

Microinvasive Glaucoma Surgery

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ABSTRACT

Aim: The aim of the article is to discuss issues concerning microinvasive glaucoma surgery.

Material and Methodology, Discussion: The article presents definitions of microinvasive procedures and their classification, and the most important types of implants as well as their implantation technique and their mechanism of action. The article also contains the most important reports concerning the indications and results of studies presented in the literature.

Conclusions: Microinvasive techniques are based on physiological aspects of aqueous humor flow in the eye and their role in the glaucoma treatment algorithm is yet to be determined.

Keywords: Glaucoma; Microinvasive surgery; Implants

DEFINITION OF MICROINVASIVE GLAUCOMA SURGERY

Microinvasive glaucoma surgery (MIGS) refers to surgical procedures with ab interno access and minimum damage to or bypass of tissues facilitating physiological aqueous humor drainage mechanisms with a high safety profile and efficacy and a small influence on the patient's quality of life [1]. Ab interno access, meaning from the anterior chamber of the eye, makes it possible to preserve the conjunctiva, eliminating scar formation and does not preclude the performance of additional conjunctival surgery in the future. The clear corneal incision used in cataract surgery makes it possible to expand the scope of the procedure to cover MIGS without the need to make additional incisions in the limbus and thus has a small influence on change of post-operative refraction.

Classification of MIGS according to anatomical criteria:

- a. Schlemm's canal surgery,
- b. suprachoroidal space surgery,
- c. surgery bypassing physiological aqueous drainage pathways [1-3].

Implantation

Ab interno procedures are performed using direct gonioscopy. They often require a change of the microscope's position during the procedure or a specific position of the patient's head. Understanding the distribution of aqueous flow resistance is important from the perspective of optimizing the implantation and positioning of microstents.

Physiology of Aqueous Drainage

Aqueous humor is drained from the eye via two physiological pathways [4,5]. The conventional path begins at the level of the irido-corneal trabecular meshwork and is responsible for approximately 83-96% of drainage [4]. From the anterior chamber, the aqueous humor moves through the trabecular meshwork to Schlemm's canal and then to intrascleral collector channels, which lead to the intrascleral venous plexus, aqueous vessels, and the venous vessels of the suprascleral space. Aqueous vessels begin as collector channels in the exterior wall of Schlemm's canal and can be seen on the surface of the eye in the corneal limbus [4,5]. Drainage by an unconventional suprachoroidal path covers all paths that do not being in the trabeculum [5]. Small amounts of aqueous humor probably pass through the cornea and vitreous, and thus through the retina and optic disc. However, the main part of unconventional drainage takes place through the anterior part of the choroid, which is why this path is referred to as suprachoroidal [5,6]. Drainage via this path takes place through the base of the ciliary muscle, which does not have an endothelial barrier to the anterior chamber [7]. Drainage by this path is reduced with age from 30-35% of young persons to 3% of total drainage from the eye after the 60th year of age [7].

Structure of Drainage Paths and Outflow Resistance

Aqueous humour flows out of the anterior chamber as a mass stream regulated by a pressure gradient [6]. In healthy human eyes, outflow facility has a value of $0.40 \frac{\mu\text{L} \times \text{min}}{\text{mmHg}}$ at 10 mmHg [8] and is reduced with age [9]. From a physiological perspective, the trabeculum, particularly the interior wall of Schlemm's canal, and the trabecular meshwork near collector channels are the main sources of resistance to aqueous outflow, and the remaining part of resistance is located in the exterior wall and surrounding tissues [10,11]. The aqueous humor flows through drainage pathways at a rate of $2.0 \mu\text{L}/\text{min}$ [10]. Elevated IOP in glaucoma is caused by an increase in aqueous outflow resistance on its drainage pathways, not by an increase in aqueous production [4]. Many authors believe that the source of outflow resistance in correct eyes is found close to or in the area of the interior wall of Schlemm's canal [10]. Outflow resistance is not constant but a function of IOP and rises as IOP rises [8].

Schlemm's Canal

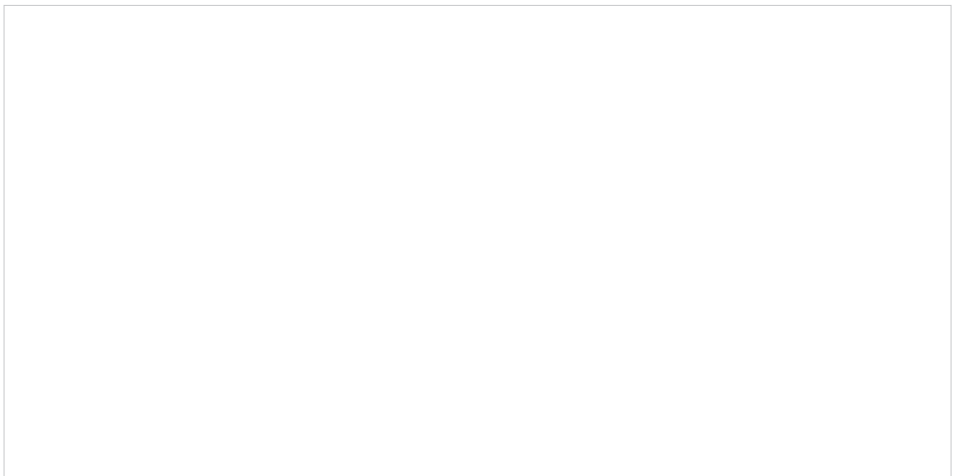
Schlemm's canal drains aqueous humor from the trabeculum into suprascleral and conjunctival veins via collector channels. This is a circuitous channel lined with endothelial cells, with a total length of 36-40 mm and a width of 190-370 μm [4]. The Schlemm's canal interior wall is built of a continuous monolayer of endothelium [12], in which the endocellular route of aqueous flow is found, as represented by giant vacuoles and pores [5].

The interior diameter of Schlemm's canal changes in response to IOP fluctuations [13,14], which is too high to generate significant resistance on the outflow path [4]. When IOP rises, the trabecular meshwork expands toward the lumen of the canal and causes it to narrow. At high IOP, parts of the canal's lumen close, increasing the probability that its walls will collapse and increase resistance in drainage routes [13], however the canal does not collapse under the influence of physiological increases in IOP [15]. Extensive collapse of the canal only occurs at a pressure of 40 mmHg, with the exception of points where septa are located [10,16].

The most frequent point of implantation in Schlemm's canal surgery is the nasal quadrant, mainly as a result of simple surgical access through a temporal corneal incision. This location covers the most collector channels and aqueous veins (Video 1,2).



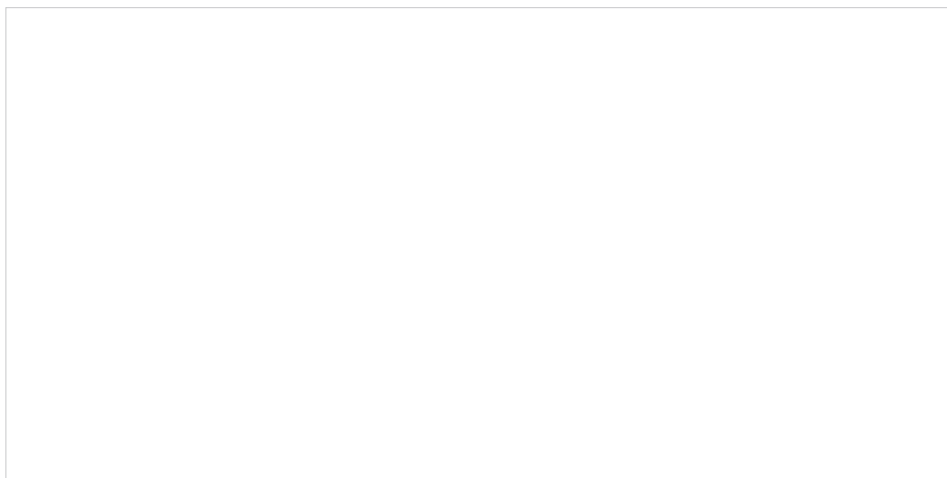
Video 1:



Video 2:

The aqueous flows out of Schlemm's canal through one of 30 collector channels and aqueous veins and then to the system of suprascleral veins [11], ophthalmic veins, and general circulation [5]. Aqueous veins have a length of approximately 1 mm and a diameter of approximately 50 μ m [11]. According to Poiseuille's law, the resistance of aqueous veins should be insignificant if they are not collapsed or compressed [17]. It can be stated that distal aqueous drainage routes do not play a significant role in generating outflow resistance [10].

Provocative gonioscopy, during which blood reflux into Schlemm's canal is observed, is the simplest method of assessing the conventional drainage pathway and facilitating localization of an uncollapsed collector and aqueous vein [18]. Assessment of the distribution of aqueous veins in canalography is a more precise method (Video 3).



Video 3:

Studies by Grieschaber et al. [19] showed a relationship between post-operative intraocular pressure level and the presence of reflux in Schlemm's canal before surgery and between the degree to which aqueous veins were filled. Zou [20] introduced the trabeculum bypass theory, which reduces resistance in this part of the drainage route. He observed increased flow through Schlemm's canal only in the quadrant where the implant was applied, and intraocular pressure reduction was dependent on initial pressure.

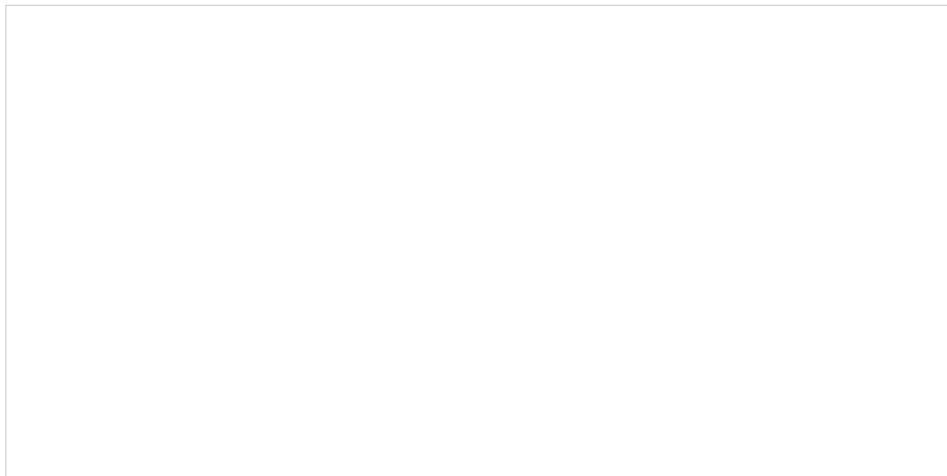
Pulsating flow

Aqueous and suprascleral veins oscillate according to heartbeat [18]. These oscillations enable continuous lamellar flow. Pressure in aqueous veins is sufficiently high and enables reverse lamellar flow from suprascleral veins at cardiac diastole. At cardiac systole, pressure in aqueous veins increases and reverses the direction of aqueous flow with simultaneous blood reflux (Video 4).

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Video 4:

Suprachoroidal space

Prostaglandin analogues can increase suprachoroidal outflow and thus lower IOP. Certain authors suggest that this outflow route may undergo greater modification with the use of medications than the conventional route [21,22]. This is also why it is attempted to use this path in MIGS. Emi et al. [23] suggest that a negative pressure gradient is generated between the suprachoroidal space and the anterior chamber. It amounts to 3-4 mmHg and creates a potential driving force for aqueous humor outflow to the suprachoroidal space. The pressure difference between the anterior chamber and the posterior suprachoroidal space increases at higher IOP.

Cyclodialysis is the separation of the longitudinal muscle of the ciliary body from the scleral spur. Aqueous humor flows directly through this cleft into the suprachoroidal space and causes

hypotony. This phenomenon was described for the first time in 1900 by Fuchs [24]. Intentional surgical cyclodialysis has been used for the treatment of glaucoma and was first described by Heine in 1905. A surgical cyclodialysis was created by inserting a spatula between the sclera and choroid through a posterior scleral incision into the anterior chamber [25]. Ultrasound biomicroscopy precisely identified cyclodialysis [26] (Figure 1).

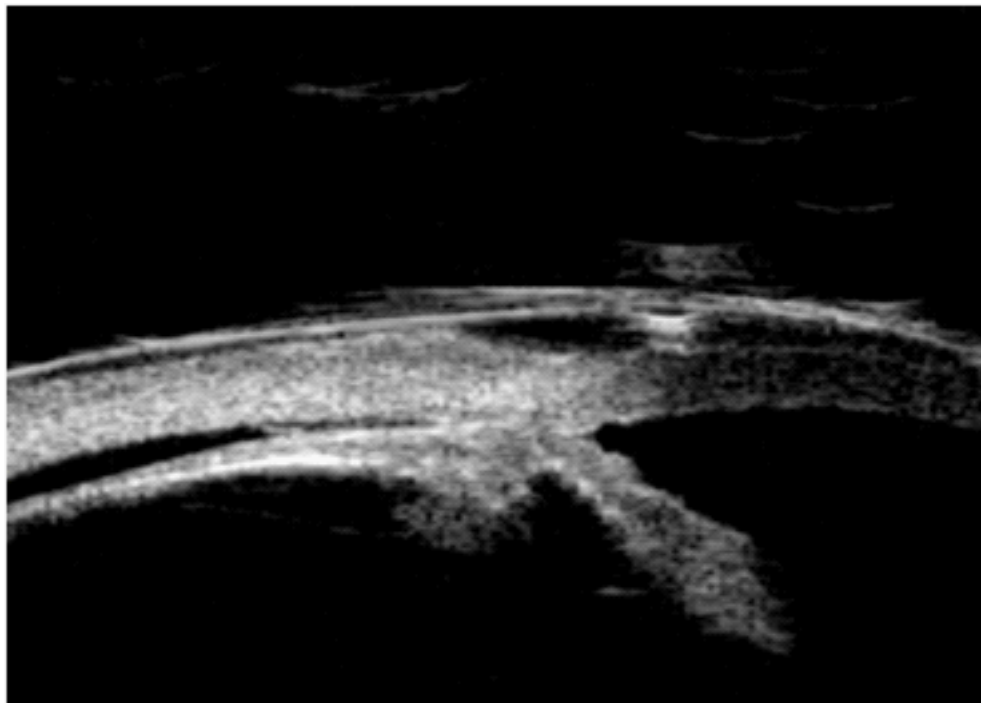


Figure 1: Cyclodialysis in UBM.

Achievement of controlled cyclodialysis for the purpose of therapeutic IOP reduction is difficult. Earlier attempts to surgically increase suprachoroidal outflow have had limited success due to complications and the difficulty of achieving controlled cyclodialysis [27-29].

MIGS CLASSIFICATION

- a. Schlemm canal surgery improving conventional outflow:
 - i. iStent
 - ii. Hydrus
 - iii. Ab interno canaloplasty
- b. Suprachoroidal space surgery strengthening outflow through the unconventional route.

- i. Cypass
- ii. iStentsupra
- c. Surgery bypassing physiological aqueous drainage pathways:
- i. XEN GelStent

iStent (Glaukos Corporation, Laguna Hills, CA, USA)

We distinguish between three microstent generations:

1st generation iStent trabecular micro-bypass,

2nd generation iStent inject,

3rd generation iStent Supra.

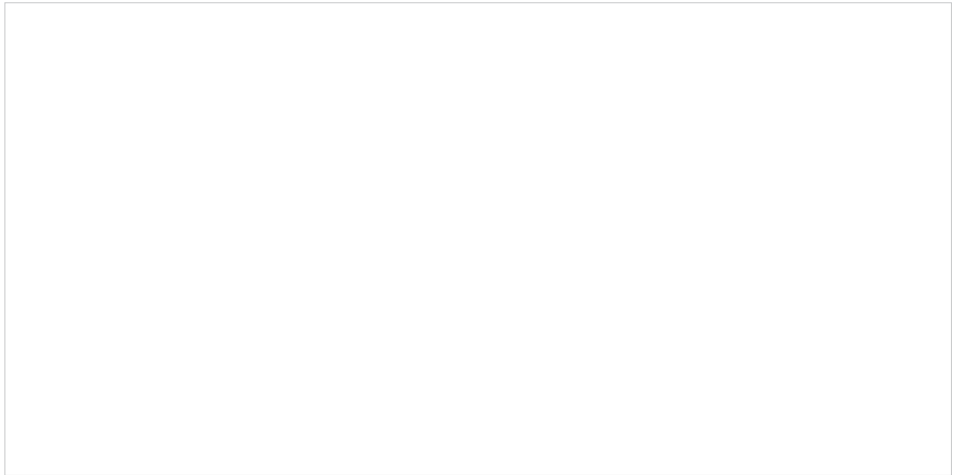
iStent Trabecular Microbypass

The iStent (CE certified & FDA approved 2012) is designed to restore natural physiological outflow by creating a patent bypass through the trabecular meshwork to Schlemm's canal (Figure 2, Figure3 and Figure 4). It has an "L"-shaped structure with a snorkel (inlet) on the short side (which sits in the anterior chamber) and an open half-pipe lumen. It is the smallest device known to be implanted in humans: 1.0 mm in length and 0.33 mm in height, with a snorkel length of 0.25 mm and diameter of 120 μm . The convex side of the iStent sits against the inner wall of Schlemm's canal and the open half-pipe against the outer wall. The size of the lumen has more than adequate capacity to accommodate flow of the aqueous humor that is produced. Two orientations of the iStent are available, one for the right eye (OD) and one for the left eye (OS). The iStent is inserted ab internally through a small temporal clear corneal incision, and placed in Schlemm's canal at the lower nasal quadrant (Video 5). Implantation of this stent into Schlemm's canal at this location:

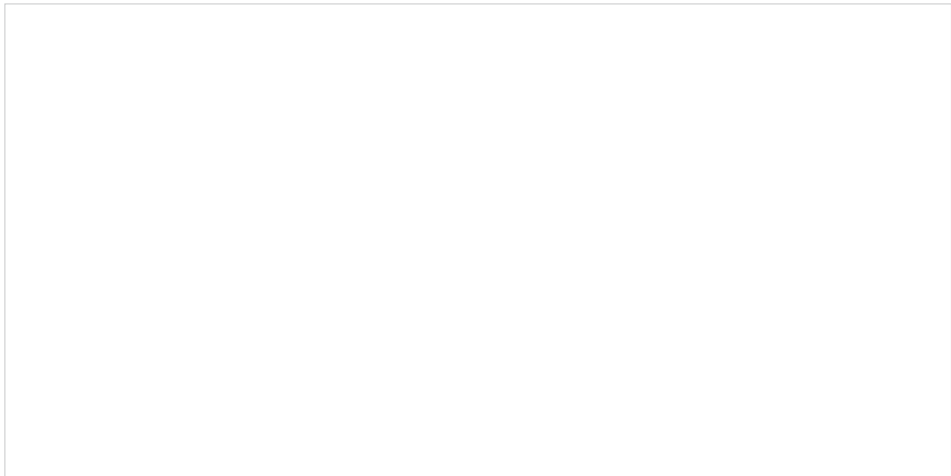
- 1) allows aqueous humor to drain directly from the anterior chamber into Schlemm's canal, bypassing the obstructed trabecular meshwork.
- 1) optimizes outflow in the area with the highest concentration of collector channels (the lower nasal quadrant) [30] (Video 6,7).



Video 5:



Video 6:



Video 7:

The iStent is manufactured from titanium, a material commonly used in medical implants with proven biocompatibility in the body. It is non-ferromagnetic for safety in magnetic resonance imaging. The heparin coating is used to ensure wetting ability of the lumen for self-priming. It is non-ferromagnetic for safety in magnetic resonance imaging. Non-clinical testing has demonstrated that the iStent Trabecular Micro-Bypass Stent (Models GTS100R and TS100L) is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions: static magnetic field of 3T or less, maximum spatial gradient magnetic field of 4,000 gauss/cm (40 T/m), maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode) [31].



Figure 2: iStent implant.

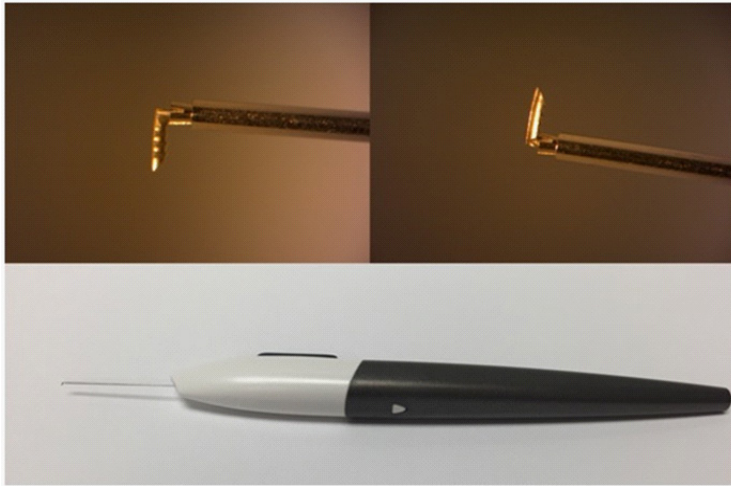


Figure 3: iStent implant with injector.

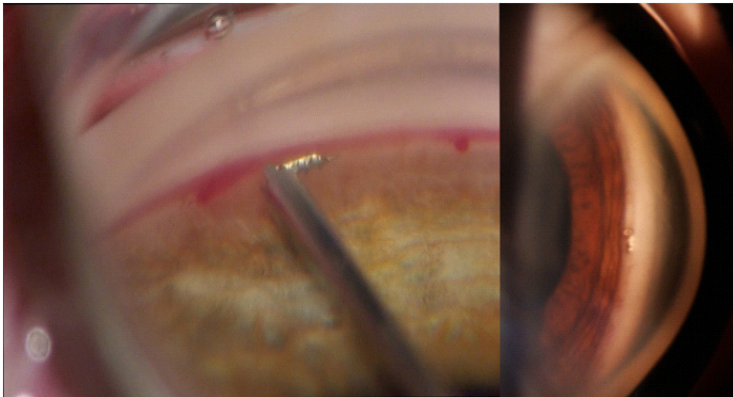
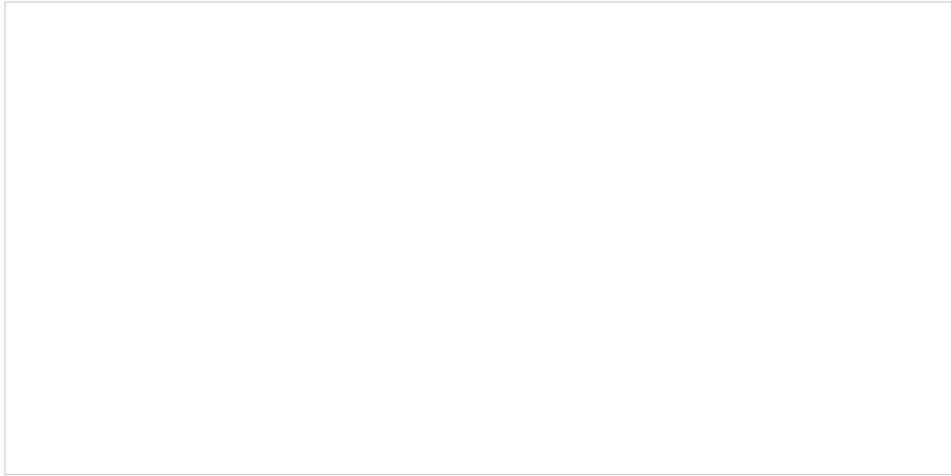


Figure 4: iStent implant in gonioscopy.

iStent inject

iStent inject (heparin-coated titanium same as iStent) is a second generation ab interno micro-bypass stent used to create patent bypass through the trabecular meshwork to Schlemm's canal. Several stents can be used to achieve a better hypotensive effect. The iStent is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle, which could lead to improper placement of the stent and pose a hazard. The iStent is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions [31](Video 8).



Video 8:

iStent Supra

iStent Supra is made from polyethersulfone (PES) and a colored titanium sleeve. It is a 4mm long tube with a hole at each end that is placed in the suprachoroidal space via ab interno access through a clear corneal incision. It is designed to create a patent lumen from the anterior chamber into the suprachoroidal space. It has retention rings to provide stability at the implant location. We can gain some knowledge from presentations that have been made at ophthalmology meetings around the globe [1].

The iStent G1 is currently the most widespread. The efficacy and safety of the microbypass by itself or in combination with phacoemulsification has been assessed in numerous studies. Most of them covered an observation time amounting to one year or less [32-34]. Samuelson presented the results of a study on iStent application with simultaneous cataract removal surgery. The study covered year-long observation of 240 eyes randomly qualified into two groups: in the first group, patients underwent cataract phacoemulsification surgery with iStent implantation, and cataract removal by itself was performed in the second group. In this study, pressure control with a lower number of applied medications was observed in a greater percentage of patients from the iStent group after 1 year compared to the control group. The safety profile was similar in both groups [35]. Craven confirmed the statistically significant therapeutic effect in the iStent group in his two-year observation study [36]. Certain studies confirm the beneficial influence of implanting multiple stents and suggest that multiple implantation reduces the number of applied medications [37]. In a non-randomized prospective case series study, Belovay and Ahmed compared pressure among patients with two and three stents. The dependencies of pressure on the number of applied stents shown in the study indicate that the surgeon may determine the number of implanted stents according to target pressure for every patient [37]. The most

frequently described complications after iStent implantation are hyphema, transitory increase in intraocular pressure, corneal edema, unpatent stent, loss of anterior chamber, difficulties with implantation, entrapment of the vitreous, improper stent positioning, necessity of repeating the procedure [33-36].

Hydrus Schlemm Canal Scaffold (Ivantis, Inc.,Irvine, CA, USA)

Hydrus Schlemm canal scaffold (CE certified) made from nitinol® (nickel-titanium alloy) is a flexible, biocompatible “scaffold” for Schlemm’s canal, containing 3 windows over its length of 8mm (Figure 5, Figure 6). Its open design enables outflow of aqueous humor. Implantation takes place ab interno through a clear corneal incision. The microstent is placed into Schlemm’s canal in a direct gonioscopic image using a preloaded hand-held injector. The implant is tasked with increasing outflow from the anterior chamber into Schlemm’s canal[38] (Video 9).The Hydrus microstent dilates approximately one quadrant of Schlemm’s canal (3 clock hours) and the most common place of implantation is the nasal quadrant. The proximal 1 mm inlet part of the microstent remains outside Schlemm’s canal in the anterior chamber, ensuring direct inflow of aqueous humor [39]. Studies conducted on eyeballs collected from human remains have shown changes in outflow after implantation of the Hydrus microstent under different perfusion pressure conditions and showed that the microstent significantly improves outflow in comparison to the control group [40].Saheb and Ahmed published data from 6-month observation of 28 eyes after phacoemulsification with Hydrus implantation. The initial value of intraocular pressure dropped from 29 mmHg to 15 mmHg. Complications included subconjunctival hematoma, hyphema, peripheral anterior synechiae [1]. In a 2-year observation, Pfeiffer et al. proved statistically significantly lower IOP in the Hydrus plus cataract surgery group compared to the cataract surgery without Hydrus group. No statistically significant differences in safety were observed. The only notable device-related adverse event was focal peripheral anterior synechiae [41].

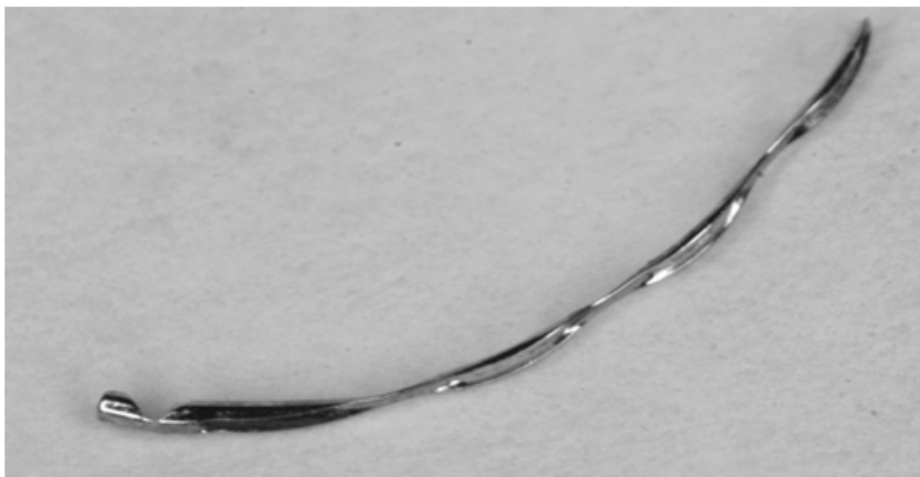


Figure 5: Hydrus implant.

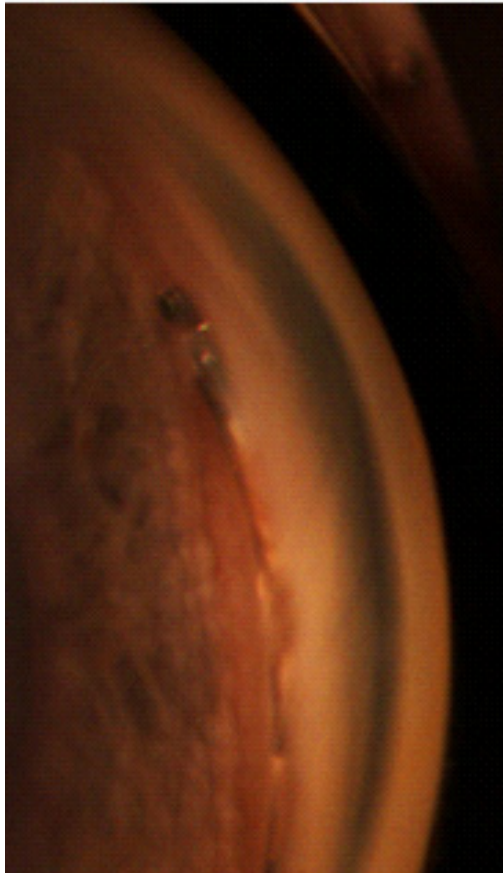
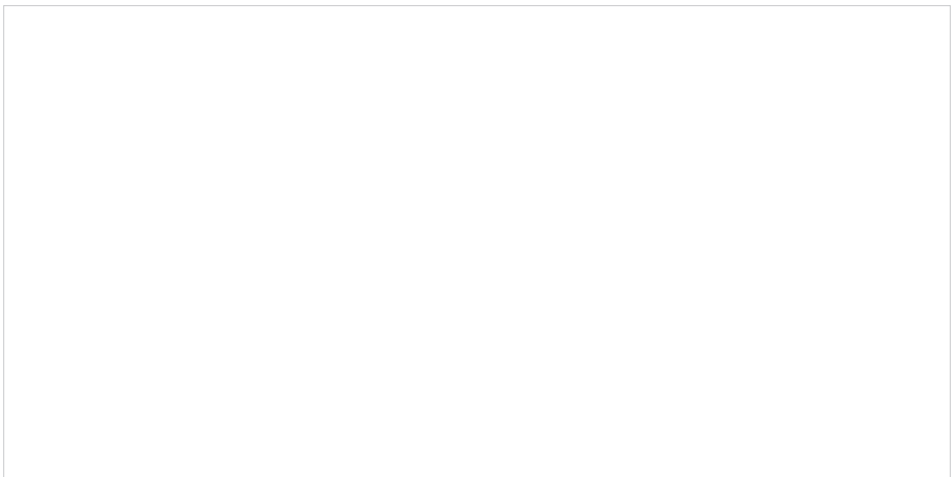


Figure 6: Hydrus implant in gonioscopy.



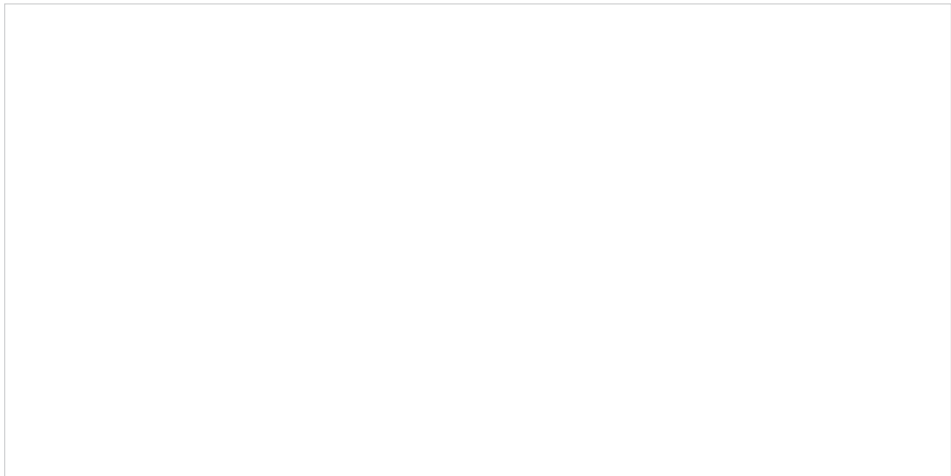
Video 9:

Ab Interno Canaloplasty (ABiC)

Ab interno canaloplasty (ABiC) was created based on ab externo canaloplasty. ABiC is designed to access, catheterize, and viscodilate all aspects of outflow resistance—the trabecular meshwork, Schlemm’s canal, and the distal outflow system beginning with the collector channels. The key difference, however, is that no tensioning suture is required to maintain the IOP reduction with the ab-interno approach and the procedure spares conjunctival manipulation for future procedures if required. Gentle application of viscoelastic during insertion allows the compressed tissue planes of trabecular meshwork and sclera to separate and any herniated trabecular meshwork tissue to withdraw from collector channels using the iTrack 250A Canaloplasty microcatheter, viscoelastic (Healon or Healon GV, Abbott Medical Optics). The indication for ABiC is patients with mild-to-moderate glaucoma on medical therapy. Exclusion criteria: neovascular glaucoma, chronic angle-closure, angle recession/peripheral anterior synechiae, or narrow-angle glaucoma. ABiC could be performed in conjunction with phacoemulsification or by itself [42]. 6-month observations are currently available on the manufacturer’s website [43].

XEN GelStent (AqueSys, Inc.,CA, USA)

XEN GelStent (CE mark in 2011) is a non-absorbable implant made from soft cross-linked collagen tube with a length of 6 mm and an interior diameter of 65 microns. The implant connects the anterior chamber to the subconjunctival space transsclerally (Figure7). The concept of the XEN implant is based on utilizing the outflow route produced by trabeculectomy, which is currently the gold standard, bypassing potential points of outflow resistance while conserving the conjunctiva. Studies evaluating safety and efficacy in reducing intraocular pressure in patients with early-stage, medium-stage, and advanced-stage glaucoma are in progress. The first reports indicate that the XEN implant is a safe method and enables effective control of intraocular pressure as well as reduction of the number of applied antiglaucoma medications. Bypassing of all potential points of outflow resistance and ab interno access eliminate the need to make a scleral flap and the complications related to it accompanying traditional antiglaucoma surgeries [44] (Video 10).



Video 10:

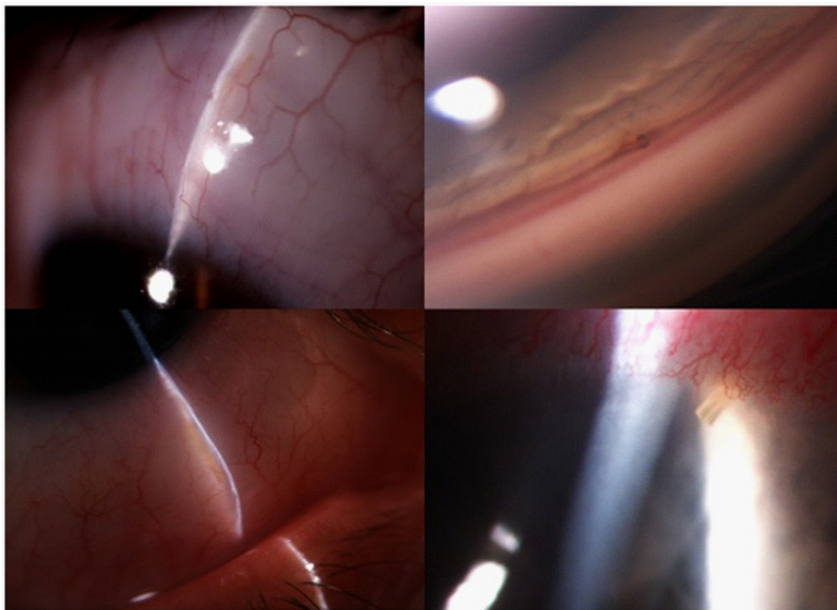


Figure 7: XEN implant.

The CyPass microstent (Transcend Medical, Menlo Park, CA, USA)

The CyPass microstent is implanted ab interno into the suprachoroidal space and was designed to achieve controlled aqueous outflow from the anterior chamber into the suprachoroidal space (Figure 8, Figure 9). This is a tube made of perforated polyamide with a length of 6.35mm and an outside diameter of 510 μ m (Figure 10). The procedure is based on implanting the microstent by means of a special injector through a clear corneal incision (1.5-2.2mm) into the supraciliary space in a direct gonioscopic image. This procedure spares the conjunctiva, and avoids the

formation of a filtering bleb [45-47] (Video 11). The first periodical report of a multi-center study concerning the CyPass microstent was published in 2013 [45]. The study included 2 groups of patients with cataract and uncontrolled and controlled primary and secondary open angle glaucoma. The time of observation had a duration of 6 months. In the 6th month of observation, a 36% pressure drop occurred in the first group, while only a drop of 1.2 mmHg occurred in the second group. The authors emphasize that the second group was made up of patients with controlled glaucoma, therefore the more important result in this group is reduction of the number of applied medications, which amounted to 71%. The most frequently described undesired side-effects include hypotony, transitory increase in intraocular pressure, inflammation in anterior chamber, blood in anterior chamber. 9% of those cases required additional surgical intervention, but no patient required removal of the stent [45].



Figure 8: CyPass implant in gonioscopy.

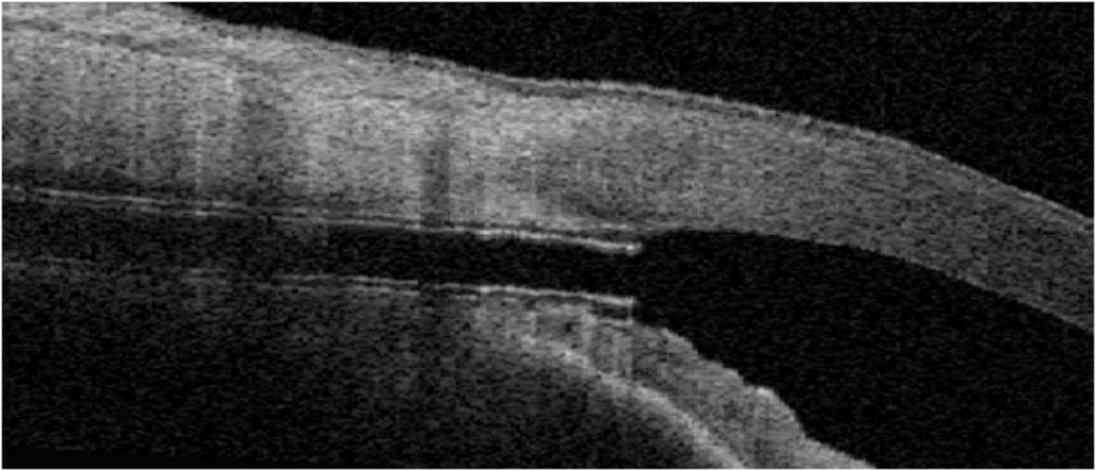


Figure 9: Cypass implant in OCT Visante.

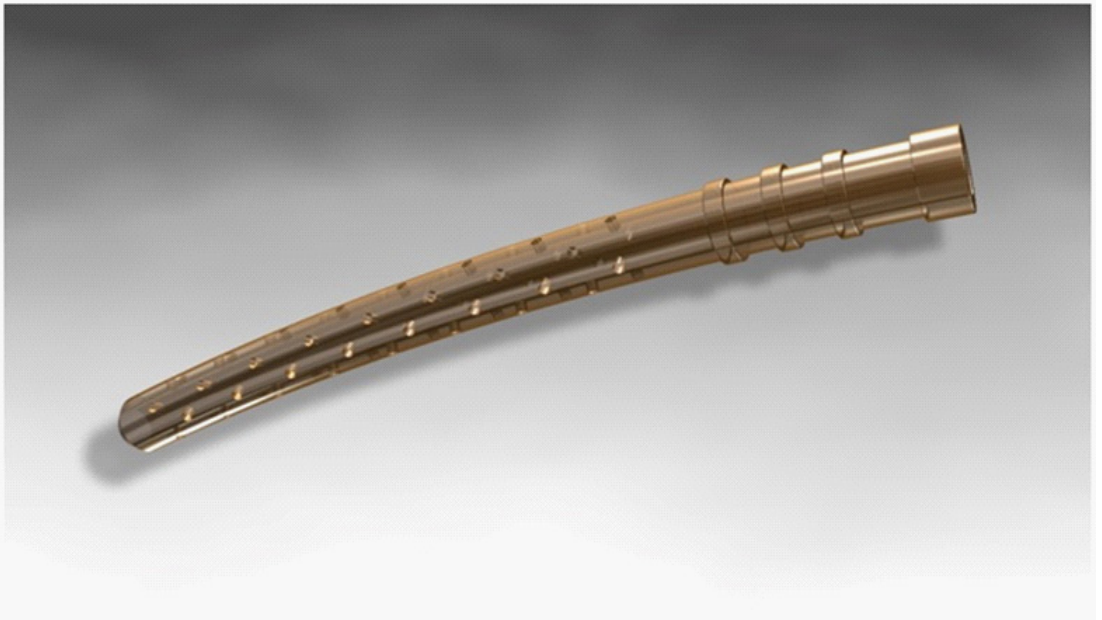


Figure 10: Cypass implant (used courtesy of Transcend Medical, Inc.)

In 2015, Garcí'A-Feijoo et al. [48] presented the results of 24-month observation. Mean IOP was reduced from 24.5 ± 2.8 mmHg to 16.4 ± 5.5 mm Hg at 12 months (34.7% reduction, $P < .0001$). Mean medication usage also decreased from 2.2 ± 1.1 to a mean of 1.4 ± 1.3 medications at 12M. There were no serious intraoperative events. The most common adverse events included IOP increases >30 mm Hg beyond 1 month (11%), transient hyphema (6%), and cataract progression (12%).

SUMMARY

The efficacy of MIGS seems promising, however the ultimate efficacy of these procedures must be evaluated on the basis of randomized clinical studies [1].

We define microinvasive procedures as glaucoma surgery with ab interno access, minimum damage to or bypass of tissues facilitating physiological mechanisms of aqueous outflow, a high safety and efficacy profile, and small influence on the patient's quality of life [1]. In light of the growing interest in and availability of these procedures, it is necessary to conduct pharmacoeconomic studies and quality of life studies in different groups of glaucoma patients to make it possible to present this method of treatment to patients as an alternative. This turn in the direction of understanding and facilitating physiology in the surgical treatment of glaucoma also creates a need to search for medications with a similar mechanism of action. MIGS techniques are based on physiological foundations, however their role in the algorithm of glaucoma treatment is yet to be determined.

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