

*Original Article***Results of photorefractive keratectomy with mitomycin C
for high myopia after 4 years***Farhad Fazel**, *Afsaneh Naderibeni****Fateme Eslami***, *Hooman Ghatrehsamani*****Abstract**

BACKGROUND: This study assessed the long-term results of photorefractive keratectomy (PRK) with mitomycin C in high myopia (≥ 7 diopter).

METHODS: In this retrospective study, visual acuity, refractive error, pachymetry, topography, contrast sensitivity, corneal haze safety, predictability and complications (with emphasis on ectasia) of 37 high myopic patients (72 eyes) who had PRK surgery with mitomycin C in the last 10 to 40 months were assessed. The exclusion criteria included previous ocular surgery other than LASIK, current ocular disease and any systemic illness.

RESULTS: The mean follow up period was 27.2 ± 7.9 months. The spherical equivalent error was significantly reduced, from a mean of -9.10 ± 2.12 diopters (D) (range of -7 to -18.25 D) before PRK to a mean of -1.81 ± 1.57 D (range of -8.5 to 0 D) after ($P = 0.001$). Postoperatively, 34.72% of eyes were within ± 0.5 D of attempted correction and 58.33% within ± 1 D and 84.72% within ± 2 D. 80.5% of eyes had a vision of 20/40 or better. Best corrected visual acuity (BCVA) was unchanged or improved in 93.05%. The safety index was 0.96 [the ratio of mean postoperative BCVA (0.84) to mean preoperative BCVA (0.87)] and efficacy index was 0.8 [the ratio of mean postoperative uncorrected visual acuity (0.7) to mean preoperative BCVA (0.87)]. Corneal haze formation was seen in 5 patients (6.9%) with grade +1. The minimum stromal residual bed was 400 μm . No eyes had progressive corneal ectasias at the time of post-op control.

CONCLUSIONS: The topical intraoperative application of 0.02% mitomycin C can reduce haze formation in highly myopic eyes undergoing PRK. Predictability of refractive results, however, was poor.

KEY WORDS: Mitomycin C, photorefractive keratectomy, high myopia.

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Excimer laser photorefractive keratectomy (PRK) has become a common surgical procedure to correct refractive disorders¹⁻⁶ but because of its side effects (mainly slow visual recovery, discomfort in the early postoperative period and corneal haze) it has been widely replaced by laser in situ keratomileusis (LASIK)⁷. Unfortunately, patients

with -5 diopter (D) myopia or more and corneal thickness less than 500 μm are not suitable candidates for LASIK or conventional PRK due to the inadequate corneal thickness and risk of haze⁸⁻¹¹. In these eyes, LASIK may induce structural instability, tissue ectasia and associated complications such as irregular astigmatism, loss of best spectacle-corrected visual

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acuity (BSCVA), and sometimes, iatrogenic keratoconus¹². In highly myopic eyes, unsuitable for laser ablation, phacic intraoperative lens (IOL) was developed to become a reasonable alternative. However, it could also be considered to treat the high myopic refractive errors by PRK if wound healing reactions such as haze formation could be suppressed effectively. PRK is easy to apply, it is not invasive such as IOL implantation and therefore, potential complications such as endophthalmitis or cataract formation are not associated with PRK. Correction of high myopia with PRK can lead to haze development, compromising final visual function^{13,14}. Haze after PRK is induced by activated and proliferating corneal keratocytes. The collagen tissue produced by activated keratocytes is much less organized than normal stromal tissue, and shows matrix-free areas and fibers with an irregular stereospatial relationship¹⁵⁻²⁰. Recently, topically applied anti-proliferative drugs have been reported in small series to be able to modulate haze formation and treat established haze²¹⁻²⁵. The most commonly used drug is mitomycin C. There are also some reports on the prophylactic use of mitomycin C to prevent haze following PRK in moderate to high myopia^{18,21,26-29}. To investigate further long-term refractive and mechanical stability and late sequelae after PRK with mitomycin C, we conducted the current study.

Methods

Of 50 high myopic patients (myopia \geq -7 D) who underwent PRK (96 eyes) with mitomycin C at Feiz hospital, Esfahan, Iran, during 2002-2004, 37 patients (72 eyes) underwent follow-up examinations after surgery (follow-up rate: 75%). The baseline demographic characteristics of patients who underwent follow-up examinations in terms of age at surgery, preoperative manifest distance refraction (mean spherical equivalent), and attempted correction was not statistically significant ($P = 0.09$). The reasons for failing to attend follow-up appointments were either change of address or work and family commitments. Patients attended lec-

tures that provided background information before deciding whether to enter the study and were counseled before surgery before providing informed consent. There were 25 female patients and 12 male patients. At the start of the study, the mean age of patients was 26.3 years (range: 20-46 years). Exclusion criteria were patients with preexisting ocular pathological features, previous anterior segment surgery, diabetes and connective tissue disorders. The preoperative mean spherical equivalent (MSE) of all patients was -9.1 ± 2.12 D (range: -7 to -18 D).

Preoperative assessment

Before surgery a detailed ocular examination was performed, including subjective and cycloplegic refraction, keratometry, corneal pachymetry, tonometry, mydriatic funduscopy and contrast sensitivity.

Operative procedure

In planning PRK, the post-ablation corneal thickness was calculated to be greater than 350 μm without epithelium. Patients received topical anesthesia without systemic sedation. With 8 mm ring 16% ethanol in an optical zone marker well for 20 seconds used. The epithelium was removed mechanically with a sponge. Then, the ablation was performed using Nidek EC 5000 excimer laser. In all treatments, the central optical zone of 6 mm and transition zone of 7.5 mm were applied. Immediately after laser ablation, a single topical application of mitomycin C 0.02% (0.2 mg/ml) diluted in balanced salt solution was applied in each eye with a weck sponge placed over the ablated stroma for 45 seconds. The corneal surface and the entire conjunctiva were then vigorously irrigated with 20 ml cold normal saline to remove the residual mitomycin C. At the end of the procedure, a bandage contact lens was applied which was removed after one week.

Postoperative treatment and assessment

After surgery, patients were instructed to take an analgesic (diclofenac sodium) every 8 hours and all eyes were received betamethasone eye

drop every 6 hours for 2 weeks, and chloramphenicol eye drop every 6 hours for one week. All patients were instructed to wear sunglasses in direct sunlight for 3 months. On the first seven days after surgery, all patients were examined with slit lamp and the areas of the epithelial defect were measured with its ruler to identify the time of complete reepithelialization. Postoperative examinations were carried out at 1 and 3 days, 1 and 4 weeks, 3, 6, and 12 months. At each visit, a full refraction and slit-lamp examination were performed. At the last follow-up (mean: 27 months), pachymetry and topography was done. Data of postoperative measurements including, uncorrected VA, best-corrected visual acuity, contrast sensitivity (Vision Contrast Test System plates CVS-1000 cs chart) mesopic and photopic, topography (ZEISS Humphrey system 1993-2000), ultrasonic pachymetry were recorded. Patients were examined with a slit lamp. For evaluation of haze, we used Hanna's grading scale from 0 (no haze) to +4 (dense white corneal haze) ³⁰.

Data Analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (version 11.5). The refractive error of those subjects who required cylindrical corrections were converted to spherical equivalents. Pearson correlation coefficients were used to evaluate correlation between continuous variables and Pearson's chi square test was used to investigate associations between categorical variables. Data were also described as mean \pm standard deviation (SD), and differences were considered significant if $P < 0.05$. The right and left eyes were analyzed independently as the surgery was conducted independently for the right and left eyes

Results

The mean interval between PRK and study was 27 months (range: 10-40 months). The age of the patients ranged from 19 to 46 years (mean: 26.35 ± 7.8). The preoperative MSE was -9.1 ± 2.12 D (range: -19 to -10 D). The attempted mean spherical correction was -12.59

G 2.96 D (range: -7 to -18 D). The MSE error was significantly reduced to -1.81 ± 1.57 D (range: -8.5 to 0 D) after PRK ($P=0.001$). The refractive and demographic data are listed in table 1. The postoperative refractive and visual data are listed in table 2.

Table 1. Demographic and refractive data of the surgery group (n= 72, 36 right eye, 36 left eye).

	Mean \pm SD	Rang
Age	26.35 ± 7.8	19 to 46
Sphere (D)	-8.22 ± 0.1	-16.5 to -7
Cylinder (D)	-1.13 ± 0.1	-4.5 to 0
Pachymetry (μ m)	532 ± 37	481 to 643
CIM (corneal irregularity measurement)	1.09 ± 0.74	0.46 to -5.55
SF (shape factor)	$0.347 \pm .182$	-0.66 to 0.62
Ablation depth without epithelium μ m	116.83 ± 8.68	75 to 162.7

Table 2. Refractive and visual outcomes after surgery.

Parameter	Preoperative	Postoperative
Spherical equivalent (D)	-9.1 ± 2.12	-1.811 ± 0.57
Cylinder (D)	-1.131 ± 0.1	-0.90 ± 0.73
BCVA	0.870 ± 0.17	0.840 ± 0.17
CIM (Corneal Irregularity Measurement)	1.090 ± 0.74	1.931 ± 0.14
SF (Shape Factor)	0.3470 ± 0.182	-0.9510 ± 0.622
Pachymetry (μ m)	532 ± 37	432 ± 38

Predictability

For all patients, the preoperative MSE at the spectacle plane was -9.1 ± 2.12 D (range: -7 to -18 D) and the attempted mean spherical correction at the corneal plane was -8.1 ± 1.6 D (range: -5.25 to -12 D). The predictability after surgery is shown in figure 1. The number of eyes (with percentages) within ± 0.5 D, ± 1 D and ± 2 D of the intended correction after surgery is shown in table 3. Twenty five eyes (34.7 %) were within ± 0.5 D of emmetropia (SE) and 40 eyes (58.3 %) within ± 1 D (SE) and 60 eyes (84.7) within ± 2 D(SE).

Safety

The mean changes in refraction for patients are shown in table 4, which shows the safety data: loss and gain of BCVA). Uncorrected visual acuity was 20/40 or better in 58 eyes (80.5%), 20/25 or better in 39 eyes (54%), and 20/20 or better in 19 eyes (26.38%).

Best Spectacle-Corrected Visual Acuity

BSCVA was unchanged or improved in 67 eyes (93.03%). Specifically, 51 eyes (70.8%) were unchanged, 9 eyes (12.5%) gained 1 line and 7

eyes (9.7%) gained 2 lines or more. Three eyes (4.1%) lost 1 line and two eyes (2.7%) lost more than 1 line of BSCVA. In patients with loss in BSCVA, haze formation developed. Mean postoperative BCVA was 0.84, mean preoperative BCVA was 0.87 and mean postoperative uncorrected visual acuity (UCVA) was 0.7. The safety index (the ratio of mean postoperative BSCVA to mean preoperative BSCVA) was 0.96 and the efficacy index (the ratio of mean postoperative UCVA to mean preoperative BCVA) was 0.8.

Table 3. Numbers of eyes, with percentages (%), within 0.5 Diopters and 1 Diopters of the intended correction.

	Number (Percentage)
Within ± 0.5 D of intended correction	25 (34.7)
Within ± 1 of intended correction	40 (58.3)
Within ± 2 of intended correction	60 (84.7)

Table 4. Safety of PRK with mitomycin C in high myopia.

VA	Lines Lost		Unchanged	Lines Gained	
	2 or more	1		1	2 or more
BCVA postoperative	2	3	51	9	7

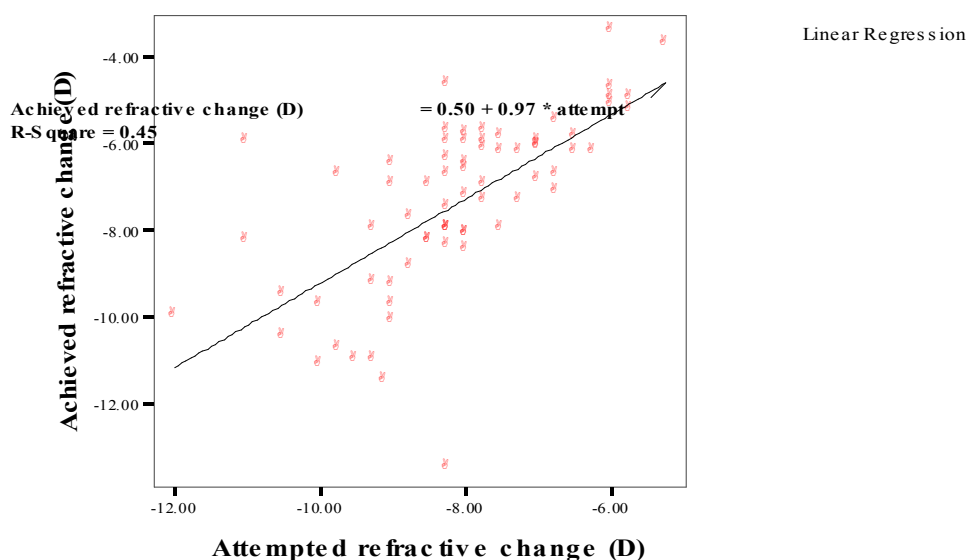


Figure 1. Predictability after surgery (D = diopter).

Contrast sensitivity

Figures 2, 3 and table 5 show the changes of contrast sensitivity in spatial frequencies of 3, 6, 12 and 18 cycles per degree in photopic and

mesopic conditions. Photopic and mesopic contrast sensitivity were preoperatively and postoperatively different.

Table 5. P values in contrast sensitivity change in spatial frequency in PRK.

Spatial frequency P value	Photopic condition				Mesopic condition			
	3 c/d	6 c/d	12 c/d	18 c/d	3 c/d	6 c/d	12 c/d	18 c/d
	0.02	0.04	0.02	0.01	0.02	0.03	0.03	0.01

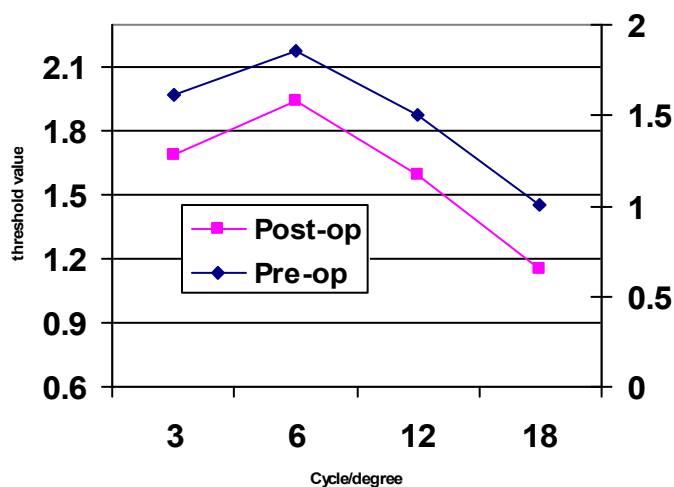


Figure 2. Contrast sensitivity under photopic conditions before and after PRK with mitomycin C in high myopia.

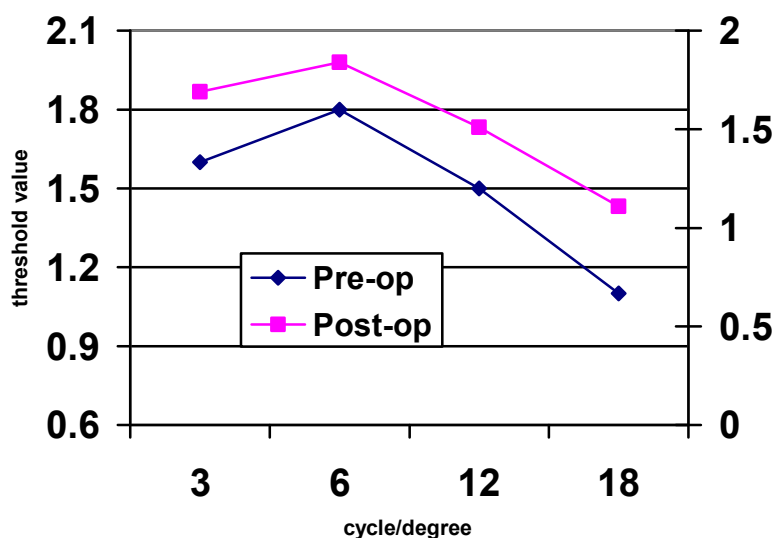


Figure 3. Contrast sensitivity under mesopic conditions before and after PRK with application of mitomycin C in high myopia.

Haze Measurements and retreatment

Corneal haze formation in 5 eyes (6.9%) was grade +1. Other degrees of corneal haze were not observed. There were no cases of retreatment (due to low residual corneal thickness and high satisfaction rate of patients) and progressive corneal ectasia among the follow-up group.

Discussion

The treatment of high myopia by PRK remains a challenge. The evidence of greater haze formation associated with regression of refractive correction, and the higher accuracy of LASIK in the treatment of high ametropias, discouraged interests in making PRK more predictable, safe and effective for highly myopic corrections^{7,18,31,32}. Yet, LASIK can not be performed in some patients with an insufficient corneal thickness resulting in an undesirable residual stromal bed or application of smaller ablation zones to correct the refractive error completely. Such a small ablation zone can lead to visual inconveniences such as impaired night vision when the pupil dilates, halos, blurred vision, and ghost images. Recently, the role of PRK has been reappraised because of corneal instability and poor visual function frequently reported by highly myopic patients undergoing LASIK^{7,33}. Conversely, haze formation continues to be the major side effect after PRK^{34,35}. If PRK plus mitomycin C safety and predictability can be verified, larger ablation depths can be used and the above complications will practically be avoided. On the other hand, correction of higher refractive errors will be possible. By collecting data in a systematic fashion and keeping as many variables as possible constant, this study was designed to examine the efficacy and long-term stability of PRK along with a 45 seconds minute application of mitomycin C 0.02% (0.2 mg/ml) on the exposed stromal bed after ablation was performed in high myopic patients. Mitomycin C is an antimetabolite and antibiotic drug. It has been used in ophthalmology in cases of intraepithelial neoplasms of the cornea and conjunctiva, ocular pemphigoid

and following surgical treatment of glaucoma and pterygium. Mitomycin C has cytotoxic effects through inhibiting DNA synthesis. The rationale of its long term effects is based on prevention of hyperproliferation of keratocytes and on apposition of new irregularity generated materials causing scars^{36,37}. The effects of mitomycin C 0.02% in preventing haze has been shown by Talamo et al³⁸, and Xu et al³⁹ in experimental models. In studies by Majmudar et al and Maldonado, it was concluded that the application of mitomycin C can remove haze following PRK and radial keratectomy²¹⁻²³. Carones et al reported the positive refractive and visual results over a 6-month period after PRK with mitomycin C 0.02% (0.2 mg/ml) for medium and high myopia¹⁸. We used the same concentration of 0.2 mg/ml to perform PRK with mitomycin C in high myopia considering the different climate and races in this Middle Eastern region. More over, the problems of haze and regression after PRK are more prominent in people of this region⁴⁰. Among factors determining the ablation depth, an important predictor of haze, correction and ablation zone size are more important. A 6 mm optical zone and a minimum of ≥ 7 diopters of correction, ethically and practically limited our study to those patients who were at a high risk of developing haze with PRK. Maximum ablation depth of cornea in our patients was 160 μm and minimal corneal depth after PRK was 400 μm in this study and no patient had corneal ectasia. It seems that residual corneal after PRK to 400 μm is safe however, another study is needed. The BCVA after surgery was 20/50 or better in 100% and 20/20 or better in 45.8% of patients. The refractive and visual results of this study are better compared to the reports concerning the same amount of correction with LASIK^{41,42} in which the predictability was 55% and $45\% \pm 1$ DSE, respectively. Considering the fact that haze influences BCVA, patients' BCVA is of great importance. In this study, 5 eyes lost one line of BCVA after surgery compared to the preoperative BCVA and 67 eyes had better BCVA or the same as preoperative conditions.

The mean BCVA was approximately the same as preoperative value. Major side effects (corneal edema, melting or perforation) or minor complications (major corneal sensitivity or tear film problems) associated with the topical use of mitomycin C were not seen. None of the eyes had significant grades of haze or degenerative reactions after surgery. Another important finding was the absence of post-LASIK corneal ectasia despite the increased attempted corrections. As a counterbalance, contrast sensitivity was decreased in these patients. However, the major limitation of the study included its retrospective and cross-sectional nature,

absence of data during the interval between 6 months and the mean 27 months, low rate of the patients completed follow-up (75%), possible age-induced refraction and lack of comparison with a control group. Ectasia after refractive surgery is a long-term problem possibly appearing a decade after the initial treatment therefore, follow up is necessary. In conclusion, using mitomycin C in PRK for myopia greater than -7 D seems safe and can reduce haze formation after surgery. However, predictability was poor (only $58.3\% \pm 1$ DSE) in the treatment of highly myopic eyes undergoing PRK with mitomycin C.

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