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Research Article

Evaluation of Efficacy and Safety of Mytomycin-C Application in Laser-Assisted Subepithelial Keratectomy (LASEK)

Emil W Chynn[1]*, Semran Thamer[2] and Tatiana Bakaeva[1]

[1]Park Avenue Safe Sight, New York, NY, USA
[2]New York University, New York, NY, USA

***Corresponding Author**: Emil W Chynn, Park Avenue Safe Sight, 102 East 25th Street, New York, NY, USA.

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Abstract

Purpose: To evaluate 1) if very low dose (0.01%) intraoperative Mytomycin-C (MMC) is effective in preventing postoperative corneal haze, (2) if a short-fixed MMC duration is as effective as a duration which varies based on refractive error, and (3) if varying MMC duration affects recovery after LASEK.

Setting: Subspecialty refractive practice

Methods: The study was conducted on 103 patients (206 eyes) who underwent LASEK for myopia, hyperopia and/or astigmatism. All right eyes received a 10-second application of 0.01% MMC intraoperatively. All left eyes served as a control and received 0.01% MMC for a duration (0 - 80 sec) varying based on degree of refractive error, as many clinicians currently do.

Results: Out of 206 eyes treated with 0.01% MMC after LASEK, 18 eyes developed trace to 1+ haze. Out of the 18 affected eyes, 10 eyes were right and 8 eyes were left, indicating that there was no statistically significant difference in haze formation between a short-fixed vs. variable MMC application time ($p = 0.0194$). There was no significant difference in mean time needed to reach the intended refraction between the two treatment groups.

Conclusion: 0.01% intraoperative MMD was effective at preventing post-op corneal haze in the vast majority of cases, some of which involved very high prescriptions. Both a short-fixed duration and one that varied based on refractive error were effective. Neither dosing schedule interfered with post-op recovery. Clinicians concerned about possible MMC toxicity can be reassured that they can decrease the concentration of MMC used, and reduce application duration, without compromising efficacy.

Keywords: *Mytomycin-C; LASEK; Keratocyte; Stroma*

Introduction

Themitomycins are a family of aziridine-containing natural products isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae* [1]. One of these compounds, mitomycin C (MMC), finds use as a chemotherapeutic agent by virtue of its antitumor activity. Initially it was developed as a systemic medication to treat gastro-intestinal, breast and bladder cancers. A recent development is its topical application in eye surgery to prevent scarring during glaucoma filtering surgery, reduce fibrosis in strabismus surgery [2] and to prevent haze after PRK, LASEK or epi-LASIK.

MMC has an anti-proliferative effects derived from its ability to generate covalent bonds in the DNA chains, and a cytotoxic effect that causes increased keratocyte apoptosis after its corneal application [3]. In surface refractive surgery, comprising photorefractive keratectomy (PRK) and subepithelial keratectomy (LASEK), it is utilized to reduce the prevalence and the intensity of the postoperative haze by diminishing the proliferation of fibroblasts in the corneal stroma [4].

Several studies have shown that topical intraoperative MMC reduces haze and improves visual acuity after surface ablation [5-7], and is safe in both normal and thin corneas [8,9] without adverse effects on the corneal endothelium [10,11]. Although one study showed a decrease in anterior stromal cells 3 months after LASEK with MMC, there was a compensating proliferation of keratocytes in the deeper corneal layers, suggesting that the ability of keratocytes to repopulate the cornea is maintained after surface ablation with MMC [12]. It has been demonstrated that performing LASEK without MMC in eyes with a preoperative SE of> -12 D is associated with suboptimal visual outcomes due to haze formation and myopic regression [13]. Importantly, predictability of final target refraction, induction of higher order aberrations, and improvement in contrast sensitivity has not been shown to differ with and without MMC [6].

Although most refractive surgeons are applying MMC for certain high prescriptions, clinicians currently vary widely in their utilization of MMC. There is still no agreement on the optimal concentration of MMC or exposure time to reduce or prevent postoperative haze after surface ablation. There are only a few studies that evaluate the efficacy of using MMC at a lower concentration than 0.02% to prevent postoperative haze after surface ablation. Camellin's study reported that using a concentration of 0.01% MMC in 86 eyes after LASEK reduced the incidence of haze when compared to 100 control eyes [16]. Camellins study found that 0.01% concentration MMC is effective but failed to evaluate effective duration times since his study utilized a "brushstroke" of MMC application [16]. Duration of MMC application varies from 10 seconds to 2 minutes [7,10,11]; However, studies have shown that application of MMC in high doses and duration can significantly affect keratocyte density in applied tissue and can even lead to long-term acellular zones in the anterior stroma at the site of ablation. Acellular zones in the stroma lacking keratocytes can result in biomechanical instability, iatrogenic ectasia and corneal melting [3]. Given the dangers of using long duration high dose MMC application, it is obvious that using a lower dose and shorter duration MMC application would be safer. While studies have shown that concentrations of MMC lower than the standard 0.02% are effective in preventing postoperative corneal haze, this study utilizes a 0.01% concentration of MMC to evaluate the efficacy of a safer, lower dose lower duration MMC application.

There is still debate about whether or not MMC decreases predictability of the refractive result and/or increases higher order aberrations and what is the optimal ideal MMC concentration and exposure time [16].

Therefore, the purpose of this study was to examine whether a low-duration and low-dose (0.01%) schedule of MMC is as effective in preventing corneal haze after LASEK as a long-duration protocol, without adverse effects on recovery.

Discussion

Methods

The study was conducted on a group of patients with no previous ophthalmic surgery who underwent primary uncomplicated LASEK for myopia, hyperopia and/or astigmatism (N = 103 (206 eyes)).All patients were treated on a VISX STAR S4 IR excimer laser.MMC was obtained in sterile powder format from the distributor, and diluted with sterile water to yield a final concentration of 0.01%. MMC was carefully diluted according to the instructions from the manufacturer to avoid the widely-known and serious adverse events that can occur if the MMC is mistakenly diluted to a too-high concentration, such as corneal melts or scleral perforations (which was the reason we investigated using a lower-than-standard concentration of MMC for this study, because we wanted to use the lowest dose effective in preventing haze, to minimize all toxic side effects). All right eyes received a 10-second application of 0.01% MMC intraoperatively. Recent studies depict successful haze inhibition with an intraoperative MMC exposure interval varying from 15 to 120 seconds, depending on the attempted correction and ablation time. As a comparative control, all left eyes (OS) received 0.01% MMC for a duration time (0 - 80 sec) varying based on degree of refractive error, as many clinicians currently do, as follows: SE of -5.00 to +2.00D received no MMC, myopic SE greater than 5.00D or cyl greater than 3.00 D received an application of 0.01% MMC for a duration equal to the ablation time, and hyperopic SE greater than 2.00 D received 0.01% MMC for a duration equal to half the ablation time. A total of 49 left eyes received MMC application.41 patients also completed a questionnaire assessing postoperative discomfort as a measure of healing time: peak pain day (PPD), pain grade (PG) on scale 0 - 10, pain free day (PFD). Recovery time was also assessed by measuring "Time to Reach Intended Refraction" (TRIR).

Results

The mean patient age was 33.9 ± 11.3 years (range: 20 - 66 years), male/female ratio = 62/40. 172 eyes had myopic refraction (mean sph = -4.46 ± 2.34D, range: -0.25 to -11.25D; mean ablation depth = 89.7 ± 35.0 μm, range: 16-198 μm), 33 eyes had hyperopic refraction (mean sph = 2.43 ± 1.20D, range: 0.50 - 4.75D; mean ablation depth = 34.3 ± 13.1 μm, range: 7 - 61 μm), 179 eyes had astigmatism (mean cyl = -1.16 ± 1.09D, range: -0.25 to -6.00D) (Table 1).

	Total Number of Patients	Number of Patients Developed No haze	Developed Trace Haze with no VA change	Developed Haze/Scar with mild VA change	Developed Haze/ Scar with Significant VA change
Number of OD with MMC application	103	93	9	1	0
Number of OD with NO MMC application	0	0	0	0	0
Number of OS with MMC application	49	41	7	1	0
Number of OS with NO MMC application	54	54	0	0	0

Postoperative healing: One MMC eye (OS) had a persistent epithelial defect beyond 10 days postoperatively which healed uneventfully by day 12 and was clinically insignificant. All patients graded their postoperative discomfort for the right and left eye equally. Mean peak pain day (PPD) was 1.5 ± 1.5 days (range: 0 - 8 days), mean pain grade (PG) was 2.2 ± 1.1 (range: 0 - 4), mean pain free day (PFD) was 3.4 ± 2.1 day (range: 0 - 10 day). All three of these parameters (PPD, PG, PFD) had no significant correlation with the duration of MMC application ($r = 0.18$, $p = 0.05$) and there was no significant difference in any of these parameters between the right and left eyes, indicating no variability in healing due to varying duration of MMC.

Postoperative haze: 16 out of 206 eyes had trace haze with no vision change, 2 eyes (one OD, one OS) had grade 1+ haze with 1 - 2 lines loss of BCVA. One of these cases, in the OS treatment group, was a patient non-compliant with topical steroids and postoperative visits, another one, in the OD treatment group, was a case of extreme myopia (SE = -11.37, ablation depth = 198 μm) treated with LASEK who developed haze at 5 months postoperatively, when she had a change in hormonal status (pregnancy). No eyes lost more than 2 lines of BCVA.

Among the 18 eyes which developed haze 17 had myopic refraction with mean SE = -7.18 ± 2.49D (range: -3.38D to -11.63D), one eye had hyperopic refraction: SE = 3.13D. Mean MMC application time was 28 ± 22 sec (range: 10 - 70 sec). 10 eyes with haze were right eyes, 8 eyes were left, which indicates no significant difference in haze formation with either protocol of MMC application.

Among myopic patients with SE > -5.00D (total of 76 eyes): 60 eyes (79%) were haze-free (mean MMC application was 25 ± 23 seconds) and 16 eyes (21%) developed grade 1 - 2 haze (mean MMC application = 30 ± 22 seconds).

Refractive outcome: Mean Time to Reach Intended Refraction (TRIR) was 1.69 ± 1.43 months (range: 1-8 months); the difference in TRIR for the right and left eye was not significant: OD (n = 103) TRIR = 1.63 ± 1.40 months (range: 1 - 8 months); OS (n = 103) TRIR = 1.74 ± 1.46 months (range: 1 - 8 months). TRIR did not correlate with MMC application time ($r = 0.11$, $p = 0.05$).

Conclusion

Intraoperative MMC application is becoming a standard procedure after surface ablation, especially after treatment of high prescriptions [13] to prevent postoperative haze and scarring. Most surgeons agree that MMC is a relatively safe and effective agent for haze prevention [5-7]; on the other hand, there are some data about its adverse effect on keratocyte population that could theoretically delay

healing [3,12]. There are controversial data about whether or not MMC application might affect refractive outcome or induce higher order aberrations [6,16]. Therefore, the optimal protocol of the MMC concentration [14,15] and exposure time [7,10,11] needs to be established, and evaluated for safety and efficacy.

Our large prospective comparative study involving 103 patients (206 eyes) showed that both a short protocol of 0.01% MMC application (10 seconds application regardless of the refraction) and a varying-time protocol (0 - 80 seconds depending on preoperative refraction) were safe and effective in preventing haze after LASEK.

Unlike other studies [16], we did not find that MMC decreased predictability of the refractive result. Refractive outcomes were both excellent and predictable-and, importantly, did not correlate with MMC time.

The risk of adverse events (visually significant haze or delayed healing) was extremely low and also did not correlate with duration of MMC. One of the two cases of visually significant haze was caused by patient non-compliance; the other was in a patient with an extreme myopic ablation who had a change in hormonal status (pregnancy). The extremely low number of adverse events does not let us analyze the causes and propose additional preventive measures, but points to patient compliance as an important factor.

In summary, 0.01% MMC application for as little as 10 seconds was shown to be effective and efficacy did not increase with longer application time. There were no statistically significant differences in haze levels among the standard dose (0.02%) and low dose (0.01%) MMC for eyes treated with small and large amounts of ablation depth. Both10-second and longer applications (up to 80 seconds) were safe and did not adversely affect healing or refractive outcome. Therefore, we recommend using ashort10-second application of 0.01% MMC for all surface ablations to shorten procedure time, minimize changes in corneal hydration status, and decrease the risk of any toxicity to the corneal endothelium-all while providing effective protection against scarring and haze formation.

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