Original Article

Haze after Photorefractive Keratectomy with and without Mitomycin in Patients with Ablation Depths below 70 Microns: A Randomized Trial

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Abstract

Purpose: To evaluate the efficacy and safety of mitomycin C (MMC) application during photorefractive keratectomy (PRK) in patients with low myopia and an ablation depth of less than 70 microns.
Patients and Methods: This study was a prospective, randomized, double-masked, placebo-controlled clinical trial the study included patients with low myopia (less than three diopters) and a corneal ablation depth of less than 70 microns, who were candidates for PRK in both eyes. Each patient underwent PRK in both eyes, with one eye randomly receiving intraoperative MMC 0.02 % (10 seconds) and the contralateral eye receiving a placebo. The main outcome measures were corneal haze and mean endothelial cell density assessed by confocal microscopy at six months postoperatively.
Results: Seventy eyes from thirty-five patients were evaluated. There was no statistically significant difference between the case and control groups in terms of mean preoperative best-corrected visual acuity, uncorrected visual acuity, sphere, cylinder, spherical equivalent, intraocular pressure, or endothelial cell count. The mean corneal haze, based on confocal microscopy readings at six months postoperatively, was significantly lower in the group receiving MMC ($P = 0.003$). The mean endothelial cell density at six months postoperatively was significantly lower in the MMC group compared to the control group ($P = 0.006$).
Conclusions: The application of MMC 0.02 % significantly reduces postoperative haze in low myopia patients undergoing PRK with an ablation depth of less than 70 microns but is linked to a statistically significant reduction in endothelial cell density.

Keywords: Photorefractive Keratectomy; Mitomycin; Myopia; Ablation; Haze; Endothelial Cell .

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Introduction

Photorefractive Keratectomy (PRK) was the first surgical procedure invented to correct refractive errors using an excimer laser [1]. This method is performed using excimer laser ablation of the corneal stroma after removal of the epithelium [1,2]. However, PRK was gradually replaced with other refractive surgical methods like laser in situ keratomileusis (LASIK) due to corneal wound-healing complications, particularly stromal haze [1-3]. Although postoperative haze following PRK is often transient and disappears after the first postoperative year, it may cause reduced postoperative visual acuity and lower patient satisfaction [4-8].

Mitomycin C (MMC) is a strong anti-metabolic agent derived from a fungus called Streptomyces caespitosus, which acts by inhibiting DNA replication, mitosis, and protein synthesis [9,10]. MMC was first suggested by Talamo et al., [11] to control the corneal wound healing response and haze after refractive laser surgery in an animal experimental study. Majmudar et al., [12] applied MMC for the first time on a limited number of patients who had corneal haze and decreased corrected visual acuity due to previous PRK or RK procedures. The use of MMC in PRK surgery has resulted in a significant reduction of haze and has renewed interest in PRK [3,13,14]. However, potential toxic effects of MMC treatment have been reported, which include decreased keratocyte and fibroblast density and corneal endothelial cell loss [13,15-17].

The depth of ablation is the most significant risk factor for corneal haze after PRK, affecting its severity [1,13,18-23]. This is due to the fact that haze formation is related to the total energy delivered to the cornea, which is directly proportional to the depth of ablation [24]. Therefore, it seems logical to avoid MMC usage in patients with low myopia and less ablation depth to reduce its potential toxic effects. It has been suggested that the prophylactic use of MMC during PRK should only be considered when the ablation depth is higher than 50-75 µm and correction exceeds 4.0 to 6.0 diopters [16,22, 24-26]. However, to our knowledge, only one previous study has been performed to evaluate the effect of prophylactic MMC on haze and its toxic effects among patients with low ablation depth [26].

This study aims to evaluate the effect of MMC on postoperative haze formation in patients with low myopia and an ablation depth of less than 70 µm and assess its potential endothelial toxicity. We hypothesize that while MMC reduces haze, it may also lead to a decrease in endothelial cell density.

Patients and Methods

Patients

This prospective, randomized, double-masked, placebo-controlled clinical trial was conducted at the Vanak Eye Clinic in Tehran, Iran, from March 2019 to February 2020. Informed consent was obtained, adhering to the Helsinki ethical principles. Confidentiality of personal data was maintained, and participants were free to withdraw at any time. This study adhered to the tenets of the Declaration of Helsinki and received approval from the Ethics Committee of Iran University of Medical Sciences (code: IR.IUMS.REC.1398.238). All participants gave written consent before entering the study. Eligible participants were candidates for PRK surgery in both eyes, aged between 20 and 45 years, with myopia of less than 3 diopters, astigmatism of less than 1.25 diopters, and an ablation depth during surgery of less than 70 microns. All patients entering the study had

a best-corrected visual acuity of 10/10 and no active corneal inflammation or infection. Only patients without ocular or systemic conditions potentially impacting corneal healing, including collagen diseases, diabetes, dry eye syndrome, and uveitis, were included in the study. Patients with excessive dry eye, keratoconus suspect patients, patients with impaired wound-healing processes, lenticular changes, anterior or posterior uveitis, retinal disease, ectatic corneal diseases, glaucoma, cataracts, a history of severe ocular trauma, or previous corneal surgery, as well as non-cooperative patients, were excluded.

Randomization and Masking

In each patient, one eye randomly received intraoperative topical Mitomycin C (MMC) 0.02 % for 10 seconds, while the other eye received a placebo (balanced salt solution) according to a computer-generated randomization list. We chose this concentration and duration of mitomycin exposure as it aligns with our routine protocol for patients with low myopia and corresponds to the short exposure duration recommended in the literature for these patients [27]. A biostatistician performed the random allocation and the surgeons performing the procedures, the study investigators and the patients were masked regarding which eye received mitomycin or the placebo. The main outcome measures were corneal haze and mean endothelial cell density, measured using confocal microscopy at six months postoperatively ensuring objective evaluation.

Preoperative Examinations

All participants underwent comprehensive preoperative examinations, including uncorrected and best-corrected vision assessment using a Snellen chart at 6 meters, and objective refraction with an autorefractometer (KR-800, TOPCON, Japan), both with and without cycloplegia. Subjective refraction, slit lamp examinations, intraocular pressure measurement using a Goldmann tonometer, corneal topography, pachymetry using a Pentacam device, and confocal microscopy with a confocal microscope (CONFOSCAN 3, Nidek, Japan) were also performed.

Surgical Technique

Both eyes of the patient were anesthetized using local eye drops. PRK surgery was performed using the Amaris 1050RS laser (SCHWIND eye-tech-solutions, Kleinostheim, Germany) excimer laser system in both eyes. An optical zone of 7 millimeters was marked on the cornea, and a specialized ring was fixed in the marked area. A diluted alcohol solution was filled inside the ring and left for 20-30 seconds to remove the epithelium. After that, the alcohol was absorbed from inside the ring using a sharp-tipped sponge, followed by rinsing the entire surface of the eye with a neutral saline solution. A specialized brush (Hockey knife) was then used to remove and clean the damaged epithelium. The remaining epithelium was thoroughly removed using a specialized cellulose sponge soaked in tear lubricant (carboxymethylcellulose) to achieve a completely smooth surface.

After the removal of epithelial cells, photoablation was performed on Bowman's layer and anterior stroma. Ablations of 0.22 to 0.25 microns per pulse were performed. Then, Mitomycin C 0.02 % (0.2 mg/mL) or a placebo (neutral saline solution) was randomly applied to one eye for 10 seconds. A silicone hydrogel contact lens, which is optically neutral, was

placed on the eye's surface postoperatively, and antibiotics and corticosteroids were prescribed. The contact lens was removed approximately 5 days after surgery during a follow-up session.

Follow-Up

At the 6-month follow-up, visual acuity, refractive errors, haze, and endothelial cell density (using confocal microscopy) was compared between the two eyes of each patient. Patients received local anesthesia drops before each eye examination. To perform confocal microscopy after entering the patient's information into the device's computer, a transparent gel drop (hydroxypropyl methylcellulose) with a thickness of 2 to 3 millimeters was applied to the tip of the front lens of the device to completely cover the lens. Continuous imaging was performed from the surface of the epithelium to the corneal endothelium. Images were obtained within 7 to 10 seconds. Three to seven complete images were analyzed each time. Significant eye movements, such as loss of fixation, occurred in 15 % of patients during confocal testing, which was resolved with repeated testing. All of our patients completed the study and attended the six-month follow-up.

Statistical Methods and Sample Size Calculation

Demographic information was extracted from clinical records. Visual acuity, refractive errors, and the health of the eye's anterior and posterior segments were evaluated using respective tools. For data analysis, means and standard deviations were used, and comparisons between groups were made using Generalized Estimating Equations (GEE). Statistical analyses were performed in SPSS version 25. The sample size was determined based on a type I error of 5 % and a statistical power of 80 % to detect a statistically significant difference in postoperative corneal haze between the MMC and placebo groups. Applying these parameters to a standard sample size formula for continuous outcomes in a paired comparison design (as each patient had one eye in each group), we calculated a required sample size of 33 participants per group (66 eyes in total) to achieve adequate statistical power. The final sample included 35 participants (70 eyes) to account for potential dropouts.

Results

Seventy eyes from thirty-five patients entered the present study and randomly underwent PRK with or without mitomycin. The average age of patients was 29.5 ± 8 years, and 21 patients were female. There was no statistically significant difference between the case and control eyes in terms of mean preoperative best-corrected visual acuity, uncorrected visual acuity, intraocular pressure, stromal haze, and endothelial cell count (Table 1).

Table 2 shows the visual acuity and intraocular pressure readings 6 months postoperatively. Again, no statistically significant difference was observed regarding the visual acuity and intraocular pressure readings between the two groups, while both groups showed significant improvement of uncorrected visual acuity (UCVA) compared to preoperative readings.

Table 3 shows the stromal haze and endothelial cell count six months postoperatively. As can be observed in this table, the mean anterior stromal layer haze ($P = 0.005$) and mean total stromal haze ($P = 0.003$) in the group receiving mitomycin C were significantly

lower than the group not receiving mitomycin C, but the mean endothelial cell density was significantly higher in the group not receiving mitomycin C (P = 0.006).

We did not encounter any serious side effects among our patients up to six months of follow-up, and all participants in the study completed their follow-up.

Discussion

Contradictions exist among researchers regarding the use of mitomycin C for individuals undergoing PRK with low ablation depth. A cautious approach to utilizing mitomycin C in patients with lower ablation depth has two main reasons. The first reason is the lower chance of postoperative haze among patients with less ablation depth, and the second reason is the probable toxic effect of mitomycin C on endothelial cells. Therefore, some authors have suggested that the prophylactic use of MMC during PRK should be considered when the ablation depth is higher than 50-75 µm and correction exceeds 4.0 to 6.0 diopters [22, 24-26].

Based on the results of the present study, even in eyes with an ablation depth of less than 70 microns, the application of mitomycin C resulted in significantly lower haze formation after PRK surgery compared to placebo. Several review and meta-analysis articles confirm the usefulness of mitomycin C in preventing haze after PRK surgery [8,13,23]. However, these aforementioned studies mostly rely on the results of studies conducted on individuals with moderate to high myopia, while our study was specifically conducted on individuals with low myopia (less than -3 diopters). To the best of our knowledge, there is only one previous study in English literature comparing the postoperative outcomes of PRK with and without the application of mitomycin C in eyes with low myopia. This study, conducted by Shojaei et al., [26], included 152 patients with an ablation depth of less than 65 µm. In their study, patients were randomly divided into two groups. The right eye of patients in the case group (78 patients) underwent PRK with intraoperative topical mitomycin C 0.02 % application for 5 seconds, and the right eye of patients in the control group (74 patients) underwent PRK using balanced salt solution as a placebo. In our study, we decided to use eyes from the same patient as the case and control to minimize the chance of bias. Additionally, Shojaei et al., [26] used slit-lamp microscopy examination for grading the corneal haze into three groups of no haze (clear cornea), trace haze, and severe haze, while to improve the reliability of haze assessment and comparison, we used confocal microscopy. Similar to our results, Shojaei et al., [26] reported a statistically significant lower haze among eyes receiving mitomycin C six months postoperatively compared to eyes receiving placebo.

In the present study, we observed that the use of mitomycin C resulted in a statistically significant lower endothelial cell density (3114±303 mm^2) six months postoperatively compared to placebo (3158±314 mm^2). Interestingly, in the study by Shojaei et al., [26] the authors did not find a statistically significant difference regarding the endothelial cell density six months postoperatively. This difference might be attributed to the fact that they used a 5-second mitomycin exposure protocol while we used a 10 second exposure protocol. It should be noted that also we found a statistically significant difference between the two groups the reduction in mean endothelial cell count in the group receiving Mitomycin C from the baseline was only about 1.5 %, which might not be clinically significant. By comparing our results, it seems

that their choice of a shorter application time for mitomycin is preferred in patients with low ablation depth since it results in similar outcomes regarding the reduction of haze but avoids a lower endothelial cell density due to the lesser toxicity of mitomycin applied for a shorter period. We used the same mitomycin concentration (0.02 %) as used by Shojaei et al., [26].

Regarding the visual acuity outcomes, we did not find any statistically significant difference either in UCVA or BCVA between eyes treated with mitomycin or placebo six months postoperatively. Our results are in line with Shojaei et al., [26] findings. It seems that among patients with low ablation depth, regardless of using mitomycin C or not, the amount of haze six months postoperatively might not be significant enough to result in a significant difference in visual acuity.

Finally, regarding the six-month postoperative IOP, there was no difference between the patients receiving mitomycin or placebo. This is in line with previous reports by Zare et al., [28] and Kymionis et al., [29].

There have been reports of corneal edema after PRK with mitomycin C; however, in these cases, factors other than mitomycin C exposure and the consequent reduction in endothelial cells—such as chronic uveitis, previous cataract surgery, or complicated surgery—appear to be the underlying causes [30].

In summary, the results of our study show that the application of MMC 0.02 % for 10 seconds compared to placebo reduced haze formation in eyes with low myopia undergoing PRK with an ablation depth of less than 70 microns, up to six months postoperatively. However, mitomycin exposure was associated with a statistically (but not clinically) significant reduction in endothelial cell count compared to placebo. These findings suggest that although the use of mitomycin C among these patients should not be totally dismissed as suggested by some authors, the pros and cons of its usage should be weighed individually by the surgeon. In those patients with a low preoperative endothelial cell density, it might be advisable to avoid using mitomycin since the remaining long-term haze in these patients is probably not significant enough to outweigh the risk of endothelial cell loss. Using mitomycin for a shorter period than we used among our patients, for example, a 5-second exposure suggested by Shojaei et al., [26] might reduce the chance of endothelial cell loss with similar results regarding haze reduction and thus might be preferred.

Our study had some strong attributes including the double-blind controlled design, the use of specular microscopy for better assessing the haze, and the use of eyes from the same patients as the case and control eyes. The relatively low number of participants based on a power of 80 % for sample size calculation might be considered a shortcoming of the present manuscript. Also, the relatively short six-month follow-up period should be considered as a shortcoming.

Given the high prevalence of PRK candidates with low myopia, the scarcity of studies on MMC use in this specific patient group, and the significant impact of postoperative haze on patient satisfaction, we suggest that further studies with larger sample sizes, longer follow-up periods, and shorter MMC exposure times are warranted to better evaluate its effects in this population.

Conclusion

The application of MMC 0.02 % significantly reduces postoperative haze in low myopia patients undergoing PRK with an ablation

depth of less than 70 microns but is linked to a statistically significant reduction in endothelial cell density. While MMC effectively reduces postoperative haze, its use in low myopia cases should be carefully weighed against potential endothelial cell loss. Shorter exposure times (e.g., 5 seconds) may mitigate toxicity while maintaining efficacy.

Conflict of interest

The authors have no conflict of interest with the subject matter of the present study.

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