Original article

Effect of mitomycin C on corneal regrowth after laser-assisted sub-epithelial keratectomy (LASEK)*

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ABSTRACT

Purpose: To study the effect of mitomycin C (MMC) on the corneal regrowth after laser-assisted sub-epithelial keratectomy (LASEK).

Methods: We performed a prospective, controlled, observer-masked study of 64 consecutive eyes scheduled to undergo LASEK to correct their myopia. The patients were divided into two age-matched groups. With Group 1 including 32 eyes in which the ablation depth was ≤50 μm and received no MMC. Group 2 consisted of 32 eyes in which the ablation depth exceeded 50 μm and were treated with intra-operative 0.02% MMC for 30 s over the ablated zone. A masked observer measured the central corneal thickness (CCT) 1 and 3 months after surgery. We compared the change in CCT between both groups up to 3 months after surgery.

Results: The mean patient age was 31.5 years (SD 4.6) and 31.6 years (SD 8.7) in groups 1 and 2, respectively (p = 0.9). Group 1 showed a mean CCT of 444.0 (SD 41.3) μm one month after surgery and 450.3 (SD 43.5) μm three months after surgery (p = 0.04). CCT values in group 2 were 399.7 (SD 31.2) μm and 407.9 (SD 32.6) μm for one and three months after surgery, respectively (p = 0.006). The difference in the CCT increases between both groups was not statistically significant (p = 0.6).

Conclusions: A single intraoperative application of 0.02% MMC for 30 seconds did not seem to cause a substantial change in the post-surgical corneal thickening expected after LASEK.

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Efecto de la mitomicina C en el engrosamiento corneal tras queratectomía subepitelial con láser excimer (LASEK)

Palabras clave:
LASEK
Ablación de superficie
Mitomicina C
MMC
Hiperplasia epitelial

RESUMEN

Objetivo: Estudiar el efecto de la mitomicina C (MMC) en el engrosamiento corneal tras keratectomía subepitelial con láser excimer (LASEK).

Métodos: Realizamos un estudio prospectivo, controlado, enmascarado de 64 ojos consecutivos operados con LASEK para corregir su miopía. Separamos dos grupos empatados por edad. 32 ojos en los que la profundidad de ablação era ≤50 micras (μm) fueron incluidos en el grupo 1 y no recibieron MMC. 32 ojos en los que la profundidad de ablação era >50 μm se...
Introduction

On the one hand, mitomycin C (MMC) has and antiproliferative effects derived from its ability to generate covalent bonds in the DNA chains and, on the other side, a cytotoxic effect that gives rise to an increased apoptosis of keratocytes after its application over the cornea.1 In surface refractive surgery, comprising photorefractive keratectomy (PRK) and subepithelial keratectomy (LASEK), it is utilized to reduce the prevalence and the intensity of the postop haze by diminishing the proliferation of fibroblasts in the corneal stroma.2 Various studies3–5 have demonstrated that after PRK the epithelium not only regenerates but also suffers postop hyperplasia, which is considered the most likely cause of the corneal thickness increase detected after surface ablation. However, other authors did not detect said epithelial hyperplasia, but a stromal thickening which would explain said corneal thickness increase in the postop period.6

Due to its antiproliferative and cytotoxic effects, MMC could bring about changes in the corneal thickening pattern after surface ablation. We did not find in the literature any study focusing on this subject, and for this reason we decided to analyze whether the application of MMC after surface ablation would involve and alteration in postop corneal thickening, considering it as an in direct measurement of epithelial hyperplasia or stromal thickening described after surface surgery.

Subjects, material and methods

A prospective, controlled, interventionist, nonrandomized study was carried out with a masked observer, comprising 64 consecutive patients (64 eyes) scheduled for LASEK for correcting their myopia. The study excluded patients with unstable refraction, previous ocular surgery or disease and those exhibiting systemic diseases which could alter the healing process such as diabetes and connective tissue disorders. The study was previously approved by the Ethics Committee of our institution.

Two groups of patients of the same age were identified and they voluntarily accepted to participate in the study. Group 1 included eyes in which the ablation depth was of 50 μm or less and who had not been treated with MMC. Group 2 included patients in which said depth exceeded 50 μm, in whom MMC 0.02% had been applied intra-op for 30 seconds over the ablation area. All the surgeries were performed by the same experienced surgeon (M.A.T.).

All the study patients took a phone ophthalmological assessment before the surgery, including uncorrected visual acuity (ucVA), best corrected with eyeglasses visual acuity (ceVA) (utilizing the Snellen optotypes, Nidek autochart projector CP 670. Nidek, Gamagori, Japan) both with cycloplegic and manifested refraction, as well as biomicroscopy exploration, tonometry (CT-80. Topcon, Tokio, Japan), ultrasound pachymetry (OcuScan RXP, Alcon Laboratories, Inc. Fort Worth, TX), corneal keratometry and topography (Dicon CT200. Vismed Inc., San Diego, CA), pupil diameter under mesopic conditions (Colvard pupil meter, Oasis, Glendora, CA) and ocular fundus assessment.

Surgical technique

In all cases, surgeries were performed under topical anesthesia with 2% lidocaine. After applying 20% diluted alcohol within a 7 mm circular marker during 40 s, the epithelial flap was separated with a Crescent-type blade (Alcon Surgical), leaving it joined with a hinge at 12 o’clock. The ablation was performed on the dry stromal substrate utilizing the Technolas 217C (Bausch & Lomb Surgical, Claremont, CA) excimer laser. In the cases scheduled for receiving MMC, the programs ablation was 10% below the refraction to be corrected in order to avoid hyper corrections. The cases in which the ablation depth exceeded 50 μm, cellulose sponge imbibed in MMC 0.02% was applied for 30 s. Subsequently, the stroma was irrigated abundantly and, after placing the epithelial lenticle, a therapeutic contact lens was inserted (Acuvue 2. Johnson & Johnson Vision Care, Inc., Jacksonville, FL). Finally, ciprofloxacin drops (3 mg/ml) and ketorolac trometamole 5 mg/ml were applied.
Postop follow-up

Assessments were scheduled one day, one week and 3 months after surgery. In the weekly and 3-month assessments, a masked observer recorded the central corneal thickness (CCT) of each eye, recording the average of 3 measurements.

Statistical analysis

The Statview + Graphics Tm (Abacus Concept Inc., Cupertino, CA) software was utilized. The comparisons were made with the double tail t for Student test for paired data for the intra-group comparison and for non-paired data for the comparison between groups. In addition, the linear regression analysis was utilized to determine the existence of a relationship between the CCT increase in the postop and the treated refractive defect. A value of $p < 0.05$ was considered statistically significant. The data are indicated with mean and standard deviation values (SD).

Results

Sixty-four consecutive patients (64 eyes) were included in the study: 32 eyes in group 1 (not treated with MMC) and 32 eyes in group 2 (MMC intra-op treatment). Table 1 illustrates the preop data for both groups.

Residual spherical refraction 3 months after surgery was of 0.1 D (SD 0.3) in group 1 and 0.05 D (SD 0.6) in group 2 ($p = 0.4$). The residual cylinder was of $-0.2$ D (SD 0.6) and $-0.07$ D (SD 0.3), respectively ($p = 0.2$).

Table 2 illustrates the pachymetric measurements before surgery and in all the postop assessments. The comparison within each group between CCT measured one month and 3 months after surgery exhibited a statistically significant increase in both groups. The difference between the CCT increase between both groups was not statistically significant ($p = 0.6$).

The linear regression analysis did not exhibit a significant relationship between the treated refractive error and the postop CCT increase in any of the 2 groups (taking into account for the group that received MMC that a hypocorrection of 10% had been programmed for the preop refractive error). The analysis results for the 64 eyes were: $r^2 = 0.01$ ($p = 0.3$); in the subgroup of 32 eyes treated with MMC: $r^2 = 0.08$ ($p = 0.1$); in the subgroup of 32 eyes without MMC treatment: $r^2 = 0.08$ ($p = 0.1$).

No relevant intra-op or postop complications arose. No haze cases exceeding degree one (slight, without effect on vision) were found in any of the postop assessments.

Discussion

In this study we found a statistically significant increase of CCT between one month and 3 months after surface ablation in both groups, regardless of the use of MMC. No significant differences were found in the percentage of CCT increase between the group that was given intra-op MMC and the group that was not. MMC does not seem to cause a clinically significant delay in corneal re-epithelization when applied intraoperative in surface ablation.\(^2\text{,7–11}\) However, none of the aforementioned studies has analyzed significant differences in the final epithelial thickness between MMC treated and untreated corneas. These differences could be a subtle sign of epithelial toxicity.

Rajan et al.\(^{12}\) analyzed the effect of 0.02% MMC on the corneal epithelium morphology after in vitro application on human corneas. At month one, the epithelium of the control group was similar in thickness and morphology to that of the group treated with MMC during 1 min but, significantly

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**Table 1 – Pre-op data of the 64 eyes included in the study.**

<table>
<thead>
<tr>
<th></th>
<th>LASEK</th>
<th>LASEK + MMC</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (eyes)</td>
<td>32</td>
<td>32</td>
<td>0.9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.5 ± 4.6 (26–48)</td>
<td>31.6 ± 8.7 (24–50)</td>
<td>0.0061</td>
</tr>
<tr>
<td>Spherical refraction</td>
<td>−2.30 ± 1.00 (−0.75 a to −4.20)</td>
<td>−5.70 ± 2.60 (0 a to −11.00)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cylinder (D)</td>
<td>−0.60 ± 0.50 (0 a to −2.75)</td>
<td>−1.6 ± 1.4 (0 a to −5.00)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Data are expressed as: mean ± standard deviation (range).
D: diopeters; LASEK: laser excimer sub epithelial keratectomy; MMC: mitomycin C.

**Table 2 – Central corneal thickness (CCT) in the 64 eyes treated with surface ablation for correcting myopic defect.**

<table>
<thead>
<tr>
<th></th>
<th>CCT preop (μm)</th>
<th>CCT 1 month postop (μm)</th>
<th>CCT 3 months postop (μm)</th>
<th>CCT increase</th>
<th>Comparison between 1 and 3 months postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>LASEK</td>
<td>507.9 ± 30.7</td>
<td>444.0 ± 41.3</td>
<td>450.3 ± 43.5</td>
<td>1.42%</td>
<td>$p = 0.04$</td>
</tr>
<tr>
<td>LASEK + MMC</td>
<td>514.5 ± 26.9</td>
<td>399.7 ± 31.2</td>
<td>407.9 ± 32.6</td>
<td>2.02%</td>
<td>$p = 0.006$</td>
</tr>
<tr>
<td>Comparison between groups</td>
<td>p = 0.3</td>
<td>p = 0.0001</td>
<td>p = 0.0001</td>
<td>p = 0.6</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as: mean ± standard deviation (range).
D: diopeters; LASEK: laser excimer sub epithelial keratectomy; MMC: mitomycin C.
thinner and less differentiated in those who received MMC during 2 minutes. Perhaps a longer follow up would have allowed the epithelium to differentiate and become thicker so that said differences would disappear. However, in our study we utilized and exposure time of 30s which, on the basis of its results, should not produce any significant thickness and morphology change in the regenerated epithelium one month after surgery.

Corneal epithelial hyperplasia has been described after surface ablation, particularly associated to a small optical areas ($\leq 5$ mm) and to deep ablations in which the change of the dioptr power of the cornea on the edge of the ablation area is more abrupt. The corneal epithelium reacts against stromal ablation with hypertrophia of the base layer cells and, if this hypertrophia is not sufficient to achieve a smooth corneal surface, additional epithelial hyperplasia to smooth out the surface even more.

As the epithelium plays a significant role in determining the corneal dioptr power, it is considered that epithelial hyperplasia after refractive surgery could be one of the causes of regression after PRK and LASIK. However, other studies with confocal microscopy on human corneae after PRK did not find said epithelial hyperplasia or any relationship between the postop epithelial thickness and refractive regression, although they did identify stromal thickness increases significantly related with postop regression.

In our study, the statistically significant differences we found between CCT at month one and month 3 after surgery supports the hypothesis of postop corneal thinning either due to epithelial hyperplasia, to stromal thickening or a combination of both. The fact that we did not find differences in the corneal thickening between the group that received intra-op MMC and the one who did not suggest that this drug, in a concentration of 0.02% and applied for 30s, does not produce a clinically significant delay in the re-epithelization of the surgical ulcer but in addition it would enable the epithelial hyperplasia described after surface ablation as well as stromal thickening.

In fact, in our results we found a great increase of CCT in the MMC group than that in the other group, although the differences were not statistically significant. This great increase could be due to the greater refractive defects treated in the group that received MMC. However, the linear regression analysis performed in both groups did not reveal a significant correlation between the preop refractive error and the postop CCT increase. Perhaps a greater number of cases would have allowed us to detect a significant correlation between both parameters, which would explain the larger CCT increase in the group treated with MMC.

Even so, it must be considered that we achieved good predictability in the refractive results in the group treated with MMC despite programming a 10% preop hypocorrection of the spherical refractive defect. This could suggest that if actually the postop refractive regression was exclusively and directly determined by the postop corneal regrowth, the use of MMC would in fact partially inhibit said postop thickening but, as indicated by our study, without canceling completely the corneal healing response after surgery and therefore without endangering corneal regenerative capacity.

Additional studies would be necessary to determine whether MMC actually effects a partial inhibition (and the extent) of corneal thickening after surface ablation.

The results of our study suggest that MMC does not seem to cancel corneal thickening after surface ablation. Obviously, more studies with a higher number of patients and with histological analysis as well as in vivo confocal microscope of human corneae are needed to clarify the effect of MMC in the healing process after surface ablation.

Conflict of interests

None of the authors have declared any conflict of interests.

References


