

Comparison of Standard and Low Dose Mitomycin C in the Prevention of Corneal Haze following Photorefractive Keratectomy

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Abstract

Purpose: Although applying mitomycin C (MMC) during photorefractive keratectomy (PRK) has shown to reduce postoperative corneal haze but there is considerable evidence of MMC toxicity in the literature and concerns exist regarding side effects and long-term complications. We conducted this study to compare the efficacy of MMC 0.02% and 0.01% in prevention of haze after PRK.

Methods: 210 eyes were included in an interventional prospective comparative study. Both eyes of each patient were enrolled in this study. After laser ablation, MMC 0.02% (standard) were applied to right eyes of patients while the concentration was 0.01% (Low dose) for left eyes. Duration of MMC exposure was up to 40 seconds. Patients were followed on days 1 and 5 and 1, 3, 6 months after surgery and examined for refraction, uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA) and corneal haze.

Results: Ablation depth was 60-120 microns in all patients. One month after PRK, mean UCVA were 0.06 and 0.04 and mean BCVA were 0.02 and 0.01 in right and left eyes respectively. In the second follow-up visit performed 6 month after surgery mean UCVA were 0.05 and 0.04 and mean BCVA were 0.01 and 0.01 in right and left eye respectively. One month after PRK, 13 right eyes and 8 left eyes had grade 1+ and 2+ of haziness, while 6 months after surgery no haze were detected.

Conclusion: Our data suggest that low dose (0.01%) MMC (LDMMC) can be as effective as standard dose (0.02%) MMC (SDMMC) in prevention of corneal haze after PRK, while reducing the side effects and future complications.

Keywords: Photorefractive Keratectomy, Corneal Haze, Mitomycin C

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Introduction

Photorefractive keratectomy (PRK) is a popular refractive surgery proven to be effective and safe for the correction of refractive errors.¹ Normal conformation of the extracellular matrix is altered after PRK. Along with changes in cellular density and phenotype, there is variable production of disorganized extracellular matrix components and generation of myofibroblasts.

The ultimate result is a decrease in tissue transparency associated with subepithelial corneal haze, which in some patients, is clinically significant.²

Many studies have shown a decrease in occurrence of haze after PRK with applying a single intraoperative mitomycin C (MMC).³ These studies suggest that the prophylactic use of a MMC 0.02% solution contributed to lower haze rates, better uncorrected visual acuity (UCVA), and more favorable refractive outcomes.^{3,4} Despite these results, literature shows considerable MMC toxicity and concerns exist regarding the side effects and long-term complications^{4,5} among which, endothelial cell dysfunction is of great importance. Pfister reported a case of corneal edema following phototherapeutic keratectomy (PTK) using the standard MMC concentration of 0.02%.⁶ Topical application of MMC has proven to block fibroblast replication in conjunctival tissue.⁷ Additional evidence by Kim et al, suggests that topical MMC induces keratocyte apoptosis and may also lead to myofibroblast death by inducing apoptosis and necrosis.⁸ Netto et al, found decreased cellularity of the anterior stroma at 1 month after MMC application. Kim et al, reported persistent low cellularity up to 6 months after PRK including MMC.⁹

The standard dose (0.02%) MMC (SDMMC), used in myopic surface ablation was empirically proposed based on experiences from glaucoma filtering procedures and pterygium removals.^{10,11}

The first exposure time experienced was 2 minutes, but many investigators are now shortening this time to 30 seconds or even 12 seconds in order to reduce potential toxicity, while maintaining the same efficacy.¹²

Reviewing the literature we found many controversies in dosing and timing of MMC application, although the duration of MMC exposure appears to be less important than its

concentration.¹³ This study is conducted to compare the standard concentration of topical MMC (0.02%) with low dose (0.01%) MMC (LDMMC) in preventing postoperative haze following PRK.

Methods

After informing the patients and obtaining written consent, 210 eyes of 105 patients were included in our clinical trial. Eyes were divided into two arms; the first arm (left eyes) received LDMMC and the second arm (right eyes) received SDMMC. Eyes with recent refractive surgery or any other corneal disorders that could possibly influence the postoperative level of corneal haze were excluded. All patients were operated on by one surgeon. Following a povidone-iodine scrub of the eyelid and skin, several drops of topical proparacaine 0.5% were placed into each eye before surgery. After primary preparations, Technolas 217z-100 was utilized for laser ablation. Ablation depth was 70-112 microns. MMC was applied to stromal bed using a cotton applicator up to 40 seconds, depending on the depth of ablation, then the surface was dried with a sponge and irrigated with BSS.

Follow-up were performed at days 1 and 5 and 1, 3, and 6 months after surgery. Pre- and postoperative UCVA, best corrected visual acuity (BCVA) and manifest refraction were recorded. Corneal topography and thickness measurement were performed by orbiscan. Haze intensity was graded as trace, 1, 2, 3, or 4 according to the Fantes scale.¹⁴ χ^2 and Student's T-test were used for data analysis. Considering 85% power and using the following formula the sample volume was 60 patients but we increased it to 105.

$$N = \frac{2(Z\alpha + Z\beta)^2 P(1-P)}{(P_0 - P_1)^2} = 60$$

Results

Between March and November 2008, 210 eyes of 105 patients (41 men and 64 women) underwent PRK with standard and low dose MMC. The mean age of patients was 26.80 years (Range: 19-51).

The mean spherical equivalent (SE) in right eyes was -4.19 ± 2.29 (Range: -8.75 to -1.575 D) and the mean SE in left eyes was -4.13 ± 2.03 (Range: -8.5 to -1.625 D) preoperatively.

Mean postoperative SE was -0.054 ± 0.26 in right eyes (Range: -1.00 to $+0.75$ D) and -0.057 ± 0.26 (Range: -1.00 to -1.00 D) in left eyes 6 months after PRK.

Mean ablation depths were 80.56 ± 25.9 and 77.56 ± 18.12 in right and left eyes respectively.

In first postoperative visit mean UCVA were 0.06 and 0.04 and mean BCVA were 0.02 and 0.01 in right and left eyes respectively.

In the second follow-up visit performed 6 month after surgery mean UCVA were 0.05 and 0.04 and mean BCVA were 0.01 and 0.01 in right and left eyes respectively.

One month after PRK, 13 right eyes and 8 left eyes had grade 1+ and 2+ of haziness, while 6 months after surgery no haze were detected.

Discussion

Prophylactic MMC application may be a valuable adjunctive treatment specially in high-risk cases. However, the potential toxicity of MMC is a matter of concern, and therefore its risk/benefit ratio must be evaluated.²⁰ Midea et al, noted that PRK with 0.02% topical MMC has no significant side effects on corneal keratocytes compared to standard PRK, as documented by in vivo corneal confocal microscopy.²¹ Goldsberry et al, also found that administration of MMC for haze prophylaxis following PRK did not have a significant effect on quantitative endothelial

cell density or qualitative morphometric parameters.²⁰ Similar results were found by some other authors.^{22,23} Netto et al noted that MMC treatment induces apoptosis of keratocytes and myofibroblasts, but the predominate effect in inhibiting or treating haze appears to be at the level of blocked replication of keratocytes or other progenitor cells of myofibroblasts.⁹ This study also found that a persistent decrease in keratocyte density in the anterior stroma could be a warning sign for future complications and treatment should be reserved for patients with significant risk of developing haze after PRK.⁹

According to our data no eye developed postoperative haze in LDMMC arm, in the other words there was not any differences in right eyes which received standard MMC dose and left eyes with LDMMC regarding postoperative haziness. Thornton et al found that the standard concentration of topical MMC (0.02%) is more effective than LDMMC (0.002%) in preventing postoperative haze following surface ablation for myopia ≥ -6.00 D and deeper ablation depth ≥ 75 microns. However, for moderate myopia and shallow depth ablation, low dosing appears to be equally effective.¹³ They used MMC with $1/10$ standard dose but we decreased MMC concentration to half which can be a probable reason for the efficacy of our method.

Conclusion

Our data suggest that LDMMC is as effective as SDMMC in prevention of corneal haze after PRK while reducing side effects and future complications.

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