

Minimally Invasive Modalities for Treatment of Glaucoma: An Update

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Abstract

Purpose of Review: In recent years, Minimally Invasive Glaucoma Surgery (MIGS) and laser-based procedures have been gaining popularity as glaucoma treatment options. As such, they represent active areas of research. This article reviews some of the notable recent and forthcoming developments in this field.

Recent Findings: The MIGS devices and cyclophotocoagulation have been focused on achieving satisfactory success rate as either combined with phacoemulsification or standalone procedure. They also have superior safety profile when compared to traditional incisional glaucoma surgeries. In addition to the promising data available thus far, more comprehensive investigations on the long-term efficacy and safety of these interventions are currently underway.

Summary: New minimally invasive surgical modalities have shown considerable potential in intraocular pressure (IOP) and the number of post-surgical medications with rare complications. The rising popularity of these devices and procedures may represent a shift in treatment paradigm from medical therapy towards earlier surgical intervention, especially in the treatment of mild-to-moderate glaucoma.

Keywords: Glaucoma; Minimally invasive glaucoma surgery; MIGS devices

Introduction

Glaucoma is a leading cause of irreversible blindness [1,2]. The number of patients with glaucoma is expected to increase dramatically as the demographic shifts, both domestically and overseas [3,4]. The only proven way to decrease the risk for glaucoma is to modulate the IOP [5]. Conventionally, the ocular anti-hypertensive medications are used as the initial treatment for glaucoma. When these fail to adequately control the IOP, surgical interventions to either increase the outflow (filtering) or decrease the production/inflow of the aqueous humor (cyclodestruction) are considered.

Over the last decade, the introduction of Minimally Invasive Glaucoma Surgery (MIGS) and more selective cyclodestructive procedures has signaled a significant shift in the approach to glaucoma management. These changes include simplification of glaucoma surgical procedure and its post-operative care as well as decrease in the number of glaucoma drops post-surgery. The rising popularity of the MIGS procedure and newer types of lasers highlight the need for a measured consideration of their merits. Thus, continued efforts to evaluate their long-term efficacy, repeatability and safety through large scale clinical trials are warranted [6].

This article summarizes the recent advancements in glaucoma laser treatment and minimally invasive glaucoma surgery. It provides a succinct description of each type of procedure or device and the published literature thus far. Forthcoming clinical trials and developments are also discussed.

Minimally Invasive Glaucoma Surgery (MIGS)

While there is no standard definition, MIGS generally aim to reduce patient dependence on medication through a relatively simple, ab-interno approach to intraocular pressure reduction without excessive conjunctival manipulation. MIGS have been categorized into 3 main groups by their mechanism of facilitating aqueous outflow: 1) Increasing the uveoscleral flow to suprachoroidal space from anterior chamber, 2) bypassing the resistance at trabecular meshwork by directly connecting anterior chamber to Schlemm's canal, and 3) conducting excess fluid to subconjunctival space. All MIGS procedures decrease IOP and the number of topical glaucoma medications, which is essential in saving lifetime medical cost and decreasing compliance burden for the patient. The third pathway works in a similar way as the traditional incisional glaucoma surgery. Devices belonging to this group have the potential to decrease IOP to low teens and treat patients with whole spectrum of glaucoma. The devices and procedures discussed in this article have been compiled in Table 1.

Suprachoroidal

CyPass microstent: The CyPass micro-stent (Alcon, Fort Worth, Texas, USA) is a fenestrated microstent made from a biocompatible polyimide material. It is placed by a curved guidewire that helps the device follow the curve of sclera during implantation.

The 2-year results of the COMPASS (Combination Cypass and Cataract Surgery) trial were published in 2016. COMPASS trial included 505 subjects with mild-to-moderate primary open angle glaucoma (POAG) and became largest MIGS study to date. The subjects were randomized to phacoemulsification with CyPass (Phacoemulsification/CyPass) or phacoemulsification only group. Significantly higher proportion (77% vs. 60%) of patients who received

the micro-stent attained greater than 20% un-medicated IOP reduction compared to those who received phacoemulsification alone. Mean IOP reduction following phacoemulsification/CyPass was 30% from baseline mean of 24.4 mmHg and number of glaucoma medication was also significantly reduced. No serious adverse events were described in either group at 24 months [7,8].

Furthermore, partial results of CyCLE (Cypass Clinical Experience) study were recently made available. CyCLE study was a multi-center, open-label registry study with 3-year follow up. Out of the 245 eyes that received phacoemulsification/CyPass, 93 had uncontrolled baseline IOP of 21 mmHg or higher and the remaining 152 eyes had controlled baseline IOP of less than 21 mmHg. In the baseline-

uncontrolled eyes, the micro-stent reduced IOP by 28% to 34% through the 3-year follow-up period. Additionally, the proportion of eyes controlled with no medication increased from 8% at baseline to 19% at 36-months. In baseline-controlled eyes, the micro-stent maintained IOP at constant levels. CyPass further reduced the number of glaucoma medications at 3 years, when 45% of the eyes did not require medication compared to 3% at baseline. Minor complications occurred in >3% of subjects, including CyPass obstruction, retinal complication, 2 lines of visual acuity loss, and anterior chamber inflammation. No major complication such as choroidal hemorrhage was reported [9].

Pathway/Mechanism	Device/Procedure	Company	References (as numbered in bibliography)
Drainage to Suprachoroidal Space	CyPass micro-stent	Alcon, Fort Worth, Texas, USA	[8,9]
	iStent Supra®	Glaukos Corporation, Laguna Hills, CA, USA	[10-14]
Bypassing Trabecular Meshwork	Gonioscopy-assisted transluminal trabeculotomy (GATT)	iTrack by Ellex iScience, US Operation headquartered in Fremont, CA	[15-17]
	Hydrus Microstent	Ivantis, Inc. Irvine, CA, USA	[18-22]
	iStent: First and Second Generation	Glaukos, Laguna Hills, CA USA	[23-30]
	Kahook Dual Blade	New World Medical, Rancho Cucamonga, CA, USA	[31-33]
	Trabectome	NeoMedix, Tustin, TX, USA	[34-37]
Drainage to Subconjunctival Space	Innfocus MicroShunt	Santen, Japan	[38,39]
	Xen implant	Allergan, Irvine, CA, USA	[40-46]
Laser	Endo-cyclophotocoagulation	Laser unit by Endo Optiks, Little Silver, NJ, USA	[48-56]
	Micropulse Transscleral Cyclophotocoagulation	IRIDEX, Mountain View, CA, USA	[57-64]

Table 1: Summary of all procedures/devices discussed.

iStent Supra®

iStent Supra® (Glaukos Corporation, Laguna Hills, CA, USA) is the third-generation microstent by Glaukos. It is a 4 mm-long heparin coated tube made of polyethersulfone and titanium, designed to reduce IOP by accessing the suprachoroidal space. It is placed under gonioscopic view through a one-millimeter clear cornea incision [10].

The number of studies evaluating iStent Supra is small. Jünemann et al. reported on 42 eyes whose mean baseline IOP was 20.4 mmHg with medication. After the device implantation, all patients were treated daily with travoprost prostaglandin analog medication. At the 12-month follow up, 98% showed greater than 20% reduction from baseline IOP on just travoprost. At twelve months, the mean IOP was 13.2 mmHg. This further decreased to 12.3 mmHg in the 32 eyes that reached 18 months of follow-up. No major adverse events were reported [11]. Meyers and Katz reported similar results when they described iStent Supra implantation in 25 patients, followed by daily topical administration of travoprost [12].

There may be a synergistic effect between iStent Supra and other MIGS devices. Martinez de la Casa described the implantation of the iStent Supra in thirty patients previously treated with two iStents in addition to postoperative travoprost. The IOP decreased from 22 mmHg preoperative to 13.2 mmHg eighteen months after surgery [13]. A prospective study by Saheb et al. analyzed subjects with refractory open angle glaucoma. A total of 80 subjects received 2 trabecular bypass stents as well as an iStent Supra stent. On postoperative day 1, travoprost was prescribed. Preoperative mean IOP was 22.0 ± 3.1 mmHg on 1.2 ± 0.4 medications, and 26.4 ± 2.4 mmHg after washout. At all study time points through 36 months, mean medicated IOP remained at or below 13.7 mmHg, with 4 eyes requiring a second medication. Post-washout IOP remained below 17.1 mmHg at annual medication washouts (Months 13, 25, 37) [14]. In addition to these encouraging results, peer-reviewed long-term clinical trials are warranted to evaluate efficacy and safety of iStent Supra.

Trabecular meshwork

Gonioscopy Assisted Transluminal Trabeculotomy (GATT): GATT is a minimally invasive, ab interno approach for a circumferential 360-degree trabeculotomy to bypass the trabecular meshwork. This procedure and its significant success rate in 85 eyes at 12 months was first described by Grover et al. [15]. Another retrospective study by Rahmatnejad et al. analyzed the outcomes of 67 eyes with primary or secondary open angle glaucoma. Mean IOP was decreased by 26.4% and 36.2% at 3 and 6 months follow up. Failure rate at 6-months was 19% and postoperative IOP spikes above 30 mmHg was significantly correlated with surgery failure. Decrease in IOP was significantly greater in Caucasians than in African Americans. Common complication were transient hyphema, persistent inflammation and hypotony [16].

In a follow-up study in 2017, Grover et al. retrospectively examined the outcomes of GATT in 35 eyes with a history of incisional glaucoma surgery. Both mean IOP and the number of glaucoma medications were significantly reduced at 24 months. The prior-trabeculectomy group and the prior-tube shunt group had an IOP decrease of 32% and 52%, respectively, at 24 months. The cumulative proportion of failure was 0.4 and the cumulative proportion of reoperation was 0.29. The risk of transient hyphema led Grover et al. to propose that this and other angle procedures are counter-indicated by inability to stop anticoagulant use and bleeding diatheses [17]. Given the promising results reported so far, prospective trials that evaluate the long term efficacy and safety of GATT compared to other established MIGS are warranted.

Hydrus microstent

Hydrus Microstent (Ivantis, Inc. Irvine, CA) is currently an investigational device in United States. Made of super-elastic biocompatible alloy, it works as an intracanalicular scaffold once implanted into Schlemm's canal *via* ab interno approach. It reduces IOP by forming a large circumferential space that maintains the trabecular outflow into the Schlemm's canal [18].

The HYDRUS II was a randomized, controlled clinical trial conducted within European Union. It enrolled 100 eyes with both open angle glaucoma (OAG) and cataract. The eyes were randomized at 1:1 ratio to undergo phacoemulsification/Hydrus or phacoemulsification only. The proportion of patients with a 20% reduction in washed-out IOP was significantly higher in the phacoemulsification/Hydrus group at 24 months compared with the phacoemulsification group (80% *vs.* 46%). The proportion of patients using no medication was also significantly higher at 24 months in the phacoemulsification/Hydrus group (73% *vs.* 38%). The only notable device-related adverse event was focal peripheral anterior synechiae (1–2 mm in length) [19].

HYDRUS II was followed by several retrospective studies. Fea et al. reported that Hydrus implant led to significantly more reduction in glaucoma medication and similar reduction in IOP when compared to Selective Laser Trabeculoplasty (SLT) at 12 months [20]. Gandolfi et al. compared the clinical outcomes of canaloplasty to Hydrus microstent. At 2-year follow-up, the efficacy profiles were comparable. The most common complication of Hydrus microstent implantation was transient hyphema lasting 1–2 weeks [21].

Ongoing clinical trials for Hydrus microstent include HORIZON, COMPARE and SUMMIT. HORIZON trial randomized 558 patients to either phacoemulsification/Hydrus or phacoemulsification-only

group. It is slated to become the largest MIGS study up to date. On the other hand, COMPARE and SUMMIT trials are evaluating Hydrus implantation as a standalone procedure. COMPARE is a comparative trial in which the patients with mild-to-moderate POAG will receive either Hydrus or two generation-one iStents. SUMMIT is to evaluate the efficacy of Hydrus in patient with severe, refractory glaucoma [22].

iStent: First and second generations

The iStent (Glaukos, USA) is a heparin-coated implant that is inserted into Schlemm's canal, bypassing the trabecular meshwork resistance [7]. The first generation iStent may offer mild IOP reduction and more than one iStent may be needed to lower the IOP [23,24]. However, iStent offer significant reduction of IOP and glaucoma medications when combined with cataract surgery [24]. In addition, when combined with cataract surgery, it has been shown to decrease the IOP more than cataract surgery alone [25].

The cost-comparison study by Berdahl et al. modeled patients receiving two iStents, SLT, or medications-only at year zero. In this model, patients could remain on initial treatment or move to another treatment option(s), or filtration surgery in year 1–5 according to probabilities determined by a clinician panel. Although the year zero expenditure was the highest in the iStent group, the overall medical cost over 5 years was also the lowest in this group. The cumulative 5-year savings with two iStents over SLT or medications-only was \$309 or \$1,797, respectively [26].

Subsequently, Glaukos modified the size, shape and the outflow system for the second-generation iStent, or iStent inject[®] (Trabecular Micro-Bypass; Glaukos Corporation). Following promising results of iStent inject facilitating outflow in cultured human anterior segments [27], Fea et al. and Voskanyan et al. demonstrated significant reduction of IOP during the 12 months of follow up [28,29]. In addition, a retrospective, intraindividual study by Gonnermann et al. reviewed patients who had phacoemulsification/Trabectome in one eye and two iStent Inject in the contralateral eye. Both groups saw significant, and comparable reduction of mean IOP and number of glaucoma medications at 12-month follow up [30].

The most common complications for the first and second-generation iStent were early postoperative stent occlusion and malposition, which was observed in 2.6%–18.0% of study subjects [23,29].

Kahook Dual Blade (KDB) (New world medical, CA)

KDB is a novel dual-blade device designed to remove a strip of trabecular meshwork. The dual blade device is tapered at the tip to allow for smooth entry into Schlemm's canal. A key feature of this instrument is that the elevation of the trabecular meshwork tissue allows for cleaner removal of the tissue, thus minimizing damage to adjacent structures [31].

The number of clinical studies evaluating KDB is small. Radcliffe et al. conducted a multicenter cohort study with follow up period of 12 months. A total of 122 patients were included. A majority of the surgeries (59.8%) were phacoemulsification/KDB. Other surgery types were combined KDB with endocyclophotocoagulation (15.6%), KDB with both phacoemulsification and endocyclophotocoagulation (13.9%), KDB alone (6.6%) and KDB plus some other procedure (4.1%). In all cases, the mean IOP and number of glaucoma medications were significantly reduced at the 12-month follow-up;

mean IOP was decreased by 30% and 70% of eyes reduced at least one IOP-lowering medication. In the combined phacoemulsification/KDB cases, IOP was reduced by 29%, with 74% of eyes needing fewer medications. No major complications were reported [32].

Adding to the potential of KDB, Khouri et al. reported a single case of KDB application in a pediatric patient who developed glaucoma following cataract extraction. Intraocular pressure reduced from 35 to 17 mmHg in the right eye and from 52 to 18 mmHg in the left eye at 3 months follow up. No complications were noted [33].

Trabectome

The Trabectome (NeoMedix, Tustin, USA) was the first FDA-approved MIGS. It is designed to remove a large section of trabecular meshwork and increase outflow of fluid by exposing Schlemm's canal and the collecting channels. 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.

In a prospective, comparative study by Mizoguchi et al., trabectome was used as a standalone procedure in patients with POAG or exfoliative glaucoma. The mean IOP for all cases was significantly decreased by 23% at 2-year follow up. The success rate at 2 years was 51.2%. No significant complications were reported [34]. Furthermore, a prospective study by Bussel et al. showed that trabectome with or without phacoemulsification can reduce IOP significantly regardless of degree of angle opening [35]. Transient hyphema seems to be the most common risk associated with trabectome.

Roy et al. conducted a retrospective, observational cohort study by reviewing the clinical outcomes of 498 eyes that had phacoemulsification/trabectome after 12-month follow-up. Patients were stratified into four groups according to the Glaucoma Index (GI) that incorporated preoperative IOP, number of medications and visual field status. The relationship between GI group and IOP/medications was analyzed. At one year, the mean IOP of GI groups 1 through 4 was reduced by 2.9 ± 4.4 , 3.6 ± 5.0 , 3.9 ± 5.3 , and 9.2 ± 7.6 mmHg. The success rate was 98%, 93%, 96% and 88% at one year for GI groups 1 to 4 ($P < 0.05$) [36].

The trabectome study group investigated into factors and patient characteristics associated with success in trabectome surgery. They analyzed a total of 658 cases with at least 12 months follow-up after phacoemulsification/trabectome or trabectome alone.

Phacoemulsification/trabectome group and trabectome group had a 94% and 79% survival rate at 12 months, respectively. Phacoemulsification/trabectome cases had 78% lower risk of failure than TA (95% confidence interval [CI]: 54-89). At 12 months, the average IOP and the average number of medications were significantly reduced in both groups. 20% of trabectome cases were required to undergo additional secondary surgery compared to only 3% of phacoemulsification/trabectome cases ($P < 0.01$). Diagnosis of pseudoexfoliation glaucoma had a 54% lower risk of failure than POAG patients (95% CI: 1-78). Furthermore, Hispanics had an estimated hazard ratio that is 60% lower than Caucasians (95% CI: 18-80) [37].

Subconjunctival

Innfocus MicroShunt: Innfocus MicroShunt (Santen, Japan) is a micro-lumen aqueous drainage device made out of biostable

thermoplastic elastomeric material that shunts aqueous drainage from the anterior chamber to the subconjunctival space. It is designed to be implanted with Mitomycin-C (MMC) with or without concurrent cataract surgery.

In a prospective study of 23 eyes in 14 patients with 3 years follow-up, Battie et al. reported a qualified success rate of 95% with a decrease in mean IOP of over 50% (23.8 mmHg to 10.7 mmHg) in addition to significant decrease in mean number of glaucoma medication [38]. The authors concluded that InnFocus MicroShunt is a safe and effective device for achieving IOP control in most subjects at 3 year follow-up.

Palmberg et al. presented at annual American Glaucoma Society meeting in 2017 the outcomes at 1 and 4 years for 79 patients who underwent either phacoemulsification/Innfocus or Innfocus only. All patients were diagnosed with POAG, from mild to severe stage. Average pre-op IOP was 24.8 ± 6.1 mmHg on 2.3 ± 1.2 medications. Mean post-operative IOP at 1 year was 13.4 ± 4.0 with 0.4 ± 0.9 medication. At 4 years, it was 11.7 ± 4.1 mmHg, using 0.9 ± 1.3 medication. At the four-year follow up, 65% of the patients did not require glaucoma medication. The qualified success rate (IOP \leq 18 mmHg with \geq 20% drop in IOP with or without medication, no re-operation) ranged from 96 to 90% from 1-4 years. Short-term adverse events included transient hypotony and transient choroidal detachments; all of which resolved spontaneously within 3 months. There were only three surgical interventions over the 4 years requiring one trabeculectomy and two placements of new devices. There were no sight-threatening long-term adverse events [39].

InnFocus is currently an investigational device in the United States after receiving U.S. Investigational Device Exception by the FDA in May 2013. A multicenter clinical trial is under way comparing the MicroShunt to primary trabeculectomy in patients who are refractory to medication (Trial number NCT01881425).

Xen microstent: Xen implant (Allergan, Irvine, California, USA) is made of soft collagen-derived gelatin. It is inserted through the trabecular angle into the subconjunctival space, creating an external drainage fistula. The Xen microstent implant (Allergan, Irvine, California, USA) was a newly modified version of the Xen implant. Although the concept is similar to trabeculectomy, in which aqueous is directed from the anterior chamber directly to the subconjunctival space, this procedure is technically simpler and can be performed more quickly.

A multicenter, retrospective interventional cohort study by Schlenker et al. analyzed 354 eyes of 293 patients (185 microstent and 169 trabeculectomy) with no prior incisional surgery. Success was defined as IOP between 6 and 17 mmHg with (qualified) or without (complete) medication. Time to 25% failure for microstent and trabeculectomy group was 11.2 months (95% CI, 6.9-16.1 months) and 10.6 months (95% CI, 6.8-16.2 months) for complete success and 30.3 months (95% CI, 19.0- ∞ months) and 33.3 months (95% CI, 25.7-46.2 months) for qualified success. White ethnicity and diabetes were associated with increased risk of failure. There were 22 and 30 distinct complications, although most were transient. Ten percent and 5% underwent reoperation ($P = 0.11$). Authors concluded that there was no detectable difference in risk of failure and safety profiles between standalone ab interno microstent with MMC and trabeculectomy with MMC [40].

Another retrospective study by De Gregorio et al. used the same standard of success, both qualified and complete. Forty-one eyes with open angle glaucoma underwent phacoemulsification/Xen. The mean

preoperative IOP was 22.5 ± 3.7 mmHg on 2.5 ± 0.9 medication classes. After 12 months, the mean postoperative IOP and number of glaucoma medication were both significantly decreased to 13.1 ± 2.4 mmHg (mean IOP reduction of 41.82%) and 0.4 ± 0.8 . Complete success was achieved in 80.4% and qualified success in 97.5%. There were no major or long-term intra- and postoperative complications during the first year of follow-up [41].

The need for frequent post-operative intervention is notable for Xen microstent. Sheybani et al. reported the rate of needling at 47%. A retrospective by Galal et al. reported that this rate decreased to 30% when the patients were given intraoperative 0.01% MMC injection [42].

Laser cyclophotocoagulation

Currently, the diode laser (810 nm wavelength) with either transscleral or an endoscopic approach is the preferred mode for laser cyclophotocoagulation (CPC) [43-45]. Continuous-wave (CW) Transscleral CPC (TSCPC) has been used widely and while this method has proved effective in treating different forms of glaucoma, [46] it has been associated with high prevalence of post-surgical complications such as hypotony, visual deterioration, phthisis bulbi as well as unpredictable outcomes which may require repetition of the surgery. The CW-CPC procedure is now viewed as the last resort option.

On the other hand, the profiles for endocyclophotocoagulation and micropulse transscleral cyclophotocoagulation (MP-TSCPC) are rising. Their efficacy in different demographics and novel methods of application has been active areas of exploration in recent years.

Endoscopic cyclophotocoagulation (ECP)

The laser unit for ECP (Endo Optiks, Little Silver, NJ, USA) incorporates a semiconductor diode laser that emits pulsed energy at 810 nm. ECP reduces the IOP by ablating the ciliary processes *via* an endoscopic probe to decrease aqueous humor production [47].

A trend in recent decades has been to combine ECP with phacoemulsification (Phaco-ECP) to treat glaucoma and cataract at the same time. These age-related eye problems frequently coexist, and the phaco-ECP has shown great promise for treating them together.

Siegel et al. retrospectively analyzed 313 eyes with mild-to-moderate glaucoma, with 261 eyes in the combined procedure group and 52 eyes in the phacoemulsification group. At 36 months, the combined procedure group had significantly higher success rate at 61.4% *vs.* 23.3% and much lower dependence on medication at 0.2 *vs.* 1.2 [48].

Francis et al. were the first to conduct a prospective study comparing phaco-ECP with phacoemulsification alone. The difference in IOP and medication reduction between the 2 groups was statistically significant at all-time points in the 24 months follow up period. Visual acuity outcomes and complication rates were similar [49].

Few recent studies have reported that the refractive outcome of combined phaco-ECP procedure is more myopic and less predictable compared to that of phacoemulsification alone [50,51]. It would be interesting to investigate both the efficacy and refractive outcome of phaco-ECP in different glaucoma subtypes, and whether different formulas for IOL calculations better suit phaco-ECP.

Two novel methods of ECP application were discussed in recent literature. In 2016, Tan et al. described a modified ECP approach

which involved the standard photocoagulation of the ciliary processes as well as the treatment of posterior ciliary processes through pars plana (ECP-plus). This study, which included 53 eyes of 53 subjects, reported a 78% cumulative treatment success after 12 months of follow up, significantly reducing IOP and number of glaucoma medication with an acceptable complication profile [52].

Another approach related to ECP, called endocycloplasty (ECPL), has been used in treatment of angle closure glaucoma. In ECPL, endoscopic diode laser energy is applied to the posterior aspect of the ciliary processes with the goal of shrinkage but not destruction. Ablation pulls the entire ciliary process, including its anterior head, posteriorly to widen the anatomic angle. Podbielski et al. were the first group to describe ECPL with and without phacoemulsification in 2010. The study enrolled 58 patients with plateau iris syndrome (PIS). At three months follow up, the mean IOP decreased from 17.3 to 13.3 mmHg; the average number of glaucoma medications decreased from 1.7 to 0.7; gonioscopy showed significant angle opening [53]. The study by Hollander et al., which examined the effect of combined phacoemulsification and conventional ECP on PIS patients, showed similar results regarding the IOP reduction and number of glaucoma medications [54].

The three most common complications reported after ECP are fibrin in the anterior chamber, hyphema and cystoid macular edema. In addition, regardless of the type of approach that was used in ECP, concerns over complications such as hypotony or choroidal detachment still exist [52,55]. The risk of hypotony may need to be considered with particular care for the ECP-plus method, which represents destruction of much larger segment of the ciliary body and adjacent structures. The hypotony may last much longer, or even be permanent because there is no intervention to shift the balance between aqueous humor production and outflow following ciliary body destruction procedure [56].

Micropulse Transscleral Cyclophotocoagulation (MP-TSCPC)

The micropulse laser is delivered *via* a semiconductor diode probe that emits a string of laser pulses, each separated by a relatively long period of thermal relaxation. The transmitted energy is highly absorbed by pigmentary epithelium in ciliary bodies and trabecular meshwork, but the surrounding tissue can regularly cool off. This is thought to result in minimal collateral damage and prevention of necrosis, which may improve repeatability of the procedure [57,58].

MP-TSCPC has shown promising results in several studies. Tan et al. in 2010 was the first to describe MP-TSCPC in a prospective interventional case series in 40 eyes with refractory glaucoma. The overall success rate was 70% after a mean of 1.3 treatment trials. The mean follow-up period was 16.3 ± 4.5 months [59]. The randomized, prospective study by Aquino et al. compared the efficacy of MP-TSCPC with that of conventional TSCPC in refractory glaucoma. At 18 months, significantly higher proportion of patients who received MP-TSCPC achieved successful outcome when compared to patients who received CW-CPC. There was no significant difference in retreatment rates and the ocular complication rate was significantly higher in eyes treated with CW-TSCPC [60].

At UCSF, we recently examined the effect of MP-TSCPC in pediatric patients given its advantages in treating adult glaucoma patients [61]. Nine eyes out of 9 pediatric patients, as well as 29 eyes of 27 adult patients who received MP-TSCPC were followed for 12 months. At 12

months, nearly all pediatric patients required additional surgical treatment. The success rate in pediatric patients was only 22% compared to 72% in adults ($P=0.02$). There was no significant change in IOP or in number of medication at 12 month from the baseline for pediatric patients. There were no significant vision threatening complications observed in either group, and thus MP-TSCPC appears to be a safe procedure for treating pediatric glaucoma but with limited effect.

Similar to conventional TSCPC, the mechanism behind the effect of MP-TSCPC is under debate; the IOP reduction may not be explained alone by decreasing aqueous production through destruction of the ciliary bodies. Johnstone et al. postulated that MP-TSCPC leads to reorganization of outflow pathway. In primate eyes, the MP-TSCPC with even subclinical energy input resulted in contraction of the ciliary muscle and posterior shift of the scleral spur and trabecular meshwork. At the clinical energy input, this structural reorganization appeared to be permanent, and may suggest that MP-TSCPC also reduces IOP by deepening the angle of anterior chamber [62].

One limitation noted for MP-TSCPC is that efficacy and safety studies have not yet assessed the optimal laser parameters. Another limitation is lack of stratifications for different types and severity of glaucoma. Previous studies on conventional CW-TSCPC have shown that higher energy leads to higher complication rates and that the risk of complications is significantly affected by the glaucoma subtypes [63,64]. These factors would be worth exploring in MP-TSCPC.

Future Direction

The last decade brought 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. Some have demonstrated efficacy similar to filtering surgery at intermediate follow up. 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 the gold standard of conventional filtering surgeries.

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