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TARGET AUDIENCE

This educational program is aimed at general ophthalmologists, ophthalmology residents and glaucoma specialists.

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"ADVANCES IN GLAUCOMA SURGERY"

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Special Focus:

An overview on options in glaucoma surgery

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CORE CONCEPTS

Trabeculectomy remains one of the most common incisional procedures for glaucoma; however, it is associated with significant complications.

MIGS (micro-invasive glaucoma surgery) has allowed clinicians to provide safer interventional therapies at an earlier stage of disease progression.

"MIGS" refers to a group of surgical procedures that aim to lower IOP in a safer and typically more physiological manner causing minimal trauma to surrounding tissue.

"MIBS" (micro-invasive bleb surgery) exhibit greater IOP-lowering potency than internal MIGS, extending indications for MIGS for more advanced glaucoma cases.

MIBS are more invasive than internal MIGS, but less so than traditional glaucoma surgeries, offering a favorable safety profile with faster recovery.

Ocular surface preparation helps to improve outcomes for MIBS by decreasing tissue inflammation, which could impact long-term survival of filtering blebs.

Typically related to distal tube obstruction with Tenon tissue, the major complication of MIBS procedures is failure to control IOP. Often this can be corrected by bleb needling.

1. Introduction

Glaucoma is the leading cause of irreversible blindness worldwide. It is a progressive disease with intraocular pressure (IOP) as the only proven modifiable risk factor to slow the progression of visual field loss.[1] There are several options to reduce IOP, including surgical intervention. In the past, glaucoma surgical options were restricted to more advanced cases or those at risk of rapid progression because of their possible complications. More recently, the surgical approach to glaucoma has significantly changed, and newer surgical options for glaucoma patients have expanded.

2. Advances in Trabeculectomy

Trabeculectomy remains one of the most common incisional procedures for glaucoma. While its efficacy in IOP lowering has been well demonstrated, it carries a significant rate of complications and requires more intense management over a relatively prolonged recovery period.[2] In the Primary Tube Versus Trabeculectomy (PTVT) Study, complications were reported in 41 and 29% of the patients in the trabeculectomy and tube shunt groups, respectively.[2]

Since the introduction of trabeculectomy, surgical technique has evolved, and perioperative modifications has been implemented to improve outcomes and reduce the complications. The safer trabeculectomy technique is marked by more postoperative interventions, including adjustment or removal of scleral flap sutures.[3] It aims to improve control of flow, and in particular, to reduce the risk of early postoperative hypotony.

Scarring is the main cause of surgical failure, and the use of antifibrotics has significantly increased over the last decades to improve surgical success. In the 1996 UK National Survey of Trabeculectomy, only 6.4% of trabeculectomy cases received an antifibrotic. In contrast, a 2013 analysis showed the use of antifibrotics in 93% of cases (MMC 63%, 5-FU 30%).[4]

3. Blebless MIGS and micro-invasive bleb surgery (MIBS)

In an effort to improve glaucoma surgery results and safety, a variety of micro-invasive glaucoma surgeries (MIGS) have been introduced, expanding surgical options for glaucoma patients. More procedures options have become popular compared with trabeculectomy.[5] The Distribution of Glaucoma Surgical Procedures in the United States data reveals that MIGS account for the overwhelming majority of glaucoma surgeries performed there.[6]

"MIGS" refers to a group of surgical procedures that aim to lower IOP in a safe and more physiological manner causing minimal trauma to surrounding tissues. Saheb and Ahmed have identified MIGS to share an ab interno micro-incisional approach, minimal trauma to target tissues, at least modest efficacy, high safety profile, rapid recovery, with minimal impact on the patient's quality of life.[7]

MIGS procedures can be classified on their outflow mechanism – Schlemm's canal, suprachoroidal or subconjunctival. Devices that target the subconjunctival space are bleb–forming procedures; they are more efficient at lowering IOP compared with other types of internal MIGS. However, as creation of a subconjunctival filtering bleb doesn't obey the traditional definition of MIGS, we prefer to regard these procedures as micro-invasive bleb surgery (MIBS) as we believe they are more aggressive than the internal MIGS; however, still considerably less invasive than traditional glaucoma surgeries.

With their greater potency in lowering IOP than internal MIGS, the MIBS allow us to extend indications for more advanced glaucoma cases. Bleb creation increases the risks of these procedures plus the need for more intense post-operative management compared with internal MIGS.

4. MIBS: Options and use

Two MIBS devices are available: the ab interno gel stent (XEN Gel Stent) and

the ab externo Microshunt (Preserflo).

The XEN gel stent (Allergan Inc., CA, USA) is a biocompatible, flexible 6-mm tube made of collagen-derived porcine gelatin cross-linked with glutaraldehyde. It facilitates the drainage of aqueous humor from the anterior chamber to the subconjunctival space. Its standardized lumen size and length regulate flow minimizing postoperative hypotony.[8,9] The Xen 45 has an inner diameter lumen of 45 µm; it is Conformité Européenne (CE) marked in the European Union, and has been approved by the US Food and Drug Administration (FDA).

Preloaded in an injector, the Xen is usually implanted through an ab-interno approach, resulting in minimal conjunctival disruption. The ability to implant the device precisely in the angle is one of the benefits for the ab interno approach. A goniolens is used to visualize the angle to ensure the needle's tip is inserted just above the pigmented trabecular meshwork, avoiding blood reflux from the Schlemm's canal (Figure 1). The injector's needle is advanced through the sclera into the subconjunctival space using a second instrument at the side port or a corneal traction suture. We aim to implant the gel stent in the supra-Tenon's space. Sub-Tenon's placement is challenging with an ab interno approach. Potential adhesions in the sub-Tenons space, near and beyond limbus, add to those challenges.[9] The endpoint we seek to release the device is that the bevel of the needle has fully emerged through the sclera with the metallic stippling easily visible to make sure the device is placed superficially in the supra-Tenon's space (Figure 2).[9] It is important to make sure that the distal end of the gel stent is not embedded or caught in tenons tissue, and the device should be completely free and mobile after implantation. If this is not observed, a primary needling is indicated. A study showed that routinely primary needling at the time of surgery reduced the rate of postoperative needling and the number of postoperative clinic visits.[10]

With this procedure, we aim to create a more posterior, low, and diffuse bleb (Figure 3). We favor device implantation at the 12 o'clock position, avoiding a nasal location as this could provoke bleb dysesthesia and carry a higher risk of conjunctival erosion.[9] Intraoperative mitomycin C (MMC) is injected sub-conjunctivally before or after device implantation to reduce post-operative scarring.

While the primary method for Xen implantation is ab interno, some surgeons prefer ab externo placement involving conjunctival dissection. There is a hypothesis that this would allow a more consistent placement of the XEN gel stent, thereby reducing the risk of intraoperative or postoperative occlusion of the distal end of the device and improving surgical outcomes. Other surgeons have advocated an open conjunctival approach to allow direct visualization ensuring the gel stent is not trapped in Tenon's capsule. A study compared the efficacy and safety of the implantation of the XEN45 with opening of the conjunctiva (ab interno and ab externo approach) to the ab interno closed conjunctiva tech-

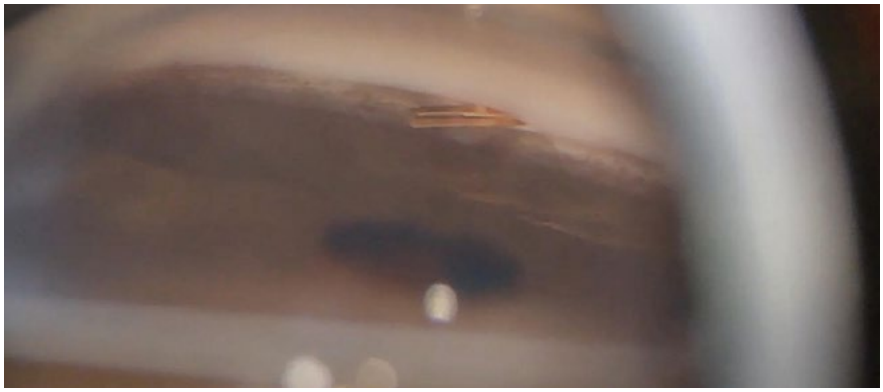

Figure 1. Gonisocopic view of the Xen gel stent entering just above the trabecular meshwork. Figure courtesy of Iqbal Ike K Ahmed, MD, FRCSC

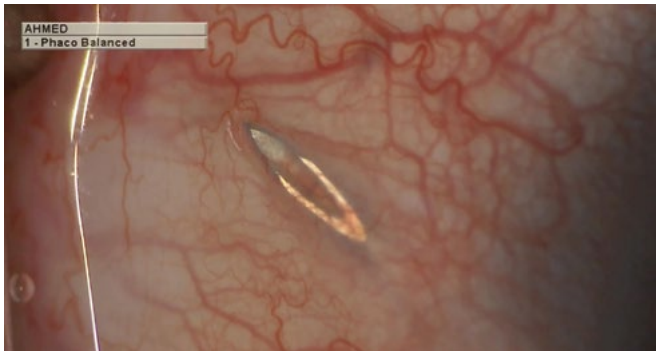

Figure 2. Needle's bevel fully in the subconjunctival space and metallic stippling clearly visible. Figure courtesy of Iqbal Ike K Ahmed, MD, FRCSC

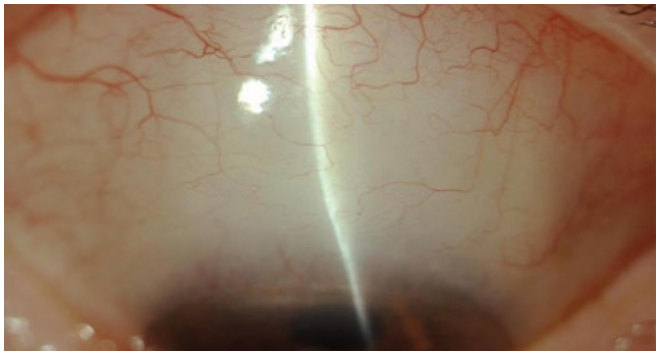

Figure 3. A diffuse and posterior bleb 3 months after Xen gel stent implantation. Figure courtesy of Iqbal Ike K Ahmed, MD, FRCSC

nique. A higher success rate (31% vs 56%, p=0.01) and lower needling rate (36.1% vs 11.8%, p=0.001) was found in the open conjunctiva group.[11] Another study found no difference in safety and efficacy in ab externo, open conjunctiva gel stent placement, and ab interno technique.[12]

Surgical outcomes from the first operated eye strongly correlate with those from the second. Fellow eyes are over 16 times more likely to fail when the first-operated eye failed.[13]

The Preserflo Microshunt (Santen, Miami, Florida, USA) is an 8.5 mm-long device composed of biocompatible material called poly (styrene-block-isobutylene-block styrene) or SIBS (Figure 4). This biomaterial is a biostable thermoplastic elastomer with physical properties that overlap silicone rubber and polyurethane. Originally designed to coat coronary stents, it has been studied in different medical fields.[14] SIBS induces less collagen deposition and myofibroblast differentiation when compared with silicone, thereby decreasing scarring and subconjunctival fibrosis, which otherwise could induce bleb failure.[15] With an internal lumen diameter of 70 µm, the Microshunt self-regulates flow, minimizing hypotony: traditional glaucoma drainage devices have a tube lumen size around four times larger: the Ahmed Glaucoma valve has an internal lumen of 305 µm.[14,15] The MicroShunt received a CE Mark in 2012, but has not yet been approved by the FDA in the USA.

Implanted ab externo, a key step of surgery is conjunctiva dissection and Tenon's disinsertion. It's important surgeons are familiar with Tenon's capsule anatomy.

Use of mitomycin is an essential augmentation.

A 1-mm fin 4.5 mm from the device's tip allows for fixation and minimizes peritubular leakage (Figure 5). The length of the Microshunt is designed to produce a posteriorly placed better-tolerated bleb with the outflow end on the scleral surface under cover of the upper eyelid.

We close the Tenon's and conjunctiva separately as two distinct layers as we believe this ensures the implant is not stuck in Tenon's and reduces the risk of leakage.

Results suggest an IOP at trabeculectomy-like levels (low teens) with a good safety profile.[16,17,18] Schlenker et al. reported complete success in 76.9% of eyes and qualified success in 92.5% of the eyes at one year after Microshunt standalone implantation. Median IOP decreased from 20 mm Hg (range, 16.5–26) to 12 mm Hg (range, 10–15), with the median number of glaucoma medication falling from four to zero.[17]

Ocular surface preparation may be a key to improve MIBS outcomes, as inflammation increases post-operative fibrosis, impacting long-term bleb survival. Pre-operatively, surgeons should consider ceasing or replacing some topical IOP-lowering medications with oral acetazolamide for a few weeks to try to optimize the ocular surface.[9] Pre-operative topical steroids to reduce ocular surface inflammation is part of our routine. This has been demonstrated to improve surgical outcomes and to reduce the need for post-operative needlings.[19]

One cause of failure is tube obstruction with Tenon's tissue; often this can be corrected by bleb needling at the slit lamp. One study reported needling in 43.2% and 30.8% of Xen and trabeculectomy eyes, respectively.[20] Preserflo needling rates were 8.5% in virgin eyes and 11.8% in eyes with refractory glaucoma over a one-year follow-up period after standalone Microshunt implantation.[17,18]

5. Conclusion

In the past, because of their possible complications, glaucoma surgical options were restricted to more advanced cases or to those at risk of rapid progression. MIGS approaches offer a better safety profile; they have changed this mindset. MIBS devices have extended non-trabeculectomy options for more glaucoma patients. Both the Xen gel stent and PreserFlo MicroShunt have demonstrated significant IOP lowering

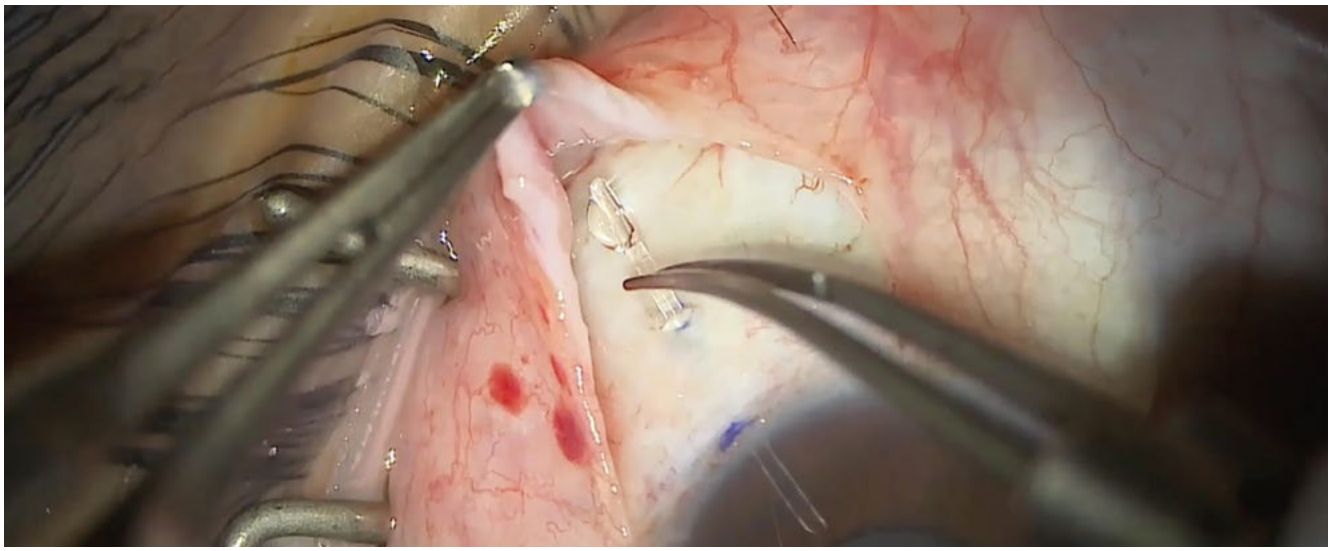

Figure 4. Preserflo MicroShunt. Figure courtesy of Iqbal Ike K Ahmed, MD, FRCSC

effects in glaucoma patients.[16,17,18,20] Although the MIBS devices depend on creating an external filtering bleb, they are associated with fewer risks than traditional glaucoma surgeries, offering a favorable safety profile procedure with faster recovery. We now have more options to offer our patients as we continue to determine which procedure is optimal for each patient, individually.

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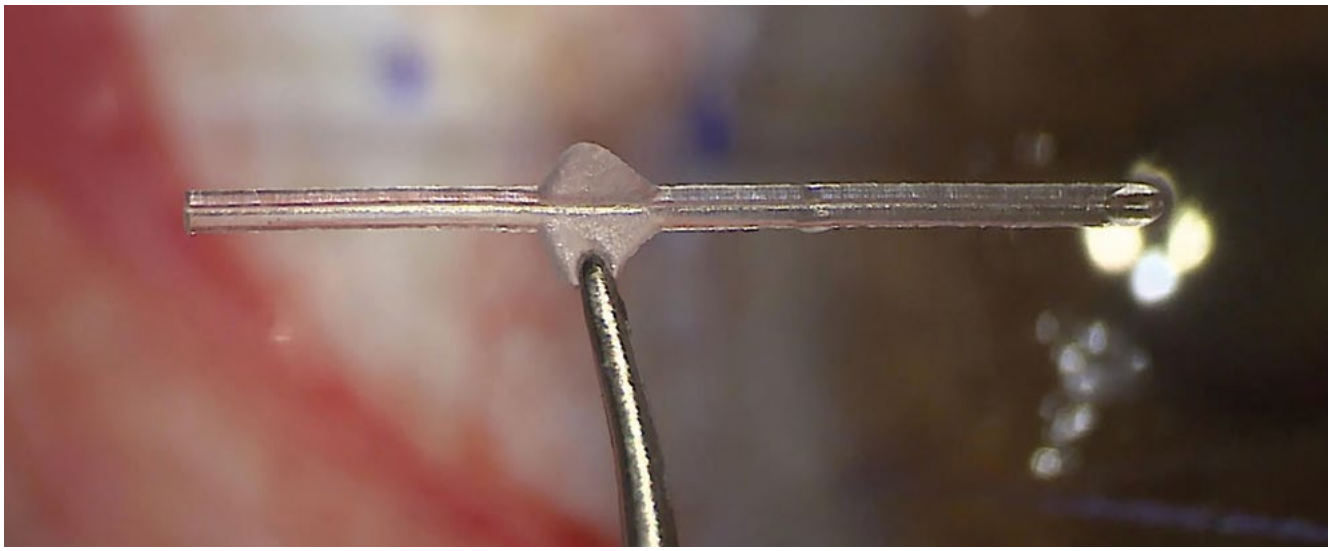

Figure 5. The Preserflo Microshunt is being implanted into the anterior chamber through a 3mm-long scleral tunnel. Figure courtesy of Iqbal Ike K Ahmed, MD, FRCSC

What's New:

Minimally invasive glaucoma surgery

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CORE CONCEPTS

A wide range of MIGS exists with different target sites and IOP lowering efficacy to treat various stages and types of glaucoma.

Trabecular bypass stents have the most robust long-term data demonstrating their clinical efficacy and safety.

The excellent safety profile and rapid visual recovery of MIGS allow earlier surgical intervention in glaucoma management.

Newer devices are evolving with promises of clinical predictability, less tissue manipulation, and faster visual recovery.

While more options are now available, comparative studies are still lacking for MIGS and perioperative predictors for success remain elusive.

1. Introduction

Reduction of intraocular pressure (IOP) remains the major modifiable risk factor to halt glaucoma progression. Minimally invasive glaucoma surgery (MIGS) was introduced nearly a decade ago with the promise of improved IOP control with less chance of vision threatening side effects than trabeculectomy and glaucoma drainage device surgery. Surgical options could, then, be applied with relative safety to earlier stages of glaucoma. Since then, several more options to treat glaucoma at different stages have been added and there have been improvements in the earliest procedures with more data to substantiate the efficacy of many of the newer operations. Due to MIGS' favorable safety profile and demonstrated efficacy, surgeons are incorporating MIGS into their surgical armamentarium to treat earlier stage glaucoma. Here we review novel surgical devices as well as recent data on existing MIGS.

2. Trabecular meshwork targeting MIGS

As the conventional pathway is responsible for most of aqueous outflow, it is no surprise that the trabecular meshwork (TM) is the target for numerous MIGS devices. The TM targeting devices can be categorized: stenting versus excision/ablation with or without Schlemm Canal (SC) expansion (canaloplasty). Stenting devices often are inserted in conjunction with cataract surgery (especially in the United States), while excisional MIGS are more often performed as a standalone procedure. TM-targeting MIGS typically are indicated for patients with mild to moderate stage medically controlled open angle glaucoma (OAG).[1-5] Limitations of TM based MIGS include uncertainty regarding the ideal surgical location, inability to assess the patency of the distal pathway beyond SC, and the local fibrotic response from surgical trauma.

One of the earliest MIGS devices, iStent (Glaukos) remains one of the most widely used due to its ease of implantation and excellent safety profile.[6] When combined with cataract surgery, iStent has been shown, in multiple studies, to offer relatively long-term IOP control with reduction in drop burden in patients with mild to moderate OAG.[5] As a standalone procedure, iStent is effective in reducing medication burden but the IOP lowering efficacy is reduced.[9] The design of iStent has evolved, the second generation introduced in 2018 with an arrow-like design and a reduced lumen of 80µM. This allowed direct en face implantation. The injector is pre-loaded with two stents, as IOP lowering efficacy correlates with the number of stents implanted.[7] Recently, iStent inject has an updated wider flange to improve implantation predictability (Figure 1). The iStent Infinite which comes with three preloaded implants awaits US FDA approval.

An eight mm long, nitinol stent with an aqueous bypass inlet portion and a distal SC scaffolding portion (Figure 2), the Hydrus microstent (Ivantis) allows drainage access to approximately 6 mm of SC. In patients with mild to moderate OAG, the Hydrus demonstrated comparable clinical efficacy with iStent when combined with cataract surgery.[3-4] Data from the HORIZON study also showed that patients who had combined phaco with Hydrus had a lower rate of immediate post-operative IOP spikes and a lower need for incisional glaucoma surgery in subsequent years.[3,8] In a direct comparative study of the first generation iStent versus the Hydrus as standalone treatment in newly diagnosed OAG, the Hydrus was found to be more effective to maintain medication-free IOP control.[9]

The second group of TM based MIGS requires no implants and allows direct access to SC by excising or ablating the TM via goniotomy or trabeculotomy ab-interno. Trabectome (Microsurgical Technology) was one of the first MIGS devices to perform goniotomy but requires a separate console to generate electrocautery. The Kahook Dual Blade (New World Medical) and Trab-Ex (MST) are single-use handpieces designed to perform up to 160° goniotomy, excising a strip of TM. Ab-interno trabeculotomy is considered when at least 180° and up to 360° of TM needs to be excised. This can be performed with the gonioscopy assisted transluminal trabeculotomy (GATT) technique (iTrack Microcatheter (Ellex) or prolene suture) or with the OMNI surgical system (Sight Sciences) (Figure 3). Both the iTrack catheter and the OMNI allow concurrent visco-canaloplasty to be performed to dilate the SC.

Goniotomy has similar clinical efficacy compared with TM bypass stents in mild to moderate OAG when used in conjunction with cataract surgery. A few small comparative studies have found better IOP control when compared with iStent.[10,11] Trabeculotomy can be used for more refractory glaucoma and is particularly effective in juvenile and sec-

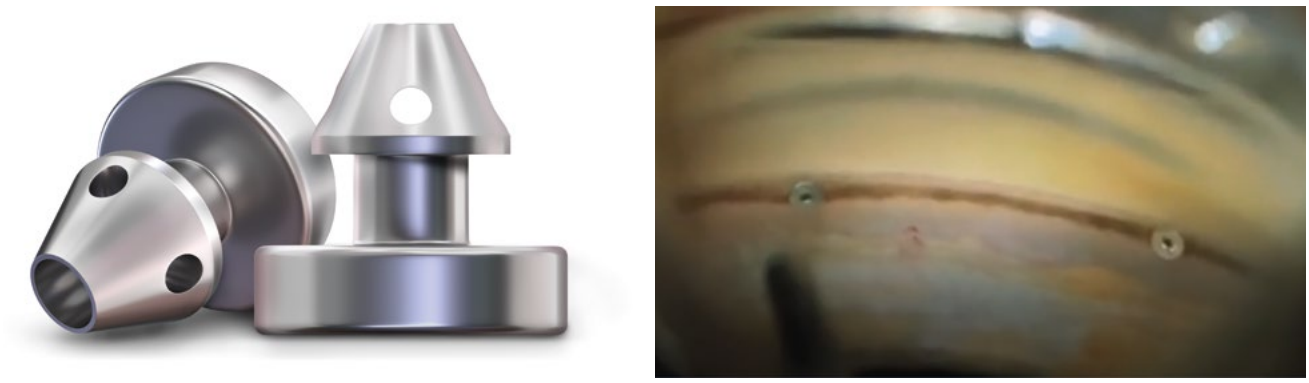

Figure 1: iStent Wide

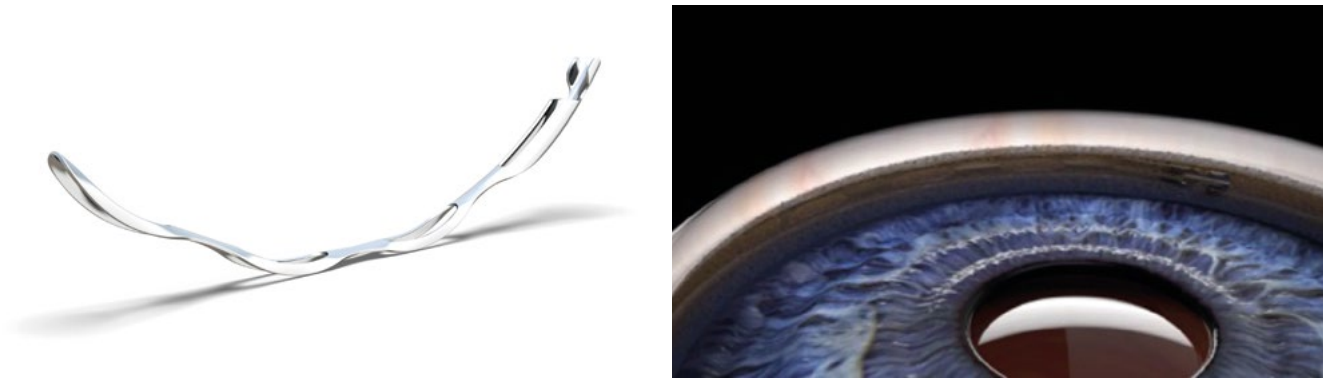

Figure 2: Hydrus microstent with curved design to span 90 degree of the Schlemm's canal.

Figure 3: OMNI surgical system allows surgeon to perform both visco-canaloplasty and trabeculotomy single handedly.

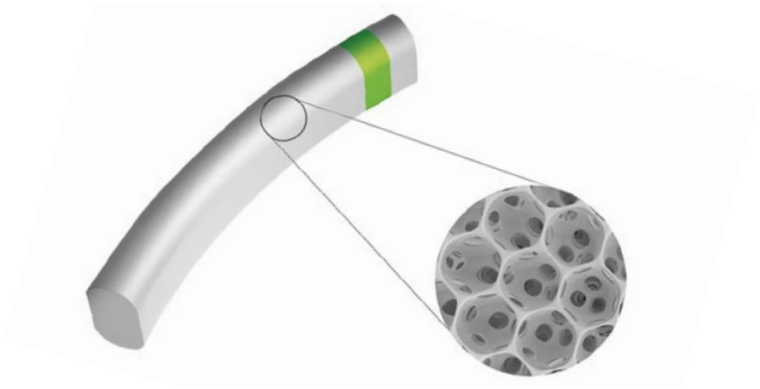

Figure 4: (© iSTAR Medical)

ondary OAG.[12] With their larger area of tissue disruption, goniotomy and trabeculotomy have higher rates of significant hyphema[12,13]; they should be used with caution in anticoagulated patients. There is also growing evidence demonstrating 180° trabeculotomy performs similarly to 360° in adult OAG.[13,14] One advantage of the TM excisional MIGS is the absence of an implant, but they require a larger extent of trabecular tissue disruption with an unclear effect on the subsequent fibrotic response locally.

Excimer laser trabeculostomy (ELT) is another form of TM targeting MIGS introduced in the 1990s. It uses a non-thermal laser to create direct micro bypass channels to the SC. ELT does not require an implant and the excimer laser minimizes tissue disruption, scarring, and bleeding. ELT has received CE mark in Europe in 2014. Several studies have demonstrated its safety and efficacy as a standalone procedure and as a combined procedure with cataract surgery.[15]

3. Supraciliary space

The uveoscleral outflow system is another targeted space to lower the IOP. The ab-interno approach to access the suprachoroidal space is preferred over the ab-externo approach to avoid conjunctival and scleral manipulation. The CyPASS supraciliary stent (Alcon) was U.S. FDA approved in 2016 for concurrent implantation with cataract surgery. The COMPASS trial showed a greater proportion of patients achieving >20% IOP reduction from baseline with CyPASS than with phacoemulsification alone,[16] this effect extending up to five years from the COMPASS-XT study[17] (though the proportion decreased from 77% to 46% over time). At five years follow-up, concern regarding corneal endothelial cell loss correlating with stent position led to voluntary withdrawal of the device from the market in 2018. Two other ab-interno devices currently under clinical trial are the iStent SUPRA (Glaukos) and the MINIject (iStar Medical). The MINIject is a 5 mm device made of a flexible porous silicone material to improve tissue biocompatibility and aqueous outflow (Figure 4). Two years clinical data on the MINIject as a standalone procedure in medically uncontrolled OAG showed all patients achieving >20% IOP reduction from baseline with nearly 50% medication free.[18] The iStent Supra is a 4mm device made with biocompatible polymer; it has completed patient enrollment for a FDA approval trial.

4. Subconjunctival space

When the aqueous pathway is compromised, shunting the aqueous to the subconjunctival space has been the mainstay of traditional glaucoma surgery. Though the subconjunctival space provides a wide area of filtration, the main challenge is Tenon's fibrosis leading to surgical failure. The use of antifibrotic agents has been crucial to reduce scarring but increases the risk of post-operative hypotony and wound leaks.

The subconjunctival MIGS devices are akin to a hybrid of trabeculectomy and valved glaucoma drainage devices. They utilize the principle of Poiseuille's equation to regulate IOP and to prevent hypotony. The length of the device allows for more posterior aqueous drainage, reducing the risk of wound leak. Mitomycin C (MMC) is required with the subconjunctival MIGS to minimize Tenon's fibrosis as part of bleb control.

The Xen gel stent (Allergan), 6 mm long with a 45µm internal lumen, was the first subconjunctival MIGS device. It is preloaded on a 27-gauge injector for ab-interno transcleral implantation. Xen seemed indicated for refractory OAG as an early study showed a 20% IOP reduction after one year in 75% of patients who had failed prior incisional glaucoma surgery.[19] When compared with trabeculectomy as primary incisional surgery in an uncontrolled group of mixed glaucoma types, the Xen gel stent demonstrated similar risk of failure as trabeculectomy.[20] In a prospective single center study with predominantly white patients, implantation of the Xen gel stent was able to sustain a 30% IOP reduction from baseline for up to two years.[21] Post-operative needling rates range up to 40% due to Tenon's fibrosis.[20,21] Thus, increased MMC concentration and modified implantation

Figure 5: Preserflo microshunt has a 1-mm fin positioned 4.5 mm from the tip allows fixation and prevents peritubular leakage.

techniques including an ab-externo approach have been proposed.[22]

The Preserflo microshunt (Santen) is an 8.5mm stent with 70µm internal lumen made of biocompatible SIBS material (Figure 5). It has received a CE mark in Europe and is pending FDA approval in the Unites States. In a comparative study with trabeculectomy, using a 0.2 mg/ml concentration of MMC, the microshunt group had a somewhat higher IOP at 12 months compared with trabeculectomy (14.4 vs 11.1 mmHg), but with a lower rate of post-operative hypotony (27% vs 45%).[23] Post-operative needling rates were found to be around 20% but reduced to 8.5% with higher concentrations of MMC.[24]

5. Newly designed non-valved glaucoma drainage device

Though much of the recent surgical innovations have been in MIGS, glaucoma drainage devices still play an important role to treat refractory glaucoma. A novel valveless glaucoma drainage device, Ahmed ClearPath (New World Medical), was designed to improve efficiency and safety during implantation. The device comes with two sizes (250 and 350 mm^2 plate); both have anteriorly-placed islets to allow easier suture fixation, particularly in patients with poor surgical exposure.

6. Summary

Since the introduction of early MIGS devices, there is growing evidence demonstrating their clinical efficacy and safety profile. This has led to a paradigm shift in glaucoma management allowing earlier surgical intervention for better IOP control without compromising visual outcome. For refractory glaucoma, subconjunctival MIGS can be a safe alternative with lower risk of hypotony. It is an exciting time in glaucoma with a growing number of novel surgical developments. More research is needed to determine which device(s) work best under which conditions so as to enable true evidence-based decisions for each individual patient.

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Clinical Issues:

Quality Use of Antifibrotics

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CORE CONCEPTS

Use of anti-fibrotics are key to modern glaucoma filtering surgery (GFS) success.

Application techniques vary for Mitomycin C (MMC).

Take care to determine your MMC dose, especially with injections.

MMC has significant potential side effects that has to be justified by the higher chance of surgical success.

Post-operative use of 5 Fluorouracil (5FU) can augment a MMC GFS bleb.

Needling of GFS blebs can be performed with both MMC and 5FU. MMC has a higher rate of success.

Other antifibrotic strategies that have been used are transforming growth factor (TGF) beta antibody, anti-vascular endothelial growth factor (VEGF), Ologen and Molteno's oral antifibrosis treatment.

1. Introduction

Antifibrotic agents, in particular, Mitomycin C (MMC) and 5- fluorouracil (5FU) have increased the success rate of glaucoma filtering surgeries (GFS). Trabeculectomy technique and the safer use of antifibrotics have been refined over the years.[1] With newer bleb-forming microinvasive glaucoma surgeries (MIGS), the XEN45 Gel Stent® (Xen) and PRESERFLO™ Microshunt (Preserflo), the quality use of antifibrotics has become even more important. Antifibrotics have also been used, less widely, in glaucoma drainage device (GDD) surgery.[2]

2. Use of anti-fibrotics are key to modern glaucoma filtering surgery (GFS) success.

Worldwide, most GFSs use antifibrotics, mainly intraoperative Mitomycin C (MMC) with adjunctive postoperative[5] Fluorouracil (5FU) being used as needed.

MMC is the most potent and most used antifibrotic. 97% of American Glaucoma Society (2016)[3] and 97.2% of the UK and Eire Glaucoma Society (2019) members reported routine use of MMC.[4] Mitomycin is used by some performing GDD. There is insufficient evidence to support its routine use.[2]

3. Application techniques vary for MMC

Aim to have a large area of MMC delivery during GFS to create a more diffuse bleb.[1] MMC can be delivered with sponges or by an intra-Tenon's injection. Using Tryphan blue can visualize MMC spread.[5] The dose and duration of MMC used depends on the eye's risk of bleb failure.[1,6] The higher the dose, the greater the risk of MMC complications.

The most common delivery of MMC in trabeculectomy is with direct application into a sub-Tenon pocket with cellulose or PVA sponges. Sub-Tenon's or intra-Tenon's injection has been less commonly utilized in trabeculectomy (5.9%).[4] With the advent of the ab-interno, bleb-forming MIGS, the Xen implant, injection of MMC has become a common practice. The Preserflo is an ab-externo device and MMC is delivered as for trabeculectomy.

4. Take care to determine your MMC dose, especially with injections.

These are some considerations when applying MMC with sponges. The doses of MMC used with sponges vary between 0.1 mg/ml (0.01%) to 0.5 (0.05%) mg/ml, with exposure times ranging between 1-5 minutes.[3] Both concentration and duration have an effect. A commonly used standard dose is 0.2 mg/ml (0.02%) for 2 minutes. There is variable absorption of the MMC by the delivering sponge as Cellulose sponges are superabsorbent. Using Tryphan Blue, Healey and Crowston showed that sponge delivery did not extend well posteriorly.[5] This may lead to more MMC effect anteriorly. Cellulose sponges may fragment when cut and leave microscopic fragments behind.[7] This has been experienced by 11.76% of surgeons surveyed in the UK.[4] Polyvinyl alcohol (PVA) sponges and uncut sponges of either material do not fragment.

Advantages of an injection are that the exact amount of MMC injected is known (Table 1) and that the volume can be directed quite posteriorly using a squint hook. To protect the conjunctival wound and limbal stem cells, ensure that the limbus is protected from exposure to MMC. Figure 1 shows my technique to mix MMC with Tryphan Blue for injection (Figures 1 and 2). A randomized study comparing the delivery techniques found more dysesthesia with injection and more encapsulation with sponges.[8] Another RCT showed a more diffuse, shallower and less vascularized bleb in the injection group.[6]

5. MMC has significant potential side effects that has to be justified by the higher chance of surgical success.

Bleb-related complications are higher with MMC, particularly with higher doses. Thin avascular blebs can lead to bleb leak with increased risk of blebitis and endophthalmitis. The rate is about 2.2% in 5 years.[3] Long-term hypotony with maculopathy is another late complication. There may be a combination of over-filtration and direct toxicity to the ciliary body.

While it is not the cause of an exposed Xen or Preserflo implant, if the conjunctiva overlying the implant is thin and avascular from MMC, the eye is at long-term risk of erosion, bleb leak and blebitis.

6. Post-operative use of 5FU can augment a MMC GFS bleb.

Subconjunctival 5FU (usually 5mg/0.1ml) is most commonly used on a "as needed" basis postoperatively. 5FU is associated with corneal epithelial toxicity, 5FU keratopathy. This can be reduced by "mopping up" excess 5FU that refluxes through the conjunctiva with local anasthetic: the local anesthetic converts 5FU into a non-toxic salt.

7. Needling of GFS blebs can be performed with both MMC and 5FU. MMC has a higher rate of success.

Bleb needling is an integral part of the post-operative care in GFS. Post-operative needling is usually done in clinic or in the operating theatre. Similar MMC doses to primary surgery are used for needling blebs. The needling rate is high with ab-interno Xen implant. Reports vary but approximately 30-50% require at least one needling. The needling and re-operation rate is not affected by the dose of MMC.[3] Many surgeons now perform initial intra-operative needling to ensure that the external opening of the Xen is not lying intra-Tenon's.[9] More than one needling may be required.

Table 1

Injected MMC options

Concentration	Volume (ml)	Dose	Dosing
0.05 mg/ml (0.005%)	0.1	5 µg	Low
0.1 mg/ml (0.01%)	0.1	10 µg	
0.2 mg/ml (0.02%)	0.1	20 µg	Average
0.2 mg/ml (0.02%)	0.2	40 µg	
0.4 mg/ml (0.04%)	0.1	40 µg	High

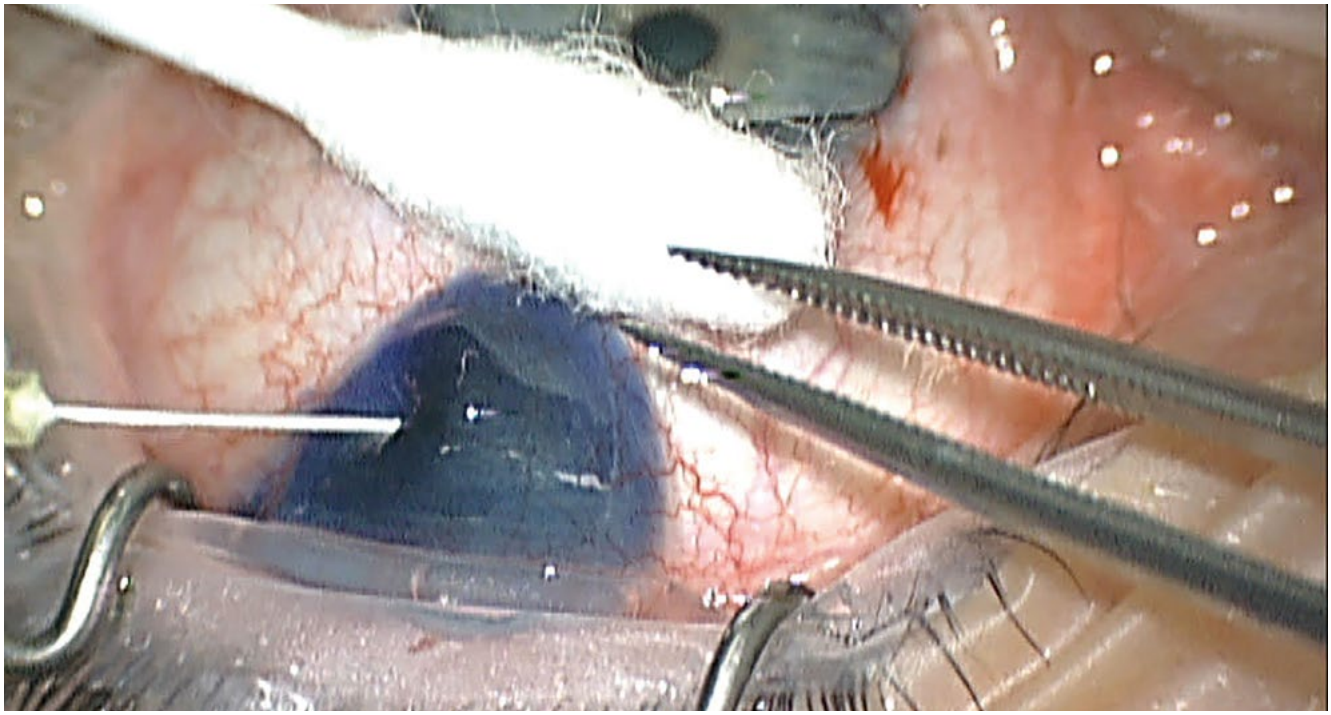

Figure 1: MMC injection technique shown with Trypan Blue.

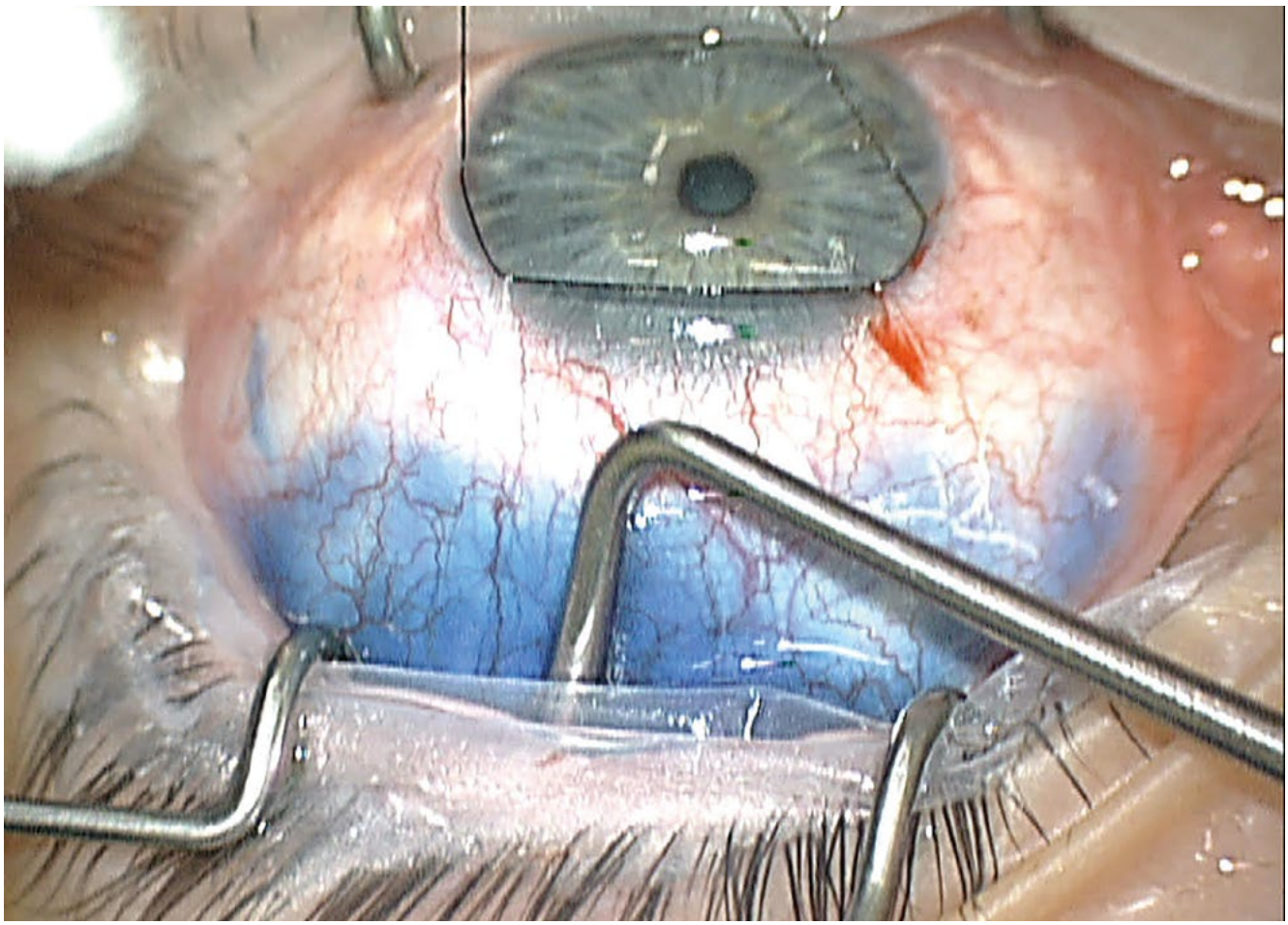

Figure 2: Use of squint hook to direct injected volume posteriorily

8. Other anti-fibrotic strategies that have been used are TGF beta antibody, anti-VEGF, Ologen and Molteno's oral anti-fibrosis treatment.

Anti-VEGF agents are postulated to have a synergistic effect with MMC and have been used sub-conjunctivally and intracamerally.[10] Molteno's oral anti-inflammatory fibrosis suppression (prednisone, colchicine, NSAID) showed good outcomes but has not been tested against MMC.[11]

9. Conclusions

MMC is the anti-fibrotic with the most effect and the most side effects. By applying it over a wide area and also by performing GFS in a safer way, ophthalmologists are working to improve surgical outcomes and to reduce poor outcomes. New ab-interno devices have given all more experience with MMC injections. Care is required with dosing MMC and 5FU as complications are dose-related.

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Practical Tips:

Secure Closure of the Conjunctival Flap

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CORE CONCEPTS

Secure closure of the conjunctiva is essential to maximize trabeculectomy success and minimize long term complications

Limbal-based flaps are generally less prone to early bleb leaks but may result in more focal, anterior blebs

We prefer closure with 8-0 Vicryl on a TG needle but 9-0 or 10-0 either Vicryl or nylon suture may be used

Limbal-based flaps are typically closed in a simple running fashion, but care should be taken to incorporate Tenon's into any conjunctival closure

We prefer a modified Wise closure for our fornix-based flaps which leaves a small lip of anterior conjunctiva when making the initial incision. We attempt to bury all knots

If no lip of anterior conjunctiva is left, typical closure involves either wing sutures or mattress sutures through the cornea

1. Introduction

Despite numerous advances in glaucoma surgery, trabeculectomy remains an essential tool that most glaucoma surgeons employ to lower intraocular pressure (IOP), especially when sub-physiological pressures are required. Advances in trabeculectomy technique such as the use of anti-metabolites have significantly increased the long-term success rates for patients. Conjunctival closure is one of the most essential steps for any sub-conjunctival glaucoma surgery, but this is especially true for trabeculectomies. Failure to achieve watertight closure frequently leads to persistent post-operative bleb leaks, which have been shown to increase the risk of serious complications such as bleb-related infections, hypotony, and early bleb failure.[1] Numerous techniques have been described for conjunctival closure after trabeculectomy. The primary determination for which technique a surgeon will use centers around whether a limbal or fornix-based flap is created.

2. Limbal-Based Trabeculectomy

Proponents of limbus based conjunctival flaps believe that a watertight closure is easier to achieve and bleb leaks are less frequent. Others believe that limbal-based conjunctival flaps may lead to more focal, anterior, and avascular blebs and thus be more susceptible to long-term complications such as bleb dysesthesia and late leaks with risk of blebitis and endophthalmitis. Recent studies have suggested that the success rates may be similar between the two.[2]

The closure of limbal-based flaps is generally more straight forward than fornix-based. We prefer 8-0 Vicryl on a TG needle (J974, Ethicon Inc., Somerville, NJ) although 9-0 or 10-0 needles can be used. The incision for a limbal-based flap is made roughly 8-10mm posterior to the limbus and direct closure is performed in a running fashion (Figure 1). It is important to close Tenon's layer in addition to the conjunctiva, which can be done via a "double-layered" two-step closure or by simply incorporating Tenon's into each bite of a single-layered closure. This frequently results in a water-tight seal and has the additional benefit of the incision being covered by the patient's upper eyelid.

3. Fornix-Based Trabeculectomy

Advocates of the fornix based approach believe that avoiding the so-called "ring of steel", the barrier induced by a scarred posterior incision, results in a more diffuse and posterior bleb. For this reason, we prefer fornix-based conjunctival flaps in the vast majority of our cases. Our technique is a slight variation of the technique that was initially described by James Wise, MD[3] and subsequently modified by Garry Condon, MD.[4] An initial conjunctival incision is made near the limbus with a lip of approximately 0.5mm of conjunctiva near the corneoscleral junction.

After the scleral flap is secured, we begin suturing at the right-sided edge of the conjunctival incision. The first pass is done outside-in so as to bury the knot, and the suture is then anchored to the corneoscleral junction. The needle is passed back out through the posterior edge of conjunctiva near the initial entry of the first pass. A traditional Wise closure is then performed. The needle is brought 3-4mm to the left of the last bite and passed through the conjunctiva in an inside-out fashion (Figure 2). A corneoscleral pass is then made beneath the lip of residual conjunctiva near the termination of the prior corneoscleral bite. The needle is brought back through the posterior conjunctiva in an inside-out manner near the previous outside-in pass. One key to this closure is keeping the corneoscleral passes longer than the distance between any two adjacent conjunctival suture bites.

This pattern is then repeated until the needle reaches the left-sided terminus of the incision. We attempt to bury the final knot by making multiple passes that incorporate conjunctiva and partial-thickness sclera near the limbus. It is essential to incorporate both Tenon's and conjunctival layers into the closure. This technique[5] reliably creates watertight closure by bringing the edge of the conjunctival flap underneath the lip of residual conjunctiva near the limbus. We routinely test the closure at the end of each case with a fluorescein strip after applying pressure to the posterior scleral flap to promote flow.

4. Other Considerations

Numerous other techniques have been described for closure of fornix-based flaps. If no limbal remnant of conjunctiva is left, many surgeons will use either wing sutures or multiple horizontal mattress sutures for closure. A recent study comparing winged sutures to the modified Wise closure suggested that the modified Wise closure may result in lower IOPs with low-

er rates of bleb leaks long-term.[6] The use of fibrin glue has also been described as an alternative to sutured closure.[7]

5. Conclusion

Meticulous conjunctival closure is essential to the success of trabeculectomies. We have found that our technique for fornix-based closure produces blebs with desirable morphology and low rates of bleb leaks. Nevertheless, numerous methods are available to the glaucoma surgeon for both limbal and fornix-based flaps which can produce excellent long-term outcomes.

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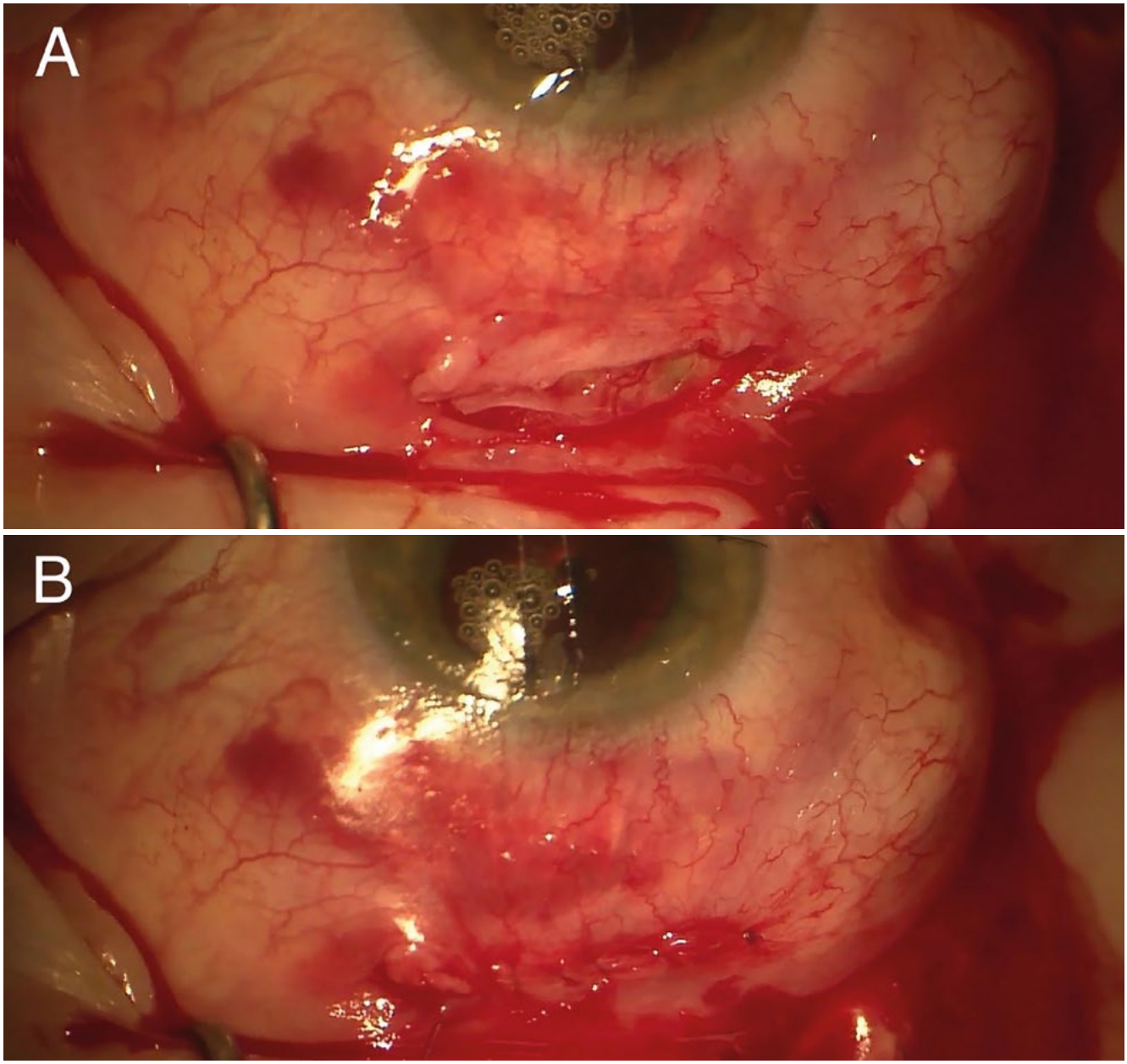

Figure 1: Limbal-based trabeculectomy, direct closure.

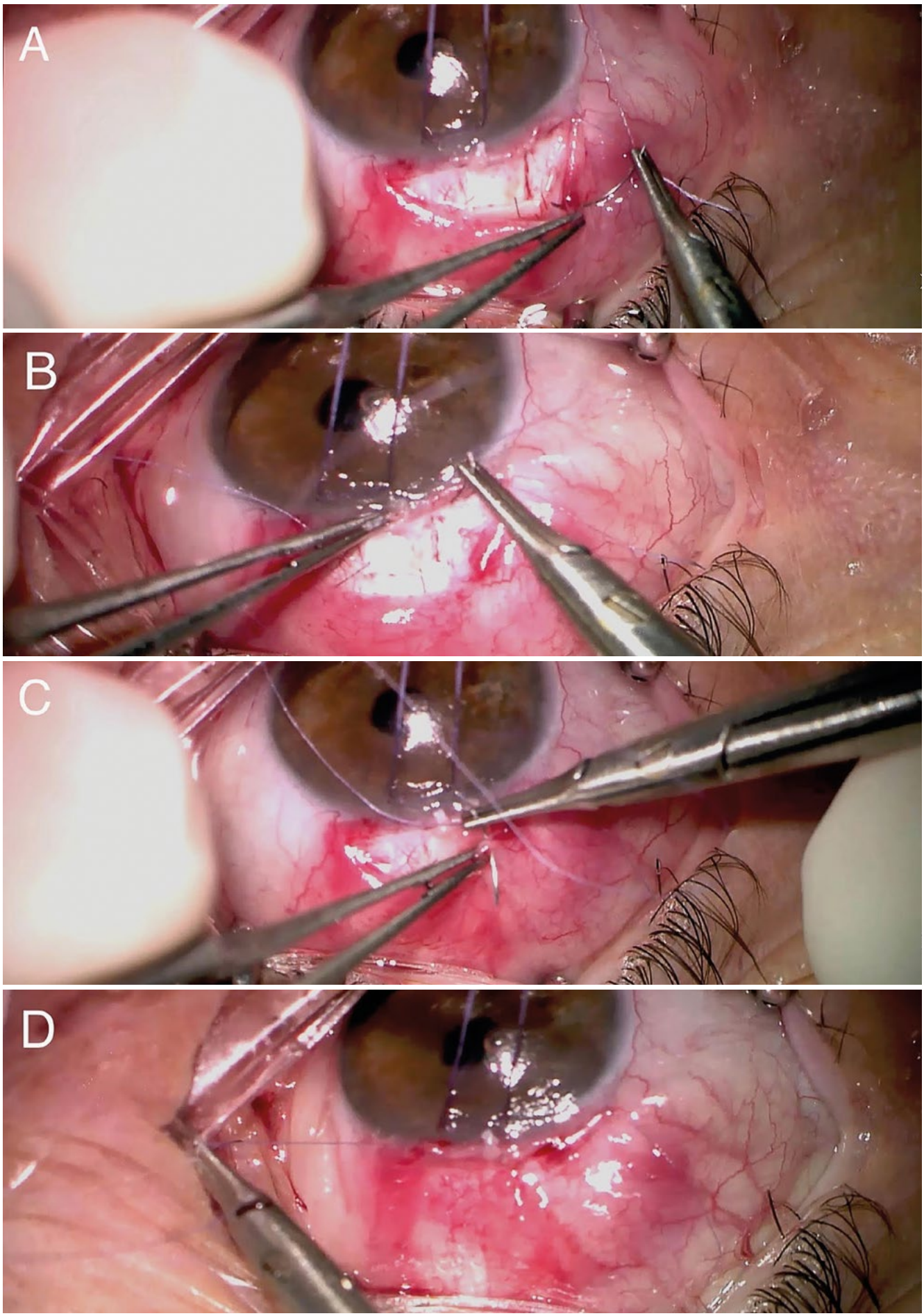

Figure 2: Fornix-based trabeculectomy, Wise closure.

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