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A SAFER SOLUTION

The benefits of standardized MMC application in ab externo glaucoma surgery.

Sponsored by Mobius Therapeutics, LLC

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Participants

Richard A. Lewis, MD (Moderator), is in private practice in Sacramento, California, and is a section editor for *Glaucoma Today*. He has served as an investigator for Glaukos Corporation and is a consultant to Mobius Therapeutics, LLC; Alcon Laboratories, Inc.; AqueSys, Inc.; Ivantis Inc.; Envisia Therapeutics; and AVS. Dr. Lewis may be reached at (916) 649-1515; rlewiseyemd.yahoo.com.

Donald L. Budenz, MD, MPH, is the Kittner family distinguished professor and chairman of the Department of Ophthalmology at the University of North Carolina at Chapel Hill. He is a consultant for Alcon Laboratories, Inc., and Liquidia Technologies Inc., and has received honoraria from Merck & Co. Dr. Budenz may be reached at (919) 966-5296.

Louis B. Cantor, MD, is chair and professor of ophthalmology, the Jay C. and Lucile L. Kahn professor of glaucoma research and education, and director of the Glaucoma Service at the Indiana University School of Medicine in Indianapolis. He is a consultant for Allergan, Inc.; Liquidia, Inc., and Mati, Inc., and he is an investigator for Bausch + Lomb, InnFocus, Glaukos, and Outcomes Science. Dr. Cantor may be reached at (317) 278-2651; lcantor@iupui.edu.

Brian A. Francis, MD, MS, is the director of glaucoma services and professor of ophthalmology at Dohney Eye Institute, UCLA School of Medicine in Los Angeles. He is a member of the advisory boards for NeoMedix, Inc., and Endo Optiks, Inc., and he is an investigator for AqueSys, Inc., and a consultant for Allergan, Inc., and Alcon Laboratories, Inc. Dr. Francis may be reached at (323) 442-6415; bfrancis@doheny.org.

INTRODUCTION

Mitosol (mitomycin for solution) 0.2 mg/vial, Kit for Ophthalmic Use (Mobius Therapeutics, LLC) is a standardized formulation of mitomycin C (MMC) prepackaged in a kit for glaucoma surgeons (Figure 1). This kit is the first FDA-approved formulation of MMC, with benefits that include reliable potency, dosing, sterility, closed transfer, and extended room-temperature storage. Recently, noted glaucoma specialists gathered to discuss how they use MMC in surgery and how the Mitosol formulation has assisted them in practice.

INJECTION TECHNIQUES, NUANCES

Dr. Lewis: Would each of you please explain your surgical technique, and perhaps even provide a case example?

Dr. Cantor: I primarily create limbal-based flaps, because I think they are superior to fornix-based flaps in terms of handling the tissue, locating the incisions, creating the flap, and controlling leakage through the sclerotomy. I feel that our surgical technique is a unit that includes all these steps, and it is hard to change one item in that method and know what impact that change has on the overall procedure.

Dr. Lewis: I also create limbal-based flaps. After conversations with colleagues at meetings concerning using subconjunctival injections, I switched to mixing MMC with

Figure 1. An open Mitosol kit containing the antimetabolite indicated as an adjunct to ab externo glaucoma surgery.

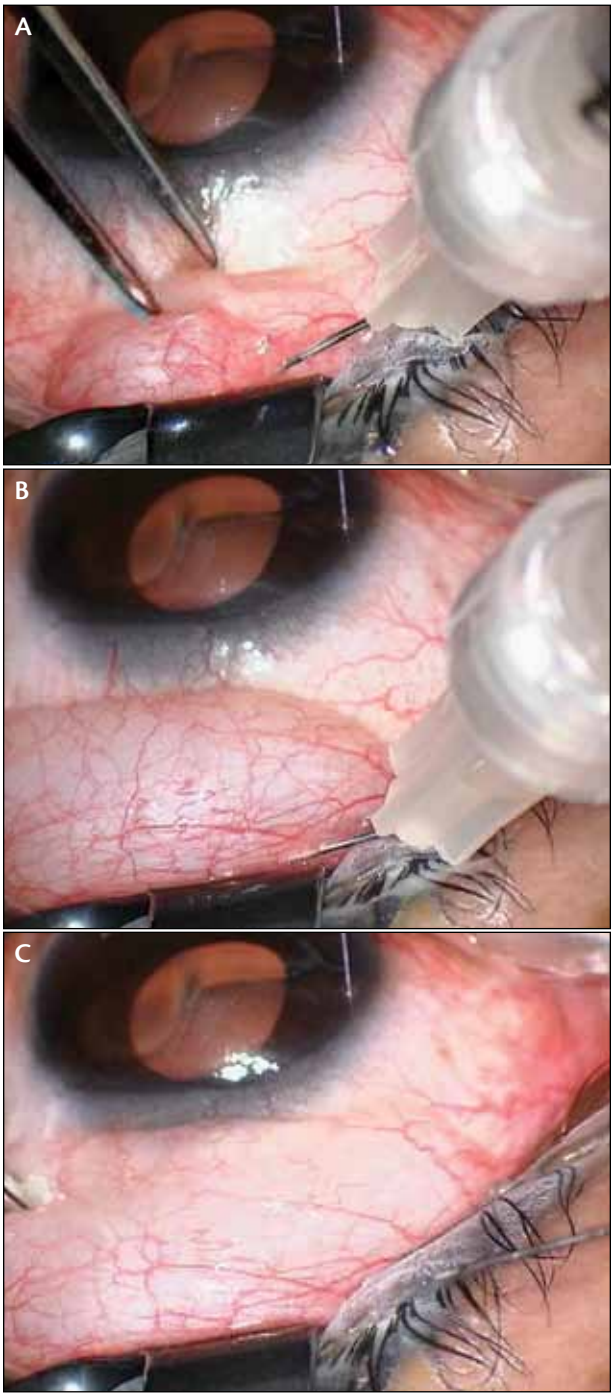

Figure 2. The surgeon begins the injection process and the initial formulation of the subconjunctival "balloon" of MMC (A). As he or she continues the injection, the balloon enlarges (B). Then, the surgeon massages the conjunctiva, forcing the MMC toward the cornea (C).

lidocaine in a subconjunctival injection. I place the traction suture, rotate the patient's eye downward, and inject the mixture. I create a small bleb and push the MMC posteriorly away from the limbus, but I allow for enough anesthetic to perform the surgery topically (Figure 2A–C). I create a limbal-based incision, which has allowed me to move away from an anterior application of MMC with a Weck-Cel sponge (Beaver-Visitec International) or instrument wipe. My issue is the time factor; once I enter the conjunctiva, the injection has dissipated.

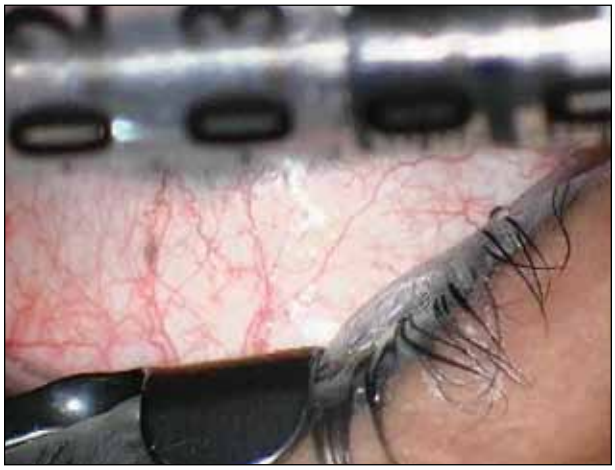

Figure 3. The surgeon begins the massage technique using the barrel of the TB syringe to massage the conjunctiva, thus forcing the MMC toward the cornea. By the end of the massaging process, the MMC is distributed in a broad, diffuse manner.

I believe that many surgeons are pretreating patients with a subconjunctival injection of MMC. They inject the solution and then wait approximately 20 to 30 minutes before needling the eye.

Dr. Francis: I switched from limbus-based to fornix-based flaps a few years ago in order to create more posterior and diffuse filtration blebs. I place MMC on instrument wipe sponges posteriorly, away from the limbal edge of conjunctiva, with a typical concentration of 0.3% for 3 minutes. I have found that this approach induces more diffuse and lower-level blebs with more posterior filtration. However, the incidence of early postoperative bleb leaks is higher, although these usually resolve with conservative measures. I am intrigued by injecting MMC with lidocaine and plan to adopt this technique soon.

Dr. Cantor: As ophthalmologists, we have an opportunity to apply standardized doses of MMC in glaucoma filtering surgery via the Mitosol kit from Mobius Therapeutics. We can see how patients' outcomes vary with standardized doses of MMC applied via a subconjunctival application or injected subconjunctivally.

Dr. Lewis: Even with trabeculectomies, the injections are posterior. You should massage the fluid or the MMC forward toward the limbus (Figure 3), because you do not want to make the injection too close to the limbus, to avoid a potential site of leakage where the bleb may end up.

There have always been concerns about injecting MMC into the anterior chamber. The potential toxicity on the endothelium, iris, and outflow system is significant. I am unaware of any literature reports of this potential complication, but it may result in a chronic inflammatory focus and cataracts. We can impose better safety regulations by standardizing MMC doses.

APPLICATION TECHNIQUES OF MMC

Dr. Cantor: My MMC application technique utilizes an intact Weck-Cel sponge. I do not like to rely on passive transfer of the drug from the sponge to the eye. My colleagues and I once conducted a small internal (unpublished) study in which we placed the Weck-Cel sponges on filter paper after soaking them in a saline solution. We weighed the filter paper before and after we allowed the MMC-soaked sponge to sit on the filter paper for 2 minutes. We found that highly variable amounts of the saline fluid transferred to the filter paper. Sponges are not designed to release fluid as a drug-delivery device. When I apply an MMC-soaked sponge during surgery, I "mash" on it or just keep gentle pressure on the sponge in order to create a pool of MMC around the surgical site. This way, I do not rely on the passive transfer of MMC from the sponge to the eye.

Dr. Budenz: Dr. Cantor's description demonstrates how variable our current practices are with regards to the application of MMC. I started using a single Weck-Cel sponge on its stick; I first soaked it and then placed it over the trabeculectomy flap with the conjunctiva draped over it. This technique created very focal ischemic blebs with variable function, but the area around the ischemic bleb was scarred. I thought that this technique may lead to late bleb leaks, because the aqueous is contained in a very small, circumscribed area, putting some pressure on the conjunctival wall. Thus, my staff and I started to cut up Weck-Cel sponges, and we now use three or four sponges in order to produce a wider area of exposure.

The problem with using multiple pieces of a Weck-Cel sponge is that the surgeon must keep track of how many sponges are used in the eye and make sure they are intact upon removal, which is not always easy. I had one case in which I thought I removed all the sponges, but one of the sponges must have broken apart during removal, because the patient returned 6 months later with a piece of sponge that had eroded through her bleb. I have heard of other such cases over the years.

Dr. Francis: I also had an issue many years ago with a small piece of Weck-Cel sponge breaking off and remaining under the conjunctiva. I had to take the patient back to surgery to remove it. After that experience, I switched to instrument wipe sponges, which seem to maintain better integrity and also do not swell up as much. I typically place three or four large sponge pieces as posteriorly as possible, away from the limbal edge of the conjunctiva.

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>
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Dr. Budenz: Eventually, I switched to creating a fornix-based flap, because Professor Peng Khaw believes it produces a low and diffuse bleb rather than a focal and high bleb, which may reduce late leaks.[1] I make an 80% to 90% partial-thickness, triangular trabeculectomy flap. I do not enter the eye until after the mitomycin has been applied and rinsed off. I place four mitomycin-soaked sponges on and around the flap and drape the conjunctiva over them to expose both the sclera and conjunctiva to MMC. I do not place a sponge directly under the flap, although some surgeons do. I believe that the MMC leeches out from the top sponge, which I drape over the flap and leave on for 2 to 3 minutes. Although Jampel showed that more than 1 minute of MMC application does not add much additional action,[2] I still use 2 minutes as my minimum application time.

Dr. Cantor: I place the sponge behind and over the scleral flap in order to cover the area. I create a pool of MMC so it is free to diffuse throughout the tenons and episclera in the area of the trabeculectomy. When I first starting using MMC, I put the sponge on the eye and left it in place with no pressure applied to the sponge and just the conjunctiva draped over the sponge. When the bleb developed, you could practically see the outline of the sponge in many eyes. It was a square, white bleb. The bleb was the shape of the sponge, reinforcing the idea that the fluid was not diffusing very far from the sponge. Following this observation, I began the technique of expressing the fluid from the sponge with gentle pressure, allowing for greater diffusion of the MMC and therefore more diffuse blebs.

Dr. Francis: I try to use as large a surface area as I can posteriorly in order to create a diffuse bleb. I think using lower concentrations of MMC with a larger surface application results in more appealing bleb morphology and a lower incidence of focal, avascular blebs that are at higher risk of leaks.

ISSUES OF AVAILABILITY AND CONCENTRATION

Dr. Francis: Just having MMC available in the OR in sealed packages is a great relief, as it takes the availability issue out of the equation. It is one less thing to worry about in glaucoma surgery.

Dr. Budenz: There have been times during the past 5 years when there were shortages of MMC. Once, I arrived in the OR to perform a scheduled trabeculectomy, and there was no MMC, even though I had ordered it. I was not told of the shortage until I was in the OR. Options at that point are (1) to reschedule the surgery or (2) to change the surgical plan and reconsent the patient. Neither are good options. Now, having access to MMC in a kit (Figure 4A and B) on the shelf like an IOL, easily available, is a huge help for us.

Dr. Cantor: The availability of MMC has varied within my practice, which has facilities that are both office- and hospital-based. We have surgery centers that are not necessarily operating under the same rules as the university hospital. In some locations, our MMC would come from the pharmacy, while in others, the nurses would mix the MMC solution in the OR. It was not uncommon to have a larger mixture of 0.4 mL of MMC in the OR. Throughout the day, depending on the case, the nurses would dilute the MMC depending on the surgeon's preference, and the surgeons had to assume the concentration handed to them was correct.

Dr. Budenz: The issue of concentration has been a big problem in my practice. Our hospital pharmacy has sent us the wrong concentration because corneal surgeons were using very low doses of MMC to treat pterygia. For my surgeries, I prefer to use 0.2 mg/mL of mitomycin for primary trabeculectomy in elderly white patients, and 0.4 mg/mL in pretty much every other clinical situation in which I use MMC. If we receive the wrong concentration, it can be a problem. Because MMC is specially ordered, if you are sent 0.2 mg/mL but want 0.4 mg/mL, there is not much you can do.

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Dr. Lewis: As an owner and operator of an ASC, it worries me when nurses mix up MMC. There is always the potential for toxicity with that drug, whether injecting it or inadvertently making a mistake. In one case, the wrong jug was mixed, and something else was added into the solution. I think MMC was due to be standardized to avoid this problem.

Dr. Cantor: MMC is very toxic and not well contained or controlled in some situations. Any of the nursing or technical staff who was pregnant would at times be asked to leave the glaucoma OR to avoid exposure. We have had incidents of MMC spilling on the floor or back table during preparation when nurses or technicians were mixing it.

Dr. Francis: Due to these toxicity and exposure concerns, we have not had the ability to mix the solution in the OR until now with Mitosol. In our ASC, we would order it from compounding pharmacies, but sometimes it was sent to the patient instead of the ASC. In our main hospital, we would order the MMC in advance from the pharmacy, but often it was not ready on time, and we would have to wait during surgery.

In addition, I typically use 0.2 to 0.3 mg/mL of MMC,

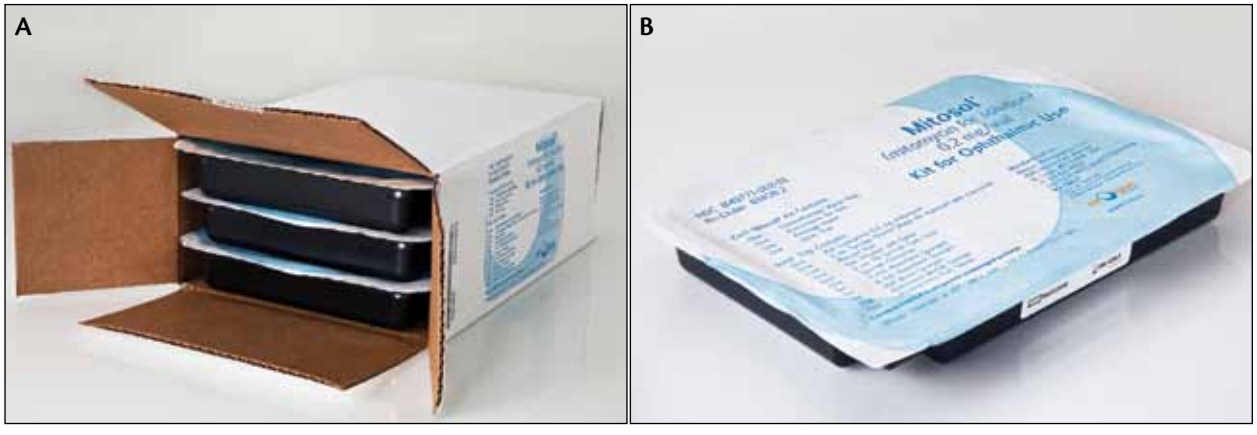

Figure 4. Mitosol kits are packaged in boxes of three (A) and do not take up much space in the OR (B).

> "[My colleagues and I] compared concentrations of 0.2 mg/mL versus 0.4 mg/mL in primary surgery, and we did not see a benefit with the higher concentration."
>
> —*Louis B. Cantor, MD*

but the pharmacy would only mix in concentrations of 0.2 and 0.5 mg/mL. Therefore, to make concentrations of 0.3 or 0.4 mg/mL, we would have to dilute it with balanced salt solution just before application. This was an imprecise method, and sometimes the sponges were already placed in the MMC prior to dilution, so I was not sure what concentration was actually in the sponges.

PREFERENCES FOR CONCENTRATION AND APPLICATION TIMING

Dr. Budenz: I use 0.2 mg/mL of MMC for primary trabeculectomies and 0.4 mg/mL on other patients, although not in every case. I am afraid to use a high dose of MMC in my elderly white patients, for example, because they are less likely to have scarring postoperatively, even without MMC, and I am afraid of inducing thin, avascular blebs. For these individuals, I use 0.2 mg/mL of MMC. However, 0.4 mg/mL of MMC can be mixed up very precisely with Mitosol, even though it is off-label. *(Mitosol is approved by the FDA at the 0.2 mg/mL dose.)*

Dr. Cantor: I use 0.2 mg/mL of MMC for the majority of my cases, including eyes that have only one risk factor for failure, such as younger age or one previous eye surgery without extensive conjunctival scarring, etc. I increase the concentration of MMC to 0.4 mg/mL in patients I consider at a higher risk of failure. Even in a primary surgery in an African American, I use 0.2 mg/mL. If the patient is an African American who has undergone previous conjunctival surgery, however, I may use 0.4 mg/mL.

My colleagues and I have conducted studies comparing different concentrations of MMC in trabeculectomy surgery. We compared concentrations of 0.2 mg/mL MMC versus 0.4 mg/mL in primary surgery, and we did not see a benefit with the higher concentration.[3] We even looked at 0.2 mg/mL versus 0.1 mg/mL of MMC and found similar results.[4] However, it is always difficult to generalize these results based on everyone's individual surgical technique, since there is so much variability.

Dr. Lewis: When MMC first came out, its concentration varied. Some surgeons were using high levels such as 0.5 mg/mL and applying it for a long period of time on the patient's eye. The feeling at that time was, what is the highest dose you can use without inducing a complication? Without tracking these patients' results, however, surgeons did not know how much MMC they could safely use.

Dr. Francis: I think the decisions about concentration and time of application are best based on personal experience. There is no right or wrong formula, but my recipe is similar to my colleagues'. If a patient is at low risk for scarring (white persons and the elderly, with no prior conjunctival surgery), I use 0.2 mg/mL of MMC. I will increase that dosage to 0.3 mg/mL for those at moderate risk for scarring, and up to 0.4 mg/mL for high-risk patients (those who are African American, young, or have had prior conjunctival scarring).

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Dr. Cantor: I usually do not vary the time of the application of MMC; I believe the effect of MMC has more to do with its concentration. The article published by Dr. Jampel several years ago[2] made an impression on me. In a tissue culture model, Dr. Jampel found that even a brief exposure time of MMC has a large impact on cell growth, and by extension, on wound healing. This very rapid effect suggested to me that the application time of MMC did not matter as much as the concentration and location. Generally, I apply MMC on the eye for 2 minutes. If I have patients who I consider at very low risk for surgical failure, such as an elderly white female with very thin conjunctival tissue, I reduce the MMC exposure time to 1 minute.

Dr. Francis: I vary the application time somewhat in the same way as I vary the concentration. My minimum application time is 2 minutes, and the maximum is 4 minutes. Although it is likely true that the majority of effect happens quickly, prolonged exposure has been hypothesized to increase the likelihood of scleral penetration and may affect the ciliary body and aqueous production as well as contribute to inflammation.

EFFECT OF MMC IN CLINICAL TRIALS AND THE FUTURE OF CLINICAL STUDIES

Dr. Lewis: I think having the FDA's stamp of approval allows MMC to be part of clinical studies. We could never use it in an FDA-regulated study before, and that was a big problem. Most surgeons were using MMC and yet, a trial could not be performed with it. With all the new microinvasive glaucoma surgery devices and other surgical devices coming out, we can now actually use MMC in trials and compare it to other products.

Dr. Cantor: Whenever somebody would propose a new wound-healing agent, there was never any other agent to compare it to. Any new wound-healing agent was previously compared to trabeculectomy alone.

Dr. Lewis: Mitosol is now the gold standard, because this is the only approved drug on the market so far. Everything else, whether it is an investigational drug or a new device, will be compared to MMC.

CONCLUSIONS

Dr. Lewis: In conclusion, the FDA-approved product, Mitosol, will help the glaucoma community. By standardizing the dose and application, Mitosol should help reduce complications and mistakes. Also, future FDA glaucoma surgical studies will have the advantage of using Mitosol as we compare trabeculectomy to the new procedures. ■

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