myopia more than 6.0 diopter (D). Visual acuity and quality indices were evaluated before and three years after the procedure and their stability was examined between the 1st and 3rd years. At 3 years after surgery, mean uncorrected visual acuity was 0.03 ± 0.06 in the logarithm of minimum angle of resolution (logMAR) unit which showed a significant improvement when compared to baseline ($P < 0.001$) and means best corrected visual acuity was 0.03 ± 0.06 logMAR, which showed no significant difference ($P = 0.730$). Manifest refraction spherical equivalent (MRSE) at 3 years ($-0.12 \pm 0.2D$) was significantly decreased when compared to baseline ($P < 0.001$), but it did not change significantly after the 1st year and was stable ($P = 0.368$). Mean coma and spherical aberration 3 years postoperatively were $-0.54 \pm 0.26 \mu m$ and $0.46 \pm 0.19 \mu m$, respectively, and neither parameter showed significant differences when compared to baseline ($P < 0.001$). No significant change was found in mesopic contrast sensitivity. The long-term results of this study showed that PRK-MMC could be regarded an effective, safe, and stable procedure in patients with myopia more than 6.0 D.

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Introduction

Refractive surgery is considered a safe modality for achieving stable and desirable visual correction in myopic patients. Photorefractive keratectomy (PRK) is one of the most widely applied procedures for correcting low to moderate myopia (1-3). Although different researches have shown comparable efficiency and safety for laser in situ keratomileusis (LASIK) and PRK for correcting low to moderate myopia, LASIK is suggested as the preferred technique in patients with high myopia (4). The safety and efficacy of PRK for moderate to high myopia have been demonstrated in short-term studies, but there is no strong evidence for its long-term outcomes (5-9). In correcting high myopia, PRK may be associated with haze formation and refractive regression as a result of keratocyte activation (10-12). Based on

available evidence, environmental factors can play a role in aggravating the situation (13). Therefore, with regards to the environmental and ethnic differences in the Middle East, the complications might be more serious (14). Efforts to improve outcomes using corticosteroids, plasmin inhibitors, and collagenase inhibitors in recent decades have not been successful (15,16). Although some studies have reported the long-term results of PRK in the treatment of myopia more than 6.0 diopters (D) (7,17), their results cannot be generalized to PRK with mitomycin-C (PRK-MMC). Moreover, these studies were done retrospectively, and the results of older techniques (e.g. laser-assisted subepithelial keratectomy) and PRK were combined.

Since mitomycin-C can prevent the rapid growth of corneal epithelial, stromal, endothelial, conjunctival, Tenon's capsule fibroblasts, and retinal pigment

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epithelial cells and has been used in different ocular operations including PRK (9,18-24), several studies have shown that the use of MMC in PRK can decrease complications such as haze formation and refractive regression resulting from keratocyte activation (25-30). This is while in-vitro studies have reported complications of MMC including myofibroblast transformation and keratocyte apoptosis (31). Long-term effects of MMC in terms of visual quality and refractive regression are still not clear (8,9,32-33). This study was conducted to evaluate three-year visual acuity and quality outcomes of PRK-MMC in patients with high myopia (>6.0 D).

Materials and Methods

In this before-after case series, 20 individuals (40 eyes) with high myopia underwent PRK-MMC at Noor Eye Hospital in Tehran in 2010. The inclusion criteria of the study were myopia more than 6.0 D, refractive stability for 18 months before surgery (less than 0.5 D change), and no use of contact lenses for 4 weeks before surgery. Moreover, individuals with any type of ocular surgery, corneal pathology, and diseases that could interfere with postoperative corneal healing were excluded from the study.

Examinations included the measurement of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) using a Snellen chart, manifest refraction spherical equivalent (MRSE) using an auto kerato-refractometer (Topcon 8800, Tokyo, Japan) and retinoscopy (ParaStop HEINE BETA 200; HEINE Optotechnik, Herrsching, Germany), contrast sensitivity (CS) testing using the CVS 1000 grating charts (VectorVision Inc., Greenville, Ohio, US), and measurement of higher order aberrations (HOAs) using the Allegretto WaveLight Analyzer (WaveLight Laser Technologie AG, Erlangen, Germany).

CS was measured under mesopic conditions (10 lux) without dilation wearing best distance correction. Extracted aberration indexes included C9 (trefoil), total coma root mean square (RMS), C8 (horizontal coma), C7 (vertical coma), C6 (trefoil), C12 spherical aberrations (SA), and total HOA RMS. Measurements were repeated three times and the best image with the least error was selected. The study was approved by the Institutional Review Board of Noor Ophthalmology Research Center (NO; M.1149) and participants signed informed consents before joining the study.

Surgical procedures

All operations were performed under topical anesthesia with proparacaine hydrochloride 0.5% by one surgeon (HH). The VISX STAR S4 Excimer laser with software version 5.30 (Abbott, Altavista, US) was used for conventional ablation without iris registration (target laser fluence=160 mj/cm², laser pulse rate=10.0 Hz). The ablation zone was set on 6mm with a 1.25 mm blend zone. After the mechanical removal (scraping) of the corneal surface and laser ablation, a sponge soaked in MMC 0.02% was placed on the ablated stromal bed (for 10 seconds per 1.0 D correction). Then, the stroma was irrigated with 30 cc balanced sterile solution. At the conclusion of the procedure, a bandage contact lens (Air Optix, Ciba vision, Alcon, TX, US) was placed. The postoperative treatment included levofloxacin eye drops (Oftaquix 5 mg/ml) and betamethasone 0.1% four times daily and preservative-free artificial tears (Hypromellose, preservative free) as needed. To reduce inflammation, diclofenac sodium 25 mg (Voltaren) was used every 6 hours for 24 hours. Daily examinations were continued until complete epithelial healing was observed. At this time, the bandage contact lens was removed, and Oftaquix[®] was discontinued, but betamethasone and artificial tears were continued for two more weeks. Also, fluorometholone 0.1% drops were prescribed to be tapered over the next three months. Follow-up visits were scheduled for 1,3,12, and 36 months after surgery. One-year results have been reported before, and here we present the three-year outcomes in comparison with baseline and one-year results.

Statistical analysis

The following formula was used to calculate total coma: Total coma RMS= $\sqrt{(C7+C8)^2}$. The safety index of PRK-MMC was calculated as postoperative CDVA divided by preoperative CDVA and efficacy was calculated as postoperative UDVA divided by preoperative CDVA. *P*-values less than 0.05 were considered significant.

In this report, generalized estimating equations (GEE) were used to compare UDVA, CDVA, MRSE, and mesopic CS at baseline and at 1 and 3 years after surgery. The effect of fellow eye correlation was adjusted for in the analysis. Bonferroni correction was applied to adjust the significance level of multiple comparisons.

Results

Of the 20 individuals who originally participated in the study, 3 people (6 eyes) did not return for the three-year follow-up due to the long distance and complete satisfaction with their visual status. Therefore, all reported results concern 17 participants (34 eyes). The mean age of the participants was 29.00 ± 5.24 years (22-40 years), and 55.6% of them were female patients. During the three-year follow-up, no complications such as haze formation or infectious keratitis were observed, and none of the patients had complaints about visual symptoms such as glare or star.

Table 1 summarizes baseline and postoperative vision and refraction data. At 3 years after surgery, UDVA was 0.03 ± 0.06 in the logarithm of minimum angle of resolution (logMAR) unit (20/21) which showed a significant difference when compared to baseline ($P < 0.001$). Mean CDVA was 0.03 ± 0.06 logMAR (20/21) after three years with no significant difference when compared to baseline ($P = 0.730$). The three-year safety and efficacy index was 1.04 ± 0.17 and 0.99 ± 0.23 , respectively. Mean UDVA and CDVA at 1 and 3 years after surgery did not differ significantly ($P = 1.000$ and $P = 0.293$, respectively).

Table 1. Visual acuity and refraction at baseline and at 1 year and 3 years after photorefractive keratectomy with the application of mitomycin-C in high myopic patients (mean \pm SD)

	Baseline (CI 95%)	After surgery		P. value [†]
		1 year (CI 95%)	3 years (CI 95%)	
UDVA (logMAR)	1.78 ± 0.32 (1.63 to 1.88)	0.01 ± 0.03 (0.01 to 0.05)	0.03 ± 0.06 (0.01 to 0.05)	<0.001
CDVA (logMAR)	0.04 ± 0.07 (0.01 to 0.05)	0.02 ± 0.01 (0.01 to 0.03)	0.03 ± 0.06 (0.00 to 0.04)	0.730
Spherical error (D)	-7.14 ± 1.60 (-7.56 to -6.28)	0.02 ± 0.13 (-0.04 to 0.04)	-0.02 ± 0.1 (-0.08 to 0.05)	<0.001
Cylindrical error (D)	-1.59 ± 1.14 (-2.00 to -1.08)	-0.20 ± 0.29 (-0.36 to -0.12)	-0.19 ± 0.37 (-0.39 to -0.11)	<0.001
MRSE (D)	-8.11 ± 1.72 (-8.16 to -7.01)	-0.10 ± 0.18 (-0.19 to -0.05)	-0.12 ± 0.22 (-0.24 to -0.06)	<0.001

[†] to compare the mean values of third-year and preoperative visits

UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity; MRSE: manifest refraction spherical equivalent

At baseline, MRSE was 6.0-8.0 D in 54.8%, 8.0-10.0 D in 38.1%, and more than 10.0 D in 16.7% of the participants, and mean MRSE was -8.11 ± 1.72 D which decreased to -0.12 ± 0.22 D at three years ($P < 0.001$) (Table 1). On the third year follow-up visit, 94.4% of the participants were within ± 0.5 D of emmetropia. Only 2 eyes (5.6%) had MRSE of 0.75 D. Comparison of mean MSRE between the first and 3rd year showed no significant change and indicated stability ($P = 0.706$).

Table 2 presents three-year changes in HOAs. After three years, the increase in a total coma ($P = 0.020$), SA ($P = 0.014$), and total HOAs ($P = 0.050$) was significantly significant, while C6 and C9 had no significant changes. Comparison of one-year and three-year results showed that total coma ($P = 0.404$), SA ($P = 0.627$), C6 ($P = 0.923$), C9 ($P = 0.702$), and total HOA ($P = 0.575$) were stable after one year with no significant changes.

Table 2. Higher order aberrations at baseline and at 1 year and 3 years after photorefractive keratectomy with the application of mitomycin-C in high myopic patients (mean \pm SD)

	Before surgery (CI 95%)	After surgery		P. value [†]
		1 year (CI 95%)	3 year (CI 95%)	
C6 trefoil (μ m)	-0.05 ± 0.18 (-0.12 to -0.02)	0.03 ± 0.23 (-0.12 to 0.09)	0.05 ± 0.17 (-0.01 to 0.05)	0.012
C7 vertical coma (μ m)	0.09 ± 0.21 (0.02 to 0.15)	-0.14 ± 0.38 (-0.23 to 0.12)	-0.12 ± 0.37 (-0.27 to 0.02)	0.020
C8 horizontal coma (μ m)	-0.02 ± 0.13 (-0.04 to 0.05)	0.09 ± 0.45 (-0.01 to 0.13)	-0.50 ± 3.40 (-1.85 to 0.83)	0.999
Total coma RMS (μ m)	0.22 ± 0.18 (0.17 to 0.31)	0.54 ± 0.27 (0.51 to 0.78)	0.54 ± 0.26 (0.45 to 0.65)	< 0.001
C9 trefoil (μ m)	-0.01 ± 0.13 (-0.08 to 0.04)	-0.01 ± 0.16 (-0.11 to 0.09)	-0.01 ± 0.31 (-0.13 to 0.11)	0.999
C12 spherical aberration (μ m)	0.05 ± 0.15 (0.00 to 0.12)	0.35 ± 0.13 (0.35 to 0.46)	0.46 ± 0.19 (0.38 to 0.52)	< 0.001
Total HOA RMS (μ m)	0.37 ± 0.22 (0.30 to 0.47)	0.77 ± 0.27 (0.78 to 1.08)	0.80 ± 0.27 (0.73 to 0.92)	< 0.001

[†] Baseline versus 3-year results

CI: Confidence intervals; HOAs: higher order aberrations; RMS: root mean square

The changes of mesopic CS in spatial frequencies 3 (CS3) after three years were not significant when compared to baseline ($P=0.335$). No significant change was found in CS6 ($P=0.115$) or CS18 ($P=0.864$) either.

Comparison of one-year and three-year results showed the stability of CS3 ($P=0.294$), CS6 ($P=0.591$), CS12 ($P=0.460$), and CS18 ($P=0.915$) (Figure 1).

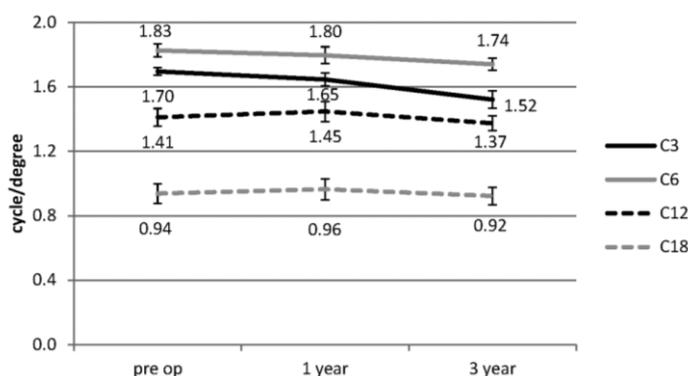


Figure 1. Logarithm of mesopic contrast sensitivity at baseline and at 1 year and 3 years after photorefractive keratectomy with the application of mitomycin-C in high myopic patients (mean \pm SE)

Discussion

The results of this long-term study showed that PRK-MMC is an effective procedure for the correction of refractive errors. Comparison of 1-year refractive outcomes with baseline showed a significant difference in all vision and refraction indices except for CDVA. Significant differences were also observed when three-year, and baseline data were compared. The significant change in UDVA is indicative of PRK-MMC efficacy in improving visual acuity in high myopia, and patients enjoy better visual clarity after surgery. Our results were similar to the 24-month results of a study by Diakonis *et al.*, (34). The main goal of PRK is improving UDVA, achieving this goal while maintaining CDVA is an important standard of safety for this type of surgery. The literature contains reports pointing to decreased CDVA as a complication of PRK in high myopic cases (35,36). In our study, although mean CDVA in the first and third year was lower compared to baseline, the decrease was not significant, and none of the participants lost Snellen lines due to corneal haze or irregular astigmatism. This finding is in favor of PRK-MMC safety. In this regard, our findings are in line with the results of a number of studies with different follow-up times ranging from 6 to 24 months (30,34,37,38).

Different short-term studies have reported the positive effects and safety of MMC use in PRK for high myopia, and the results of our confirm its long-term

positive effects and safety (12,25,34,39,40). It should be noted that despite the MMC protocol in other studies (30 seconds to 2 minutes), we used MMC for 10 seconds per diopter correction to minimize the risk of adverse effects (34,39,41). According to our findings, it seems that reducing the MMC application time allows patients to benefit from its advantages such as reduced risk of haze without experiencing its side effects.

In terms of predictability, although there is evidence of satisfactory refractive outcomes of PRK without MMC (7,17). Results with PRK-MMC are more favorable (33). In our study, all 34 eyes were within ± 1.0 D of emmetropia at 3 years after surgery, and 94.5% of them were within ± 0.5 D. Mean MRSE improved significantly after surgery when compared to baseline, indicating the acceptable predictability of PRK-MMC in high myopia. The results of this study in terms of predictability are in agreement with the findings of studies by Carones *et al.*, Lee *et al.*, and Diakonis *et al.*, with follow-up periods of 6, 13, and 24 months, respectively (30,34,42).

It has been shown that in high myopia patients, refractive regression, as a complication, usually occurs in the first postoperative year. Our study showed that residual refractive error remained unchanged in the first and third-year post operation, showing the refractive stability of PRK-MMC. The results of the three-year follow-up of the present study are congruent with the findings of some other studies with one-year follow-ups

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(9,33,34).

In light of the reported relationship between HOAs and visual outcomes like night vision, double vision, shadows and halos, and glare (43,44), HOA changes were evaluated in this study. We found a significant increase in a coma and mean total HOAs RMS while CS did not change significantly. It should be noted that the significant increase in total mean HOAs RMS could decrease day and night visual clarity and the increase in a coma could cause monocular diplopia, ghosting, and glare (45) although these complications were not observed in our patients.

As for the indexes of mesopic CS, mean CS3 showed a gradual decrease from baseline through the third year. Despite an increase in the first year, mean CS6 was significantly decreased in the third year when compared to baseline. Mean CS12 and CS18 showed a similar pattern and decreased in the first year but then increased in the third year when compared to baseline, although the increase was not significant. However, the decrease in mean C18 in the first year versus baseline was significant. The results of CS3 and CS12 were similar to the report by Wallau *et al.*, with a follow-up period of 6 months (9).

Due to the pre-test/post-test nature of this study, the results should be interpreted with caution. The GEE method was used for analysis on account of the loss to follow-up in the first- and third-year visits in order to provide a valid estimate of the standard errors of repeated measurements and avoid underestimated *P*-values while maintaining study power.

Although some randomized controlled trial (RCT) studies have been done, (27,40) it is necessary to perform RCT studies with longer follow-up periods and adequate sample sizes in order to determine the safe dose, best application duration, and permanent effects of MMC in PRK.

The results of this long-term study showed that PRK with the application of 0.2 mg/ml MMC for 10 seconds per diopter correction could provide good visual outcomes with no complications. Therefore, PRK-MMC could be used as a safe and effective surgical technique for stable long-term results in high myopia (6.0 D) patients.

Acknowledgment

The authors declare no conflict of interest.

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