Transconjunctival MMC for Needle Revisions

Recent findings suggest that a new technique is successful in the revitalization of nonfunctioning trabeculectomy.

BY ANDREW G. IWACH, MD, AND MARIANA MATA-PLATHY, MD

Needling a failing filtering bleb is one means of reviving a nonfunctioning trabeculectomy in a glaucomatous eye. The antifibrotic agent mitomycin C (MMC) has become a popular option for increasing the survival of blebs by decreasing the eye's wound-healing ability. We believe that combining the use of MMC with a needling procedure enhances the long-term success of many previously failing blebs. This method has been useful in our practice and is described herein.

A UNIQUE CHALLENGE

Risk factors such as uveitis, neovascular glaucoma, previous surgery, pseudophakia, aphakia, and black race may reduce the success of a filtration procedure. In addition, the success of glaucoma surgery is largely determined by wound healing. After filtering surgery, scar tissue forms as a result of increased vascular permeability and the leakage of plasma proteins at the filtration site; it is to this location that fibroblasts migrate and where collagen undergoes reorientation.

The failure of filtration surgery due to fibroblast infiltration leaves few options for controlling the IOP in a glaucomatous eye. Bleb revision by means of needling is one of few available options to enhance filtration, and MMC is an antineoplastic agent that has been shown to increase the duration of bleb function longer than other antifibrotic agents in such eyes.[1,2]

Figure 1. The authors placed a superior intracorneal traction suture with 8–0 VICRYL. The failing bleb had this appearance preoperatively. (Reprinted with permission from Iwach AG, Delgado MF, Novack GD, et al. Transconjunctival mitomycin-c in needle revisions of failing filtering blebs. *Ophthalmology*. 2003;110:724-742.)

INTRAOPERATIVE TRANSCONJUNCTIVAL MMC APPLICATION

The needling technique for failing filtering blebs varies among surgeons, as does the use of antifibrotics and the postoperative care regimen. We favor intraoperative transconjunctival MMC application (ITMA) as an adjunct in the modification of blebs by means of needling. We perform the procedure in the OR under sterile conditions. The anesthesiologist administers an intravenous sedative to the patient. We perform a peribulbar block with 2% lidocaine mixed 1:1 with 0.75% bupivacaine. After preparing the skin surrounding the eye with a 5% povidone iodine solution, we place a drop of this mixture on the eye. The face is draped, and a lid speculum is positioned. We place an 8–0 VICRYL suture (Ethicon Inc., Somerville, NJ) superiorly intracorneally for traction (Figure 1). We then pass a 25-gauge disposable needle subconjunctivally through the dense scar tissue of the bleb (Figure 2). Typically, multiple passes are needed to revitalize the preex-

isting trabeculectomy site and increase the filtering area. We attempt to raise the scleral flap when possible to further disrupt scar tissue and maximize aqueous outflow. The size of the filtering area increases after the needle's removal. Reformation of the bleb is immediately noticeable (Figure 3).

Next, we close the entry site with a single 8–0 VICRYL suture. We soak a cut piece of Weck cell sponge in MMC 0.5 mg/mL and hold the sponge to the conjunctival tissue associated with the enlarged filtering area for 6 minutes. After removing the sponge, we irrigate the area with BSS. The eye receives a subconjunctival injection of 0.5 mL betamethasone (6 mg/mL), followed by drops of atropine 1%, gentamicin 0.3%, and prednisolone acetate 1%. The eye is then patched and shielded. The patient continues administering these drops during the follow-up period. Prednisolone dosing depends on the level of inflammation but is typically q.i.d. The administration of atropine depends on the patient's IOP and anterior chamber depth. Both drops are tapered within 4 weeks of surgery, whereas antibiotics are typically discontinued after the first week.

POSTOPERATIVE CARE

The number of visits during the postoperative period varies by case, depending on the characteristics of the eye and the patient. We see patients on the day after surgery, and subsequent visits are scheduled as needed. Some patients receive postoperative subconjunctival 5-fluorouracil injections (5 mg) in the clinic. We have found that those receiving 5-fluorouracil require between one and 11 injections. The number and timing varies based mainly upon the appearance of the tissue and bleb and less on the IOP. Blebs with active fibrosis and vascularization receive a greater number of injections. Ocular hypotensive medications may be needed as well.

To date, we have encountered no intraoperative complications with the ITMA procedure. Postoperatively, small hyphema, choroidal detachment, and blebitis have occurred in a small percentage of cases. All of these complications have resolved within a few weeks with conservative medical management. Some conjunctival epithelial staining may be noted at the site of the ITMA, but it resolves within the first postoperative week.

> "This procedure is a safe option for restoring bleb function in patients who may benefit from a lower IOP."

CONSIDERATIONS

Known advantages of applying MMC transconjunctivally include minimal conjunctival dissection and manipulation, greater control by the surgeon, and a lower risk of the direct spread of the agent into the anterior chamber compared with the injection of MMC into the subconjunctival space, adjacent to or into the bleb. We prefer to perform this procedure in an OR rather than in the clinic at a slit lamp for several reasons. In the OR, there is a lower theoretical risk of infection, we can better visualize the tissues, the eye is more stable during the procedure, and the patient is more comfortable. In addition, the OR is a more controlled environment than the clinic for the use of antimetabolites.

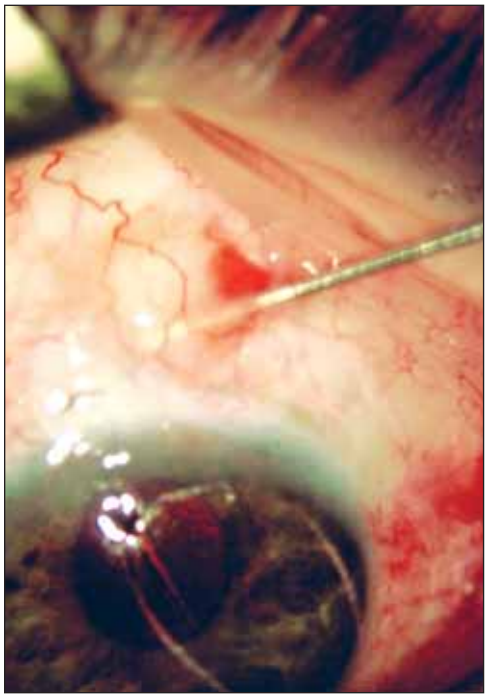

Figure 2. A 25-gauge needle is advanced subconjunctivally through scar tissue. (Reprinted with permission from Iwach AG, Delgado MF, Novack GD, et al. Transconjunctival mitomycin-c in needle revisions of failing filtering blebs. *Ophthalmology*. 2003;110:724-742.)

BENEFITS

When strictly defining success as including a 30% reduction in IOP, our preliminary results and those of our colleagues are that 76% of cases undergoing the ITMA procedure are successful at 12 months and require few ocular hypotensive medications. At 24 months, 72% are successful.[3]

Bleb revision by means of needling with subsequent ITMA allows the incision of scarred tissue with associated restoration and revital-

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Fixed-Combination Glaucoma Drops

Their place in practice and recent developments.

BY RICHARD A. LEWIS, MD

In the early 1970s, patients with glaucoma commonly received b.i.d. treatment with a topical fixed-combination medication comprising pilocarpine 2% and epinephrine 1%. Although this agent gained wide acceptance as providing enhanced compliance and efficacy, other combination products that became available did not attain the same level of commercial success. When the beta-blockers introduced later in that decade proved to offer q.d. or b.i.d. dosing and more effective lowering of IOP, the popularity of miotic agents and combination products for the treatment of glaucoma declined.

In 1998, the fixed-combination agent COSOPT (timolol 0.5% and dorzolamide; Merck & Co., Inc., West Point, PA) became available. Despite concern that b.i.d. dosing of the medication compromises the effectiveness of the topical carbonic anhydrase inhibitor, which requires t.i.d. dosing, COSOPT has been commercially successful. The agent is often used as an adjunct or second tier to the prostaglandin analogues.

Why is there not a greater number of fixed combinations for treating glaucoma, especially when such a large percentage of glaucoma patients take more than one IOP-lowering medication? Among patients with primary open-angle glaucoma, almost half use more than one eye drop; the most common combination is a prostaglandin and a beta-blocker. In the Ocular Hypertension Treatment Study,[1] 40% of subjects in the treatment group took two or more medications at 60 months to achieve the targeted 20% reduction in IOP. In light of the potential severity of glaucoma and patients' known problems using their medications, a fixed-combination agent used q.d. could be helpful. What determines the success of a fixed combination? The answers to these questions are complex and depend on issues of patient compliance, regulatory requirements, and drug efficacy and safety.

> "It is challenging to develop a fixed-combination agent that enhances patient compliance, effectively lowers IOP, and achieves regulatory approval, but it is also an opportunity."

COMPLIANCE AND EFFICACY

Assuming patients' compliance with prescribed therapy increases when they are asked to take a medication once versus multiple times daily, it seems logical that a fixed-combination eye drop prescribed q.d. would be successful if it proved to be more effective at IOP-lowering than both its individual components and other competing therapies.[2] In the case of COSOPT, the fixed combination was shown in clinical trials to lower pressure to a greater extent than either timolol or dorzolamide alone. All fixed-combination medication are required to fulfill this FDA requirement. COSOPT was approved for b.i.d. dosing, however, which is not optimal for enhancing compliance. Moreover, the agent is not as efficacious as the prostaglandin analogues.

RECENT DEVELOPMENTS

It is challenging to develop a fixed-combination agent that enhances patient compliance, effectively lowers IOP, and achieves regulatory approval, but it is also an opportunity in glaucoma therapy. Pfizer Inc. (New York, NY), Allergan, Inc. (Irvine, CA), and Alcon Laboratories, Inc. (Fort Worth, TX), have each conducted multiple clinical trials to develop a fixed combination of a prostaglandin analogue and timolol for q.d. application. Although Pfizer Inc. received approval in the European Union for Xalcom (latanoprost and timolol), the company was unsuccessful in obtaining FDA approval for the medication. Pfizer Inc.

did not satisfy the FDA requirement that its combination product be more effective than its individual components. Allergan, Inc., is awaiting FDA review of its fixed combination of Lumigan (Allergan, Inc.) and timolol as well as of COMBIGAN (brimonidine 0.2% and timolol 0.5%), which is currently available in Canada.

The FDA should decide whether to approve Extravan (Alcon Laboratories, Inc.) by the end of this year. This fixed-combination agent is composed of Travatan 0.004% (Alcon Laboratories, Inc.) and timolol 0.5%. In a pivotal phase III clinical study, Extravan administered q.d. produced a statistically significant and clinically relevant reduction in IOP from baseline. Specifically, the agent decreased patients' (N=155) pressure by 6.8 to 8.6 mm Hg versus 7.3 to 8.4 mm Hg in subjects (N=151) concomitantly receiving Travatan and timolol as separate agents and 4.6 to 7.0 mm Hg in patients (N=81) taking timolol alone. At every 8-AM time point, Extravan delivered therapeutically equivalent pressure reductions to those achieved in the Travatan-plus-timolol concomitant administration group.

Another study compared the safety and efficacy of three treatment groups: (1) Extravan q.a.m. (N=82); (2) Travatan 0.004% q.p.m. (N=84); and (3) timolol 0.5% b.i.d. (N=92). Extravan produced statistically significant and clinically relevant reductions in IOP from baseline, with mean decreases of up to 12 mm Hg or 38%. The agent produced statistically significantly lower mean IOP at all visits compared with timolol. When dosed in the morning, the agent exerted maximum IOP-lowering efficacy at the 8-AM time point (the peak of the diurnal IOP curve). At that time point, it lowered IOP by 2 mm Hg more than Travatan alone. Whether the FDA will consider this amount to be a sufficient pressure reduction remains to be determined.

CONCLUSION

As practitioners raise the pressure-lowering goals of glaucoma treatment in terms of providing maximum compliance, safety, and efficacy, fixed-combination medications will likely gain in popularity. In all probability, such agents will once again become first-line therapy. ❑

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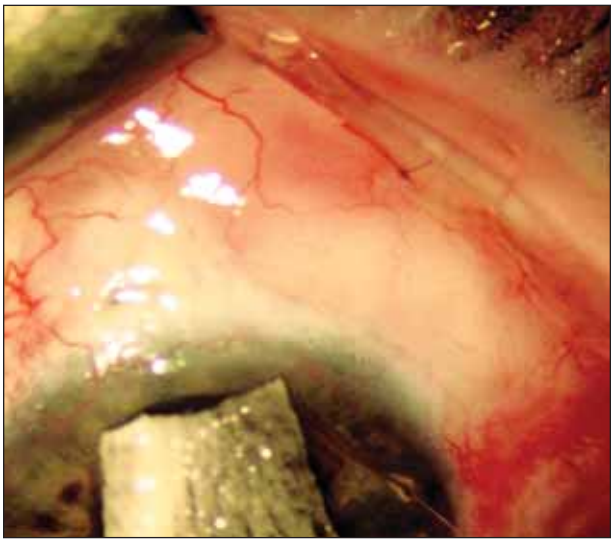

Figure 3. The restored bleb had this appearance postoperatively. (Reprinted with permission from Iwach AG, Delgado MF, Novack GD, et al. Transconjunctival mitomycin-c in needle revisions of failing filtering blebs. *Ophthalmology*. 2003;110: 724-742.)

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ization of the bleb space. We have been performing this procedure for approximately 4 years with good results. When combined with meticulous surgical technique and individualized postoperative care, we believe ITMA is an appropriate adjunct to bleb revision by means of the needling of failing filtering blebs. This procedure is a safe option for restoring bleb function in patients who may benefit from a lower IOP. ❑

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