The Off-label Use of Mitomycin C

Glaucoma surgery.

By Steven D. Vold, MD

Isolated from the fungus *Streptomyces caespiatus*, mitomycin C (MMC) inhibits DNA synthesis, which prevents cells from dividing and growing.\(^1,2\) It is this quality that led the FDA to approve MMC for the treatment of advanced stomach and pancreatic cancer in combination with other chemotherapeutic agents. MMC is also currently widely used in ophthalmology, including glaucoma surgical care.

WHY OPHTHALMOLOGY?

After the FDA approves any new drug, physicians can legally prescribe the medication for off-label purposes. They must make therapeutic decisions based on a thorough evaluation of the product information and solid scientific evidence, however, and maintain records of its use and effects.\(^3\) MMC’s inhibition of cellular proliferation is what makes the agent attractive to ophthalmologists. They primarily use MMC to slow or halt wound healing, thereby reducing postoperative scarring and potentially preventing the regrowth of previously excised ocular tissue. In addition, applying MMC over the ciliary body is believed to reduce aqueous production via a cyclodestructive mechanism.

Ophthalmologists have effectively used MMC in glaucoma filtering surgery, wound- or bleb-revision procedures, dacrocyctorhinostomy, corneal refractive surgery, pterygia management, and the treatment of ocular surface squamous neoplasia, primary acquired melanosis with atypia, and conjunctival melanoma.\(^4\)

GLAUCOMA FILTERING SURGERY

The Agent’s Utility

The success of glaucoma filtering surgery is largely determined by the patient’s wound-healing response. Conjunctival and scleral scarring affect long-term outcomes.

The use of MMC in glaucoma filtering surgery has become widespread since its first description in the early 1980s. Many surgeons now consider the application of antifibrotic agents during this procedure to be the standard of care. To date, MMC is the only such agent to demonstrate efficacy for improving surgical outcomes in combined trabeculectomy and cataract surgery.\(^5\) Nonetheless, the agent’s routine use in glaucoma filtering surgery certainly can be debated due to its association with postoperative complications such as hypotony, choroidal effusions, maculopathy, bleb leaks, wound dehiscence, endophthalmitis, and cataract.\(^6\)

Surgical Technique

Filtering surgery and the use of MMC have evolved. The agent can be administered via subconjunctival or sub-Tenon injections or through a direct application using a variety of sponges or filter paper. Currently recommended topical concentrations generally range from 0.2 to 0.5 mg/mL, with a duration of application from 30 seconds to as long as 5 minutes in some cases. When administering MMC, surgeons carefully avoid exposing the edges of the wound to the antifibrotic so that the conjunctival incision heals properly.

In the past, ophthalmologists placed sponges soaked in MMC anteriorly, near the surgical limbus, and frequently inserted them beneath the scleral flap in trabeculectomy. Unfortunately, this surgical technique resulted in frequent anterior, avascular blebs that predisposed patients to bleb dysesthesia and bleb-related infection and hypotony. Surgeons now place MMC-soaked sponges more posteriorly, and many of them favor fornix-based conjunctival incisions and close them tightly to produce more diffuse, low-lying blebs that are less prone to bleb-related complications.

CONCLUSION

The judicious use of MMC is a mainstay of the surgical care of glaucoma patients. The agent’s popularity in filtering surgery is assured for the foreseeable future, but other compounds that modulate wound healing are currently being evaluated. Moreover, the development and approval of more minimally invasive surgical tech-
niques may ultimately reduce glaucoma surgeons’ need for antifibrotic agents.

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Pterygium surgery.

By Gaston O. Lacayo III, MD

The FDA approved mitomycin C (MMC) for the treatment of certain cancers, but over the past 20 years, this antineoplastic agent has become a popular, off-label adjunctive treatment for a variety of ophthalmic conditions. Most commonly, MMC serves as an antifibrotic agent to prevent scarring after trabeculectomy surgery. Surgeons, however, have found increasingly effective ways of using the agent for a variety of corneal conditions, including pterygium surgery and corneal haze prophylaxis in refractive surgery.1

The postoperative use of MMC in the treatment of pterygium was first reported in 1963, and the intraoperative use of MMC has since become progressively more common.2

Simple pterygium excision with a bare-sclera technique is associated with high rates of recurrence (between 29.2% and 88.9%).3 Surgeons have developed numerous techniques to attempt to reduce the rate of recurrent pterygium, which are commonly more aggressive and difficult to treat than primary pterygia. The primary closure of the conjunctiva, rotational autografts, free conjunctival autografts, and amniotic membrane grafts are all used with varying amounts of success.4 Combining conjunctival autografts with the use of MMC has significantly reduced the rate of recurrence (2%) compared with prior techniques.5

Standard intraoperative concentrations of ophthalmic MMC range from 0.01% to 0.04% (0.1-1.4 mg/mL) with a duration of 1 to 5 minutes. The surgeon determines the concentration and duration. Many ophthalmologists use 0.02% for 2 minutes on primary cases and for 4 to 5 minutes for recurrent or aggressive pterygium. Extreme care is warranted with regard to the dosage of, duration of, and location where MMC is applied due to serious side effects. They include scleral thinning, scleral melting, corneal epithelial toxicity, and early cataract formation—even years after the agent’s original use.6

SURGICAL TECHNIQUE

A peribular injection or topical lidocaine jelly is used on the ocular surface for anesthesia. (Figure 1A). Lidocaine 1% with 1:100,000 epinephrine helps balloon up a subconjunctival wheal under the pterygium. The surgeon uses Sharp Westcott scissors to excise the pterygium head from the limbus and cornea. Balanced salt solution injected into the subconjunctival space inflates and delineates the fibrovascular matrix within the sub-Tenon tissue, which the surgeon then carefully excises away from the conjunctiva and rectus muscle. Limited electrocautery reduces scleral scarring and ischemia. A diamond burr polishes the cornea and creates a smooth transition from the limbus to the cornea.

After cutting surgical spears into small pieces and...
soaking them in 0.02% MMC, the ophthalmologist places individual pledges below the leading edge of the remaining conjunctiva (Figure 1B). He or she must be careful not to expose the bare sclera to the MMC and to limit the exposure over the rectus muscle. The pledges are then removed after the determined time (1-5 minutes), and the eye is thoroughly irrigated with balanced salt solution to remove any amount of residual MMC from the ocular surface.

A free conjunctival autograft or amniotic membrane covers the bare sclera. Fibrin glue helps to fixate the graft onto the globe. The surgeon tucks the remaining three sides of the graft below the host conjunctiva to provide a continuous transition zone over which the epithelial cells can migrate onto the graft. Postoperatively, patients are treated with topical antibiotic and steroid drops. The former are discontinued once the corneal epithelium has healed, and the steroid is tapered off and discontinued over a period of 1 to 3 months.

CONCLUSION

The role of MMC in ophthalmology continues to expand. Current studies indicate that this agent is a viable and safe adjunctive treatment in pterygium surgery. Although both intraoperative and postoperative topical applications of MMC are effective at preventing the recurrence of pterygium, the agent’s intraoperative use has several advantages. The main benefit is the surgeon’s control over the drug’s concentration and the duration of application, thereby avoiding the problems of non-compliance and toxicity, which increase dramatically with cumulative doses. Although longer follow-up is needed to validate the future role of MMC in ophthalmic surgery, recent developments have corroborated past findings and shown great promise for continued success.

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Refractive surgery.

By Peter McGannon, MD, and Parag A. Majmudar, MD

The term off label has developed an unwarranted negative connotation during the past several years. The vast majority of pharmaceutical products used routinely within ophthalmology were initially approved by the FDA for another indication. This in no way implies that the physicians who use these therapies off label are rogue doctors. Rather, it points to the immense impracticality of conducting a new controlled clinical trial every time a new indication is considered. Each individual clinician or surgeon, acting in the best interest of his or her patient, must therefore carefully evaluate the peer-reviewed results of phase 4 clinical trials (post-FDA approval) prior to incorporating a new treatment into practice.

Mitomycin C (MMC) inhibits cellular proliferation. Although only approved by the FDA for the treatment of advanced stomach and pancreatic cancer in combination with other agents, this antibiotic has become a popular adjunctive ophthalmic treatment during the past 25 years. It is most commonly used in pterygium and glaucoma filtering surgery, but refractive surgeons now widely use MMC to modulate wound healing after PRK to prevent corneal haze. Although the exact etiology of corneal haze formation is unknown, it may relate to the disorderly deposition of collagen and glycosaminoglycans by proliferating fibroblasts (Figure 1).

IS MMC EFFECTIVE?

Talamo et al first suggested the use of MMC for preventing haze in PRK in an animal model. Subsequently, our group reported the first use of a single application of MMC for the treatment of post-RK and post-PRK corneal haze. The agent was later used to prevent haze in eyes at high risk of corneal haze such as those undergoing PRK for high myopia, and numerous articles now support this application of MMC. Carones et al performed a prospective, randomized study of the topical application of MMC 0.02% for 2 minutes. There was more haze in the control group (63%) compared to the treated group (0%). This study also found that there was less regression, and therefore greater refractive accuracy, in the treated group. These beneficial effects have been confirmed by several subsequent studies.

WHEN TO USE MMC

A number of factors may be involved in the formation of haze, including the type of laser, laser energy, homogeneity of the laser beam, variations in surgical tech-
nique, and variability in wound healing. The identification of which patients are at risk of developing haze after PRK (ie, the indications for MMC) is imprecise. Using an arbitrary dioptric cutoff (ie, > -6.00 D of myopia) is less than optimal, because visually significant haze may develop after a treatment for low myopia that uses a large optical zone.

We believe the most significant factor in the development of haze is the total amount of excimer laser energy delivered. Since we are unable to directly measure that parameter, we can use the depth of ablation, which is likely directly correlated. Historically, -6.00 D was considered the threshold for developing haze with the first generation of excimer lasers, and this amount corresponds to an ablation depth of approximately 75 µm. Our indication for using MMC is therefore an ablation depth of 75 µm or greater, which may allow for the standardization of the procedure across the range of excimer lasers used today. MMC may also be a helpful adjunct during surface ablation over prior RK, prior LASIK, or prior penetrating keratoplasty.4

DOSE AND APPLICATION TIME

The original description of MMC in PRK used a concentration of 0.2 mg/mL (0.02%) as a single intraoperative application of 2 minutes.2 We strongly recommend applying the MMC with a 6-mm circular sponge or corneal light shield (Figure 2). This technique helps to limit the contact of MMC with the central cornea, thereby reducing the risk of complications from limbal exposure. Initial experience with this protocol has been widely successful, but surgeons have explored two alternate approaches in an attempt to minimize potential toxicity: (1) a lower concentration of MMC and (2) a shorter duration of application.

Thornton et al reported the use of low-dose 0.02 mg/mL (0.002%) MMC versus the standard dosage of 0.2 mg/mL (0.02%) at different exposure times. They found that the standard concentration was more effective than low-dose MMC for ablation depths of 75 µm or more at all exposure times.5 Low-dose MMC was equally effective, however, for ablation depths of less than 75 µm. Our group has investigated reduced exposure times using the standard concentration and found that MMC’s efficacy is maintained with applications as short as 12 seconds.6 The effectiveness of the treatment appears to diminish more with variations in the concentration than in the application time, but further study is required. Currently, we recommend a concentration of 0.2 mg/mL (0.02%) with an application time of 12 seconds for “virgin” corneas and 2 minutes for corneas with preexisting haze. After the application, it is imperative to irrigate the cornea with at least 30 mL of balanced salt solution to avoid prolonged exposure of the tissue to MMC.

RISKS

Despite MMC’s clear efficacy in preventing stromal haze, concerns remain regarding the agent’s use. Significant ocular morbidity has been reported with the long-term use of MMC, including corneal edema, glaucoma, corneoscleral perforation, iritis, and photophobia. These effects were observed, however, after the long-term topical administration of a high dose of MMC. Strict adherence to the protocol we recommended earlier in this article has not resulted in any reported adverse effects for the past 12 years. The specter of endothelial toxicity and MMC’s penetration into the anterior chamber has undoubtedly kept many surgeons from using the agent. Its effect on endothelial cells is currently controversial, with a recent study finding endothelial cellular loss correlating with application time.7 Several other studies have reported no endothelial toxicity.8-10 Additional concerns include a possible depletion of keratocytes, ectasia, and abnormal wound healing. Some animal (Continued on page 61)
models have demonstrated decreased keratocytes in the anterior stroma, whereas human studies using confocal microscopy have shown no significant decrease in the density of keratocytes after 5 years. There have been no reports of ectasia or abnormal wound healing from the use of MMC. In our research and experience, we have found the topical use of MMC to be low risk when the practitioner adheres to the suggested dosage and application time.

A final consideration is overcorrection after PRK with MMC. The inhibition of compensatory wound healing may explain this effect. To avoid the problem, we currently reduce the patient’s spherical correction by 10% and subsequently enter this value as the planned laser correction. Our use of this nomogram has resulted in excellent refractive accuracy.

**CONCLUSION**

Most off-label uses of medications are not imagined when the FDA originally approves these drugs. Careful study, analyses of outcomes, and worldwide surgical experience have led to the widely accepted use of MMC in refractive surgery. Most of the ophthalmologists who use this agent judiciously believe it has improved their outcomes.

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