Effects of mitomycin-C on tear film, corneal biomechanics, and surface irregularity in mild to moderate myopic surface ablation: Preliminary results

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PURPOSE: To assess the effect of mitomycin-C (MMC) on the tear film, corneal biomechanics, and surface irregularity in surface ablation (photorefractive keratectomy [PRK]) for low to moderate myopia.

SETTING: Refractive Surgery Unit, Farabi Eye Hospital, Tehran, Iran.

DESIGN: Double-masked randomized clinical trial.

METHODS: In patients with spherical equivalent myopia of −0.75 to −3.87 diopters (D) and astigmatism up to −1.75 D, the first eye was randomly assigned to the application of MMC 0.02% or a balanced salt solution for 15 seconds. The fellow eye received the alternate in a masked fashion after excimer photoablation.

RESULTS: The study enrolled 60 patients. In fellow eyes, the changes in the tear-film index were comparable 1 month and 6 months postoperatively. There was no significant difference in changes in total higher-order aberrations, spherical aberration, coma, or Q values (Pentacam HR) between fellow eyes at 1 month and 6 months. There was a trend toward a higher asymmetry index at 1 month; however, a statistically significant drop was observed at 6 months in the MMC group (P<.01). It was hypothesized that stromal remodeling was delayed, but better, in MMC-treated eyes. No haze was recorded at 6 months in either group.

CONCLUSION: Use of MMC in PRK did not appear to contribute significantly to surface irregularity, transient tear-film dysfunction, or biomechanical weakening of the cornea compared with PRK without MMC.

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Mitomycin-C (MMC) is now indispensable in ocular surface and anterior segment surgery. In surface ablation, application of the 0.02% solution for 12 to 120 seconds is variably recommended for corrections of 4.00 diopters (D) or more or for an estimated ablation depth of more than 60 μm.

It is well established that laser in situ keratomileusis (LASIK) causes tear-film dysfunction; however, the information on tear function after surface ablation is not substantive. Also, it has been shown that surface ablation weakens corneal biomechanical properties.

Ocular higher-order aberrations (HOAs) after excimer laser ablation also increase. This adverse effect is inevitable; however, surface ablation induces fewer such events. There is general agreement that the induced aberrations are related to reshaping of the front surface of the cornea after the surgery and that in LASIK, the flap is the cause.

In this study we evaluated the safety of using MMC in photorefractive keratectomy (PRK) for low to moderate myopia. We studied the tear film, surface irregularity (induced HOAs), and corneal biomechanics.
PATIENTS AND METHODS

Between July 2010 and March 2011, this study prospectively enrolled 18- to 45-year-old patients with spherical equivalent (SE) myopia of −0.75 to −3.87 D, astigmatism up to −1.75 D, and refractive stability for more than 1 year. Excimer laser PRK was performed at the Refractive Surgery Unit, Farabi Eye Hospital, Tehran. Patients received a full explanation of the study; those who signed a written informed consent form were included. The study followed the tenets of the Declaration of Helsinki, and the Institutional Review Board of Tehran University of Medical Sciences approved the protocol. The protocol was registered at the Iranian Registry of Clinical Trials.

Exclusion criteria were anisometropia of 1.50 D or more, cycloptoria, a history of ocular surgery or ocular surface disease, keratoconus, and vitreoretinal disorders. Fellow eyes were randomly assigned to application of MMC 0.02% (MMC group) or balanced salt solution (control group) for 15 seconds at the conclusion of the surgery.

Comprehensive preoperative examinations included cycloplegic refraction, a modified Schirmer test, tear breakup time (TBUT), and Scheimpflug imaging (Pentacam HR, software version 6.02r10, Oculus Optikgeräte GmbH). Corneal biomechanics were measured with a dynamic bidirectional applanation device (Ocular Response Analyzer, Reichert Ophthalmic Instruments). The examinations were repeated 1 month and 6 months after surgery. Observers, including the surgeon, were masked to which eye received MMC.

Surgical Technique

The same surgeon (S.F.M.) performed all PRK procedures using the Planoscan algorithm of the Technolas 217z100 excimer laser platform (Bausch & Lomb); the optical zone was set at 6.0 mm. In all cases, the intended refraction was emmetropia as dictated by subjective refraction and a duochrome test. After exposure to 20% alcohol for 15 seconds, the central 0.02% (MMC group) or balanced salt solution (control group) for 15 seconds at the conclusion of the surgery.

The Schirmer test was performed under topical tetracaine hydrochloride 0.5% (Anestocaine). At 1 minute, a score of 2, 1, or 0 was recorded if the strip was wet for more than 10.0 mm, between 5.0 mm and 10.0 mm, or for less than 5.0 mm, respectively. The TBUT was measured after topical anesthesia and fluorescein were instilled. A score of 0, 1, or 2 was given for TBUT times of more than 15 seconds, between 10 and 15 seconds, or less than 10 seconds, respectively.

Patients were questioned at baseline and postoperatively about the following tear-film symptoms: foreign-body sensation, a sense of dryness, vision fluctuation, and visual fatigue and/or spontaneous eyelid drooping. Every positive symptom contributed 1 score, and a symptom score of 0 to 4 was recorded.

The 2 objective scores (Schirmer test and TBUT) and the modified subjective score were added and used as the tear-film index. Higher scores indicated a better tear-film status.

Statistical Analysis

Data were analyzed using SPSS software (version 16, SPSS, Inc.). Data normality was tested using the Kolmogorov-Smirnov test; none of the outcome variables significantly deviated from normality. Bonferroni adjustment was performed, and a P value less than 0.01 was considered significant. All comparisons were performed in a paired fashion (ie, preoperative versus postoperative and right eyes versus left eyes). Changes in outcome measures were determined in a paired fashion for statistical testing. One-month data on corneal shape, irregularity, and aberrations were not included in the statistical analysis.

Outcome Measures

All the outcome measures were assessed at baseline and 1 month and 6 months postoperatively.

Tear-Film Status

The Schirmer test was performed under topical tetracaine hydrochloride 0.5% (Anestocaine). At 1 minute, a score of 2, 1, or 0 was recorded if the strip was wet for more than 10.0 mm, between 5.0 mm and 10.0 mm, or for less than 5.0 mm, respectively. The TBUT was measured after topical anesthesia and fluorescein were instilled. A score of 0, 1, or 2 was given for TBUT times of more than 15 seconds, between 10 and 15 seconds, or less than 10 seconds, respectively.

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Corneal Biomechanics

Corneal hysteresis (CH) and the corneal resistance factor (CRF) were derived from the dynamic bidirectional applanation device. Measurements were repeated 3 times, and the most reliable capture was used.

Corneal Surface Irregularity

Scheimpflug imaging maps were standardized for a 6.0 mm zone centered over the pupil, and height deviations were referenced to a best spherical fit. Readings of the Q value (6.0 mm central cornea), spherical aberration, coma, and total root-mean-square HOAs (up to the 5th Zernike order) were extracted from the Scheimpflug imaging report. A meridional height difference was calculated as the mean absolute anterior height differences between 3 pairs of points on the 4.0 mm ring (6 points) at 30-degree, 90-degree, and 150-degree axes measured by Scheimpflug imaging. This yielded an irregularity index in microns.

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RESULTS

Of the 68 patients included in the study, 60 (120 eyes) completed the 6-month follow-up. The mean age was 26.76 years \((SD = 4.9)\) (range 19 to 41 years); 42 patients (70%) were women. The mean cycloplegic SE refraction was \(-2.37 \pm 0.73 \text{ D}\) (range \(-4.0\) to \(-1.0 \text{ D}\)) in all patients, \(-2.36 \pm 0.70 \text{ D}\) in the MMC group, and \(-2.38 \pm 0.77 \text{ D}\) in the control group; there was no statistically significant difference between the MMC group and the control group. \((P = .85)\). The mean astigmatism was \(-0.50 \pm 0.40 \text{ D}\) (range \(-1.75\) to \(-0.00 \text{ D}\)).

Six months after surgery, the mean cycloplegic SE refraction was \(-0.04 \pm 0.11 \text{ D}\) and \(-0.04 \pm 0.19 \text{ D}\) in the MMC group and the control group, respectively \((P = .18)\). The median corrected distance visual acuity and uncorrected distance visual acuity was 20/20 in both groups \((P = .1)\). No eye lost visual acuity.

Table 1 shows the change in the tear-film index between 1 month and 6 months postoperatively. Preoperatively, the median tear-film index was 3 (range 1 to 8) in the MMC group and 3 (range 1 to 7) in the control group \((P = .68)\). One month after surgery, the index decreased to 2 (range 1 to 6) and 2 (range 1 to 6), respectively \((P = .78)\). At 6 months, the index returned to the baseline value in both groups. The median tear index was statistically significantly worse at 1 month than at baseline \((P = .04)\).

Table 1 also shows the changes in CH and the CRF from 1 month to 6 months.

The changes in total HOAs, spherical aberration, coma, the Q value, and the asymmetry index were comparable in the MMC group and the control group at 1 month and 6 months (all \(P > .05\)) (Table 2).

Early-onset trace haze (ie, visible with broad beam) developed in 7 eyes in the MMC group and 5 eyes in the control group; 1 eye in the MMC group and 2 eyes in the control group had mild haze (ie, visible with slit beam) \((P = .8)\). There was no case of haze at 6 months in either group. Exaggerated epithelial healing (a hurricane pattern, thickened epithelium, and/or epithelial haze) was observed in 3 eyes (2 MMC-treated and 1 balanced salt solution–treated eye) at the 1-month follow-up.

DISCUSSION

It seems plausible that our hypotheses would be best tested in eyes with high myopia; however, we cannot ethically randomize such eyes to receive a balanced salt solution or MMC. Therefore, we performed the study in a population with low to moderate myopia. Both MMC-treated eyes and the fellow control eyes achieved excellent refractive outcomes without complications or visual acuity loss. The routine use of adjuvant MMC in surface ablation is controversial; some reserve it for high myopic ablations \((>-6.0 \text{ D})\), some for ablations deeper than 50 to 100 \(\mu\text{m}\), and others when the ratio of the ablation depth to corneal thickness is greater than 0.18. \(^{1,6}\) Some surgeons use MMC in all cases of surface ablation on the premise that haze is not simply predicted by the above-mentioned factors and to achieve more consistent results. \(^7\) The corneal endothelium has been the focus of previous studies of the safety of MMC in PRK; \(^8,9\) however, in this study we focused on the tear film, corneal biomechanics, and surface irregularity.

The induction or exacerbation of dry eye after LASIK has been attributed to several factors; namely,

<table>
<thead>
<tr>
<th>Parameter/Group</th>
<th>Mean Change ± SD</th>
<th>(1) Month Postop (n = 36)</th>
<th>(6) Months Postop (n = 60)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tear-film index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>-0.25 ± 1.34</td>
<td>0.31 ± 1.96</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-0.36 ± 1.83</td>
<td>0.32 ± 2.26</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>.78</td>
<td>.83</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CH (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>-2.43 ± 2.11</td>
<td>-1.64 ± 1.37</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-2.40 ± 1.93</td>
<td>-1.52 ± 1.49</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>.95</td>
<td>.64</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CRF (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>-2.13 ± 1.77</td>
<td>-2.62 ± 1.33</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-1.80 ± 1.76</td>
<td>-2.25 ± 1.53</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>.47</td>
<td>.15</td>
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</tbody>
</table>

CH = corneal hysteresis; CRF = corneal resistance factor; MMC = mitomycin-C
conjunctival goblet cell damage by the microkeratome suction ring and corneal nerve severing and ablation. This latter implies a neurotrophic mechanism because in the current thinking, ocular surface innervation is considered part of the lacrimal apparatus. Fortunately, patients recover and the ocular surface indices return to preoperative values; only in rare instances do symptoms continue beyond 2 years. Although information about surface ablation and tear function is not substantive, the consensus is that LASIK causes more sustained tear dysfunction as a result of more extensive neural damage. The tear-film indices in our patients were worse 1 month postoperatively than preoperatively; however, by 6 months, values returned to baseline. We hypothesized that MMC worsens the tear-film status through goblet cell toxicity and a delayed healing response; however, this is not substantiated because the tear-film indices were comparable in the MMC group and control group at both postoperative examinations. It has been suggested that surface ablation induces less dry eye than LASIK; however, tear-film dysfunction should be expected in the early postoperative days because of the extensive healing process that is taking place. Our scale system cannot be substituted for more formalized approaches (eg, Ocular Surface Disease Index or tear osmolarity test). Future studies should use these approaches to evaluate the tear film after surface ablation.

Biomechanical weakening in keratorefractive surgery is more pronounced in LASIK than in surface ablation because of the effect of the LASIK flap. There is scant evidence that adjuvant MMC in surface ablation exacerbates this weakening effect. Wallau and Campos suggest that inhibition of healing may result in poorer biomechanical indices. We did not find this; however, given that our patients had mild to moderate myopia, we did not expect a significant deterioration in biomechanical indices. Thus, additional deterioration in these indices caused by MMC application would be smaller. Therefore, that we did not find MMC causes such deterioration does not exclude a potential role. Further studies are needed to resolve the controversy.

In a randomized trial, Wallau and Campos found a greater induction of HOAs with the use of MMC. It is plausible that MMC use, at least in the short term, is associated with more aberrations due to the inhibition of healing and delayed stromal remodeling. However, similar to Nakano et al. and de Benito-Llopis et al., we did not find an increase in aberrations. Camellin found that MMC can induce more irregularity within 1 month and delay recovery as a result of the

<p>| Table 2. Changes in corneal surface irregularity and HOAs at 1-month and 6-month follow-ups after PRK with and without adjuvant MMC. |</p>
<table>
<thead>
<tr>
<th>Parameter/Group</th>
<th>Mean Change ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOAs (μm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>.27 ± .32</td>
<td>.29 ± .30</td>
</tr>
<tr>
<td>Control</td>
<td>.17 ± .35</td>
<td>.17 ± .30</td>
</tr>
<tr>
<td>P value</td>
<td>.22</td>
<td>.06</td>
</tr>
<tr>
<td>Q value</td>
<td></td>
<td></td>
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<tr>
<td>MMC</td>
<td>.28 ± .27</td>
<td>.41 ± .22</td>
</tr>
<tr>
<td>Control</td>
<td>.26 ± .28</td>
<td>.39 ± .29</td>
</tr>
<tr>
<td>P value</td>
<td>.71</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Horizontal coma (μm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>.00 ± .28</td>
<td>.08 ± .18</td>
</tr>
<tr>
<td>Control</td>
<td>.08 ± .30</td>
<td>.10 ± .27</td>
</tr>
<tr>
<td>P value</td>
<td>.34</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Vertical coma (μm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>.00 ± .23</td>
<td>−.02 ± .16</td>
</tr>
<tr>
<td>Control</td>
<td>−.02 ± .27</td>
<td>−.07 ± .23</td>
</tr>
<tr>
<td>P value</td>
<td>.69</td>
<td>.2</td>
</tr>
<tr>
<td><strong>Asymmetry index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>2.70 ± 1.87</td>
<td>0.95 ± 2.03</td>
</tr>
<tr>
<td>Control</td>
<td>2.07 ± 2.39</td>
<td>1.50 ± 2.19</td>
</tr>
<tr>
<td>P value</td>
<td>.18</td>
<td>.2</td>
</tr>
</tbody>
</table>

HOAs = higher-order aberrations; MMC = mitomycin-C
induced aberrations. Our observation supports this; there was relatively higher induced surface irregularity at 1 month in the MMC group; however, there was a much sharper drop in the induced irregularity at 6 months (Figure 1). Thus, it seems reasonable to hypothesize that although MMC delays healing, the cornea ends up with a smoother surface over the longer term.

In fact, the interaction seems to be much more complex. Excessive healing (haze), remodeling, tear-film status, and biomechanical properties may have a role in the surface irregularity and the induced and measured aberrations. Mitomycin-C has been shown to delay stromal wound healing and reduce excessive healing and haze formation. Animal studies found that within hours of MMC application, keratocyte apoptosis increases and repopulation decreases. The population of myofibroblasts and the density of the extracellular matrix decrease in the first 4 weeks, and the corneal wound-healing response is suppressed. The cytotoxic effect of MMC causes apoptosis, and its antimitotic effect reduces myofibroblast repopulation. Another study also found delayed reepithelialization after the application of MMC. In future studies, confocal microscopy or scanning electron microscopy should be used to correlate the optical irregularities (HOAs) with the unevenness of the corneal surface.

It has been suggested that MMC may cause a trend toward overcorrection because it inhibits the healing response, which on its own can cause regression. Therefore, standard nomograms may have to be adjusted accordingly. In this small series of eyes with mild to moderate myopia or myopic astigmatism, no eye was found to be overcorrected as a result of the MMC application.

In conclusion, adjuvant MMC did not seem to exacerbate the adverse effects of keratorefractive photoablation in terms of the tear status, biomechanical weakening of the cornea, or induced surface irregularity (aberrations). Although MMC is potentially toxic to the corneal epithelium, stromal kerocytes, and corneal endothelium, the effects were of negligible clinical significance in our study. Sometimes, these effects are desirable; for example, in haze reduction. In addition, MMC application—through healing suppression and delayed stromal remodeling—may result in a smoother corneal surface. Considering the range of approaches and tests used to assess biomechanics, tear-film status, and corneal surface irregularity, further studies should be performed to substantiate our observations.

**WHAT WAS KNOWN**
- Excimer laser refractive photoablation causes surface irregularity, inducing HOAs; it also causes transient tear-film dysfunction and biomechanically weakens the cornea.

**WHAT THIS PAPER ADDS**
- Results support the safety of MMC; ie, that the use of MMC does not increase the adverse effects of keratorefractive surgery.

**REFERENCES**


OTHER CITED MATERIAL