Prophylactic Effects of Mitomycin-C on Regression and Haze Formation in Photorefractive Keratectomy

Hassan Hashemi, MD[1,2]; Mohammad-Reza Taheri,MD[2]; Akbar Fotouhi, MD, PhD[3]

ABSTRACT

Purpose: To study the effect of prophylactic application of mitomycin-C on regression and corneal haze formation after photorefractive keratectomy (PRK) for high myopia.

Methods: Fifty-four eyes of 28 high myopic patients were enrolled in this prospective study. All eyes underwent PRK with application of 0.02% mitomycin-C for two minutes and irrigation with 15-20 ml of normal saline. Follow-up visits were scheduled for the first 7 days and 1,3 and 6 months after surgery. Hanna grading (in the scale of 0 to 4+) was used to assess corneal haze.

Results: Mean spherical equivalent refraction (SE) was -7.08 ± 1.11 diopters (D), preoperatively. All eyes were examined on the first 7 days and one month after surgery; 48 eyes (88.9%) were evaluated 3 and 6 months post-surgery. Six months after surgery, all eyes had uncorrected visual acuity (UCVA) of 20/40 or better and 37 eyes (77.1 %) achieved UCVA of 20/20 or better, 45 eyes (93.7%) had SE within ±1.00D of emmetropia. One month postoperatively, 2 eyes (3.7%) had grade 0.5 haze, while at 3 and 6 months after surgery no visited eye had haze at all. There was no decrease in best corrected visual acuity after 6 months. In spatial frequencies of 6 and 12 cycle/degree, contrast sensitivity decreased immediately after PRK but increased to the preoperative values by the 6th postoperative month.

Conclusions: Mitomycin-C can prevent the development of corneal haze when treating high myopia with PRK. In patients with insufficient corneal thickness for laser in situ keratomileusis (LASIK), mitomycin-C makes a useful adjunct to PRK to provide an alternative treatment for myopia. However, further research with longer follow-up is suggested.

[1] Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Noor Eye Clinic, Tehran, Iran
[3] Health Faculty, Tehran University of Medical Sciences, Tehran, Iran

Introduction

In keratorefractive surgery, patients with myopia greater than -5.0 diopters (D) and corneal thickness less than 500 microns are ineligible for laser in situ keratomileusis (LASIK) or refractive keratectomy (PRK) due to the risk of corneal haze.[1-14] Smaller ablation zones enable surgeons to perform LASIK in relatively thin corneas, but this approach predisposes patients to postoperative complications such as glare and halos.[15] Should corneal haze formation in myopic eyes undergoing PRK be prevented, there would be less concern over corneal thickness, ablation zones and even flap

induced aberrations which are major problems in LASIK.[16]

Mitomycin-C 0.02% has previously been used in the treatment of post-PRK corneal haze.[17] The corneal haze seen following PRK may be due to the process of wound healing. In laboratory animals, it has been shown that this process probably begins with keratocyte apoptosis which then leads to overproduction of cells.[18] Mitomycin-C is an antibiotic with anti-metabolitic properties which can inhibit keratocyte proliferation without affecting normal corneal cells. There are reports on prophyhlactic use of mitomycin-C for inhibition of haze formation after PRK for moderate to high myopia.[15,19]

In this study, we evaluated the effect of mitomycin-C as an adjunct to PRK on regression and corneal haze in high myopic (>-5.0 D) patients.

Methods

In this interventional case series, 54 eyes of 28 patients with spherical equivalent refraction of -5.0 D or greater were enrolled. Corneal thickness in these eyes did not meet the criteria for LASIK, because residual stromal bed would be less than 250 microns. However, predicted corneal thickness after PRK was over 350 microns. Exclusion criteria were any ocular or systemic disease that could potentially interfere with corneal healing (such as collagenoses and diabetes mellitus), dry eye syndrome, anterior or posterior uveitis, glaucoma, retinal disorders, lens opacities, history of severe eye trauma or ocular surgery, corneal ectatic conditions such as keratoconus and corneal dystrophies.

All eyes underwent standard PRK. All operations were performed under local anesthesia by a single surgeon. The corneal epithelium was cut 8.0 mm wide and 70 microns deep with a microtrephine and lifted using a hockey knife. Laser ablation was performed with the Technolas 217-C excimer laser. In all cases, the ablation zone was 8.4 to 8.9 mm in diameter including a 5.5-6.0 mm central optical zone and a 2.9 mm transitional zone. The algorithm was adjusted based on our experience. To avoid overcorrection, the applied correction was 5% less than that for LASIK.

The ablated area was immediately soaked with mitomycin-C 0.02% for 2 minutes using a cellulose sponge. Then the corneal surface and the entire conjunctiva were irrigated with 20 ml of normal saline. At the end of the procedure, a bandage contact lens was fit on the cornea and removed in 3 days. An oral analgesic (diclofenac sodium) was prescribed for patients orally every 8 hours. Patients were instructed to use artificial tears and fluorometholone eye drops every 4 hours for two weeks, every 6 hours in the third and fourth weeks, every 8 hours during the second month, and every 12 hours in the third month. Chloramphenicol eye drop was also prescribed every 6 hours for 3 days. All medications were discontinued at the end of the third month. Patients were advised to wear sunglasses for 3 months.

Preoperative examination included uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), refraction (manifest, subjective, and cycloplegic), slit lamp examinations, intraocular pressure measurement, corneal topography, ultrasound pachymetry, keratometry, indirect fundoscopy, and contrast sensitivity with Vector Vision 1000 (with and without glare, 6 and 12 cycles/degree). During the first 7 postoperative days, all eyes were examined with the slit lamp and the epithelial defect was measured to record healing time. On the 7^{th} and 14^{th} postoperative day, UCVA, BCVA and refraction were measured. Examinations performed at month 1, 3 and 6 after surgery were UCVA, BVCA, refraction (manifest, subjective, and cycloplegic), slit lamp examination, intraocular pressure measurement, ultrasound pachymetry, keratometry, topography, and contrast sensitivity with and without glare. Corneal haze was evaluated according to Hanna scale which rates haze from zero (no haze) to 4^{+} (dense and white corneal haze).

Results

Fifty-four eyes of 28 patients with mean age of 29.3 (range, 20 to 45) years were operated. A total of 48 eyes (88.9%) were examined 3 and 6 month after surgery. Preoperatively, mean spherical equivalent refraction (± standard deviation) was -7.08±1.1 (range, -5.0 to -9.9) D and 51 eyes (94.4%) had BCVA of 20/25 or better, which was 20/20 or better in 33 (61.1%). Mean preoperative and postoperative central corneal thickness was 488.6±11.9 and 380.8±28.7 microns, respectively. The epithelium had completely healed in 53.7% of the eyes by the third postoperative day and in 92.6% by day 4. One patient had a large epithelial defect on day four after initial healing which was treated successfully with a bandage contact lens for 3 days. The efficacy of the procedure is shown in Figure 1.

Three months after surgery, refraction was within ±0.5D of emmetropia in 33 eyes (68.7%) and within ±1.0D in 43 (89.6%), while at sixth months, corresponding figures were 39 (81.3%) and 45 (93.7%), respectively. The refractive changes occurring over these 6 months (Figure 2) show that refraction stabilized during the first month. Mean (± standard deviation) spherical equivalent refraction at 6 months was +0.35±0.54 (range, -0.88 to +1.5) D.

UCVA at the third postoperative month was 20/40 or better in 47 eyes (97.7%), and 20/20 or better in 32 (66.7%). At 6 months, all eyes had UCVA of 20/40 or better, which was 20/20 or better in 37 eyes (77.1%). No eye lost visual acuity.

During the first postoperative month, 2 eyes (3.7%) had grade 0.5 corneal haze. No eye had any grade of haze at the 3rd and 6th postoperative visits. Changes in contrast sensitivity during follow-up are shown in Figure 3. Contrast sensitivity, measured at 6 and 12 cycles/degree with and without glare, showed a reduction in both frequencies immediately after PRK, compared to the preoperative values, and a mean increase of 1.5 lines at the sixth month. There were no intraoperative or postoperative complications.

Discussion

The risk of corneal haze and regression makes PRK in high myopia a matter of debate and controversy.[19] This risk may be even greater in our country, Iran, due to darker skin color and exposure to sunlight.[20] However, insufficient corneal thickness leaving the cornea with an unacceptable residual bed makes LASIK impossible or limits it to smaller ablation zones. This in turn may cause disturbances in night vision when the pupil dilates, or halos and glare.[16,21] Should the safety and efficacy of PRK in these eyes be confirmed, larger ablation zones can be used to avoid such complications.

Mitomycin-C is an antibiotic with anti-metabolitic properties used mainly as a systemic chemotherapy agent. It has also been used in ophthalmology in conjunctival and corneal epithelial neoplasms, ocular pemphigus, and in conjunction with glaucoma and pterygium surgery. Mitomycin-C exerts cytotoxic effects through inhibiting DNA synthesis. The logic behind its use in PRK is prevention of stromal keratocyte proliferation and thus inhibition of subepithelial fibrosis which are the major causes of regression and haze after laser ablation. The effect of mitomycin-C 0.02% on corneal haze has been studied on experimental models by Talamo et al.[21] and Xu et al.[22] Majmudar and colleagues[17] have reported that mitomycin-C can eliminate the corneal haze occurring after PRK and radial keratectomy (RK).[17] Results of prophylactic use of mitomycin-C to inhibit haze formation after PRK for high myopia have been reported by Carones et al.[19] In this study, we continue previous studies on the prophylactic effects of mitomycin-C as an adjunct to PRK in a group of Iranian patients with high myopia.

In the present study, no immediate toxic effects such as conjunctival chemosis and delayed or irregular epithelial healing were observed. Only one patient had a large epithelial defect on the

fourth day after initial healing, which resolved within three days wearing a bandage contact lens. During the 6 month follow-up period, no complication previously reported with topical application of mitomycin-C, such as corneal edema, melting, or perforation was seen. Therefore, the topical application of this agent with the aforementioned concentration and duration was safe in this study. Although the results of this study indicate the efficacy of such treatment, great caution is advised in using this agent until further studies confirm its long-term safety.

Based on our previous experience, a nomogram 5% less than that for LASIK was used which brought refractions closer to emmetropia at the 6th postoperative month. In the report by Carones et al[19], patients showed 0.5 D hyperopic shift in 6 months, while in the present study, a myopic shift of 0.43 D was seen.

The results of this study, in terms of visual acuity and refraction, are better than those reported with LASIK[23,24], PRK, or LASEK.[25,26] Considering the fact that corneal haze affects corrected vision, BCVA is an important part of the study. In this study, no eye lost any line of BCVA which provides supporting evidence for the safety of this treatment. None of the eyes showed any degree of haze on the 3rd and 6th month visits; a fact that favors the effectiveness of mitomycin-C in corneal haze prophylaxis. In addition, the efficacy of this treatment, in terms of visual quality, is further approved by the 1.5 line improvement in contrast sensitivity.

In conclusion PRK with mitomycin-C can be used to correct high myopia with acceptable efficacy. It can be considered as an alternative treatment for eyes with myopia greater than -5.0 D and inadequate corneal thickness for LASIK. Long-term effects of this treatment should be investigated.

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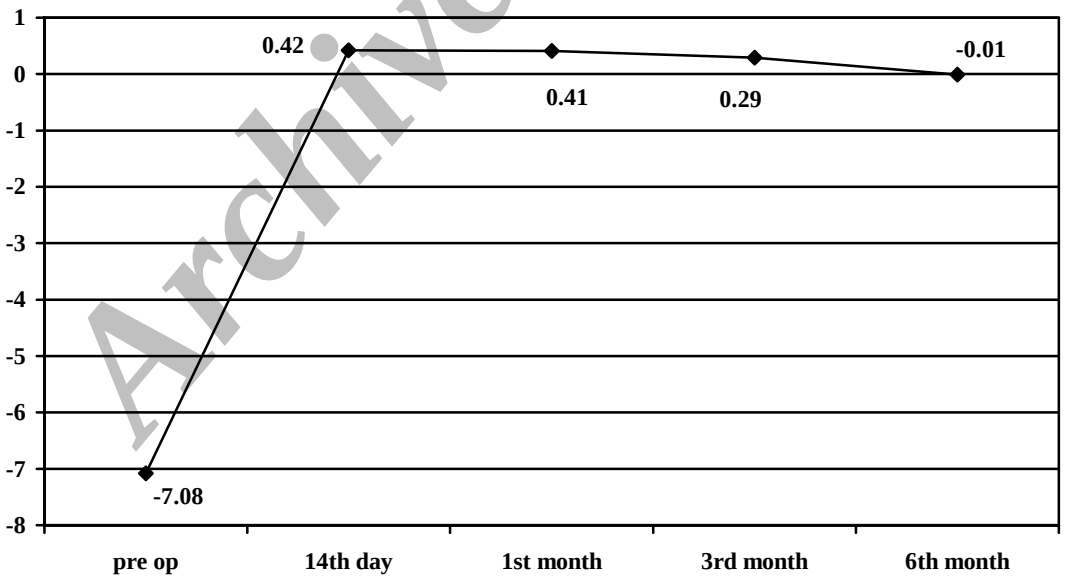

Figure 2. Changes in mean spherical equivalent refraction (D).

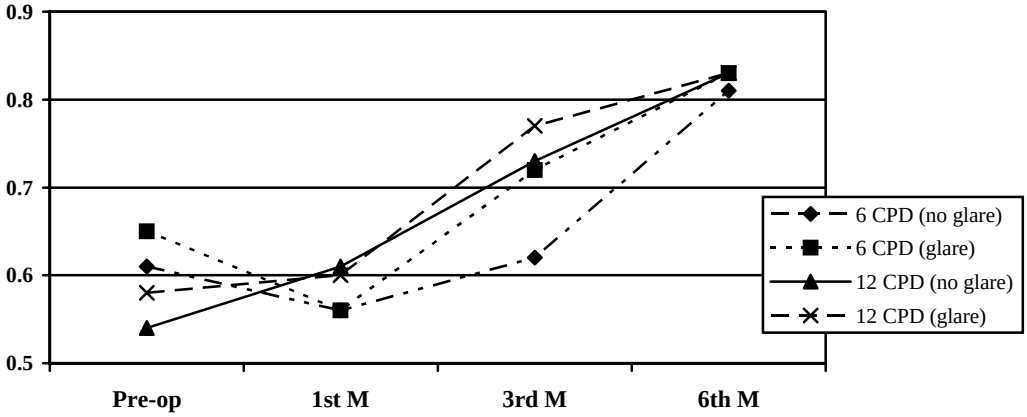

Figure 3. Changes in contrast sensitivity in spatial frequencies of 6 and 12 cycles per degree with and without glare (CPD = cycles per degree; M = month).