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Which Patients Would Most Likely to Benefit: MIGS or MEGS, Which One Is It?

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Abstract: The availability of ab interno minimally invasive glaucoma surgery (MIGS) has promoted an international interest in this procedure. Our purpose is to define the role of MIGS in the constant evolving glaucoma treatment algorithm. Current MIGS approaches to lowering intraocular pressure (IOP) include increasing trabecular outflow (iStent trabecular microbypass stent, iStent inject, Hydrus Microstent, Kahook Dual Blade goniotomy, Trabectome ab interno trabeculectomy, Excimer laser trabeculotomy, and goniotomy-assisted transluminal trabeculotomy), increasing uveoscleral outflow with suprachoroidal shunts (Cypass microstent), and developing subconjunctival filtration (XEN gel stent and InnFocus microshunt). The efficacy of each depends on the achievement of desired target IOP reduction in a specific patient. The determination of whether a procedure is either a MIGS or minimally effective glaucoma surgery (MEGS) procedure is based on their efficacy and complications. Aqueous humor angiography suggests that success of trabecular bypass MIGS may not be patient-dependent only, but it may be affected by the location and flow of aqueous through collector channels. The future use of aqueous angiography may permit customized treatment of trabecular meshwork dependent MIGS procedures.

Key Words: ab interno glaucoma surgery, MIGS, minimally invasive glaucoma surgery, novel glaucoma procedures

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Trabeculectomy and glaucoma drainage implants are the most commonly performed surgical procedures worldwide and remain the standard of care for glaucomatous neuropathy resistant to medical therapy.[1] Although both procedures efficiently lower IOP, they have a high complication rate.[2,3] Recently a new class of procedures and novel devices, MIGS, has emerged. Despite the increased popularity of MIGS procedures, no consensual definition of MIGS exists in the standard medical lexicon.

Initially MIGS was developed as an alternative to medical therapy for the treatment of mild primary open angle glaucoma. This intervention was proposed to address the problems of adherence to medical therapy, and to minimize the adverse events and quality of life issues related to topical glaucoma medications.[4] As opposed to traditional glaucoma procedures that are indicated in advanced or medically uncontrolled glaucoma, MIGS devices were intended for earlier use in the glaucoma treatment algorithm. Newer MIGS devices have been used in patients with severe or refractory glaucoma and uncontrolled IOP, including those with history of previous failed glaucoma surgery.[5–8] As the number and types of MIGS devices increased, the surgical criteria and definition have evolved. In 2012, Saheb and Ahmed[9] defined MIGS as a microinvasive glaucoma surgery that should satisfy a set of preferable qualities. To meet the criteria, the procedure should be performed through ab interno clear corneal incision with no conjunctival involvement and it should only cause minimal trauma to target tissue with little disruption of normal ocular anatomy. By their definition, it should provide at least modest efficacy and deliver a high safety profile with rapid recovery. Later in 2015, the Food and Drug Administration (FDA) provided guidance to investigators on studies for premarket approval for implantable MIGS devices.[10] The FDA described MIGS as an implant used with either ab interno or ab externo approach that was associated with little or no scleral dissection, and minimal or no conjunctival manipulation.

Despite the changes in the surgical approach to newer MIGS devices, all are regarded as being less invasive and having a higher safety profile than traditional glaucoma filtering procedures with a more rapid recovery. A pertinent question is whether the reduced surgical risk of MIGS procedures comes at the expense of reduced efficacy, especially when used in patients with advanced disease. Dr. Robert Weinreb raised this concern at the 10th European Glaucoma Society Meeting in 2012 (Personal communication January 14, 2019) by questioning whether these devices are minimally invasive (ie, MIGS) or minimally effective (ie, MEGS). To meaningfully answer this question, the desired efficacy of any glaucoma procedure must be defined. The surgeon must first define the estimated IOP lowering required to prevent further glaucomatous damage, which would represent the patient's target IOP. By establishing a target IOP level, or IOP range, clinicians can gauge whether a specific procedure is likely to achieve their goal.

The magnitude of the IOP lowering among MIGS procedures depends in large part on their mechanism of action that can be divided into 3 anatomical areas: Schlemm canal, the suprachoroidal space, and the subconjunctival space. Treatment of Schlemm canal can improve trabecular outflow. Devices targeting this space include iStent trabecular microbypass stent (the first MIGS device to be approved by the FDA), iStent inject, Hydrus Microstent, Kahook Dual Blade goniotomy, Trabectome

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ab-interno trabeculectomy, Eximer laser trabeculotomy, and Gonioscopy-assisted transluminal trabeculotomy. The second site is the suprachoroidal space, which can improve the uveoscleral outflow through a connection between the anterior chamber and the suprachoroidal potential space. An example of such suprachoroidal device is the CyPass Microstent which was recently withdrawn from the market. Finally, targeting the subconjunctival space creates an alternative outflow pathway for aqueous humor and is dependent on the formation of a filtering scar. The Xen Gel stent and the InnFocus Microshunt are examples of this approach.

TRABECULAR MESHWORK BYPASS

The MIGS procedures targeting the trabecular meshwork aim to bypass the usual outflow pathway to enhance aqueous humor outflow through the collector channels.

Trabecular Stents

The trabecular microbypass stent (iStent; Glaukos, Laguna Hills, CA), a 1-mm snorkel-shaped device composed of heparin-coated titanium, is placed through the trabecular meshwork into Schlemm canal. Insertion of the implant is performed through a corneal incision using a preloaded inserter and a gonioscopy lens. The iStent received FDA approval in June 2012, for the implantation combined with cataract surgery in patients with mild to moderate open angle glaucoma (OAG) to reduce the glaucoma medication burden. A prospective, randomized, multicenter clinical trial involving patients with mild to moderate OAG evaluated outcome of cataract extraction alone (n = 123) versus cataract extraction combined with iStent implantation (n = 117) at 29 US sites.[11] A greater proportion of iStent patients achieved IOP ≤21 mm Hg without medications at 1 year compared with phacoemulsification alone group (72% vs 50%, $P < 0.001$). The mean number of ocular hypotensive medications at 12 months was lower in the iStent group (0.2 ± 0.6 vs 0.4 ± 0.7, $P = 0.016$). Adverse events mainly include transient events expected after cataract surgery and occurred at similar rates in both groups. The effectiveness and safety of this study were replicated in other studies of trabecular microbypass stent cataract surgery in mild to moderate glaucoma patients.[12,13] Recent studies with iStent surgery as a sole procedure (not in conjunction with cataract surgery) demonstrated a possible incremental efficacy with use of multiple stents.[14] The second generation iStent inject (Glaukos, Laguna Hills, CA) contains 2 preloaded stents designed for perpendicular insertion into Schlemm canal through the trabecular meshwork. A prospective, randomized, multicenter clinical trial of patients with mild to moderate primary open angle glaucoma (POAG) evaluated the outcome of cataract extraction alone (n = 118) versus cataract extraction combined with iStent inject implantation (n = 387).[15] A greater proportion of iStent inject patients achieved a ≥20% reduction in medication-free diurnal IOP from baseline at 24 months (75.8% vs 61.9%, $P = 0.005$). There was a greater mean reduction in medication-free diurnal IOP from baseline to 24 months in the treatment group compared with the control group (7.0 ± 4.0 mm Hg vs 5.4 ± 3.7 mm Hg, $P < 0.001$). The overall rate of adverse events was comparable between the 2 groups. No patients developed hypotony. Stent obstruction was noted in 24 patients (6.2%) and only 3 underwent laser procedures to treat the obstruction.

The intracanalicular scaffold (Hydrus Microstent, Ivantis Inc., Irvine, CA), a crescent shaped trabecular bypass device, is threaded into Schlemm canal from an ab interno approach. The mircostent dilates and expands the diameter of three clock hours of Schlemm canal to promote flow into the collector channels. Placement is traditionally performed in combination with cataract extraction through a corneal incision with a preloaded inserter and a gonioscopy lens. The FDA has approved the use of the Hydrus microstent in conjunction with cataract surgery in patients with mild to moderate POAG. The Hydrus II prospective study randomized OAG patients to receive Hydrus microstent combined with cataract surgery (n = 50) or cataract surgery alone (n = 50).[16] At 24 months, more patients in the Hydrus group had at least 20% reduction in washed out diurnal IOP than that in the control group (80% vs 46%; $P = 0.0008$). The mean washed out diurnal IOP in the Hydrus group was significantly lower compared with the control group at 24 months (16.9 ± 3.3 mm Hg vs 19.2 ± 4.7 mm Hg; $P = 0.0093$). These results were corroborated by a larger prospective randomized trial, namely the HORIZON study. The study similarly randomized cataract patients with mild to moderate POAG to undergo Hydrus microstent and phacoemulsification (n = 369) or phacoemulsification alone (n = 187).[17] More patients in the microstent group had at least 20% reduction in diurnal IOP compared with cataract surgery alone group (77.3% vs 57.8%, $P < 0.001$) and were more likely to be medication free at 24 months (78% vs 48%, $P < 0.001$). Postoperative hypotony did not occur and adverse events were similar between the two groups. Peripheral anterior synechiae formation was observed in 6 patients in the Hydrus group with focal iris tissue adhesions to the device, but had no apparent effect on IOP.

Ab Interno Trabeculectomy/Trabeculotomy

This category of MIGS involves ab interno ablation or stripping of the inner wall of Schlemm canal to allow aqueous humor in the anterior chamber to flow directly into the collector channels.

Trabectome ab interno trabeculectomy (Trabectome; NeoMedix Inc., Tustin, CA) employs an electrode to ablate a strip of the trabecular meshwork and inner wall of Schlemm canal through a disposable handpiece. The surgeon operates through a temporal clear corneal incision. A large retrospective case series reported the outcome of ab interno trabeculectomy in patients with uncontrolled OAG undergoing Trabectome-only (n = 738) or Trabectome-phacoemulsification surgery (n = 366).[18] The decrease in IOP was 40% at 24 months, 41% at 36 months, and 32% at 60 months in patients undergoing Trabectome-only. Among the combined Trabectome-phacoemulsification cases, the decrease in IOP was 18% at 12 months and 20% at 30 months. The mean medication use decreased from preoperative mean of 2.9 ± 1.3 to a postoperative mean of 1.8 ± 1.4 in the Trabectome-only group, and from 2.93 ± 1.29 to 2.0 ± 2.83 in the combined Trabectome-phacoemulsification group. Complications and adverse events include transient elevation of IOP reported in 65 of 1127 cases (5.8%). Intraoperative blood reflux occurred in 78% eyes but typically cleared over a few days and was not consistently correlated with IOP elevation. Case series evaluating outcomes after Trabectome ab interno trabeculectomy have reported success rates from 51% to 90% after Trabectome alone, and from 64% to 94% after Trabectome combined with phacoemulsification.[19]

Excimer laser trabeculostomy (ELT, Aida, Glautec AG, Nurnberg, Germany) cuts a hole through the trabecular meshwork

into Schlemm canal with energy delivered through a quartz fiberoptic probe connected to a xenon chloride pulsed excimer laser. A prospective randomized study compared the results of POAG eyes assigned randomly to ELT or selective laser trabeculoplasty.[20] At the last follow-up, IOP decreased from 25.0 ± 1.9 mm Hg to 17.6 ± 2.2 mm Hg and from 23.9 ± 0.9 mm Hg to 19.1 ± 1.8 mm Hg in eyes treated with ELT and selective laser trabeculoplasty, respectively ($P < 0.0001$).

The Kahook dual blade (KDB, New World Medical, Rancho Cucamonga, CA) is a single-use ophthalmic blade designed for goniotomy and simultaneous ab interno trabeculectomy with removal of trabecular meshwork strip. A prospective noncomparative study evaluated the efficacy of KDB goniotomy combined with cataract surgery performed on patients with mild to severe OAG (n = 52).[21] At 12 months, mean IOP decreased from 16.8 ± 0.6 mm Hg to 12.4 ± 0.3 mm Hg and mean medications decreased from 1.6 ± 0.2 to 0.8 ± 0.1 medications. A retrospective multicenter case series observed the efficacy of KDB in patients with severe or refractory glaucoma (n = 53).[22] Mean IOP was reduced from 18.4 ± 6.1 mm Hg to 13.9 ± 3.5 mm Hg at 6 months and mean medications decreased by 1.2 ± 1.3 medications from baseline.

In gonioscopy-assisted transluminal trabeculotomy (GATT), an illuminated microcatheter (iTrack™ fiberoptic micrcatheter, Ellex Medical Lasers Ltd, Mawson Laskes, SA, Australia) or suture, is passed through a goniotomy opening in the trabecular meshwork to cannulate Schlemm canal. A 360-degree ab interno trabeculotomy is then performed by mechanical cleavage of the trabecular meshwork, with or without concurrent delivery of viscoelastic to the distal outflow system. This facilitates treatment of a larger area of the trabecular meshwork compared with other MIGS trabecular bypass procedures. Early retrospective reports on eyes with POAG (n = 57) in which GATT was performed with or without cataract extraction, found an average IOP reduction of 39.8% at 12 months.[23] The number of IOP-lowering medications used decreased by 1.1 ± 1.8 medications at 12 months. Postoperative complications included hyphema in 35% (30/85) and steroid-induced IOP elevation in 5 eyes. A long term retrospective study included POAG patients undergoing isolated GATT or GATT combined with cataract surgery.[24] At 24 months, IOP decreased by 10.4 mm Hg and 8.4 mm Hg in the GATT alone and GATT combined with cataract surgery group, respectively. Both groups were on fewer medications at 24 months, with an average decrease in glaucoma medications of 1.4 and 1.9 fewer medications in the GATT alone and GATT combined with cataract surgery group, respectively. Common postoperative complications include hyphema in 31% (62/198) that resolved in the early postoperative course without intervention.

SUPRACILIARY MICROSTENTS

The CyPass microstent (Alcon Inc, Fort Worth, TX) is implanted into the suprachoroidal space posterior to the scleral spur via an ab interno clear cornea incision to create a patent conduit for increased aqueous outflow via the uveoscleral pathway. The COMPASS trial, a 2-year prospective, randomized, multicenter study, evaluated the outcome of CyPass microstent implantation with cataract surgery versus cataract surgery alone.[25] At 24 months, more microstent subjects (77%) than cataract surgery alone subjects (60%) achieved a $\geq$20% reduction in unmedicated diurnal IOP. Mean unmedicated IOP was 17.0 ± 3.4 mm Hg and 19.3 ± 3.3 mm Hg in microstent group and the cataract alone group, respectively. Through the 24-month follow-up, ocular adverse events in CyPass cases include iritis (7.8%), corneal edema (32%), hypotony (2.9%), IOP elevation (4%), stent obstruction (2.1%), cystoid edema (1.3%), and BCVA loss $\geq$10 letters (8.8%), most of which resolved with no permanent sequelae on vision. On August 29, 2018, Alcon voluntarily withdrew CyPass from the market and later in September 2018 the FDA issued a Class I recall. This action was due to safety concerns based on 5-year post surgery analysis data from the COMPASS study that revealed a possibly higher rate of corneal endothelial cell loss associated with CyPass implantation.

SUBCONJUNCTIVAL STENTS

This group of MIGS devices route aqueous humor directly to the subconjunctival space in a manner similar to trabeculectomy or glaucoma drainage implants surgery. Unlike the traditional ab externo trabeculectomy and glaucoma drainage devices, one device, the XEN 45 Gel Stent, can be implanted ab interno without dissecting the conjunctiva or sclera. In contrast with the previously mentioned trabecular bypass MIGS, these subconjunctival procedures are independent of the trabecular outflow system and lower IOP by draining aqueous humor directly into subconjunctival space.

The XEN 45 Gel Stent (AqueSys Inc., Irvine, CA) is a 6-mm gelatinous tube designed to avoid early postoperative hypotony by reducing the inner diameter of the tube to provide adequate resistance. Through a corneal incision, the surgeon passes a preloaded stent on a 27 gauge needle inserter across the anterior chamber and through the trabecular meshwork and sclera into the subconjunctival space. The spontaneous formation of a bleb after device insertion confirms the proper position of the device. The XEN FDA package labeling indicates its use for the management of refractory glaucoma, including patients with a history of previous failed surgical treatment and failure to control IOP with medical therapy. A prospective noncomparative study evaluated the outcome of XEN stent with Mitomycin C (MMC) in patients with refractory glaucoma (n = 65), including patients with a history of prior failure of filtering or cilioablative procedures.[8] At 12 months, 76.3% of patients achieved $\geq$20% IOP reduction from baseline on the same or fewer medications and mean IOP reduction from baseline was 6.4 ± 1.1 mm Hg. Overall, mean medication use decreased from 3.5 ± 1.0 medications at baseline to 1.7 ± 1.5 medications at 12 months. 16 patients (24.6%) experienced transient hypotony that did not require surgical intervention. Choroidal effusion, suprachoroidal hemorrhage, or hypotony maculopathy has not been reported. 14 patients experienced a total of 18 occurrences of IOP increase $\geq$10 mm Hg from baseline. 1 case of stent exposure was reported. During the 12-month follow-up, needling was performed in 21 (32.3%) patients. Recent studies have compared the results of XEN with traditional filtering surgery. A retrospective multicenter cohort study evaluated the outcomes of XEN 45 insertion with MMC (n = 185) versus trabeculectomy with MMC (n = 169) in patients with POAG or secondary glaucoma with no history of prior incisional filtering glaucoma surgery.[26] The adjusted hazard ratio of failure of the XEN 45 relative to trabeculectomy was 1.2 for complete success and 1.3 for qualified success, with no significant

difference between the 2 procedures. Postoperative in-clinic maneuvers or interventions, including laser suture lysis and needling, were not considered as failures. At the last follow-up, 24.3% of microstent eyes and 33.0% of trabeculectomy eyes received medications. Needling was performed on 43% of XEN eyes and 31% of trabeculectomy eyes. 50% of trabeculectomy eyes underwent laser suture lysis. There were 22 and 30 distinct complications in the microstent and trabeculectomy groups, respectively. Complications in the microstent eyes include leak (n = 3), hyphema (n = 2), vitreous hemorrhage (n = 2), choroidals (n = 1), hypotony maculopathy (n = 2), uveitis (n = 2), blocked microstent (n = 1), exposed microstent (n = 1), microstent-iris touch (n = 2), dellen (n = 2), and malignant glaucoma (n = 4).

The investigational InnFocus MicroShunt is an ab externo bleb-forming procedure that involves insertion of a 8.5-mm polymeric tube through the limbus into the anterior chamber after dissection of a scleral pocket. A nonrandomized prospective study carried out in the Dominican Republic evaluated the outcome of InnFocus Microshunt in patients with POAG uncontrolled on maximal tolerated medical therapy (n = 23) during a 3-year follow-up period.[27] The mean percent reduction in IOP from baseline (23.8 ± 5.3 mm Hg) was 55% at 3 years with a mean IOP of 10.7 ± 3.5 mm Hg. 7 patients experienced adverse events, including hypotony (n = 3), shallow or flat anterior chamber (n = 3), hyphema (n = 2), choroidal effusion or detachment (n = 2), elevated IOP requiring removal of fibrin in AC (n = 1) or needling of bleb (n = 1), vitreous hemorrhage (n = 1), and bleb leak (n = 1).

DISCUSSION

MIGS devices play an important role in the glaucoma treatment algorithm, with potential wide application as evidenced by their use in a wide range of glaucoma severity. Devices targeting the trabecular meshwork have shown to be effective and safe in patients with mild to moderate glaucoma as an alternative to topical treatment in those with adherence problems or ocular toxicity. Although trabecular bypass results are promising, these MIGS procedures are not likely to be effective if the surgical goal is a marked reduction in IOP or control of a very high IOP.

If the primary site of resistance to aqueous humor outflow is the meshwork, these procedures would bypass the site of obstruction and facilitate access to Schlemm canal and the distal outflow system. However, if obstruction is further downstream, then the efficacy of this device would likely to be limited. Another hypothesis for the variability in IOP reduction is the segmental and nonuniform nature of aqueous humor outflow through the entire circumference of the trabecular meshwork. Huang et al demonstrated aqueous angiography (a real-time and physiologic aqueous humor outflow imaging technique) with segmental aqueous humor outflow patterns in human eyes.[28,29] This segmentation suggests that success of trabecular bypass MIGS may critically depend on placing the device in specific regions. Advances in aqueous angiography may help clinicians localize collector channels with significant flow preoperatively and predict the optimal trabecular stent location. Additionally, such information could allow physicians to determine whether a trabecular bypass device would be the most efficacious surgery for a particular patient.

With respect to safety of the trabecular bypass devices, the risk of late-onset endophthalmitis and bleb-related complications is eliminated. Postoperative hyphema is a relatively common complication, with a reported incidence of 35% in GATT, making it less than ideal in patients with a bleeding predisposition.[23,24] In the subconjunctival stent category, several studies have supported the use of the XEN 45 Gel Stent in refractory and more advanced glaucoma compared with trabecular bypass devices.[8,26] Despite the encouraging early results, the reported incidence of cases requiring needling was as high as 43% at 1-year follow-up, despite the application of subconjunctival MMC to prevent scarring.[26]

CONCLUSIONS

The eye responds with scarring after glaucoma implant surgery, irrespective of the device location. This explains why prolonged follow-up of all glaucoma surgeries to date shows worsening results with time.[30–33] Prospective randomized controlled studies with longer follow-up periods are needed to verify the durability and long term safety of MIGS procedures and devices, especially when compared with traditional glaucoma filtering surgeries. This will be the only reliable way to determine the long term efficacy of these procedure (ie, MIGS or MEGS).

Margaret Wolfe Hungerford once wrote in Molly Bawn—"*Beauty is in the eye of the beholder*," and so it is in judging the IOP-lowering effect of these procedures.

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