CME Monograph

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Mitomycin, MIGS, and Microstents

The Role of Antimetabolites in Glaucoma Surgery

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from an expert roundtable discussion held on August 16, 2017.

ACTIVITY DESCRIPTION

Intraocular pressure (IOP) levels in the low teens can be consistently achieved with surgical interventions, and this is of greatest benefit to younger patients and those with advanced disease. To achieve IOP levels consistently in the low teens, a bleb-based procedure is usually needed. Novel devices may provide the IOP reductions expected from trabeculectomy, with more favorable safety profiles, more straightforward surgical techniques, and faster recovery times. The successful outcomes of these new procedures require antimetabolite augmentation. This monograph provides readers with an evidence-based review of antimetabolites and leading glaucoma specialists' practical approaches to their use in glaucoma surgery. Together, these advances may allow ophthalmologists to feel more comfortable offering surgery earlier in the course of the glaucoma process.

TARGET AUDIENCE

This educational activity is intended for glaucoma specialists and other ophthalmologists caring for patients with glaucoma.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the rationale for the use of antimetabolites in modulating wound healing
- Develop individualized treatment plans for patients undergoing glaucoma surgeries with the use of intraoperative antimetabolites
- Review the use of intraoperative antimetabolite augmentation in bleb-based glaucoma surgeries
- Differentiate the risks and benefits of antimetabolite use in glaucoma surgery from those of the procedure itself and the approach

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The Role of Antimetabolites in Glaucoma Surgery

Introduction

Glaucoma is not a static disease. It changes over time, and we need to consider this continuum throughout the patient's lifetime. We have many options for disease control, from noninvasive medications and laser treatments to minimally and moderately invasive surgical procedures. This array of therapeutic options provides us with the ability to titrate invasiveness and safety and power, all at the same time, depending on what is needed, at any given time of any patient's course of his or her disease. We can perform primary glaucoma surgery when needed, and we have options for tweaking glaucoma management at the time of cataract surgery. We can consistently achieve intraocular pressure (IOP) in the low teens with surgical interventions, and this is of greatest benefit for our younger patients and those with more than mild disease. Our experience with a variety of novel glaucoma surgeries has taught us that to achieve IOP levels consistently in the low teens, we usually need a bleb-based procedure. Novel devices may provide the IOP reductions we expect from trabeculectomy but with more favorable safety profiles, more straightforward surgical techniques, and faster recovery times. The availability of these new procedures has led us to rethink our approach to antimetabolite augmentation, leading to a shift from sponge-based to injection-based applications. Together, these advances may allow us to feel more comfortable offering surgery earlier in the course of the glaucoma process.

–Iqbal Ike K. Ahmed, MD

Access the Instructional Videos Described in This Monograph

- Mitomycin C applied to the sclera via sponges during a trabeculectomy
  http://tinyurl.com/mmctrab
- Diffuse, well-vascularized bleb
  http://tinyurl.com/vascularizedbleb
- Dr Herndon's technique for injecting MMC into the subconjunctival space during glaucoma surgery
  http://tinyurl.com/herndonMMCinjection
- Dr Sheybani's technique for injecting MMC in eyes with vascularized conjunctiva
  http://tinyurl.com/sheybaniMMCinjection
- Dr Lim's preparation and injection of MMC
  http://tinyurl.com/limMMC
- Large, cystic, avascular bleb overhanging the cornea and the technique for revising it
  http://tinyurl.com/avascularbleb

Wound Healing After Glaucoma Surgery

The evolution of glaucoma surgery has been driven by the need to overcome the healing process that threatens surgically created drainage fistulae. Histopathologic evaluation of filtering and nonfiltering blebs provided insight into the nature of bleb failure.[1] In functioning blebs, the bleb wall consists of intact conjunctival epithelium overlying a loose collection of connective tissue composed of scattered collagen fibrils, in which clear spaces thought to be microcysts were seen.

The microcysts seen in functioning blebs are thought to play a key role in aqueous filtration. Aqueous in these microcysts may flow across the conjunctival epithelium into the tear film[2] or may gain direct access to subepithelial blood vessels and reenter the systemic circulation in this way.[3] In contrast, nonfunctioning blebs demonstrate dense, thickened collagen, along with fibroblasts and blood vessels, and no microcysts in the connective tissue underlying the epithelium.[1]

The wound-healing process is a cascade of events that begins immediately following surgery and has been extensively reviewed by Skuta and Parrish.[4] In response to the trauma of surgery, conjunctival and episcleral blood vessels initiate the clotting process by releasing blood, fibrinogen, fibronectin, and plasminogen, which form a matrix to stop focal bleeding. Inflammatory cells, including macrophages and monocytes, are recruited to the new clot, and new capillaries and fibroblasts also migrate in from the edges of the surgical wound. Over time, the inflammatory cells degrade the clot, and the newly recruited fibroblasts produce collagens and glycosaminoglycans to form granulation tissue. In the final stages of wound healing, the granulation tissue remodels to a dense collagenous scar, as described previously in nonfiltering blebs.[1]

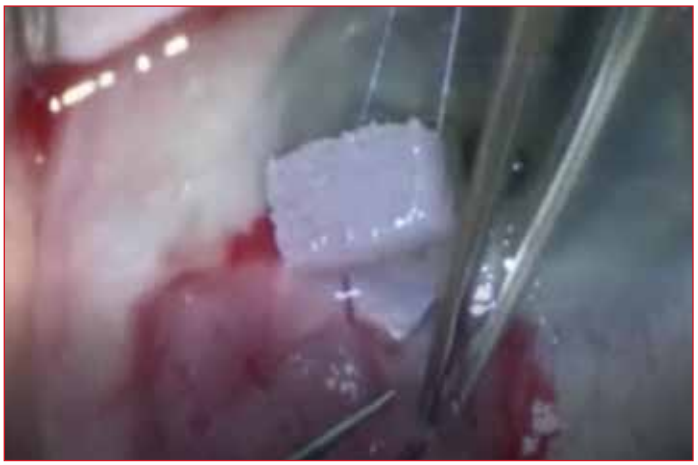
Wound Healing Modulation With Antimetabolites

Historical attempts to modulate wound healing have focused on corticosteroids[5-7] and even beta-irradiation.[8] The modern era of wound-healing modulation focuses on antimetabolites. Antimetabolites are compounds that interfere with normal cellular metabolic processes. They are commonly employed in medicine as agents to treat cancer or microbial infections. Two of these—5-fluorouracil (5-FU) and mitomycin C (MMC)—are also used to modulate the wound-healing process.

The antimetabolite 5-FU is a pyrimidine analogue that interferes with DNA synthesis, thus blocking cell division, which inhibits fibroblast proliferation and enhances bleb formation and function.[9,10] The Fluorouracil Filtering Surgery Study demonstrated lower trabeculectomy failure rates with 5-FU compared with controls (51% vs 74%; $P < .001$), but with a higher rate of bleb leaks (9% vs 2%; $P = .032$). The treatment protocol was intensive, with subconjunctival injections of 5.0 mg (0.5 mL) 5-FU given twice daily through the first postoperative week and once daily through the second week.[11] A systematic review concluded that 5-FU effectively reduced the risk of trabeculectomy failure.[12]

As stated previously, MMC is an antimetabolite used as systemic chemotherapy. Mitomycin C is activated via enzymatic reduction into metabolites that inhibit cell replication by inhibiting DNA synthesis, RNA transcription, and protein synthesis.[13,14] In tissue culture, MMC induces apoptosis of Tenon fibroblasts.[15] In 1990, researchers from Taiwan first described the use of MMC in human eyes to augment trabeculectomy.[16] The application of MMC is technically less onerous than that of 5-FU, requiring a single intraoperative application to the surgical field. Historically, pledgets soaked in MMC in concentrations ranging from 0.1 to 0.5 mg/mL were placed in the subconjunctival space of the superior fornix and delivered MMC for 1 to 5 minutes before their removal; this was followed by a thorough rinse with a balanced salt solution. Delivery of MMC via a subconjunctival injection prior to fashioning the conjunctival peritomy has recently been described.[17] For the first 2 decades of its use to augment glaucoma surgery, MMC was available only as the off-label use of formulations intended for systemic use. More recently, the US Food and Drug Administration has approved Mitosol, a commercially available formulation of MMC for ophthalmic use.[18] It is supplied as a 0.2-mg/vial dose that can be diluted with sterile water to the desired concentration before use.

Visit http://tinyurl.com/mmctrab to see a video of mitomycin C applied to the sclera via sponges during a trabeculectomy.



Video courtesy of Leon W. Herndon Jr, MD

Clinical trials have demonstrated greater surgical success—in terms of IOP reduction, visual field stability, and the need for additional glaucoma surgery—with MMC-augmented trabeculectomy compared with trabeculectomy alone.[19,20] The primary safety issues with MMC are the potential for corneal endothelial cell loss[21] and for ciliary epithelial toxicity, which may contribute to hypotony in excess of that expected due to bleb filtration enhancement.[22] The latter is of particular concern in highly myopic eyes, in which the intraocular exposure to MMC may be enhanced because of the thinner sclera characteristic of these eyes. A systematic review of the literature concluded more than a decade ago that the use of intraoperative MMC at the time of trabeculectomy reduced the risk of surgical failure and provided greater IOP reductions compared with placebo.[23]

Many randomized clinical trials have compared the relative benefits of trabeculectomy augmented with either 5-FU or MMC. A systematic review of the best of these trials concluded that MMC-augmented trabeculectomy produced lower IOP than did 5-FU–augmented trabeculectomy, but had comparable success rates overall.[24] Given that MMC's efficacy is at least as good as that of 5-FU, the substantially less demanding treatment burden associated with MMC (a single intraoperative application vs many applications over several weeks) use has led to decreased use of 5-FU for glaucoma surgery as a primary antimetabolite, although 5-FU is often used to rescue failing MMC blebs, either with or without simultaneous needling.[25]

The improved efficacy of trabeculectomy augmented with antifibrotic agents comes at a cost. Suppression of the fibroblastic response to surgical trauma can produce a thinner bleb and lower IOP, but the

thin-walled bleb is prone to leaks, which in turn increases the risk of hypotony, hypotony maculopathy, and infections, including blebitis and endophthalmitis. Long-term follow-up of the Collaborative Initial Glaucoma Treatment Study—in which newly diagnosed patients with open-angle glaucoma were randomly assigned to treatment with either topical medications or primary trabeculectomy with optional 5-FU augmentation—demonstrated equal risks of developing hypotony, blebitis, and endophthalmitis in eyes that did or did not receive optional 5-FU.[26] As noted previously in the Fluorouracil Filtering Surgery Study, bleb leaks were more common in eyes receiving 5-FU than in those not receiving 5-FU.[11] As for MMC, long-term follow-up of a randomized clinical trial of trabeculectomy with MMC vs no MMC revealed no difference in safety outcomes, including leaks, hypotony, blebitis, and endophthalmitis.[19] In the trabeculectomy (with MMC) arm of the Tube Versus Trabeculectomy Study through 5 years of follow-up, the cumulative incidence of bleb leaks, hypotony maculopathy, and blebitis/endophthalmitis was 6%, 5%, and 5%, respectively.[27] Long-term follow-up of a clinical trial comparing trabeculectomy augmented with either MMC or 5-FU revealed no difference in the rate of bleb leaks (4% per year in both groups) through a mean of approximately 4 years of follow-up.[28]

It is important to realize that despite these studies that individually show no incremental risk increase associated with antimetabolite use, the collective experience of the glaucoma community over several decades of glaucoma surgery both with and without antimetabolite augmentation is that the use of MMC or 5-FU does increase bleb-related complications, such as leaks, hypotony, and infection.[29] The disconnect between clinical eperience and clinical studies likely arises, at least in part, from the design of surgical studies, most of which are not adequately powered to detect small differences in the rates of these rare complications.

Other antifibrotic agents have been evaluated in combination with trabeculectomy, including an antibody to transforming growth factor β2 and inhibitors of vascular endothelial growth factor, placental growth factor, human epidermal growth factor 2, and tumor necrosis factor α.[30,31] To date, none of these has emerged as a viable alternative to MMC.

Mitomycin C Use in Glaucoma Procedures Beyond Trabeculectomy

Combined Phacoemulsification and Trabeculectomy

Given the benefit of MMC in standalone trabeculectomy, it stands to reason that MMC would also confer benefits to eyes undergoing combined trabeculectomy and phacoemulsification cataract surgery. An early clinical trial compared IOP reduction in eyes that underwent combined phacoemulsification-trabeculectomy with and without intraoperative MMC and found no difference.[32] A more robust placebo-controlled and double-masked clinical trial found that combined surgery augmented with MMC produced larger blebs, greater IOP reductions, reduced reliance on IOP-lowering medications, and fewer reoperations for glaucoma than did placebo, but with a higher rate of bleb leaks.[33] These benefits of MMC in combined procedures were confirmed in a subsequent study.[34]

Tube-Shunt Surgery

The potential benefits of MMC in tube-shunt implantation are less intuitive. Particularly with nonvalved implants, the fibrovascular reaction and capsule formation around the device's plate is a fundamental component of outflow resistance to avoid postoperative hypotony, and suppressing this healing response would seem counterproductive. Despite this theoretical concern, the literature is replete with studies evaluating the effects of MMC in both valved and nonvalved tube implantation. In a nonrandomized pilot study, eyes undergoing Molteno implantation with MMC had a higher IOP-lowering success rate than did a historical control group receiving the same operation by the same surgeons, but without MMC; however, the complication and reoperation rate for issues related to overfiltration and hypotony were higher in the MMC arm.[35] In this study, the rate of complications due to overfiltration (including hypotony, choroidal detachments, and flat anterior chambers) was significantly higher in the MMC group than in the historical control group. A more robust randomized trial of the same procedure found no benefit or safety cost with the use of MMC for Molteno implantation.[36] One eye receiving MMC developed persistent hypotony, but the only late bleb leak occurred in the placebo group.

Microinvasive Glaucoma Surgery

In recent years, a family of related surgical procedures has been developed with the goal of providing meaningful IOP reductions more safely than traditional procedures, such as trabeculectomy and tube-shunt implantation. These microinvasive glaucoma surgeries (MIGSs) have generally sought to bypass the obstructed trabecular meshwork by shunting fluid either into Schlemm canal or the supraciliary space.[37,38] It has been recently recognized, however, that bleb-less procedures seem unable to consistently deliver IOP-lowering efficacy similar to that achieved with trabeculectomy, with more favorable safety profiles than trabeculectomy.[39] To address this need, a pair of novel bleb-based MIGS procedures has been described.[40,41] The XEN Gel Stent is a short tube composed of porcine collagen and implanted via an ab interno approach from the anterior chamber through the trabecular meshwork and sclera into the subconjunctival space **(Figure 1)**.[40] The MicroShunt device is also a short tube, composed of polystyrene, but implanted via an ab externo approach following conjunctival peritomy through the sclera and trabecular meshwork into the anterior chamber **(Figure 2)**.[41] Both have luminal diameters designed to optimize the balance between outflow to lower IOP and outflow resistance to prevent hypotony. Both depend on a subconjunctival filtration bleb for ongoing IOP reduction, which in turn requires a lack of scarring at the distal tube end so that outflow is not impeded. Therefore, these procedures would reasonably be expected to be enhanced—albeit with the potential attendant safety issues—by use of adjunctive MMC. With the MicroShunt device, subconjunctival access is achieved surgically via a peritomy, providing access to apply MMC by sponge,[41] although MMC can also be injected into the subconjunctival space preoperatively. With the XEN Gel Stent, a conjunctival incision is not required, but can be performed; thus, MMC can be delivered either by sponge directly to the sclera or via a subconjunctival injection.[42]

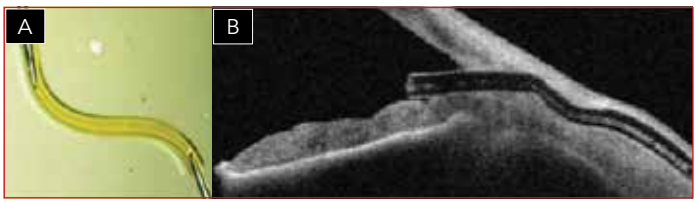


Figure 1. The XEN Gel Stent implant design (A) and intended position in the eye (B)[40]

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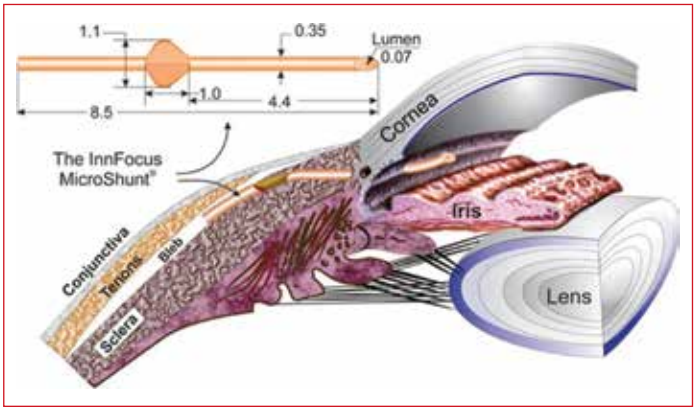

Figure 2. MicroShunt design and its intended position in the eye[41]
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Optimal Use of Mitomycin C

Patient Selection

The patients most likely to benefit from augmentation of trabeculectomy with MMC are those with risk factors for surgical failure. Known risk factors for trabeculectomy failure have been thoroughly reviewed by others and include previous conjunctival incisional procedures (such as previous failed trabeculectomy and retina procedures), secondary glaucoma (such as neovascular or uveitic glaucoma), black race, long-term use of topical IOP-lowering therapies, and young age.[43]

Mitomycin C Delivery

Early in the era of MMC-augmented trabeculectomy, there was little consensus on optimal dosing. The concentration could be varied. The exposure time could be varied. The mechanism of delivery could be varied.

Kitazawa and colleagues conducted an early randomized trial in which fellow eyes of 22 patients with primary open-angle glaucoma received MMC, either 0.02 mg/mL or 0.2 mg/mL applied for 5 minutes intraoperatively.[44] Intraocular pressure reduction was consistently greater with the higher concentration, but so was the incidence of side effects (including hypotony maculopathy and cataract progression). Sanders and colleagues conducted a similar study in eyes at high risk of failure, comparing 0.2 mg/mL to 0.4 mg/mL applied for 2 minutes, and found comparable IOP outcomes in both concentration groups, but a higher complication rate in the 0.4 mg/mL group.[45]

The duration of exposure has also been proposed as a meaningful exposure variable. Stone and colleagues reviewed the outcomes of 57 eyes receiving variable exposure times of MMC 0.3 mg/mL, with exposure time based on the number of risk factors for failure.[46] Although exposure time was not associated with success rate or IOP reduction, there was a difference in complications, which were higher in the lower-risk, shorter-exposure eyes. This led the investigators to conclude that MMC may not be necessary or prudent in eyes at low risk of surgical failure.

The location of MMC delivery has also been evaluated in several studies. Agarwal and colleagues compared MMC delivery in the subconjunctival space (above the flap) with that in the intrascleral space (below the flap) in a randomized trial and found no differences in efficacy or safety outcomes.[47] Mietz and Krieglstein evaluated postoperative MMC application, in which an MMC-soaked sponge was applied to the bleb externally on postoperative days 1 to 3.[48] Compared with placebo in this randomized trial, the MMC group achieved better IOP reduction, with no increase in complication rates. Robin and colleagues conducted a randomized trial to determine whether concentration or exposure time was more important for MMC application.[49] They compared MMC 0.2 mg/mL applied for 2 minutes; MMC 0.4 mg/mL applied for 2 minutes; MMC 0.2 mg/mL applied for 4 minutes; and placebo. Intraocular pressure reductions were seen in all 3 MMC groups, and the investigators suggested that a possible dose-response relationship existed for both concentration and duration with IOP reduction.

More recently, the route of MMC delivery has been evaluated. In addition to the traditional direct scleral application via sponges, some surgeons have begun applying MMC via a subconjunctival injection in the immediate preoperative period.[50] The rationale for this new approach is that injection of MMC under intact conjunctiva ensures a more diffuse area of application, which may promote more diffuse blebs. Other potential advantages include more efficient delivery time and elimination of the risk of retained MMC-soaked sponges.[51] A recent randomized trial comparing MMC delivery via subconjunctival injection vs soaked sponges reported similar IOP reductions between groups but significantly more shallow, more diffuse, and less vascularized blebs in the subconjunctival delivery group.[50]

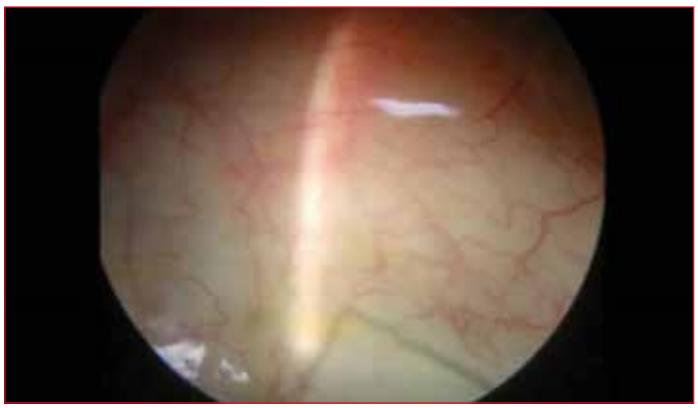
Clinical Pearls for Optimal Use of Mitomycin C in Glaucoma Surgery

Mitomycin C and Trabeculectomy

Dr Ahmed: What is the rationale for using MMC with glaucoma filtering surgery?

Dr Sheybani: With all conjunctival based surgeries—whether trabeculectomy or the newer bleb-based minimally invasive procedures—the primary cause of failure is subconjunctival fibrosis. From both the trauma of surgery and the constant bathing of the tissues by aqueous humor, inflammatory cytokines are delivered to the surgical site and stimulate inflammation and fibrosis. Antimetabolites such as MMC suppress this reaction and reduce the risk of surgical failure; they can produce diffuse blebs.

Visit http://tinyurl.com/vascularizedbleb to see a video by Dr Sheybani of a diffuse, well-vascularized bleb.



Video courtesy of Arsham Sheybani, MD

Dr Ahmed: How often do you use MMC with your trabeculectomies?

Dr Herndon: I use it all the time. Even with high-risk eyes, I still use it for 30 seconds to a minute of exposure time.

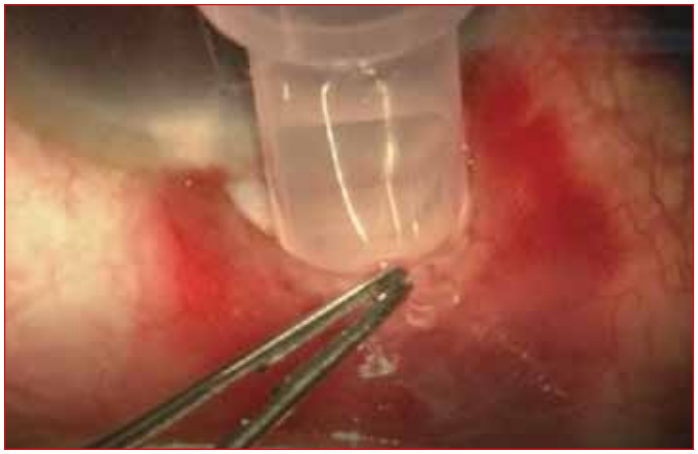
Dr Sheybani: I use it routinely. If I am worried about potential complications in a high-risk patient, I tend to perform a different procedure rather than proceeding with trabeculectomy without MMC. If I opt to perform a trabeculectomy, I want to give it the best shot at working, so I will use MMC.

Dr Lim: I was initially more cautious when I first started practicing 17 years ago and would use 5-FU for patients with lower risk factors for scarring. Now I use MMC in all of my trabeculectomies, and I think it is because the 5-FU trabeculectomies tended to often fail.

Dr Ahmed: Please describe how you use MMC for trabeculectomy.

Dr Herndon: I use MMC 0.4 mg/mL. It is formulated by our pharmacy and delivered to the operating room ready to use. I used to apply it with a soaked sponge, but now I inject the full concentration of 0.4 mg/mL, 0.3 cc of total volume, after I cut the scleral flap. The injection approach is faster than the sponge approach, and there is no risk of retained sponge fragments. I inject it posterior to the flap, under the Tenon layer, using a tuberculin syringe without a needle. My goal is to deliver it as diffusely as possible to create a diffuse bleb. After 2 to 3 minutes, I irrigate with 5 to 10 mL of balanced salt solution before proceeding.

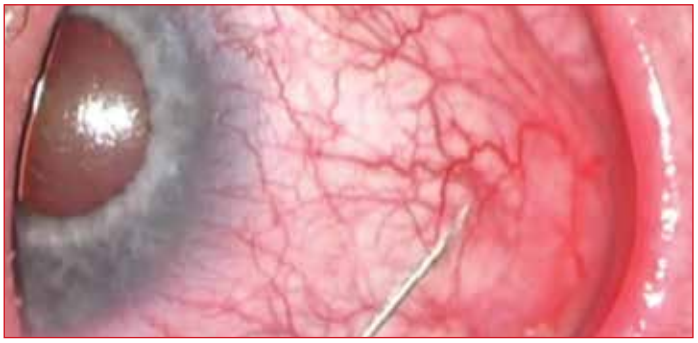
Visit http://tinyurl.com/herndonMMCinjection to see Dr Herndon's technique for injecting MMC into the subconjunctival space during glaucoma surgery.



Video courtesy of Leon W. Herndon Jr, MD

Dr Sheybani: I use commercially formulated MMC. The product is supplied as a 2-mg aliquot, which I dilute to 0.4 mg/mL. I deliver 20 µg in white patients and 40 µg in pigmented patients or those with a high risk of scarring. I inject it into the subconjunctival space rather than the sub-Tenon space using a short 30g needle. If needed, I use a cotton-tipped applicator through the conjunctiva to spread the injection more diffusely. It is important to avoid nicking a conjunctival vessel to prevent the development of a hemorrhage. This is particularly important in eyes with conjunctival inflammation and enlarged conjunctival vessels.

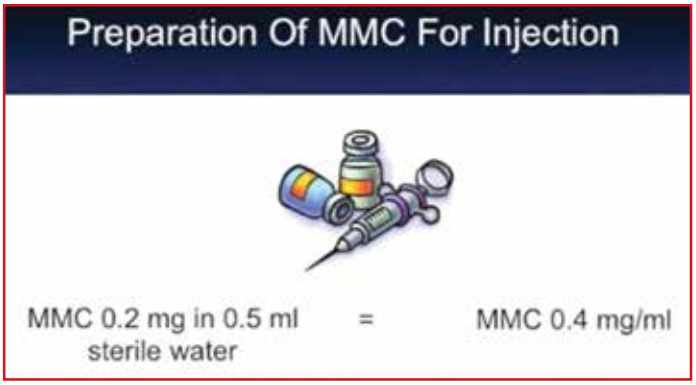
Visit http://tinyurl.com/sheybaniMMCinjection to view a video demonstration of Dr Sheybani's technique for injecting MMC in eyes with vascularized conjunctiva.



Video courtesy of Arsham Sheybani, MD

Dr Lim: I deliver MMC by injection in 100% of my cases. I use a 30g needle, and I inject approximately 8 or 9 mm posteriorly well away from the superior rectus. I use a muscle hook with some irrigation to move the bolus of MMC around under the conjunctiva and Tenon. I use much less MMC than my fellow panelists. When I first started injecting MMC, occasionally I would see white, avascular, thin blebs, so I lowered the concentration in some patients. I usually inject a concentration of 0.1 mg/mL, and I even drop down to 0.05 mg/mL in more elderly white people. This ends up being only 10 or 15 µg at most. However, after listening to my colleagues, I may consider raising my dose in a patient with a higher risk of scarring. I irrigate with normal saline after opening the conjunctiva, but I know many surgeons do not; therefore, I do not think it is absolutely necessary.

Visit http://tinyurl.com/limMMC to view a video demonstration of Dr Lim's preparation and injection of MMC.



Video courtesy of Michele C. Lim, MD

Dr Ahmed: I also inject MMC rather than apply it with sponges. Before I open the conjunctiva, I inject approximately 0.1 mL of a 0.2 mg/mL solution, and I try to inject into the Tenon tissue approximately 8 to 9 mm posterior to the limbus. I do not typically irrigate it away once I have performed the peritomy. Dr Herndon, you conducted a study comparing sponge vs injection techniques for applying MMC. What did you find?

Dr Herndon: The study is in the process of publication. We found that eyes receiving MMC by injection had lower IOP than those receiving MMC by sponge. Also, the need for supplemental 5-FU injections was much greater with sponge delivery.

Mitomycin C and Tube Shunts

Dr Ahmed: What is the current practice regarding the use of MMC with tube-shunt surgery?

Dr Lim: I do not use MMC with my tubes because I have yet to see enough evidence to show that it is beneficial.

Dr Sheybani: Neither do I. In my experience, the fibrotic reaction precipitated by silicone tubes is greater than that with trabeculectomy. I am not sure MMC is powerful enough to control this reaction. I have begun injecting triamcinolone into the sub-Tenon space over the plate of Molteno shunts.

Dr Herndon: I used triamcinolone with Baervedlt implants for a while, but this produced several cases with hypotony because the capsule did not form completely.

Dr Ahmed: I have recently begun using MMC with my Ahmed valves. I follow the protocol being investigated by the research team headed by Ying Han at the University of California, San Diego.[52] I inject MMC once intraoperatively and twice postoperatively into the bleb.

Mitomycin C and Microinvasive Glaucoma Surgery

Dr Ahmed: The evolution of MIGS has reached the point at which bleb-based MIGS procedures are now emerging. These are the subconjunctival microstents: the XEN Gel Stent and MicroShunt. Let us start with the XEN Gel Stent. Is MMC routinely used with this device?

Dr Sheybani: In preliminary studies, the failure rate for the XEN Gel Stent without the use of MMC was quite high.[40,53] In subsequent studies using MMC, success rates have been higher.[41,54] In the US Food and Drug Administration registry trial, MMC 0.2 mg/mL was applied by sponge to the subconjunctival space prior to the ab interno device implantation, and the 12-month success rate (IOP reduced by at least 20%) was 75%.[54] The eyes in this trial were at high risk of failure; 85% had failed prior glaucoma surgery, and more than half were using 4 or more glaucoma medications. A 75% success rate is quite remarkable in such high-risk eyes.

Dr Ahmed: How do you apply MMC when performing XEN Gel Stent surgery?

Dr Sheybani: The device is meant to be implanted with an ab interno approach. This has the advantage of not incising the conjunctiva and thus reduces scarring. Following the protocol from the registry trial negates this benefit because it necessitates a conjunctival incision to apply the MMC-soaked sponges. I prefer to apply MMC via a subconjunctival injection when implanting a XEN Gel Stent to minimize conjunctival manipulation and scarring. I deliver it in the same concentration as with trabeculectomy. A recent study retrospectively compared outcomes of trabeculectomy and XEN Gel Stent implants.[42] In this study, MMC was applied by injection in the XEN Gel Stent group and by either injection or sponge in the trabeculectomy group. Surgical failure rates and safety profiles of the 2 procedures were comparable.

Dr Lim: Avoiding a conjunctival incision is a key advantage of the XEN Gel Stent implantation technique. I think subconjunctival injection of MMC for that procedure is logical.

Dr Ahmed: What are the MMC usage patterns with the MicroShunt?

Dr Lim: The MicroShunt is placed via an ab externo approach and requires taking down the conjunctiva as we do with trabeculectomy. This affords the option to apply MMC by either injection or sponge.

Dr Ahmed: There is some evidence that the location of MMC application matters in MicroShunt surgery. A retrospective study found that applying MMC (0.4 mg/mL) far posteriorly lowered IOP by 38% and reduced medication use by 72%.[55] However, applying MMC 0.4 mg/mL or 0.2 mg/mL closer to the limbus lowered IOP by 52% and 55%, respectively, and reduced medication use by 85% and 88%, respectively.

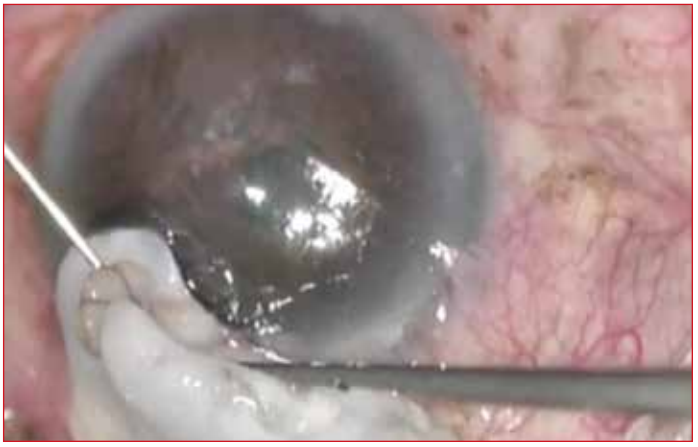
Mitomycin C Safety Issues

Dr Ahmed: What safety issues should we be concerned about when using MMC?

Dr Herndon: Certainly, MMC increases the risk of bleb leaks, infection, and hypotony,[56] but there is a trade-off in terms of efficacy. If we do not use MMC, we will see far fewer complications but far more surgical failures.[19]

Dr Sheybani: It is important to point out that it is the surgical procedure and not MMC that causes these complications; MMC just makes them more common and more severe. Before the use of MMC for trabeculectomy, we still got large, cystic, avascular blebs. All these complications—from bleb leaks to hypotony to infections—occurred in the pre-MMC era. It is likely that exposure of extraocular tissues to aqueous humor contributes to the suppression of wound healing to some extent, and the use of MMC enhances this effect. Because most of us use MMC with most or all of our trabeculectomies, we cannot know whether it is the surgery or the drug that is causing any given complication. As Dr Herndon said, it is a trade-off, and I think a worthwhile one. It is an important point to understand.

Visit http://tinyurl.com/avascularbleb to view a large, cystic, avascular bleb overhanging the cornea and the technique for revising it.



Video courtesy of Arsham Sheybani, MD

Take-Home Points

- There are many options for patients who require surgery for glaucoma, from traditional procedures (trabeculectomy and tube shunts) to bleb-less and now bleb-based MIGS procedures
- The use of antimetabolites such as MMC can favorably modulate

wound healing and improve surgical success rates

- Surgical failure due to excessive wound healing is a common complication of all bleb-based procedures
- Bleb-less procedures generally have better safety profiles but do not always deliver the level of IOP reduction seen with bleb-based procedures
- The XEN Gel Stent and MicroShunt are 2 novel bleb-based MIGS procedures designed to provide the optimal balance of efficacy and safety
- The advent of bleb-based procedures performed through an ab interno approach permits avoidance of a conjunctival incision. In these cases, some surgeons advocate for the delivery of MMC via subconjunctival injection rather than via sponge application
- The use of MMC can increase the risk of complications associated with bleb-based procedures, so it must be used judiciously

References

1. Addicks EM, Quigley HA, Green WR, Robin AL. Histologic characteristics of filtering blebs in glaucomatous eyes. *Arch Ophthalmol.* 1983;101(5):795-798.
2. Kronfeld FC. The chemical demonstration of transconjunctival passage of aqueous after antiglaucomatous operation. *Am J Ophthalmol.* 1952;35(52):38-45.
3. Teng CC, Chi HH, Katzin HM. Histology and mechanism of filtering operations. *Am J Ophthalmol.* 1959;47(1 Part 1):16-33.
4. Skuta GL, Parrish RK 2nd. Wound healing in glaucoma filtering surgery. *Surv Ophthalmol.* 1987;32(3):149-170.
5. Sugar HS. Clinical effect of corticosteroids on conjunctival filtering blebs; a case report. *Am J Ophthalmol.* 1965;59:854-860.
6. Duke-Elder S, Ashton N. Action of cortisone on tissue reactions of inflammation and repair with special reference to the eye. *Br J Ophthalmol.* 1951;35(11):695-707.
7. Araujo SV, Spaeth GL, Roth SM, Starita RJ. A ten-year follow-up on a prospective, randomized trial of postoperative corticosteroids after trabeculectomy. *Ophthalmology.* 1995;102(12):1753-1759.
8. Cohen LB, Graham TF, Fry WE. Beta radiation; as an adjunct to glaucoma surgery in the Negro. *Am J Ophthalmol.* 1959;47(1 Part 1): 54-61.
9. Blumenkranz MS, Claflin A, Hajek AS. Selection of therapeutic agents for intraocular proliferative disease. Cell culture evaluation. *Arch Ophthalmol.* 1984;102(4):598-604.
10. Gressel MG, Parrish RK 2nd, Folberg R. 5-fluorouracil and glaucoma filtering surgery: I. An animal model. *Ophthalmology.* 1984;91(4):378-383.
11. Van Buskirk EM. Five-year follow-up of the Fluorouracil Filtering Surgery Study. *Am J Ophthalmol.* 1996;122(5):751-752.
12. Wormald R, Wilkins MR, Bunce C. Post-operative 5-fluorouracil for glaucoma surgery. *Cochrane Database Syst Rev.* 2001;(3): CD001132.
13. Singh P, Singh A. Mitomycin-C use in ophthalmology. *IOSR J Pharm.* 2013;3(1):12-14.
14. Abraham LM, Selva D, Casson R, Leibovitch I. Mitomycin: clinical applications in ophthalmic practice. *Drugs.* 2006;66(3):321-340.
15. Crowston JG, Akbar AN, Constable PH, Occleston NL, Daniels JT, Khaw PT. Antimetabolite-induced apoptosis in Tenon's capsule fibroblasts. *Invest Ophthalmol Vis Sci.* 1998;39(2): 449-454.
16. Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous topical application of mitomycin-C in refractory glaucoma. *J Ocul Pharmacol.* 1990;6(3):175-182.
17. Galal A, Bilgic A, Eltanamly R, Osman A. XEN glaucoma implant with mitomycin C 1-year follow-up: result and complications. *J Ophthalmol.* 2017;2017:5457246.
18. Mitomycin solution (Mitosol) for glaucoma surgery. *Med Lett Drugs Ther.* 2013;55(1412):24.
19. Reibaldi A, Uva MG, Longo A. Nine-year follow-up of trabeculectomy with or without low-dosage mitomycin-c in primary open-angle glaucoma. *Br J Ophthalmol.* 2008;92(12): 1666-1670.
20. Martini E, Laffi GL, Sprovieri C, Scorolli L. Low-dosage mitomycin C as an adjunct to trabeculectomy. A prospective controlled study. *Eur J Ophthalmol.* 1997;7(1):40-48.
21. Sihota R, Sharma T, Agarwal HC. Intraoperative mitomycin C and the corneal endothelium. *Acta Ophthalmol Scand.* 1998;76(1):80-82.
22. Mietz H. The toxicology of mitomycin C on the ciliary body. *Curr Opin Ophthalmol.* 1996;7(2):72-79.
23. Wilkins M, Indar A, Wormald R. Intra-operative mitomycin C for glaucoma surgery. *Cochrane Database Syst Rev.* 2001;(1): CD002897.
24. Lin ZJ, Li Y, Cheng JW, Lu XH. Intraoperative mitomycin C versus intraoperative 5-fluorouracil for trabeculectomy: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2012;28(2):166-173.
25. Suzuki R, Susanna-Jr R. Early transconjunctival needling revision with 5-fluorouracil versus medical treatment in encapsulated blebs: a 12-month prospective study. *Clinics (Sao Paulo).* 2013;68(10): 1376-1379.
26. Zahid S, Musch DC, Niziol LM, Lichter PR; Collaborative Initial Glaucoma Treatment Study Group. Risk of endophthalmitis and other long-term complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Am J Ophthalmol.* 2013;155(4):674-680.
27. Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC; Tube Versus Trabeculectomy Study Group. Postoperative complications in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. *Am J Ophthalmol.* 2012;153(5):804-814.e1.
28. Palanca-Capistrano AM, Hall J, Cantor LB, Morgan L, Hoop J, WuDunn D. Long-term outcomes of intraoperative 5-fluorouracil versus intraoperative mitomycin C in primary trabeculectomy surgery. *Ophthalmology.* 2009;116(2):185-190.

29. Fan Gaskin JC, Nguyen DQ, Soon Ang G, O'Connor J, Crowston JG. Wound healing modulation in glaucoma filtration surgery–conventional practices and new perspectives: the role of antifibrotic agents (part I). *J Curr Glaucoma Pract.* 2014;8(2):37-45.
30. Khaw P, Grehn F, Holló G, et al; CAT-152 0102 Trabeculectomy Study Group. A phase III study of subconjunctival human anti transforming growth factor beta(2) monoclonal antibody (CAT-152) to prevent scarring after first-time trabeculectomy. *Ophthalmology.* 2007;114(10):1822-1830.
31. Fan Gaskin JC, Nguyen DQ, Soon Ang G, O'Connor J, Crowston JG. Wound healing modulation in glaucoma filtration surgery–conventional practices and new perspectives: antivascular endothelial growth factor and novel agents (part II). *J Curr Glaucoma Pract.* 2014;8(2):46-53.
32. Shin DH, Simone PA, Song MS, et al. Adjunctive subconjunctival mitomycin C in glaucoma triple procedure. *Ophthalmology.* 1995;102(10):1550-1558.
33. Cohen JS, Greff LJ, Novack GD, Wind BE. A placebo-controlled, double-masked evaluation of mitomycin C in combined glaucoma and cataract procedures. *Ophthalmology.* 1996;103(11):1934-1942.
34. Carlson DW, Alward WL, Barad JP, Zimmerman MB, Carney BL. A randomized study of mitomycin augmentation in combined phacoemulsification and trabeculectomy. *Ophthalmology.* 1997;104(4):719-724.
35. Perkins TW, Cardakli UF, Eisele JR, Kaufman PL, Heatley GA. Adjunctive mitomycin C in Molteno implant surgery. *Ophthalmology.* 1995;102(1):91-97.
36. Cantor L, Burgoyne J, Sanders S, Bhavnani V, Hoop J, Brizendine E. The effect of mitomycin C on Molteno implant surgery: a 1-year randomized, masked, prospective study. *J Glaucoma.* 1998;7(4):240-246.
37. SooHoo JR, Seibold LK, Radcliffe NM, Kahook MY. Minimally invasive glaucoma surgery: current implants and future innovations. *Can J Ophthalmol.* 2014;49(6):528-533.
38. Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clin Ophthalmol.* 2016;10: 189-206.
39. Chen DZ, Sng CCA. Safety and efficacy of microinvasive glaucoma surgery. *J Ophthalmol.* 2017;2017:3182935.
40. Sheybani A, Dick HB, Ahmed II. Early clinical results of a novel ab interno gel stent for the surgical treatment of open-angle glaucoma. *J Glaucoma.* 2016;25(7):e691-e696.
41. Batlle JF, Fantes F, Riss I, et al. Three-year follow-up of a novel aqueous humor microshunt. *J Glaucoma.* 2016;25(2):e58-e65.
42. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy [published online ahead of print June 7, 2017]. *Ophthalmology.* doi:10.1016/j.ophtha.2017.05.004.
43. Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. *J Glaucoma.* 2001;10(3):237-249.
44. Kitazawa Y, Suemori-Matsushita H, Yamamoto T, Kawase K. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. *Ophthalmology.* 1993;100(11):1624-1628.
45. Sanders SP, Cantor LB, Dobler AA, Hoop JS. Mitomycin C in higher risk trabeculectomy: a prospective comparison of 0.2- to 0.4-mg/cc doses. *J Glaucoma.* 1999;8(3):193-198.
46. Stone RT, Herndon LW, Allingham RR, Shields MB. Results of trabeculectomy with 0.3 mg/ml mitomycin C titrating exposure times based on risk factors for failure. *J Glaucoma.* 1998;7(1):39-44.
47. Agarwal HC, Saigal D, Sihota R. Assessing the role of subconjunctival versus intrascleral application of mitomycin C in high-risk trabeculectomies. *Indian J Ophthalmol.* 2001;49(2):91-95.
48. Mietz H, Krieglstein GK. Postoperative application of mitomycin c improves the complete success rate of primary trabeculectomy: a prospective, randomized trial. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(11):1429-1436.
49. Robin AL, Ramakrishnan R, Krishnadas R, et al. A long-term dose-response study of mitomycin in glaucoma filtration surgery. *Arch Ophthalmol.* 1997;115(8):969-974.
50. Pakravan M, Esfandiari H, Yazdani S, et al. Mitomycin C-augmented trabeculectomy: subtenon injection versus soaked sponges: a randomised clinical trial. *Br J Ophthalmol.* 2017;101(9):1275-1280.
51. Shin DH, Tsai CS, Kupin TH, Olivier MM. Retained cellulose sponge after trabeculectomy with adjunctive subconjunctival mitomycin C. *Am J Ophthalmol.* 1994;118(1):111-112.
52. University of California, San Francisco. Ahmed glaucoma valve surgery with mitomycin-C (AMCT). ClinicalTrials.gov Web site. https://clinicaltrials.gov/ct2/show/NCT02805257. Updated June 17, 2016. Accessed August 29, 2017.
53. Sheybani A, Lenzhofer M, Hohensinn M, Reitsamer H, Ahmed II. Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: pilot study. *J Cataract Refract Surg.* 2015;41(9):1905-1909.
54. Grover DS, Flynn WJ, Bashford KP, et al. Performance and safety of a new ab interno gelatin stent in refractory glaucoma at 12 months [published online ahead of print August 4, 2017]. *Am J Ophthalmol.* doi:10.1016/j.ajo.2017.07.023.
55. Riss I, Batlle J, Pinchuk L, Kato YP, Weber BA, Parel JM. One-year results on the safety and efficacy of the InnFocus MicroShunt™ depending on placement and concentration of mitomycin C [in French]. *J Fr Ophtalmol.* 2015;38(9):855-860.
56. Holló G. Wound healing and glaucoma surgery: modulating the scarring process with conventional antimetabolites and new molecules. *Dev Ophthalmol.* 2017;59:80-89.

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See detailed instructions at **To Obtain *AMA PRA Category 1 Credit*™** on page 2.

1. Which is an important feature of functioning filtration blebs?
   a. Thickened collagen
   b. Microcysts
   c. Fibroblasts
   d. Granulation tissue

2. Which is NOT typically a process involved in wound healing?
   a. Clotting
   b. Autoimmunity
   c. Inflammatory cell migration
   d. Collagen production

3. The antimetabolite 5-FU modulates wound healing by inhibiting:
   a. Macrophage activity
   b. Cytokine release
   c. Fibroblast proliferation
   d. Aqueous production

4. Mitomycin C modulates wound healing by inhibiting:
   a. Cell replication
   b. Conjunctival blood flow
   c. Protein degradation
   d. Aqueous outflow

5. What is a key advantage of MMC over 5-FU when used to improve trabeculectomy outcomes?
   a. MMC has no side effects
   b. 5-FU produces inferior surgical success rates
   c. MMC requires no special handling or formulation
   d. MMC has a more favorable application regimen

6. The use of MMC with trabeculectomy does NOT increase the risk of:
   a. Hypotony
   b. Bleb leaks
   c. Corneal epithelial toxicity
   d. Thin-walled blebs

7. Regarding the bleb-based MIGS procedures, which of the following can be augmented with MMC?
   a. iStent
   b. Trabectome
   c. Xen Gel Stent
   d. CyPass

8. Which is NOT generally considered a risk factor for failure of bleb-based glaucoma surgery?
   a. Prior conjunctival surgery
   b. Uveitis
   c. Old age
   d. Black race

9. According to a recent randomized clinical trial, which of the following is an expected benefit of MMC applied via subconjunctival injection (as opposed to via soaked sponges)?
   a. Lower IOP
   b. More diffuse blebs
   c. Fewer complications
   d. Faster visual recovery

10. The total dose of MMC delivered to the surgical bed is NOT typically dependent on:
    a. The concentration of MMC used
    b. The duration of time MMC is applied
    c. The location where MMC is applied
    d. The surgical procedure being performed

ORIGINAL RELEASE: December 1, 2017
EXPIRATION: December 31, 2018

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OUTCOMES MEASUREMENT

☐ Yes ☐ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Describe the rationale for the use of antimetabolites in modulating wound healing	5	4	3	2	1
• Develop individualized treatment plans for patients undergoing glaucoma surgeries with the use of intraoperative antimetabolites	5	4	3	2	1
	5	4	3	2	1
• Review the use of intraoperative antimetabolite augmentation in bleb-based glaucoma surgeries	5	4	3	2	1
• Differentiate the risks and benefits of antimetabolite use in glaucoma surgery from those of the procedure itself and the approach	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes
4 3 2 1

Please describe the change(s) you plan to make: _____

_____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?_____

4. Number of patients with glaucoma I see per week
☐ 0 ☐ 1-5 ☐ 6-10 ☐ 11-25 ☐ More than 25

5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.
☐ Patient Care ☐ Practice-Based Learning and Improvement ☐ Professionalism
☐ Medical Knowledge ☐ Interpersonal and Communication Skills ☐ Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10