Outcomes of Photorefractive Keratectomy with Intraoperative Mitomycin-C

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Purpose: To report the efficacy, safety, predictability and complications of photorefractive keratectomy (PRK) with intraoperative application of mitomycin-C (MMC).
Methods: This historical cohort study was performed on 1,250 eyes of 625 patients who underwent PRK using the Technolas 217 excimer laser machine by a single surgeon with intraoperative use of MMC 0.02% up to 2 minutes, depending on depth of ablation. A complete ophthalmologic examination was performed which included refraction, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA) and slitlamp biomicroscopy. Outcomes were analyzed after one year of follow-up.
Results: The mean preoperative spherical equivalent refractive error was -4.85±2.27 (range, -2.50 to -13.5) diopters (D). Mean depth of ablation was 89±22 microns and mean time to reepithelialization was 4.5±1.7 days. At final follow-up, UCVA of 20/20 and 20/40 or more was achieved in 92.1% and 99.2% of eyes, respectively. One year postoperatively, 69.4% and 91% of eyes were within ±0.50 D and ±1.00 D of emmetropia. Overall, 62 eyes (4.9%) developed one or two lines of decrease in BCVA, and 50 eyes (4%) developed corneal haze which was grade 1 or 2 in most cases; grade 3 and 4 corneal haze was found in 4 and 2 eyes, respectively. No other adverse event was noted during the study period.
Conclusion: PRK with intraoperative application of MMC provides excellent visual outcomes with acceptable safety and predictability, and entails minimal side effects.

Key words: Photorefractive Keratectomy; Mitomycin

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INTRODUCTION

Photorefractive keratectomy (PRK) is one of the surgical procedures employed for the correction of various types of refractive errors including myopia, hyperopia and astigmatism.[1] One of the major complications of PRK is corneal haze, which can result in loss of best-corrected visual acuity (BCVA). Although the mechanism of corneal haze is incompletely understood, recent studies suggest that corneal stromal wound healing and activation of keratocytes contribute to this process.[2] As early as 1991, Talamo et al[3] described the use of mitomycin-C (MMC) for modulation of corneal wound healing. MMC is a natural antibiotic-antineoplastic compound which acts as an alkylating agent after enzyme activation resulting in DNA cross-linking. Regarding the renewed interest in surface ablation procedures,

the evaluation of various aspects of these procedures seems necessary. In the current study, we report the safety and efficacy of PRK with intraoperative application of MMC in a large number of patients.

METHODS

This historical cohort study was performed on 1,250 eyes of 625 simple myopic and myopic astigmatic patients who were referred to Persian Eye Clinic, Isfahan, Iran and underwent PRK from July 2006 to December 2007 by a single surgeon using the Technolas 217 excimer laser machine (Bausch & Lomb, New York, USA). All subjects were at least 18 years of age and were in good ocular and general health without any sign of corneal or anterior segment pathology, eyelid disease, uncontrolled glaucoma, untreated retinal pathology, progressive or unstable myopia, and previous intraocular or corneal surgery. Refractive error had been stable for at least one year. All procedures conformed to the tenets of the Declaration of Helsinki and informed consent for surgery was obtained from all patients. A comprehensive ocular examination including uncorrected visual acuity (UCVA), BCVA, refraction (cycloplegic and subjective), slitlamp biomicroscopy, Goldmann applanation tonometry, dilated fundus examination, corneal topography, pachymetry, and noncontact specular microscopy was performed in all subjects.

All patients were examined every day during the first postoperative week to monitor corneal epithelial healing, and 1, 3, 6 and 12 months thereafter. Time to complete epithelialization was recorded which was considered as delayed if not complete by 7 days. At each postoperative visit, autorefraction (Topcon 2000 automated refractometer, Japan), UCVA, BCVA and slitlamp biomicroscopy were performed. Study outcomes at final follow-up (one year postoperatively) were utilized for analysis.

Corneal haze was evaluated using a slitlamp and graded as follows: 0= clear cornea, no haze; 0.5=barely perceptible haze seen only with tangential illumination; 1=trace haze of minimal density seen with difficulty using direct illumination; 2=moderate haze easily visible with direct slit illumination; 3=marked haze partly obscuring anterior chamber observation or iris details; and 4=severe haze obscuring anterior chamber or iris details.[4]

RESULTS

Overall 1,250 eyes of 625 patients including 434 (69%) female and 191 (31%) male subjects with mean age of 31.5±12 (range, 18-47) years were operated. Mean spherical equivalent refractive error was -4.85±2.27 (range, -2.5 to -13.5) diopters (D) and mean astigmatism was -2.35±1.25 (range, 0 to -3.5) D. Spheric equivalent was less than -6.00 D in 90.5% of the cases. Mean depth of ablation was 89±22 microns and mean time to complete reepithelialization was 4.5±1.7 days. Table 1 summarizes the safety, efficacy and predictability of PRK with MMC based on preoperative refraction.

BCVA showed no change in 893 (71.4%) eyes, 1-2 lines of improvement in 295 (23.6%) eyes, and 1-2 lines of decrease in 62 (4.9%) eyes, one year postoperatively. At final follow-up, UCVA of 20/20 or more and 20/40 or more was achieved in 92.1% and 99.2% of the operated eyes. At final follow-up, 69.4% and 91% of the eyes were within ±0.50 D and ±1.00 D of emmetropia, respectively.

Fifty eyes (4%) demonstrated various degrees of corneal subepithelial haze which was grade 1 or 2 in 44 (88%) eyes, grade 3 in 4 (8%) eyes, and grade 4 in 2 (4%) eyes. In eyes with corneal haze, mean ablation depth was 97±12 microns and mean duration of MMC application was 78±18 seconds; both values were significantly higher than average. All cases with grade 3 or 4 and some cases with grade 2 corneal haze had some degree of regression together with loss of BCVA and all had preoperative myopia exceeding -6.00 D. All cases with corneal haze had been treated with frequent topical corticosteroids which resulted in variable improvement at final follow-up. There were 5 cases of delayed epithelial healing which responded to conservative treatment within 2 to 3 weeks. No case of infectious keratitis or corneal ectasia occurred after one year.

Table 1 Safety, efficacy and predictability of photorefractive keratectomy with mitomycin-C

		Preoperative Refraction		P value
		< -6.00 D	≥ -6.00 D	
Safety	1 or 2 lines decrease in BCVA	51 (4.5)	107 (90.6)	<0.001
	No decrease in BCVA	1081 (95.4)	109 (92.4)	<0.001
Efficacy	UCVA ≥10/10	1057 (93.3)	94 (79.7)	<0.001
	UCVA ≥5/10	1127 (99.4)	113 (95.8)	0.063
Predictability	± 0.50 D	800 (70.7)	67 (56.8)	<0.001
	± 1.00 D	1043 (92.2)	95 (91)	0.085

D, diopter; BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity

DISCUSSION

PRK is a well established method for surgical correction of myopia.[5] Development of corneal haze, most commonly seen after PRK and rarely after laser-assisted in situ keratomileusis, is a well-documented complication of the procedure. MMC inhibits keratocyte proliferation and induces keratocyte apoptosis, and is therefore used to prevent the development of corneal haze after PRK and other surface ablation techniques.[6,7]

There are several reports on the effect of MMC in preventing corneal haze formation after PRK. Talamo et al[3] first studied MMC in 10 rabbits which were followed for 10 weeks after PRK. They randomized them into 3 groups: 2 weeks of erythromycin ointment only; 2 weeks of topical dexamethasone and erythromycin ointment; and 2 weeks of topical 0.05% MMC, dexamethasone and erythromycin. Light microscopy revealed little or no scarring in the MMC group, moderate scarring in the steroid group, and the most severe response in the erythromycin-only group. In another study on 20 rabbit eyes which were treated with a 6-mm sponge soaked in 0.02% MMC for 5 minutes after a 10-D myopic PRK, corneal haze significantly decreased both clinically and histopathologically 2 to 26 weeks postoperatively.[8] MMC is also used for treatment of established subepithelial fibrosis after corneal refractive surgery.[9]

The efficacy and predictability of PRK with intraoperative application of MMC has already been reported in several studies. Carones et al[10] noted better UCVA and BCVA and more accurate refractive outcomes with prophylactic use of a single dose of MMC 0.02% at the end of PRK as compared to controls. In another study on 124 eyes of 62 patients by Bedei et al,[11] they reported similar results. In our study on a larger number of cases, 92.1% of eyes achieved UCVA of 20/20 or better and 99.2% had UCVA of 20/40 or better one year after PRK. Postoperative refraction was within ±0.50 D and ±1.00 D of emmetropia in 69.4% and 91% of treated eyes respectively. Our findings are comparable to those reported by Lee et al[12] who observed UCVA of 20/20 or better in 86% and UCVA of 20/40 or better in 98% of eyes after PRK with MMC, and that 86% and 93% of eyes were within ±0.50 D and ±1.00 D of target refraction postoperatively.

We encountered corneal haze one year after surgery in only 4% of treated eyes. One patient developed grade 4 corneal haze which improved to grade 3 after one year with frequent topical corticosteroids but lost 2 lines of BCVA. Four eyes with grade 3 corneal haze also showed variable improvement at last visit but with loss of one or two lines of BCVA. In a study including two groups of PRK patients, no case of corneal haze was found in the MMC group after 6 months, whereas 63% of the control group developed corneal haziness.[10] In a prospective clinical trial on 36 high myopic patients, Gambato et al[13] performed PRK with MMC on one eye and PRK with artificial tears on the fellow eye and reported corneal haze in 20% of controls versus nil in the MMC-treated eyes after one year.

Regarding MMC safety, we observed no immediate toxic effect such as conjunctival chemosis, however 5 eyes had delayed corneal epithelial healing. Moreover, no late onset complications such as corneal edema, melting or perforation were observed. In a study by

Leccisotti[14] it was shown that MMC did not delay epithelialization or induce adverse effects 12 months after surgery. Rajan et al[15] suggested that epithelial healing after MMC is characterized by prolonged latency and decreased migration depending on exposure time. MMC application did not result in increased loss of keratocytes, but it significantly delayed keratocyte repopulation in the anterior stroma. Application of MMC 0.2 mg/ml for 1 minute resulted in optimum modulation of healing characterized by reduced keratocyte activation but normal epithelial differentiation. Endothelial toxicity of MMC is a matter of debate, some studies have reported probable adverse effects by MMC on the corneal endothelium in addition to intraocular toxicity;[16-18] however, others have not confirmed endothelial toxicity.[19,20] We believe that longer follow-up is required to determine delayed complications of MMC and recommend judicious application before long-term adverse effects can be ruled out.

Prophylactic use of MMC with PRK can be beneficial in patients with risk factors for corneal haze, such as high myopic eyes and those requiring deeper ablations. Although the results of this study were significantly better in patients with myopia less than -6.00 D, the safety, efficacy and predictability of the procedure seem acceptable with higher refractive errors. In 2005, Gambato et al[13] published a prospective, randomized, study in which 72 eyes of patients with myopia higher than 7 D were randomized to a topical 0.02% MMC soaked sponge for 2 minutes or a BSS soaked sponge. Corneal haze peaked at 6 months; one year postoperatively, the MMC group had no corneal haze whereas 20% of eyes in the control group developed significant haze. There were no adverse effects due to MMC over 36 months of follow-up.

In conclusion, PRK with prophylactic MMC application seems to provide acceptable safety and predictability with minimal side effects and excellent visual outcomes for treatment of myopia and myopic astigmatism.

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