Review Article

Minimally Invasive Glaucoma Surgery (MIGS)

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Abstract
Glaucoma, a chronic progressive optic neuropathy, is the second leading cause of irreversible blindness world-wide. The only treatable risk factor till date is lowering of intra-ocular pressure (IOP), thus, being the mainstay of treatment. Constant search for alternative surgical means for effective, sustainable reduction of IOP with higher safety profile, an ab- interno approach causing minimal trauma to ocular tissues, faster recovery with minimum impact on quality of life has led to a new class of procedures named Minimally Invasive/ Micro-invasive Glaucoma Surgery (MIGS). MIGS can act by bypassing any obstruction at the trabecular meshwork (iStent, Hydrus micro-stent, Trabectome, Kahook dual blade goniotomy), by enhancing aqueous outflow through Schlemm's canal (Ab interno Canaloplasty) or through the supra-choroidal space (iStent supra). They can also act through shunting aqueous outflow into the sub-conjunctival space (XEN gel implant) or by reducing aqueous production by ciliary body ablation (endo-cyclo-photocoagulation). The revolutionary MIGS comprising several different procedures and devices can be staggering for the glaucoma specialists. The aim of the present review is to provide an understanding of the currently available classes of MIGS encompassing the design, safety and efficacy profile to help the ophthalmologists to tailor the surgical approaches for greater individual care.

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***Keywords:** MIGS, Intra-Ocular Pressure, Trabecular Meshwork Bypass, Supra-Choroidal Stent, Sub- Conjunctival Implant*

Introduction

Glaucoma, a multifactorial disease, is one of the leading causes of irreversible but preventable blindness worldwide.[1] Thus, early diagnosis and prompt treatment is of prime importance. It is a chronic optic neuropathy with characteristic structural damage to the optic nerve and associated visual field loss. The number of people with glaucoma worldwide is expected to rise from 64 million to 76 million in 2020 and 111 million in 2040, with Africa and Asia being affected more heavily than the rest of the world.[2,3] At present, the only alterable risk factor for glaucoma is the intra-ocular pressure (IOP).[4] Hence, lowering IOP forms the mainstay of treatment to date.

Topical medications have proven record of efficacy as the primary means to lower pressure but on long term application have compliance and cost issues along with side effect profile.[5] Laser treatment has also shown promising results but are marred with response rate and attrition.[6] The surgical treatment including trabeculectomy (gold standard) and glaucoma drainage devices are quite efficacious but associated with high rate of complications and usually reserved for advanced cases.[7] There is ceaseless search for a safer and more effective alternatives. The term MIGS, for minimally invasive / microinvasive glaucoma surgery, coined by Dr. Iqbal Ike Ahmed in the year 2009[8] promises to fill in the gap between this therapeutic regime.

MIGS definition

Currently, there is no universal or widely acknowledged definition of MIGS. According to the workshop of the American Glaucoma Society and US Food and Drug Administration (FDA) held in February 2014, MIGS was characterized by the "implantation of a surgical device intended to lower IOP via an outflow mechanism with either an ab interno or ab externo approach, associated with very little or no scleral dissection".[9] According to Saheb and Ahmed[10], the term MIGS refers to a group of surgical procedures which share five preferable qualities namely-

1. An ab interno approach through a clear corneal incision which spares the conjunctiva of incision.
2. Minimal disruption of normal anatomy.
3. An IOP lowering efficacy that justifies the approach.
4. High safety profile avoiding serious complications compared to other glaucoma surgeries.
5. Rapid recovery with minimal impact on the patient's quality of life.

Classification of MIGS

The four main approaches of reducing IOP by MIGS include-

1. Increasing outflow across the trabecular meshwork (TM) and through Schlemm's canal (SC).
2. Enhancing uveo-scleral outflow through supra-choroidal space.
3. Shunting aqueous into the sub-conjunctival space.
4. Decreasing aqueous production by ablation of the ciliary processes.

A). Trabecular meshwork bypass

Mechanism of action : Juxta-canalicular Trabecular Meshwork has been traditionally identified as the site of greatest resistance to aqueous outflow.[11] This class of MIGS aims to remove (by ablation and excision) or bypass (through stents) the afore-mentioned tissue, allowing more direct access to aqueous humor from anterior chamber into Schlemm's canal.

Indications :

Mild to moderate primary open-angle glaucoma, pigmentary glaucoma, pseudo-exfoliation glaucoma, ocular hypertension with modest IOP target of 15-16 mm Hg

Contra-indications :

1. Eyes with primary or secondary angle closure glaucoma.
2. Eyes with active neo-vascularization.
3. Eyes with hazy cornea and angle dysgenesis
4. Patients with elevated episcleral venous syndrome such as retrobulbar tumor, thyroid eye disease, Sturge-Weber syndrome.

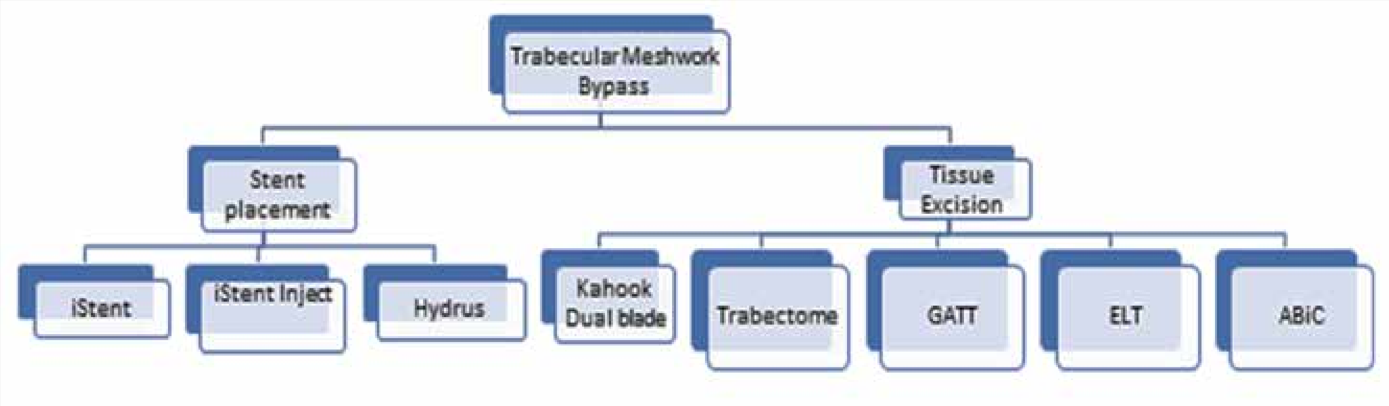

***Chart 1 :** Trabecular meshwork bypass*

Adverse effects :
Clinical trials and case series have consistently reported minimal adverse effects post implantation, that resolved spontaneously most of the times. The most common complications included hyphema (due to blood reflux from Schlemm's canal), stent malposition or temporary obstruction, focal peripheral synechiae, transient increase in IOP.[12,13,14,15,16,17]

This group is sub-divided into-
a). Trabecular meshwork bypass by stent placement-
1. iStent (Glaukos, Laguna Hills, CA) : First and the tiniest

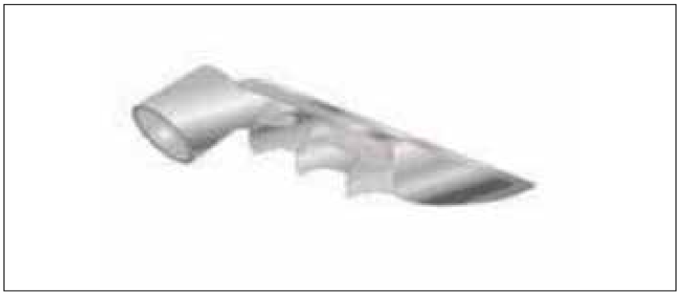

***Figure 1 :** istent micro- stent*

MIGS to receive FDA approval in 2012.
Design: The device is heparin -coated, non-ferromagnetic titanium stent with a ridged snorkel design. It measures 1 mm x 0.3 mm while the snorkel is 0.25mm in height with a central lumen of 120 microns which projects into the anterior chamber. The body of the device contains three retention arches to ensure its proper positioning into Schlemm's canal in the nasal angle.[18] It is implanted with the use of a disposable pre-loaded inserter by an ab interno, clear corneal approach under gonioscopic visualization.

Efficacy : Innumerable studies have been done since 2008 comparing effectiveness of phacoemulsification alone to phacoemulsification with iStent placement. iStent implantation resulted in an IOP reduction of more than 20% (around 25%) in 70% of the patients in most of the studies with significant decrease in the number of medications used at 1 year.[19,20] The iStent study Group showed that the iStent's efficacy was modest but allowed a prolonged reduction in IOP and medication burden.Studies with iStent stand-alone procedure have shown 23-27% [21,22] decrease whereas multiple iStent placement showed 40-44% decrease in IOP with 59% patients were off all medications at 1 year.[23,24]

2.iStent inject (Glaukos, Laguna Hills, CA) : This is the second-generation TM bypass stent which received FDA approval in 2018.

***Figure 2 :** istent inject micro- stent*

Design : It is the smallest medical implant approved for use in the human body during surgical procedures. It is a heparin-coated, non-ferromagnetic titanium stent, 360 microns in height by 230 microns in diameter with a central lumen of 80 microns. Each stent consists of a tapered head that resides in Schlemm's canal, thorax that straddles the TM and a flange that inhabits the anterior chamber (AC). iStent inject stents are delivered via ab interno approach under gonioscopic visualization. The single use injector (G2-M-IS injector system) comes pre-loaded with two stents, which are to be placed nasally into the TM and Schlemm' s canal with 30-60 degrees apart.

Efficacy : Various prospective studies such as the ones done by Arriola-Villalobos, Voksanyan, and Fea et al have shown IOP reduction of 35-39% with improved medication burden following iStent inject, where 65-75% subjects were completely off medication at 1 year.[25,26,27] Another study showed that implantation of 2 iStent injects is comparable to treatment with two agents (latanoprost and timolol) in reducing IOP at 1 year.

Figure 3 : *Hydrus micro- stent*

3. Hydrus (Ivantis Inc, Irvine, CA, USA) : It received FDA approval in August 2018.

Design : The crescent shaped micro-stent is 8 mm in length and 290 microns in diameter, with three windows and an inlet that resides in the anterior chamber. It is made up of nitinol (biocompatible titanium and nickel alloy) that is super-flexible with a shape memory. It is implanted in the nasal or the inferior temporal quadrant with a pre-loaded injector via clear corneal approach. The micro-stent has intracanalicular scaffold that occupies 3 clock hours of Schlemm's canal but does not block collector channel ostia in the posterior portion of the canal.

Hydrus works on the trimodal mechanism – allowing aqueous humor to bypass the trabecular meshwork

dilating Schlemm's canal 4-5 times the natural width countering the collapse of the canal induced by increased IOP.[28]

Enabling outflow through more collector channels.

Efficacy : Umpteen studies have evaluated the efficacy and safety of Hydrus with concurrent cataract extraction and phaco-emulsification alone. The Hydrus I and II study (more than 20% reduction in IOP seen in 80% of patients with 73% being medication free at 24 months),[29] HORIZON study (at 24 months post -surgery 77.3% of eyes experienced at least 20% reduction in IOP with significantly greater reduction in hypotensive eye drops)[30] to name few. The COMPARE study, comparing Hydrus with iStent showed better efficacy of Hydrus (at 12 months, 39.7% eyes showed more than 20% decrease in IOP from washed out baseline versus 13.3% in iStent group, 46.6% patients were medication free vs 24.0% in iStent group).[31]

b). Trabecular meshwork bypass by tissue excision (trabeculotomy):

1. Kahook Dual Blade Goniotomy (New World Medical, Rancho Cucamonga, CA) : Introduced in US in 2015.

Design : Stainless steel disposable, dual blade with a sharp tip designed with taper for smooth entry through trabecular meshwork. The heel fits easily within Schlemm's canal for

Figure 4 : *Kahook Dual Blade*

smooth advancement, ramp of the blade generates gentle stretch whereas the dual blade creates parallel incisions of trabecular meshwork. This causes near complete removal of trabecular meshwork with negligible surrounding tissue damage and less fibrosis over time enhancing long term outcome.[32] It is done via ab interno approach under gonioscope visualization.

Efficacy : Several studies have reported that 58- 70% of eyes achieved IOP reduction of more than 20% and reduction in at least 1 medication with KDB at 1 year follow-up.[33,34,35,36] KDB has also shown better results compared with Trabectome and iStent.[37,38] Particular success has been seen in patients with secondary open angle glaucoma such as pseudo-exfoliation glaucoma and pigmentary glaucoma owing to the removal of extracellular and pigments along with TM.[39] In recent studies, KDB has also been used in congenital glaucoma[40] as well as advanced and refractory glaucoma showing more than 20% decrease in IOP in 57.7% of cases.[41]

2.Trabectome (NeoMedix Corporation, Tustin, CA): It was invented by George Baerveldt, Irvine and Roy S Chuck [42]and received FDA approval in April 2004 for microsurgical management of adult and pediatric glaucoma.

Figure 5 : *Trabectome*

Design : The system consists of a disposable 19.5 gauze handpiece, console with automated irrigation and aspiration and an electrocautery generator with foot pedal to control progressive steps of irrigation, aspiration and ablation. The handpiece has a ramping foot plate to slightly lift and stretch TM and protects adjacent tissue from thermal damage. Tip of the handpiece has a bipolar 550 KHz electrode which generates plasma that ionizes and ablates TM to create an opening from AC into Schlemm's canal and collector channels. Constant infusion maintains AC whereas tissue debris is removed by aspiration.[43]

Efficacy : An average IOP decrease by 18-40% has been documented with up to 40% fewer medications at 2 years.[44,45] Trabectome is also effective in narrow angle glaucoma.[46] failed trabeculectomy[47] tube shunts[48] and refractory glaucoma[49] though with comparatively lesser success rate.

3.Eximer Laser Trabeculostomy (ELT) : Conceived by Dr Berlin in 1987,[50] ELT was first used clinically by Dr Vogel and Lauritzen in 1997[51] and obtained European CE approval in 2014.

Design : It is performed with a short pulsed (80 ns) 308 nm Xenon-Chloride excimer laser applied directly to the TM by means of a fiber-optic delivery system. The pulse energy available is 1.2 mJ at the fiber tip, the laser pulse duration is between 10 to 60 ns and the repetition rate is 20 Hz.[52] The photo-ablative energy precisely removes the tissue which obstructs the aqueous outflow with minimal thermal damage to adjacent tissues. Usually, 10 microchannels are created over 90 degrees, 500 microns apart. It enables 'pneumatic canaloplasty' that dilate Schlemm's canal and collector channels.[53] ELT is an ab interno procedure performed under direct visualization of gonioscope or endoscope.

Efficacy : The studies done have shown moderate IOP lowering, between 20 and 40% reduction from baseline with mostly decrease in 1 glaucoma medication having minimal complications.[54,55] ELT fared better than SLT.[56]

4.Gonioscopy Assisted Transluminal Trabeculotomy (GATT) : First described by Grover et al in 2014.[57]

Design : The system consists of microsurgical forceps and iTrack microcatheter with a 200-micron diameter shaft with a lubricating coating and an illuminated distal tip, which can be constantly or intermittently illuminated to monitor catheter location. An ab interno procedure under gonioscopic visualization, the microcatheter or suture (typically 5-0 or 6-0 nylon or prolene) is passed through a 1-2 clock hour goniotomy in the nasal quadrant into the Schlemm's canal then advanced for 360 degrees with the help of micro-forceps.[58] It is then pulled centrally, applying traction to lyse through the TM thus creating a 360-degree trabeculotomy.

Efficacy : GATT surgeries have shown to be similar in effectiveness as ab externo trabeculotomies with overall success in 68-90% of patients.[59] The average IOP decrease is 30-40% with decrease in medication used. Grover et al reported preliminary results of GATT for treating primary congenital glaucoma and juvenile OAG.[60] There are studies showing GATT to be a viable treatment option for the treatment of refractory glaucoma[61] and in post trabeculectomy.[62] Due to the nature of the procedure, it is contra- indicated in people who require anticoagulation, or have bleeding diatheses.

5.Ab Intero Canaloplasty (AbiC) : This MIGS procedure is done using the iTrack microcatheter system (Ellex iScience, Fermont, CA) which has 250 microns microcatheter with

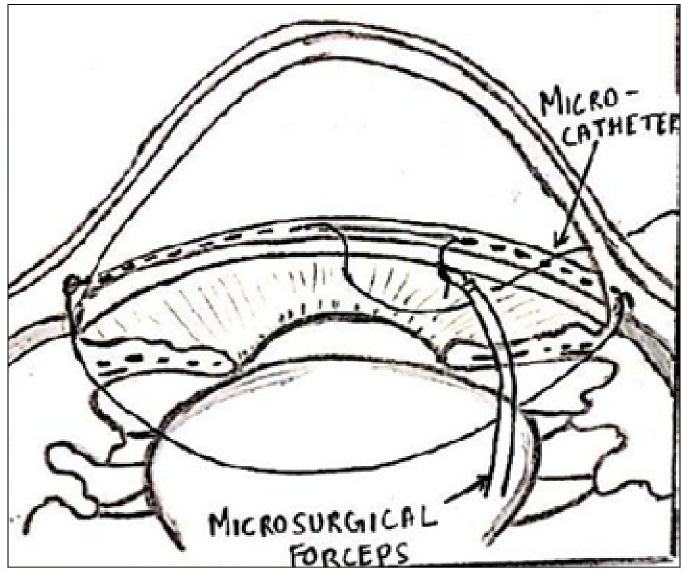

Figure 6 : *Gonioscopy Assisted Transluminal Trabeculotomy (GATT)*

atraumatic bulbous tip and a greasy coating for easier passage, fiber optic that enables illumination of the tip to monitor and a visco-injector. The aqueous outflow is enhanced through cannulation of Schlemm's canal with the microcatheter, which is then withdrawn as an ophthalmic visco-surgical device is injected to visco-dilate all potential sites of outflow resistance such as Schlemm's canal and the proximal collector channels. It has been postulated that visco-dilation may also create micro-perforations within the TM to help in aqueous outflow.

Efficacy : According to the myriad of studies, the average IOP decrease reported is 30-40% at 12 months with at least 2 fewer glaucoma medications.[63,64,65]

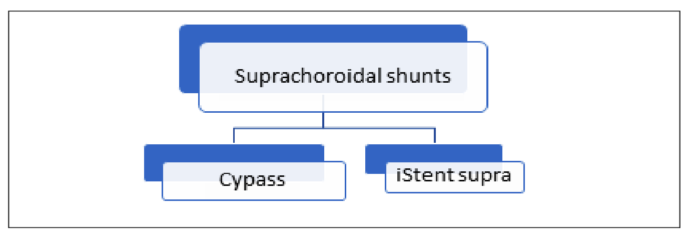

Chart 2: *Suprachoroidal shunts*

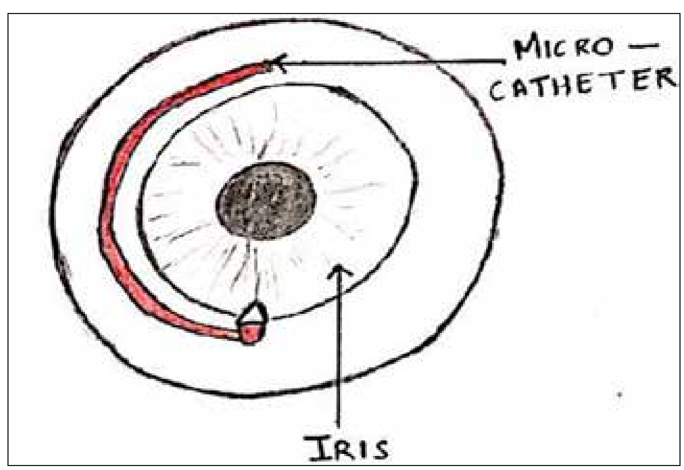

Figure 7: *Ab Intero Canaloplasty (AbiC)*

***Figure 8 :** iStent Supra*

B). Suprachoroidal shunts :

Mechanism Of Action : supraciliary shunts direct aqueous outflow in a controlled fashion to suprachoroidal space essentially increasing physiological uveoscleral pathway. It creates a permanent conduit between anterior chamber and supraciliary space.

Adverse Effects : Transient increase in IOP/ post-operative inflammation/ early hypotony, hyphema, peripheral anterior synechiae and partial obstruction of the stent were the few complications reported.[66,67]

1.Cypass- Received FDA : approved in 2016.

Design : It is a flexible, fenestrated micro-stent sized 6.35 mm x 510 microns with a 300 microns lumen and composed of biocompatible, polyimide material. It comes preloaded on a retractable guide- wire conformed to the shape of the sclera to facilitate dissection and insertion between the anterior chamber/sclera and suprachoroidal space.

Efficacy : It was voluntarily withdrawn from the global market by Alcon on August 28, 2018 owing to the COMPASS-XT study, evaluating the long-term safety of the CyPass Micro-stent, that showed a statistically significant increase in endothelial cell loss in the CyPass group after 5 years of follow up.68

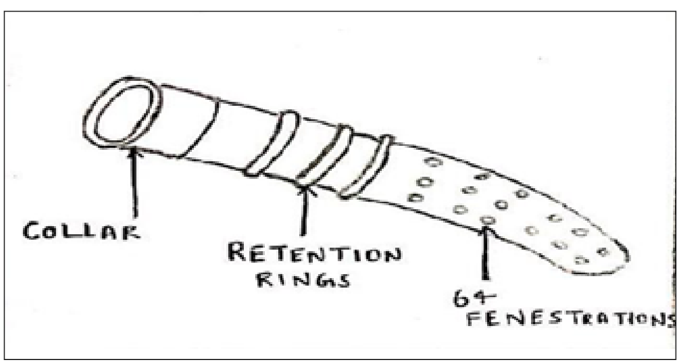

***Figure 9 :** Cypass- Micro Stent*

2. iStent Supra (Glaukos Corporation) : This third generation of iStent, received European CE mark in 2010.

Design : The device is a heparin-coated, 4 mm curved tube with a 0.16 - 0.17 mm lumen, made of biocompatible poly-ethersulfone (PES) with a titanium sleeve and retention ridges to hold it in place. The iStent Supra is guide mounted, which is used to direct the device between the anterior chamber/sclera and suprachoroidal space via an ab interno approach under gonioscopic guidance.

Efficacy : In different studies, iStent supra was effective along with Travoprost eye-drops in reducing more that 20% IOP with reduction in 1 medication in advanced glaucoma.[69,70] To gain FDA approval, Glaukos has completed enrollment (February 2017) for a prospective RCT including 505 subjects with moderate to mild primary OAG and cataract.

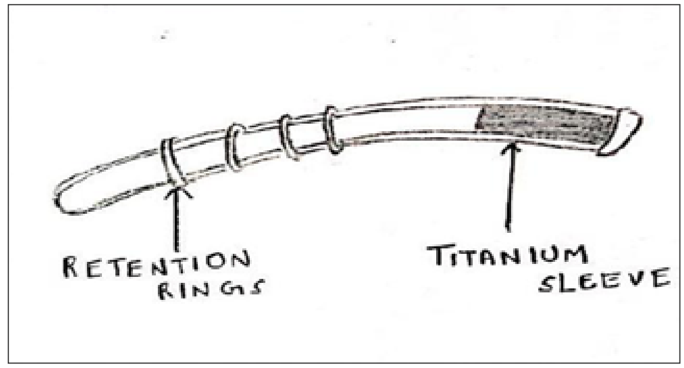

***Figure 10** : iSent Supra Micro By pass*

C). Subconjunctival filtration : This category includes XEN gel stent.

Mechanism of action : Subconjunctival MIGS procedure bypass internal drainage systems and allow aqueous to drain into the sub- conjunctival space. They are bleb forming procedure, like trabeculectomy, the archetype surgery.

Indications- They are approved for use in the treatment of moderate- advance primary and secondary open angle glaucoma

Refractory glaucoma in whom maximal medical therapy is not sufficient or are post failed glaucoma surgery.

It can be performed in phakic or pseudophakic patients.

Contra-indications : Angle closure glaucoma

Patients with conjunctival scarring, active inflammation

Active neovascularization, silicon oil or vitreous in AC.

1.Xen gel stent (Allergan, Dublin, Ireland) : Received FDA approval in 2016.

Design : Hydrophilic tube, composed of porcein derived gelatin cross- linked with glutaraldehyde. It is relatively straight and rigid when dry, flexible, and soft when hydrated. It is 6mm in length and is of three types XEN 140, XEN 63, XEN 45 based on the varying lumen size. The XEN 45 currently approved by FDA has inner lumen of

***Figure 11 :** Xen gel*

45 and outer diameter of 150 microns. The design of XEN with a very small lumen versus its length leads to outflow resistance according to Hagen- Poiseuille equation of fluid dynamics, also eliminating risk of hypotony.[71]

It is pre-loaded on a disposable 27 gauze injector system, inserted into anterior chamber via an ab interno approach, usually in the supero-nasal / superior quadrant and tunneled through sclera to deploy the device into the sub- conjunctival space. After implantation, the stent creates a filtering bleb. It can be augmented with Mitomycin -C to reduce bleb fibrosis.

Adverse effects include- exposure of the stent through a gape in conjunctiva, stent migration into anterior- chamber, or fragmentation of stent.

There may also be obstruction of the stent with blood, lens fragments or visco-elastics that may require bleb needling.
Transient hyphema and hypotony have also been reported that usually did not require any intervention.

Efficacy : Based on the studies done, XEN showed promising results with 29-41 % decrease in average IOP[72,73] with almost 45% patients being medication free. Post- operatively, bleb -needling was required in 30-40% of patients.[74]

D). Decreasing aqueous production by ciliary body ablation: This approach is employed in endo-cytophotocoagulation (ECP).

Mechanism of action : lowers the production of aqueous humor by ablating the ciliary processes (site of aqueous humor production) thereby reducing IOP. It causes localized shrinkage of ciliary processes with temporary occlusive vasculopathy.[75] Direct visualization of the ciliary processes permits a more targeted approach with nominal collateral damage.

Indications :
Unlike cyclophotocoagulation, ECP is no longer reserved for end stage cases.[76]

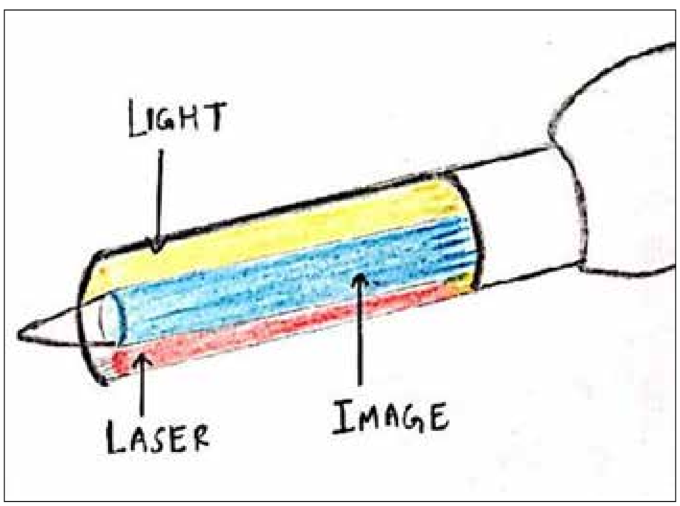

Figure 12: *Endo-Cytophotocoagulation (ECP).*

Performed for mild- moderate-severe glaucoma in conjunction with cataract extraction with the advantage of being conjunctival sparing.
Refractory open angle, angle closure glaucoma or especially in plateau iris

Paediatric glaucoma
Neovascular glaucoma
Contraindications
Active inflammation

Caution should be taken in phakic cases as ECP can lead to zonular damage or cataract progression.

ECP : It was developed by Martin Uram in 1992.[77]
Device : It is implemented using a probe attached to a laser unit (Endo Optiks, Little silver, NJ) which integrates a Diode laser. Pulsed continuous wave energy is emitted at 810 nm, using 175 W variable xenon light source, a helium-neon laser aiming beam and video camera imaging. The fiber-optics within the probe transmits all the elements. The probes are available in 19,20 or 23 gauze sizes with a field of view ranging from 70- 140 degrees. The probe tips are either straight or curved and inserted via clear corneal approach. The connected video monitor provides for endoscopic viewing and a foot pedal allows for surgeon control of the laser. Laser setting start at 0.2-0.25 Watts, continuous cycle and power is titrated to achieve blanching and contraction of ciliary processes. Typically, treatment consists of 200-300 degree of the angle.

For most refractory cases, ECP Plus can be performed. It is doing ECP but extending the treatment 1-2 mm onto pars-plana for more aggressive IOP lowering effect. This requires pars plana approach and is preceded by pars plana vitrectomy.

Adverse effects: IOP spikes, hyphema, increased postoperative inflammation, intra-ocular lens dislocation, cystoid macular edema, posterior and anterior synechiae, posterior capsular opacification, ciliary block glaucoma, choroidal detachment/ hemorrhage, retinal detachment were the complications reported by ECP Collaborative Study group.[78] Severe complications mostly occurred in eyes with neovascular glaucoma.

Efficacy: ECP has shown favorable results in the various studies conducted so far. ECP alone reduced average IOP to 34% with reduction in 1 medication.[79] When used after tube shunt surgery, ECP has been shown to be safe and effective.[80] ECP combined with phacoemulsification showed success (IOP reduction of more than 20%) in 56% of patients.[81] Success rate of 43% was noted in pediatric patients.[82]

To conclude
MIGS: is a relatively new category of procedures showing by and large acceptable safety profiles and humble efficacy. While MIGS surgeries currently appear unlikely to replace traditional incisional glaucoma surgeries, they do fill an

important void between the medical therapy and surgery for mild to moderate glaucoma and can often lower medication burden. As the horizon of MIGS is expanding, more studies with larger study group and extended follow-up is required to increase our understanding.

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