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Newer Surgical Options for Glaucoma

Behzad Amoozgar[1] · **Ingrid Chang**[1] · **Jane Kuo**[1] · **Ying Han**[1]

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Abstract
Purpose of Review Conventional filtering surgeries such as trabeculectomy and tube-shunt surgery have traditionally been considered the gold standard for management of glaucoma. However, they have a significant complication profile due to the invasive nature of the surgery, and have a relatively high risk of failure such as exuberant fibrotic responses leading to obstruction of the created outflow system. Due to these limitations of traditional incisional surgeries, new surgical techniques for management of glaucoma are of particular interest, especially in the setting of increasing prevalence of glaucoma with an aging population. These new procedures target either inflow or outflow system of the eye in order to manage the intraocular pressure (IOP). The recent innovative techniques share a common goal of effective intraocular pressure control while decreasing the complication profile and minimizing failure rate. This article reviews the primary challenges of developing a successful glaucoma surgery and the recent advancements in glaucoma laser and surgeries.
Recent Findings Recent surgical modalities have been designed to target eye inflow or outflow system. The advancements in their designs are based on detailed knowledge about eye fluidic system. These new developments have been associated with higher success rate and lower complications. More detailed investigations are currently being conducted regarding the long-term safety and repeatability of these interventions.
Summary Advanced surgical modalities have shown promising results in modulating IOP, minimizing the complications, lessening the exaggerated inflammatory-fibrotic response, and reducing the number of post-surgical medications.

Keywords Intraocular pressure · Minimally invasive glaucoma surgery · Trabeculotomy · Trabecular meshwork · Micropulse laser

Introduction

Glaucoma is the leading cause of irreversible blindness in the world (1, 2). Given the significant increase in the prevalence of glaucoma with advancing age, the number of patients with glaucoma is expected to increase dramatically (3, 4). The prime modifiable risk factor for glaucoma is intraocular pressure (IOP) (5). In order to achieve IOP control, glaucoma eye drops and laser surgeries are frequently employed as first line in management. However, glaucoma surgeries are commonly used when conservative measures fail to achieve IOP lowering, and the surgeries do so by either increasing the outflow (filtering) or decreasing the production or inflow (cyclodestructive) of the aqueous humor.

Though conventional trabeculectomy has good success rates in certain population, published data regarding the failure and complication rates have contributed to its over all decline in popularity. Glaucoma drainage devices are being used with increasing frequency in the surgical management of glaucoma as an alternative to trabeculectomy. Advantages of glaucoma drainage implants over trabeculectomy include relative ease of surgical technique and fewer postoperative complications (6, 7). A review of surgical trends from Medicare claims data demonstrated a 410% increase in the number of glaucoma drainage devices placed between 1994 and 2012, while a concurrent 72% decrease in the number of trabeculectomies was

✉ Ying Han
Ying.Han@ucsf.edu

[1] Department of Ophthalmology, University of California, Box 0730, 10 Koret Street, San Francisco, CA 94143-0730, USA

observed (8). Another recent publication assessing trends in glaucoma surgery between 1993 and 2012 in Scotland, England, and Wales found a decline in the use of trabeculectomy and a concomitant increase in the use of aqueous shunts to extraocular reservoir and Endoscopic Cyclophotocoagulation (ECP) (9). Desai et al. surveyed physician members of the American Glaucoma Society concerning their procedural preferences in particular clinical settings. They found that physician preference for aqueous shunt to extraocular reservoir and laser-related cyclodestructive procedures increased significantly between 1996 and 2008. However, the preference for conventional trabeculectomy use decreased significantly over the same time period (10). Since 2005, newer types of glaucoma surgeries, so called minimally invasive glaucoma surgery (MIGS), have been gradually invented to simplify glaucoma procedure and minimize complications. The continued movement away from conventional incisional surgery (trabeculectomy and tube-shunt surgery) and toward alternative options to control IOP highlights the need for well-designed clinical trials comparing these relatively new procedures in order to evaluate their efficacy and safety (8). The review article summarizes the recent advancements in glaucoma surgery and provides a succinct description of each type of surgery or implant and the published literature thus far.

What Challenges Do We Face?

In order to develop effective surgical procedures, certain criteria need to be met. First, the surgical procedure should lower or stabilize the IOP in a predictable manner to prevent glaucomatous progression. Second, the surgical procedure should be safe with a manageable complication profile. Third, the surgery should limit excessive manipulation of ocular structures, which can trigger inflammatory-fibrotic processes and increase the risk of failure. Lastly, since medication compliance continues to be a significant issue for glaucoma patients, newer surgical modalities should address and minimize these difficulties (11).

Enhancing Outflow: Past, Present, and Future

Conventional incisional glaucoma surgeries, such as trabeculectomy and tube-shunt implant enhance outflow and have been considered the gold standard in management of glaucoma since its introduction. However, their popularity has decreased significantly since 2000.

There are three mechanisms of MIGS to enhance outflow of the aqueous humor. One is to bypass the resistance at the trabecular meshwork by directly connecting the anterior chamber to the Schlemm's canal and the collecting channels. The second one is to conduct the aqueous humor into the suprachoroidal space from the anterior chamber. Both types of newer glaucoma surgeries have the potential to treat patients with early to moderate glaucoma. It may help decrease the number of topical glaucoma medications, and thus decrease the medical cost and improve medication compliance. The third one is to conduct excess fluid to the subconjunctival space, which shares a similar mechanism as traditional incisional glaucoma surgery. It has the potential to decrease the IOP to low teens and treat patients with whole spectrum of glaucoma, including patients with severe glaucoma.

The Newer Glaucoma Surgeries to Bypass the Resistance at the Trabecular Meshwork

Trabectome

The Trabectome (NeoMedix, Tustin, USA) is the first FDA-approved MIGS. It is designed to remove a large section of the trabecular meshwork, exposing the Schlemm's canal and the collecting channels, therefore increasing outflow of fluid. The Trabectome consists of an ab interno trabeculotomy that utilizes a high-frequency electrocautery to vaporize the trabecular meshwork and the inner wall of the Schlemm's canal under gonioscopic view. It allows a diathermic ablation of 60°–120° of the trabecular meshwork. The technique is performed using a disposable hand piece connected to a machine which can also be utilized for irrigation and aspiration (12). The advantages of this modality are the removal of both the area of greatest resistance to the aqueous outflow and the tissue debris. This can alleviate inflammation and scarring resulting from surgery (13).

Studies showed that transient hyphema seems to be the most common risk associated with Trabectome, and this modality overall has a good safety profile (14). In a recent study evaluating the long-term results of Trabectome in 70 eyes with open angle glaucoma (OAG), postoperative success was 70% after 18 months follow-up and no serious complication was observed (15). Akil et al. compared result of Trabectome between patients with pigmentary glaucoma and primary open angle glaucoma (POAG). In their study, the reduction in IOP at 12 months was similar in both groups (16). Furthermore, Bussel et al. in their prospective study showed that Trabectome combined with phacoemulsification only can reduce IOP significantly regardless of degree of angle opening (17). These studies showed that the benefits from Trabectome are not limited to a specific type of glaucoma. Trabectome is currently FDA-approved in the USA as a procedure that can be performed with or without concurrent cataract surgery.

iStent: The Three Generations

The iStent (Glaukos, USA) is a 1 mm heparin-coated implant that is inserted into the Schlemm's canal, bypassing the trabecular meshwork resistance (18). The first generation of

iStent may offer mild IOP reduction, and more than one iStent may be needed to lower the IOP (19–21). Later, Glaukos modified the size, shape, and the outflow system of the iStent and introduced the second-generation iStent or iStent inject® (Trabecular Micro-Bypass; Glaukos Corporation). The iStent inject has one head and four evenly spaced ports embedded into it. These ports lead to a narrow thorax and then a wider mid-region. An injector which can be charged by the implant is used for implantation of the iStent inject. Following promising results on the outflow facility of cultured human anterior segments after implantation of iStent inject (22), Fea et al. and Voskanyan et al. demonstrated significant reduction of IOP during the 12 months of follow-up post operation (23, 24). The most common complication in usage of the first and second generation iStent was early postoperative stent occlusion and malposition, which was observed in 2.6–18.0% of study subjects (21, 23).

iStent has shown significant reduction of IOP and glaucoma medications when combined with cataract surgery (19, 25). In addition, when combined with cataract surgery, it has been shown to decrease the IOP more than cataract surgery alone (26, 27).

Glaukos also created the third-generation iStent Supra®, a 4-mm tube made of polyethersulfone (PES) and titanium that is designed to reduce IOP by accessing the suprachoroidal space. One European study demonstrated that 98% of their patients (42 subjects) met their primary endpoint with a 20% reduction in IOP on only one medication. The mean IOP decreased by 47% from 20.8 to 13.2 mmHg (28). The first generation iStent has FDA approval when combined with cataract surgery. The newer generations of iStent are anticipating FDA approval in 2018.

Trab360 (Sight Science)

Trab360 is a combination of a stainless steel trabeculotome body and a soft and blunt trabeculotome with an advanced retraction wheel that is integrated into a single-handed, single-use instrument. This manual instrument can cut and remove up to 360° of the trabecular meshwork via an ab interno approach. A small retrospective study was presented at the American Society of Cornea and Refractive Surgery in 2015 by Sarkisian et al. (29) This study included 26 eyes that underwent Trab360, and at final follow-up, 25 out of 30 eyes (83%) achieved surgical success defined as IOP between 6 and 21 without further glaucoma surgery. The authors conclude that use of Trab360 seemed as safe and effective as circumferential ab externo trabeculotomy. More studies are needed to further evaluate its efficacy. This device is FDA-approved in the USA.

Hydrus Microstent

Hydrus Microstent (Ivantis, Inc. Irvine, CA) is an emerging MIGS device made of super-elastic biocompatible alloy, which works with the similar concept as iStent and used as intracanalicular scaffold once implanted into the Schlemm's canal via an ab interno approach. It maintains the trabecular meshwork's outflow into the Schlemm's canal through the formation of a large circumferential space (30). Fea et al. in their recent study compared efficacy and safety of selective laser trabeculoplasty (SLT) and Hydrus implant. They found that the Hydrus implant has a good safety profile, with significantly more reduction in medication and similar reduction in IOP compared to that of SLT at 12 months of follow-up (31). The Hydrus Microstent is currently an investigational device in the USA.

Kahook Dual Blade (New World Medical, CA)

Kahook Dual Blade (KDB) is a novel dual-blade device that uses precise micro-machining and laser-cutting technology to remove the trabecular meshwork. The dual-blade device is designed with a taper at the tip to allow for smooth entry of the blade into the Schlemm's canal. A key feature of this instrument is that the elevation of the TM tissue allows for cleaner removal of the tissue, thus minimizing damage to adjacent structures. In a laboratory evaluation of human cadaveric corneal rim tissues, Seibold et al. found that the Kahook blade achieves a more complete removal of the TM without injury to surrounding structures compared to microvitreoretinal blade and Trabectome, and all devices reduced IOP in a human eye perfusion model. The single-use, disposable ophthalmic knife was FDA-registered in 2015 and is now commercially available throughout the USA (32, 33). Long-term follow-up is needed to evaluate this technique.

Gonioscopy-Assisted Transluminal Trabeculotomy

Gonioscopy-assisted transluminal trabeculotomy was first described by Grover et al. in 2014 (34). It is a minimally invasive, ab interno approach to a circumferential 360° trabeculotomy. In Grover et al.'s study, they retrospectively examined the clinical outcomes of 85 eyes with glaucoma that underwent GATT. At 1 year, there was a mean decrease in IOP of 11.1 mmHg (40%) in patients with POAG and 17.2 mmHg (53%) in patients with secondary glaucoma. Eight patients (9%) failed due to the need for further glaucoma procedure. The authors conclude that this procedure produces results similar to other trabeculotomies. Similar to other angle surgeries, this procedure may cause transient hyphema (30%), and thus Grover et al. proposed that contraindications for this and other angle procedures include inability to stop anticoagulant use and bleeding diatheses.

Canaloplasty and Stegmann Canal Expander

Canaloplasty with or without the iTrack microcatheter (iScence Interventional, Menlo Park, CA) is another ab externo procedure restoring flow through the Schlemm's canal into the aqueous collecting channels. This procedure is a non-penetrating and bleb-less surgery which combines a 360° viscocanalostomy with a circumferential distension of the Schlemm's canal (12). Published literature reports that canaloplasty, alone or in combination with cataract surgery, lowers the IOP and the number of glaucoma medication use significantly (35–37).

Stegmann Canal Expander (Ophthalmos, Schaffhausen, Switzerland) (SCE) is an ab externo implantable device that enhances aqueous outflow and is developed to simplify the canaloplasty procedure (38). This fenestrated single-use instrument is made of polished surgical polyimide and is supported by a carrier that holds up the SCE during handling and implantation. It is placed into the Schlemm's canal via an ab externo approach to create a permanent distension of the canal and of the trabecular meshwork, increasing the drainage of the aqueous humor. In a recent observational study on 22 patients with POAG, implantation of SCE lowered IOP significantly (91% complete success rate) without complications related to the device during 1-year follow-up. This study reflected the potency of this modality to replace surgical procedures with significant high rate of complications such as trabeculectomy (39). Despite these benefits, canaloplasty with or with out SCE requries conjunctival and scleral incision, which may limit ocular surface space for future glaucoma surgery.

The Newer Glaucoma Surgeries to Conduct Fluid to the Suprachoroidal Space

The suprachoroidal pathway has attracted attention as a potential site for drug application which mainly includes prostaglandin and as a surgical site for management of glaucoma. This pathway was first investigated in the cynomolgus monkey by cyclodiastasis or separation of the ciliary body from the scleral spur (40). There are two devices for ab externo procedures that utilize this concept: CyPass Micro-Stent and STARflo.

CyPass Micro-Stent

The CyPass Micro-Stent (Transcend Medical, Menlo Park, CA, USA) is a fenestrated microstent made of a biocompatible polyimide material which is placed by a curved guidewire. The guidewire is curved which helps the device to follow the curve of the sclera during implantation. Saheb and colleagues examined the CyPass Micro-Stent using OCT technology and demonstrated successful aqueous drainage into the suprachoroidal space throughout a 12-month follow-up period (41). CyPass Micro-Stent combined with cataract surgery was shown to reduce IOP (35% reduction in patients with preoperative IOP > =21) and IOP-lowering medications during 12 months of follow-up with minimal complications (42). The CyPass Micro-Stent was recently FDA-approved for use in primary open angle glaucoma when combined with cataract surgery.

STARflo

STARflo is made by iSTAR medical in Belgium. This device is made of controlled microporous geometric material which is made from silicon. This silicon material is chosen with hopes of preventing excessive fibrotic response. STARflo has unique head-neck body design which helps prevent extrusion of the implant. Two versions of this implant have been introduced. The latter version has been upgraded so it can be more easily introduced to the suprachoroidal space (43). Following successful animal studies, this implant was used in a preliminary clinical trial which showed that it can significantly reduce both IOP and number of glaucoma medications (44). STARflo is currently an investigational device in Europe.

The Newer Glaucoma Surgeries to Conduct Fluid to the Subconjunctival Space

EX-PRESS Glaucoma Filtering Device

EX-PRESS glaucoma filtering device is an implantable stainless steel device roughly the size of a grain of rice. This device was originally designed to be implanted at the limbus directly under the conjunctiva. However, due to high rates of hypotony and device extrusion, the technique was modified for implantation under a partial-thickness scleral flap. Currently the EX-PRESS consists of a backplate which prevents the device from intrusion and a spur for avoiding extrusion. EX-PRESS has a lower rate of immediate postoperative complications such as hemorrhages and inflammation compared to that of traditional trabeculectomy (45). When compared to trabeculectomy, differences in long-term surgical outcomes are insignificant (46, 47). In addition, the use of EX-PRESS may be limited by its cost. EX-PRESS glaucoma filtering device is FDA-approved.

Innfocus MicroShunt

Innfocus MicroShunt is a microlumen aqueous-drainage device made out of biostable thermoplastic-elastomeric material that is designed to shunt aqueous drainage from the anterior chamber of the eye to the subconjunctival space. It is designed to be implanted with mitomycin-c, with or without concurrent cataract surgery. At 3 years of follow-up, Batlle et al. reported a qualified success rate of 95%, with a decrease in mean IOP

of roughly 50% (23. to 10.7 mmHg), in addition to decrease in mean number of glaucoma medication use (48). In this small prospective study of 23 eyes in 14 patients, the authors concluded that surgery with the InnFocus MicroShunt is a safe and effective method of achieving IOP control in most subjects at 3-year follow-up (48). This device is currently an investigational device in the USA.

Xen Microfistula

Xen implant (Aquesys, USA) is a stent made of a permanent soft collagen-derived gelatin which is inserted through the trabecular angle into the subconjunctival space, creating an external drainage fistula. New modification in Xen implant was the introduction of the Xen microfistula implant (Aquesys, Inc. Aliso Viejo, CA, USA). Although the concept is similar to trabeculectomy in which the aqueous is directed from the anterior chamber directly to the subconjunctival space, this procedure is technically simpler and can be performed quickly. The implant is inserted via an ab interno approach, and once it is inserted in the desired location, the soft gelatinous tube swells after being hydrated in the eye which facilitates retention of the implant. By design, it does not require a conjunctival incision, scleral flap creation, or use of sutures with significantly less manipulation of tissue compared to traditional filtering surgery, which may be a potential advantage (49). In a small pilot study by Ahmed et al., implantation of this gelatinous stent resulted in a significant reduction in IOP when combined with cataract surgery (50). However, there is lack of significant data regarding its use, and is currently being studied as an investigational device in the USA.

Reducing the Inflow: Past, Present, and Future

From the time of their emergence as glaucoma surgery methods in 1970, the laser-destructive procedures have been vastly updated and modified (51, 52). Currently, diode laser (810-nm wavelength) with either transscleral or an endoscopic approach is the preferred mode for laser cyclophotocoagulation (CPC). The reason for this preference is the high absorption of laser by melanin pigment inside the eye and the more direct anatomical application of the laser, which induces less post-surgical inflammation (53–55).

There have been several different mechanisms postulated regarding the effect of laser on the inflow and outflow of the aqueous in the eye. For instance, in CPC approach, the effect on IOP reduction cannot be explained solely by the destructive effects of the laser on the ciliary bodies causing decreased aqueous productions. Researchers have theorized that blood autoregulation and immunologic response could have potential roles in the increase of outflow (56, 57).

Contact transscleral CPC (TSCPC) using the continuous wave (CW) diode laser has been used widely as a common mode of delivery. This method has been proven effective in treating all forms of glaucoma (58), however, due to a high prevalence of post-surgical complications such as hypotony, visual deterioration, phthisis bulbi, and unpredictable outcomes which may lead to repetition of the surgery, this procedure is now viewed as the last resort option (58, 59).

Endoscopic Cyclophotocoagulation

ECP is a glaucoma surgery that was introduced 20 years ago (60). This procedure was designed to reduce the IOP by partially ablating the ciliary processes to decrease aqueous humor production and secretion (61). The concept is based on aiming an endolaser via an endoscopic probe with options of reaching the proper tissue either from an anterior or posterior approach. The laser can be delivered to the target tissue under direct visualization at appropriately titrated energy levels, minimizing collateral scleral and ciliary body stromal damage (62, 63).

The laser unit for ECP (Endo Optiks, Little Silver, NJ, USA) incorporates a diode laser that emits pulsed (by an operator) continuous wave energy. The most commonly used laser is a semiconductor diode laser emitting at 810 nm (61, 64). Compared to other approaches, ECP appears to be a more selective form of CPC with direct visualized targeting of ciliary body epithelium destruction and thus minimizing damage to surrunding cells.

Modified ECP approach conducted by Tan et al. involved the standard photocoagulation of the ciliary processes and the treatment of the posterior ciliary processes through the pars plana (ECP-plus). This study showed a 78% cumulative treatment success after 12 months of follow-up with an acceptable complication profile (65).

The three most common complications reported after ECP procedure are fibrin in the anterior chamber, hyphema (66), and cystoid macular edema. In addition, regardless of the type of approach that was used in ECP, concerns regarding complications such as hypotony or choroidal detachment still exist (65).

Micropulse Transscleral Diode Laser Cyclophotocoagulation

Micropulse implementation in the field of ophthalmology was first investigated about two decades ago (67). It was first applied in the management of retinal complications (68–70), and about one decade later, researchers found that micropulse transscleral diode laser cyclophotocoagulation (MP-TSCPC) has the potential to become a powerful option for glaucoma surgical interventions (71).

The laser applied in the micropulse method is performed with an 810, 577, or 532 nm semiconductor diode laser, with a

train of 100 (or 200 and even 300) μs laser pulses, each one spaced by a relatively long thermal relaxation time resulting in a 10 or 15% duty cycle.

In contrast to conventional TSCPS, the pulsatile nature of the procedure allows the surrounding tissue to cool-off between the pulses which results in minimal damage to surrounding tissues and prevention of necrosis (72, 73). This transmitted energy is highly absorbed by the pigmentary epithelium that exists in the ciliary bodies and the trabecular meshwork, which is why this procedure is currently viewed as a candidate for targeting the ciliary epithelial cells and the trabecular meshwork epithelium with relative sparing of surrounding tissues (68).

Similar to TSCPC, the mechanism behind the effect of micropulse is debatable and somewhat controversial. It has been speculated that the effect of MP-TSCPC is not limited to a direct effect on the ciliary epithelium (74, 75).

In various clinical trials, MP-TSCPC showed promising results. It offered effective IOP lowering, and yet a decreased rate of complications compared to traditional TSCPC with continuous wave (76, 77). In the Tan et al. study, the mean age of patients was 63.2 ± 16.0 years with a mean follow-up period of 16.3 ± 4.5 months. The overall success rate after a mean of 1.3 treatment trials was significant (70%) (76). Kuchar et al. investigated the results of MPTCP in patients with advanced glaucoma with a mean follow-up of 2 months. There was a 73.7% success rate for initial treatments. Three patients (15.8%) underwent a second treatment, increasing the overall success rate to 89.5% (78). The MP-TSCPC has many advantages over conventional procedures, which include low rate of complications and repeatability without significant consequences.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a new device that has been recently developed by Eye Tech Care. It is a non-invasive system based on HIFU. This entirely novel strategy allows the operator to selectively destroy the ciliary body tissue via highly focused ultrasound beams. HIFU passes through biological tissues easily and hence can target deep tissues without the need for a surgical incision. This treatment can be administered on an outpatient basis and is performed under local anesthesia.

HIFU was introduced first in the USA by Coleman et al. (Sonocare Therapeutic Ultrasound System; Sonocare, Inc., Ridgewood, NJ, USA) and was later introduced in Europe. In contrast to previous instruments implemented, the new modified device, called ultrasonic circular cyclocoagulation (UCCC), has a less bulky probe that can be applied with direct contact to the eye and requires less operating time (79). The advantage over MP-TSCPC is that we have semi-direct visualization in obscured media cases which is enhanced by preoperative high-resolution and computerized modeling of the ocular structures. Hence, in modified and modern sonography instrument, the damage impacting the surrounding tissue is limited (80). In HIFU, the treatment parameters include a 21-MHz frequency with a 2.45-W acoustic power, while the activation of each transducer lasting 4 or 6 s, depending on patient groups. The proper control over the tissue destruction is based on the main concept of resting interval between inductions of high energy which is a shared concept among both HIFU and MP-TSCPC (81).

Melamed et al. in their prospective interventional non-comparative study on patients with refractory glaucoma showed that this modality has good repeatability and safety profile (82). Overall, this method resulted in a significant reduction in IOP and minimal side effects in clinical trials (81, 83).

Future Direction

Over the last decade, there have been major advancements and innovations in glaucoma surgeries. New devices are developed which are not only effective in lowering IOP, but have also demonstrated good safety profile with greater ease of delivery and relative sparing of surrounding ocular tissues. However, long-term success rates have yet to be determined, and more prospective randomized double-blinded clinical trials are needed to determine the relative efficacy and safety profile of these new interventions compared to those gold standard of conventional filtering surgeries.

Compliance with Ethical Standards

Conflict of Interest Jane Kuo, Behzad Amoozgar, Ingrid Chang, and Ying Han declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Kof special interest
•• Of outstanding interest

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