

Mitomycin-C in Corneal Surface Excimer Laser Ablation Techniques

A Report by the American Academy of Ophthalmology

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Objective: To review the published literature assessing the efficacy and safety of mitomycin-C (MMC) as an adjunctive treatment in corneal surface excimer laser ablation procedures.

Methods: Literature searches of the PubMed and Cochrane Library databases were last conducted on August 19, 2014, without language or date limitations. The searches retrieved a total of 239 references. Of these, members of the Ophthalmic Technology Assessment Committee Refractive Management/Intervention Panel selected 26 articles that were considered to be of high or medium clinical relevance, and the panel methodologist rated each article according to the strength of evidence. Ten studies were rated as level I evidence, 5 studies were rated as level II evidence, and the remaining 11 studies were rated as level III evidence.

Results: The majority of the articles surveyed in this report support the role of MMC as an adjunctive treatment in surface ablation procedures. When MMC is applied in the appropriate concentration and confined to the central cornea, the incidence of post-surface ablation haze is decreased. Although a minority of studies that evaluated endothelial cell density (ECD) reported an MMC-related decrease in ECD, no clinical adverse outcomes were reported.

Conclusions: Over the past 15 years, the use of MMC during surgery in surface ablation has become widespread. There is good evidence of the effectiveness of MMC when used intraoperatively as prophylaxis against haze in higher myopic ablations. Although there are reports of decreased endothelial counts after the administration of MMC during surgery, the clinical significance of this finding remains uncertain, because no adverse outcomes were reported with as much as 5 years of follow-up. Optimal dosage, effectiveness as prophylaxis in lower myopic and hyperopic ablations, and long-term safety, particularly in eyes with reduced corneal endothelial cell counts from prior intraocular surgery, have yet to be established. *Ophthalmology* 2015;122:1085-1095 © 2015 by the American Academy of Ophthalmology.

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to review the published literature to assess the safety, efficacy, and predictability of mitomycin-C (MMC) as an adjunctive treatment in corneal surface excimer laser ablation procedures.

Background

Corneal haze resulting from subepithelial scarring is a well-recognized complication of photorefractive keratectomy

(PRK).¹ Corneal injury (e.g., from surgery) incites immediate and long-term changes in the cornea at the molecular and cellular level. These reactive changes include activation, proliferation, recruitment, and migration of various corneal cell types to the site of injury, and involve multiple cytokines and growth factors.² Remodeling of the extracellular matrix occurs after the abnormal activation and proliferation of stromal keratocytes, and can result in the disorderly formation and deposition of new collagen, resulting in corneal haze. Commonly, this can lead to irregular astigmatism and loss of uncorrected visual acuity (UCVA) or best-corrected visual acuity (BCVA). The incidence of corneal haze was higher with first-generation excimer lasers, possibly because of early excimer laser-beam profiles.³ However, advances in excimer laser technology have greatly reduced, but not completely eliminated, the phenomenon of corneal haze after PRK. Risk factors for the development of corneal haze include deeper ablations, ultraviolet light exposure, high astigmatism, and prior corneal surgery.^{4,5}

Pharmacologic modulation of this healing response has been investigated for many years, and antifibrotic agents that inhibit fibroblast function were postulated to be useful in the treatment and prevention of post-excimer laser surgery corneal scar formation. Mitomycin-C is a chemotherapeutic antibiotic isolated from *Streptomyces caespitosus* and is a noncell-cycle-specific alkylating agent. Mitomycin-C covalently binds to and results in cross-linking of DNA; therefore, it has antimetabolite activity, because it inhibits cellular replication in a dose-dependent fashion.⁶

Mitomycin-C has been used extensively in glaucoma filtration surgery to inhibit fibrovascular proliferation, which may lead to bleb failure.⁷ It has also been used as adjunctive therapy in pterygium excision,⁸⁻¹⁰ in the treatment of conjunctival and corneal neoplasms,¹¹⁻¹³ and in the management of ocular mucous membrane pemphigoid.¹⁴

Talamo et al¹⁵ first reported the use of MMC as a modulator of wound healing in an animal model of PRK in 1991. They demonstrated that topically applied MMC in conjunction with corticosteroid eye drops inhibited subepithelial collagen synthesis in an additive fashion when applied for 14 consecutive days after excimer laser keratectomy. Schipper et al¹⁶ compared MMC with balanced salt solution (BSS) in a rabbit model of PRK in 1997 and found that histologic evidence of scarring was seen in only 1 of 8 corneas compared with 5 of 8 in the BSS group. Majmudar et al¹⁷ reported the first human use of MMC as a modulator of wound healing after refractive surgery in 2000. Eight eyes with visually significant subepithelial scarring after radial keratotomy or PRK were treated with scar debridement and a single, 2-minute intraoperative application of topical MMC 0.02%. In each of these cases, corneal scarring had recurred (in some cases multiple times) when conventional debridement was undertaken. After debridement of scar tissue with MMC, not 1 eye had recurrence of corneal haze. After initial reports, MMC began to be widely used as a therapeutic agent in cases of corneal scarring after PRK.

As a natural extension, a number of investigators began to explore the role of prophylactic MMC. Carones et al¹⁸ reported results of the prophylactic use of MMC in refractive surgery. A single application of 0.02% MMC during surgery was used for 2 minutes after completion of the PRK laser ablation. By 6 months after surgery, no eyes (0 of 30 eyes) developed corneal haze greater than grade 1 (based on the scale by Fantès et al¹⁹), compared with 19 of 30 eyes in the control group (without MMC) that developed haze rated higher than grade 1. The use of MMC in surface ablation is now widespread. In 2009, an American Society of Cataract and Refractive Surgery survey reported that 88% of member surgeons used MMC as corneal haze prophylaxis.²⁰

Food and Drug Administration Status and Resource Requirements

Mitomycin-C (chemical name 7-amino-9 α -methoxyymitosane) is approved by the US Food and Drug Administration (FDA) as an adjunctive therapy for disseminated

adenocarcinoma of the stomach or pancreas (trade name Mutamycin, Bristol Meyer Squibb, Princeton, NJ; and Mitozytrex, SuperGen, Inc, Dublin CA) and as an adjunct to glaucoma filtering surgery (trade name Mitosol; Mobius Therapeutics, LLC, St. Louis, MO). Its use in corneal refractive surgery is considered off-label.

Intravenous MMC is packaged as a powder and requires reconstitution with sterile water. This can be performed by a compounding pharmacy or at the time of surgery by trained personnel. Mitomycin is considered carcinogenic, and appropriate precautions must be followed when handling and mixing, especially by pregnant females. This includes proper disposal of needles, syringes, vials, sponges, and unused medications. Caution must be exercised to ensure the appropriate concentration of MMC, because dilution errors can lead to significant ocular morbidity.

Questions for Assessment

The focus of this assessment is to address the following questions: (1) Does intraoperative use of MMC inhibit haze formation in surface ablation? and (2) Does intraoperative use of MMC affect corneal endothelial cell density (ECD)?

Description of Evidence

Literature searches conducted October 13, 2011, November 10, 2011, September 16, 2013, and August 19, 2014, in PubMed and the Cochrane Library resulted in 239 potentially relevant citations; 15 of these were in non-English languages and were excluded. The titles and abstracts were reviewed by the authors, and 161 were selected for full text review. Of these, 26 met inclusion criteria. The methodologist (R.M.S.) then assessed these 26 studies according to the strength of evidence. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies. With the use of these criteria, the literature search identified 10 level I studies (including 2 reports from the same study population), 5 level II studies, and 11 level III studies. The search terms used are described as follows:

PubMed #1 - ("Mitomycin"[nm]) AND ("Keratectomy, Subepithelial, Laser-Assisted"[mh] OR "Keratomileusis, Laser In Situ"[mh] OR "Photorefractive Keratectomy"[mh] OR "Keratotomy, Radial"[mh] OR "Corneal Surgery, Laser"[mh]).

PubMed #2 - ((Mitomycin*[tiab]) OR (MMC[tiab])) AND (laser in situ[tiab] OR LASIK[tiab] OR laser epithelial keratomileusis[tiab] OR LASEK[tiab] OR photorefractive keratectomy[tiab] OR PRK[tiab] OR epi-LASIK[tiab] OR epi-LASEK[tiab] OR radial keratotomy[tiab] OR refractive [tiab] OR keratorefractive[tiab]).

PubMed #3 - ((Mitomycin*[tiab]) OR (MMC[tiab])) AND ((intacs[tiab]) OR (intrastromal corneal ring*[tiab]) OR (cornea*[tiab] AND ring*[tiab])).

PubMed #4 - (mitomycin*[tw] OR MMC[tw]) AND (surface ablat*[tw]).

Cochrane Library #1 - (Mitomycin* OR MMC):ti,ab,kw and (laser in situ OR LASIK OR laser epithelial keratomileusis OR LASEK OR photorefractive keratectomy OR PRK OR epi-LASIK OR epi-LASEK OR radial keratotomy OR refractive OR keratorefractive):ti,ab,kw.

Cochrane Library #2 - (MeSH descriptor Mitomycin explode all trees) AND (MeSH descriptor Keratectomy, Subepithelial, Laser-Assisted explode all trees OR MeSH descriptor Keratomileusis, Laser In Situ explode all trees OR MeSH descriptor Photorefractive Keratectomy explode all trees OR MeSH descriptor Keratotomy, Radial, this term only OR MeSH descriptor Corneal Surgery, Laser explode all trees).

Cochrane Library #3 - (mitomycin* OR MMC):ti,ab,kw AND (intacs):ti,ab,kw or (intraströmål corneal ring*):ti,ab,kw or (cornea* AND ring*):ti,ab,kw.

Cochrane Library #4 - (surface ablat*):ti,ab,kw and (mitomycin* OR MMC):ti,ab,kw.

Published Results

Refer to [Table 1](#) for a summary of results.

Outcomes

Mitomycin-C Use as Prophylaxis with Primary Procedures: Photorefractive Keratectomy. The history of laser vision correction dates back to the introduction of PRK in 1983.²¹ Early results, especially for higher myopic corrections, demonstrated late-onset corneal haze due to corneal myofibroblast proliferation.^{22,23}

Adjunctive MMC has been used for all degrees of myopia and hyperopia to prevent corneal haze after PRK.^{18,24–30} Carones et al¹⁸ (level I) conducted a prospective randomized trial of 60 eyes of 60 consecutive patients with spherical equivalent (SEQ) correction between -6.00 and -10.00 diopters (D) and inadequate corneal thickness who were undergoing LASIK. In the study group, each eye underwent PRK, followed by application of MMC 0.2 mg/ml (0.02%) for 2 minutes. The control group received PRK without MMC. No MMC eye had haze greater than grade 1 during the 6-month follow-up compared with 19 of 30 control eyes (63%). Twenty-six eyes (87%) in the study group and 14 eyes (47%) in the control group were within ± 0.50 D of the attempted correction at 6 months follow-up. The authors concluded that MMC was a safe and effective method of haze prevention and that it resulted in greater refractive accuracy. Likewise, Hashemi et al³⁰ (level II) found that PRK with adjunctive MMC was safe and effective in preventing haze formation in highly myopic eyes in a prospective study of 54 eyes of 28 myopic patients. Six months after surgery, 77.1% achieved a UCVA of 20/20, all eyes were 20/40 or better, and 93.7% were within 1.00 D of intended correction. At 1 month after surgery, only 3.7% of patients (2 eyes) had grade 0.5 haze, which resolved by 3 months in the 2 affected eyes without further treatment.

Thornton et al³¹ (level II) analyzed 92 eyes that underwent surface ablation without MMC and compared them retrospectively with 83 eyes that received 0.02 mg/ml (0.002%) MMC during laser-assisted subepithelial keratectomy (LASEK). Eyes treated with low-dose MMC (0.002%) demonstrated statistically less haze at all post-operative time points and in each myopic subgroup ($P < 0.001$). This finding was supported by Bedei et al²⁴ (level I), who followed 124 eyes (62 control, 62 with 0.2 mg/ml [0.02% MMC]) for 1 year and reported significantly less haze in the MMC group than in the control group ($P = 0.005$). They also found a favorable effect on refractive regression at 1 year of follow-up. Patients in the study group had significantly better BCVA than controls at 1 year ($P = 0.013$). In the MMC group, 3 eyes (4.8%) lost 1 line of Snellen acuity and no eyes lost more than 1 line. In the control group, 13 eyes (20.9%) lost 1 line of Snellen acuity and 1 eye (1.6%) lost 2 lines. In the MMC group, 43 eyes (69.3%) were within ± 0.50 D of target refraction, and in the control group, only 31 eyes (50.0%) were within ± 0.50 D of target at 1 year. Argento et al³² (level III) also supported the finding of decreased haze formation with MMC use in a retrospective study of 58 patients; however, visual outcomes were similar in both groups. Shalaby et al³³ (level III) supported the use of MMC for prevention of haze formation in both primary PRK and phototherapeutic keratectomy (P.T.K.), as well as secondary procedures (post-PRK or radial keratotomy) in a retrospective analysis of 34 eyes.

In a retrospective analysis of 536 patients (1011 eyes) who underwent PRK with application of 0.02% MMC during surgery for 30 seconds to 2 minutes (depending on ablation depth), Lee et al³⁴ (level III) showed excellent visual outcomes at 13 months. The mean preoperative SEQ was -7.82 D. Six months after surgery, the mean SEQ was -0.14 ± 0.62 D; 86% were within ± 0.50 D and 93% were within ± 1.00 D of expected refraction. Ninety-eight percent of patients had a UCVA of $\geq 20/40$, and 86% of patients had a UCVA of $\geq 20/20$.³³ Regression of > 1.00 D occurred in 7.6% of eyes at 6 months follow-up and was more common in patients with higher refractive errors before surgery. Haze occurred in 32 eyes (3.2%) but was limited to grade 1 in most cases (grade 2, 3 eyes; grade 3, 2 eyes). A recent level III article³⁵ retrospectively evaluated the long-term refractive and visual outcomes of PRK with intraoperative application of MMC 0.02% for 2 minutes. The mean SEQ after surgery was -0.09 ± 0.53 D, with a mean follow-up of 44.73 ± 18.24 months. Although 4 eyes (11%) had mild haze at 3 months, none of the eyes demonstrated haze at the 12-month interval after surgery.

Although multiple studies have examined the use of MMC in higher myopic ablations, few have looked at the efficacy of MMC with hyperopia. Leccisotti³⁶ (level I) published a prospective study of 88 eyes (with a mean SE of $+3.51$ D) that underwent hyperopic PRK/MMC and compared them with a control group of 91 eyes (SE $+3.50$ D) that underwent PRK without MMC. The mean haze score at 18 months (graded on a scale of 0–4) was 0.05 ± 0.11 in the MMC group compared with 0.23 ± 0.46 in the control group ($P < 0.05$). They also

Table 1. Summary of Included Studies

Study	Level of Evidence	Study Design	Premise	No. of Eyes	Mean Follow-Up	Parameters Evaluated	Results
Carones et al, 2002 ¹⁸	I	Prospective	PRK/MMC vs. PRK alone	60	6 mos	Haze level; refractive accuracy	MMC 0% haze, control 63% haze; MMC 87% within ± 0.5 D, control 47%
Bedei et al, 2006 ²⁴	I	Prospective	PRK/MMC vs. PRK alone	124	12 mos	Haze level; refractive accuracy; safety	MMC group had less haze, greater refractive accuracy and BCVA, and fewer Snellen lines lost
Leccisotti, 2009 ³⁶	I	Prospective	Hyperopic PRK/MMC vs. hyperopic PRK	88	18 mos	Haze level; visual acuity	MMC group had less haze and better UCVA
Wallau and Campos, 2008 ²⁸	I	Prospective	PRK/MMC vs. LASIK	88	6 mos	Subjective visual outcomes; haze; HOAs; contrast sensitivity	PRK/MMC group had no haze, better subjective visual acuity, better contrast sensitivity, and fewer HOAs
Leccisotti, 2008 ²⁵	I	Prospective	PRK/MMC vs. PRK alone	104	NR; 12 mos maximum follow-up	Refractive error	MMC group had mean overcorrection of +0.47 D
Gambato et al, 2011 ⁵³	I	Prospective	PRK/MMC confocal results	56	5 yrs	ECD	MMC did not induce ECD changes 5 yrs after surgery
Hofmeister et al, 2013 ⁵⁰	I	Prospective	PRK/MMC (variable exposure times) vs. PRK alone	56	12 mos	Haze score; ECD	No differences in haze score or ECD among PRK/MMC for 60, 30, or 15 sec vs. PRK alone
Shojaei et al, 2013 ⁴⁸	I	Prospective	Low-myopia PRK/MMC for 5 sec vs. PRK with saline placebo	152	NR; 6 mos maximum follow-up	Haze score	MMC group had less haze vs. control (1.4% vs. 11.8%)
Nassiri et al, 2014 ⁵⁹	I	Prospective	PRK/MMC with alcohol debridement vs. mechanical debridement	88	3 mos	ECD; stromal keratocytes	No change in ECD between eyes or between baseline and 3 mos; no difference between groups in keratocyte numbers
Sia et al, 2014 ²⁷	I	Prospective	PRK/MMC or LASEK in dominant eye; PRK alone in contralateral eye	334	12 mos	Haze score	Less haze in the PRK/MMC group vs. LASEK and control
Hashemi et al, 2004 ³⁰	II	Prospective	PRK/MMC (no control)	54	6 mos	Haze level; refractive accuracy	High percentage of patients 20/20 UCVA and zero haze rate
Thornton et al, 2007 ³¹	II	Retrospective	Low-dose (0.002%) MMC vs. control	83	NR; 2 yrs maximum follow-up	Haze level; visual acuity	Less haze in MMC group; no differences in UCVA
Thornton et al, 2008 ⁴⁹	II	Prospective	Low-dose (0.002%) MMC vs. standard dose (0.02%) MMC	221	NR; 12 mos maximum follow-up	Haze score	Significantly less haze in the standard dose group for higher myopia
Virasch et al, 2010 ⁴⁷	II	Retrospective	Varying application time of MMC 0.02%	269	17 mos	Haze score	No difference in haze score among 12-sec, 60-sec, and 120-sec MMC application
Razmjoo et al, 2013 ⁵¹	II	Prospective	Standard vs. low-dose MMC in PRK	170	6 mos	Haze	No differences in haze in low myopia
Camellin, 2004 ²⁶	III	Prospective	LASEK/MMC vs. control (no MMC)	86	1 yr	Haze; HOA	Less haze in MMC, but also higher HOAs
Lee et al, 2005 ³⁴	III	Prospective	PRK/MMC	1011	13 mos	Haze level; refractive accuracy	3.2% had haze and 86% had 20/20 UCVA
Argento et al, 2006 ³²	III	Retrospective	PRK/MMC vs. control	58	NR; 6 mos maximum follow-up	Haze	Decreased haze vs. control
Nassiri et al, 2008 ⁵⁸	III	Retrospective	PRK/MMC	76	6 mos	ECD	Decreased mean ECD in MMC group (2740) vs. control (2727) at 6 mos
Srinivasan et al, 2008 ³⁸	III	Retrospective	PRK/MMC enhancement after LASIK	30	7 mos	Haze level; visual acuity	No haze and improved UCVA
Shalaby et al, 2009 ³³	III	Retrospective	MMC in PRK and PTK, and post-RK	34	NR; 6 mos maximum follow-up	Haze; visual acuity	No significant postoperative haze

(Continued)

Table 1. (Continued.)

Study	Level of Evidence	Study Design	Premise	No. of Eyes	Mean Follow-Up	Parameters Evaluated	Results
Forseto et al, 2010 ⁴³	III	Prospective	PRK/MMC after PKP and DALK	36	16 mos	Manifest refraction; decrease in cylinder; haze	Reduced cylinder (58%), 42% within ± 0.50 D, haze in 8%
Hodge et al, 2011 ⁴²	III	Retrospective	PRK/MMC after PKP for keratoconus	47	12 mos	Haze; reduction in cylinder	40%–60% decrease in cylinder, no eyes >2+ haze
Crawford et al, 2013 ⁶⁰	III	Prospective	Systemic absorption of topical MMC	30	NA	Systemic absorption of MMC	No systemic absorption
Diakonis et al, 2014 ³⁵	III	Retrospective	MMC 0.02% in PRK	37	45 mos	Haze; visual acuity; mean SEQ	Mean postoperative SEQ reduced to -0.09 ± 0.53 D, no haze at 12 mos, 95% of eyes gained 0–2 lines of corrected distance visual acuity
Shi et al, 2014 ³²	III	Prospective	MMC 0.04% vs. 0.02%	496	12 mos	Haze; ECD	Less haze in the 0.04% MMC group, no differences in ECD

D = diopter; DALK = deep anterior lamellar keratoplasty; ECD = endothelial cell density; HOA = higher-order aberration; LASEK = laser-assisted subepithelial keratectomy; MMC = mitomycin-C; NA = not applicable; NR = not reported; PKP = penetrating keratoplasty; PRK = photorefractive keratectomy; PTK = phototherapeutic keratectomy; RK = radial keratotomy; SEQ = spherical equivalent; UCVA = uncorrected visual acuity.

showed that MMC improved the predictability and efficacy of visual results. The mean UCVA in the MMC group was 0.13 ± 0.11 logarithm of the minimum angle of resolution (logMAR) in the MMC group and 0.21 ± 0.20 logMAR in the control group ($P < 0.05$).

Several studies^{18,25,26,36} have shown that MMC may prevent the normal regression that occurs with wound healing. Because of the resulting overcorrection of refractive error, a nomogram adjustment has been recommended to compensate for this change. Leccisotti³⁶ (level I) found an overcorrection of 6% with MMC in a prospective study of 88 eyes. Leccisotti²⁵ (level I) also conducted a prospective, randomized, double-masked, same-day paired eye study of 52 patients with spherical error between -6.50 and -10.00 D. The results showed that MMC induced a mean $+0.47$ D overcorrection (5.8% of attempted correction). Likewise, Camellin²⁶ (level III) showed an overcorrection and less predictable refractive outcomes in LASEK for myopia (range, -1.20 to -10.80 D) when MMC was used in 86 eyes, compared with 100 control eyes. The mean SEQ after surgery at 1 year was $+0.50 \pm 0.93$ D in the MMC group and 0 ± 0.34 D in the control group. An increase in higher-order aberrations was also noted in the MMC group at 1 month and 1 year after surgery. Although this study found that MMC was associated with less-predictable refractive outcomes (if nomogram adjustments were not made) and increased higher-order aberrations, it also found that there was a statistically significant decrease in the subepithelial haze score in the MMC group compared with the controls.

A recent level I study²⁷ from the US Army examined the differences among PRK, PRK/MMC, and LASEK in moderate and high myopia. The study evaluated 167 patients who were randomized to PRK/MMC or LASEK treatment in their dominant eye and conventional PRK without MMC in the fellow eye. At 12 months after surgery, visual outcomes were comparable among the treatment groups. Corneal haze of any grade was less common in PRK/MMC compared with PRK at 1 month (21.4% vs. 31.0%; $P < 0.01$) and 3 months (12.8% vs. 35.9%; $P = 0.03$) after surgery; it was also less common in PRK/MMC compared with LASEK at 1 month (21.4% vs. 55.9%; $P < 0.01$), 3 months (12.8% vs. 42.4%; $P < 0.01$), and 6 months (12.2% vs. 36.4%; $P = 0.03$) after surgery. Haze rate (grade ≥ 0.5) was comparable between LASEK and PRK. Clinically significant haze (grade 2 or higher) developed after PRK (4 eyes) and LASEK (2 eyes) but not after PRK/MMC.

Several studies directly compare the outcomes of LASIK with those of PRK/MMC. Wallau and Campos²⁸ (level I) performed a randomized contralateral eye study of 88 eyes of 44 patients who underwent myopic PRK/MMC in 1 eye and myopic LASIK in the fellow eye. Reported outcomes at 6 months after surgery revealed that eyes undergoing PRK/MMC had better subjective visual outcomes (20 patients [47%] reported “excellent” vision in their LASIK-treated eye compared with 29 patients [65%] who reported “excellent” vision in their PRK-treated eye).^{28,29} In addition, eyes that underwent PRK/MMC had better contrast sensitivity and fewer higher-order aberrations

than the LASIK-treated eyes ($P = 0.01$). No significant haze was noted in the PRK-treated eyes, and the patients experienced no complications of MMC.^{28,29} Corneal hysteresis measurements were higher in the patients treated with LASIK compared with the patients treated with PRK/MMC; however, no hysteresis measurements were made before surgery, and therefore the causality of this association and its clinical relevance are speculative. Although the authors used a concentration of 0.002% MMC for 1 minute, they noted that the optimal concentration and timing of MMC are still unknown. The authors also observed hyperopic overcorrection and recommended using an offset nomogram in these cases.

There is evidence that MMC is an effective adjunct to primary PRK, reducing haze formation in higher ablations without complications. Postoperative refractive error is found to be stable and accurate, although there is evidence for 6% to 10% overcorrection observed with MMC use that can be remedied by using an offset nomogram.^{18,25,26}

Mitomycin-C Use with Surface Ablation Treatments after a Previous Procedure: LASIK. Residual refractive error after primary LASIK is a common indication for surgical re-treatment. Methods of performing re-treatment include flap lifting, recutting a new flap, or re-treating the surface with PRK. Lifting flaps can induce epithelial ingrowth as a potential complication, and recutting a flap can result in the inadvertent amputation of a sliver of corneal tissue from a previous flap. Lifting the flap to perform further tissue ablation can cause encroachment into the residual stromal bed thickness and may contribute to the development of iatrogenic ectasia.

Because of these concerns, the idea of adding refractive correction to the surface of a previous LASIK flap is attractive. Unfortunately, the development of haze and regression in patients enhanced by PRK after primary LASIK is common,³⁷ thus negating the potential safety of less flap manipulation. To address this concern, Srinivasan et al³⁸ (level III) performed PRK/MMC for residual refractive error after primary myopic LASIK in a series of 30 eyes of 23 patients. The patients were treated with 0.02% MMC for a period of 30 seconds to 2 minutes after the laser ablation. A bandage contact lens was placed and subsequently removed after epithelial resurfacing was complete within 3 to 5 days. The mean UCVA improved from 20/50 to 20/28, and no eyes developed postoperative haze at a mean follow-up of 7 months (range, 4–12 months).

Modern technology has greatly reduced the incidence of flap complications. However, in the past, visual rehabilitation in these cases with surface PRK and adjuvant MMC prophylaxis has been used^{39,40} with encouraging results, although this practice has not been evaluated in well-designed trials.

Mitomycin-C Use with Surface Ablation Treatments after a Previous Procedure: Penetrating Keratoplasty. Despite advances in techniques, the final visual outcome of penetrating keratoplasty (PKP) is often limited by significant refractive error resulting from high levels of astigmatism and anisometropia. Photorefractive keratectomy-induced haze⁴¹ led to the use of LASIK after PKP. However, this

introduced other potential complications, such as button-holed flaps, stress dehiscence of the graft-host interface, epithelial in-growth under the flap, and poor predictability of the refractive correction, presumably as a result of irregularities associated with flap healing.

Hodge et al⁴² (level III) reported a series of 47 eyes of 41 patients who underwent PRK/MMC for residual refractive error after PKP for keratoconus. After ablation, MMC 0.02% was applied for 15 to 60 seconds on the basis of the level of correction and the authors' discretion, and a bandage lens was applied for 4 days. Patients were stratified into low-cylinder (<6.00 D, mean preoperative cylinder +5.18 D) and high-cylinder (>6.00 D, mean +9.09 D) treatment groups. At 12 months, there was a 60% reduction in refractive cylinder in the low-cylinder group and a decrease of 41% in the high-cylinder group. None of these eyes developed haze greater than grade 2, and there was no difference between low-cylinder and high-cylinder groups with respect to the development of haze.

Forseto et al⁴³ (level III) reported the results of a prospective study of PRK/MMC to correct refractive errors after PKP and lamellar keratoplasty. This study included 36 eyes of 31 patients who had undergone PKP or deep anterior lamellar keratoplasty for a variety of indications. Mitomycin-C (0.02%) was applied for 1 minute after the photoablation. A bandage contact lens was applied until re-epithelialization was complete. After surgery, 15 eyes (42%) had an SEQ refraction within ± 0.50 D of emmetropia, and 22 eyes (61%) were within ± 1.00 D of emmetropia at the most recent follow-up period. There was an average reduction of 57.5% of the baseline refractive cylinder. All eyes experienced an improvement in UCVA. Haze developed in 3 eyes. The haze was graded as 1+ in 2 eyes and 2+ in 1 eye. Only 1 eye developed a loss of 2 lines of BCVA. Smaller series have reported similar findings.^{44,45}

Dosing

The dosing of MMC is a topic of debate among refractive surgeons. Its first use in ocular surgery consisted of topical application with sponges on the bare sclera during pterygium and glaucoma-filtering surgery. The selected concentration and duration of MMC inhibited proliferation of keratocytes and fibroblasts well and was sufficient in some cases to cause avascular necrosis and tissue melts. Although the cornea and sclera are both avascular, the cornea does not depend solely on nearby blood vessels for nutrition and gets much of its needed nutrients from the tear film and the aqueous. This difference could theoretically reduce the chance of complications. However, in considering the episodic reports of complications during glaucoma and pterygium surgery, the concentration and application times were reduced as experience using it increased over time.

As noted earlier, Majmudar et al¹⁷ in 2000 were the first to report the use of MMC on human corneas as treatment, not prophylaxis, of corneal haze after radial keratotomy and PRK. Mitomycin-C 0.02% was applied for 2 minutes with a sponge and then copiously irrigated with BSS. Subsequently, the dosing strategy reported by Majmudar et al¹⁷ was used prophylactically during primary PRK to

prevent postoperative haze.^{18,24,25,34,46} However, because of concerns of potential complications reported after glaucoma and pterygium surgery, some surgeons investigated decreasing the duration of exposure to MMC during surgery. In 2005, Lee et al³⁴ reported the use of variable contact times depending on the depth of the laser ablation. Within their retrospective review (level III) of 536 patients (1011 eyes) who underwent PRK with the Nidek EC5000 (Nidek Inc, Fremont, CA) excimer laser, they evaluated 3 different exposure times: 30 seconds for ablations between 80 and 100 μm , 1 minute for depths between 100 and 120 μm , and 2 minutes for depths >120 μm . The mean SEQ of their study group before surgery was -7.82 D, and 728 eyes (72%) had >6.00 D of myopia. For this treatment protocol, they reported a postoperative haze rate of 0.49% (5 eyes) and only 2 eyes lost 1 line of BCVA.

In 2010, Virasch et al⁴⁷ (level II) reported a retrospective study of 269 eyes receiving PRK with 0.02% MMC with varying contact times: 120 seconds, 60 seconds, and 12 seconds. The mean refractive error in these 3 groups was similar (-6.49 , -6.77 , and -7.10 D, respectively); however, there was a large difference in the numbers treated among the groups (74, 36, and 159, respectively). The reductions in contact times were based on the cumulative experience of the surgeon, and the largest group studied was for the 12-second contact time, which theoretically included the eyes most prone to develop haze after surgery. Of note, 38 of the eyes in the 12-second cohort were treated for >9.00 D of myopia. This was a relatively small study, given the low incidence of postoperative haze. Because the study was underpowered to find a difference, and no difference in BCVA or haze scores was found among the groups, no conclusions should be drawn. However, the authors conclude that the 12-second application time may be as efficacious as longer treatment times.

A more recent article by Shojaei et al⁴⁸ (level I) examined very short application times of MMC 0.02% in eyes with low myopia (ablation depth <65 μm). Seventy-six patients were randomized to receive a 5-second application of MMC versus saline. At 6 months, the haze grade was significantly lower in the MMC group, with only 1 eye (1.4%) demonstrating trace haze, compared with 9 eyes (11.8%) in the control group, which had a trace to 1+ haze ($P = 0.01$). Endothelial density was not significantly different between the 2 groups.

Anecdotal experience by one surgeon who erroneously diluted MMC to 0.002% (instead of 0.02%) with very good results in terms of haze prevention led investigators to assess the effect of "low-dose" MMC retrospectively, and later in a prospective fashion.^{31,49} In their initial retrospective analysis, Thornton et al³¹ (level II) reported that eyes treated with low-dose MMC (0.002%) ($n = 83$) demonstrated statistically less haze at all time points after surgery and in each myopic subgroup ($P < 0.001$) compared with eyes that received no MMC ($n = 92$). However, there was no difference in UCVA after surgery between the groups.

The same group⁴⁹ (level II) prospectively performed a comparison of low-dose MMC (0.002%) with standard-dose MMC (0.02%). Variable application times from 30 to 120 seconds were used depending on the level of haze

and discretion of the surgeon. Significantly less haze was noted among the standard-dose (0.02%) MMC eyes for high myopia and higher ablation depths (>75 μm). In contrast, there was no significant difference in haze levels between 0.02% and 0.002% MMC among patients with moderate myopia and lower ablation depths (<75 μm) at 6 and 12 months follow-up. The subset of contralateral eyes randomly receiving low-dose MMC (0.002%) for 30 seconds in 1 eye and 2 minutes in the fellow eye showed no significant difference in haze between these application times. The authors concluded that the standard concentration of topical MMC (0.02%) was more effective than low-dose MMC (0.002%) in preventing postoperative haze after surface ablation for myopia ≥ -6.00 D and deeper ablation depth ≥ 75 μm . However, for moderate myopia and shallow ablation depth, low-dose MMC appeared to be equally effective.

Hofmeister et al⁵⁰ (level I) examined the dose-response of MMC after PRK for myopia (range, 4.40 to -8.00 D). A total of 28 patients were randomized to 60-, 30-, or 15-second exposure to a 0.01% concentration of MMC in 1 eye, and the fellow eye received placebo. There was no statistically significant difference in haze score between MMC and control eyes at 12 months, although there was significantly less haze in MMC-treated eyes at 1 month and 3 months. At 12 months of follow-up, no eye had more than trace haze. Endothelial cell densities were not significantly different among groups. The authors concluded that with modern excimer ablations, MMC may not be needed to prevent haze, although a limitation of this study was the relatively low number of patients enrolled.

Another recent article by Razmjoo et al⁵¹ (level II) examined contralateral eye randomized dosing of MMC (0.01% in 1 eye vs. 0.02% in the fellow eye) in 85 patients. At 6 months, 2 of 85 eyes in the 0.01% MMC group had grade 1 haze versus none in the 0.02% MMC group. The authors noted that the results were not statistically significant, and they recommended using the lower dosage to reduce any potential side effects.

In contrast, only 1 level III article⁵² evaluated a higher concentration of MMC in PRK (0.04% vs. 0.02%). The authors randomized 261 patients (496 eyes) to receive 0.04% MMC (133 patients, 245 eyes) or 0.02% MMC (128 patients, 251 eyes). The MMC solutions were dropped onto the ablation region during surgery, and the duration (range, 30–110 seconds) was dependent on the degree of myopia before surgery. Haze was significantly less in the 0.04% group compared with the 0.02% group at 1 year ($P < 0.05$). No statistically significant difference was identified between the density of corneal endothelial cells before surgery and the density at 1, 6, and 12 months after surgery ($P > 0.05$). This study is limited by the fact that the authors did not report results stratified by concentration, which makes the results difficult to interpret. Caution should be exercised in using a higher concentration of MMC, however, given the uniformly good results with MMC 0.02%. In addition, dosing MMC by dropping it on the cornea puts limbal stem cells at risk compared with using a sponge soaked in MMC.

It is important to keep in mind that postoperative haze has a relatively low incidence, which makes the study of its occurrence difficult and requires large numbers of patients to detect statistically significant differences. Many of the studies reporting variable contact times had relatively small numbers of subjects, but, collectively, there were no studies that found a significant increase in haze after surgery when 0.02% MMC was used for contact times as brief as 12 seconds. It is difficult to assess if low-dose MMC produces a higher incidence of postoperative haze on the basis of the limited amount of information available on outcomes of low-dose MMC treatments, but there is suggestion that the standard concentration (0.02%) may be more protective than lower concentrations in cases of high myopia or greater treatment depths.

Safety

Mitomycin-C exerts its antiproliferative effects by binding the 2 strands of the DNA double helix and preventing replication of cells (cytotoxic effect). Although the greatest concern should be the potential effect of MMC on rapidly proliferating cells, it is also important to study the possibility of cytotoxic effects on nonproliferating cells, such as the corneal endothelium, because this may result in endothelial decompensation, stromal edema, and visual compromise.

Most of the clinical studies that have assessed ECD after surface refractive treatments have not demonstrated signs of MMC-induced toxicity (e.g., decrease in cell density or postoperative complications).^{24,34,46,53–55} In these studies, there were no significant ECD alterations after use of 0.02% MMC during surgery for several exposure time intervals, ranging from 12 to 120 seconds, with follow-up ranging from 3 months to 5 years. In a long-term study of 28 patients, Gambato et al⁵³ (level I) evaluated corneal safety of MMC during PRK 5 years after surgery using *in vivo* confocal microscopy. They showed that use of 0.02% MMC during PRK did not induce long-term ECD reduction or any other corneal changes. Goldsberry et al⁵⁶ reported that there were no significant changes in quantitative or qualitative endothelial parameters (e.g., density, coefficient of variation, and percentage of hexagonal cells) in patients undergoing PRK/MMC, with a mean follow-up of 1 year. Although the study was limited by a small sample size, the authors used an independent endothelial cell reading center, which may have improved the accuracy of their conclusions about endothelial cell loss.

In contrast, 2 studies^{57,58} in the literature have reported statistically significant corneal endothelial cell loss in association with MMC use. Morales et al⁵⁷ reported that the use of 0.02% MMC for 30 seconds after PRK in 9 patients caused significant corneal endothelial cell loss of 14.7% and 18.2% at 1 and 3 months after surgery, respectively. Nassiri et al⁵⁸ (level III) also reported that the prophylactic use of intraoperative 0.02% MMC caused corneal endothelial cell loss compared with eyes not treated with MMC during PRK. However, the absolute ECD in the 76 MMC-treated eyes decreased from 2740 cells/mm² before surgery to 2727 cells/mm² at 6 months

(a decrease of only 0.47%). However, the same authors reported the results of a prospective randomized comparative study⁵⁹ (level I) of PRK/MMC during surgery in alcohol-assisted versus mechanical epithelial debridement in 88 eyes (44 patients) with myopia up to -6.00 D. In this study, there were no statistically significant differences in ECD or morphometric parameters between eyes or between baseline and 3 months after surgery. Compared with baseline values, the density of mid- and posterior stromal keratocytes showed no significant change in either group, whereas it decreased significantly in the anterior stroma in both groups 3 months after surgery.

No studies of MMC have reported sight-threatening complications after surgery, such as endothelial decompensation or corneal edema, up to 5 years after surgery. Nevertheless, MMC should be used with caution. Other potential toxicities of MMC include damage to stem cells and a potential negative effect on stromal keratocytes, although no level I or II studies have been conducted. A US Army study (level III) showed that in 30 patients who underwent PRK with topical MMC 0.02% for 30 seconds had no measurable levels of MMC in the blood, and it concluded that there was an extremely low likelihood of systemic absorption or toxicity following current techniques for refractive surgery.⁶⁰

Conclusions

Over the past 15 years, the use of MMC during corneal surface excimer ablation has become widespread. The studies identified in this literature review included 10 that provided level I evidence, and all were deemed to be of high or medium clinical relevance. Although all studies in this field are limited by the relatively low overall incidence of corneal haze after surface ablation, the relevant level I studies indicate that the use of MMC during surgery inhibits haze formation and improves visual acuity outcomes in surface ablation, particularly in highly myopic eyes.

There are some important pearls that can be gleaned from this analysis with respect to the use of MMC in surface ablation. Patient selection is an important consideration. Although there are surgeons who use MMC prophylactically in every case of surface ablation, there is some evidence that this may not be necessary. In eyes with low degrees of myopia, for which evidence on MMC use is not established, the optimal concentration of MMC remains to be determined. It may be preferable to use no MMC, lower-duration MMC, or low-dose MMC, such as 0.002%, in these cases to maximize the benefit/risk ratio. Further long-term studies are also needed to assess the health of these corneas. The possibility of stromal keratocyte dropout and the potential risk of endothelial toxicity may manifest itself in the future.

When using MMC, it is important for surgeons to remember that care must be taken to ensure the appropriate dilution of MMC, and application should be confined only to the central cornea. Mitomycin-C should not be allowed to come into contact with conjunctiva, sclera, or limbal stem cells, because this can potentially lead to delayed re-epithelialization and sterile melting.

In addition, surgeons should adjust their nomogram to prevent hyperopic outcomes. Normally, there is an initial overcorrection after surface ablation, followed by myopic regression. Mitomycin-C may prevent the compensatory wound healing that creates the myopic regression; therefore, the planned ablation should be decreased to prevent a hyperopic outcome.

Future Research

Although none of the studies identified examined other potential uses of MMC or novel application methods, there are a number of opportunities for future research. Currently, an area of great concern is to ensure that MMC application is confined to the cornea and not allowed to come into contact with limbal stem cells. Future research will lead to the development of more targeted drug delivery specifically to the corneal stroma in the area where the newly formed myofibroblasts are known to proliferate.

To fully understand the effects of MMC, there will need to be continued basic science studies of its biological impact. For example, Santhiago et al⁶¹ identified decreased cellularity in the anterior stroma after MMC exposure and questioned whether late effects of MMC will arise with respect to compromised corneal stromal cellularity, structure, and function. However, de Benito-Llopis et al⁶² showed that in 32 patients there was decreased keratocyte density in the anterior stroma versus control, but an initial higher density in the mid- and posterior stroma, 3 years after surface ablation with 0.02% MMC. This normalized to levels comparable to control by 3 years, suggesting that there may be a reorganization of the stromal cell population soon after surface ablation with MMC, but that corneal cellularity tends to normalize over time. Three years after surgery, the mean cell density throughout the cornea seems to maintain normal values. This study is limited by the fact that PRK/MMC eyes were compared with nontreated control eyes; therefore, it is not possible to separate the effects of PRK or MMC. Diakonis et al⁶³ evaluated corneal structural changes in 13 patients receiving PRK/MMC in 1 eye versus epi-LASIK (no MMC) in the contralateral eye. Throughout a mean follow-up of 29 months, qualitative analyses of the subepithelial nerve plexus, haze development, and keratocyte distribution were similar in the 2 groups. There was no statistically significant difference in ECD between the groups throughout the follow-up. Despite these recent studies, the optimal concentration of MMC and duration of exposure to MMC that balances efficacy and safety have yet to be determined.

Perhaps the most important area of research will be the identification of patients at risk for corneal haze after surface ablation. In the past, the decision to use MMC was based on a dioptric cutoff of -6.00 D. Majmudar⁶⁴ recommended using ablation depth as a way to standardize the cutoff, but this is still an arbitrary guideline, and it is known that some patients with shallow ablations may develop corneal haze. Although the widespread use of MMC has been associated with excellent refractive outcomes and few complications, improved predictability of haze

development will help ensure that only those patients most at risk receive this potentially toxic treatment.

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Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; **BSS** = balanced salt solution; **D** = diopter; **ECD** = endothelial cell density; **LASEK** = laser-assisted subepithelial keratectomy; **LASIK** = laser-assisted in situ keratomileusis; **MMC** = mitomycin-C; **PKP** = penetrating keratoplasty; **PRK** = photorefractive keratectomy; **PTK** = Phototherapeutic keratectomy; **SEQ** = spherical equivalent; **UCVA** = uncorrected visual acuity.

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