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Microinvasive glaucoma surgery (MIGS) devices have transitioned into mainstream use in recent years. Several devices, including the iStent trabecular microbypass stent, the Cypass microstent and the XEN-45 implant, have obtained the United States Food and Drug Administration (US-FDA) approval in addition to the Conformité Européene Mark.

The high safety profile of MIGS allows it to be used earlier than conventional glaucoma surgeries within the glaucoma treatment algorithm, and it is typically combined with cataract surgery in patients with mild-to-moderate primary open-angle glaucoma (POAG).

Long-term data on the efficacy and safety of MIGS devices are limited. In this special issue, P. Arriola-Villalobos reported the first study on the iStent Inject with more than 12 months follow-up. Similar to previous studies on the iStent trabecular microbypass stent, the efficacy of the iStent Inject is modest, with only 28% of patients achieving IOP $\leq 18$ mmHg without postoperative medications at 5 years. Though there are two stents in each injector, postoperative gonioscopy revealed only one functional stent in 35% of the patients. This is because the iStent Inject can be “over-implanted” and completely embedded within trabecular tissue, with no contact with aqueous in the anterior chamber. Even if the proximal end of the device is visible in the angle, “under-implantation” is still possible as the distal end may not extend to the Schlemm’s canal. Incorrect placement of trabecular bypass devices might be more prevalent than anticipated and may partially explain why they have been termed “minimally effective glaucoma surgery.” Hopefully, newer versions of these devices would allow consistent access to the Schlemm’s canal.

This special issue on MIGS has highlighted that these devices are slowly making inroads into Asian countries, pioneered again by the iStent trabecular microbypass stent. The US-FDA has approved the iStent trabecular microbypass stent for use only in conjunction with cataract surgery, and the foray of this device outside USA has allowed it to be “phaco-minus.” D. Shiba et al. reported the first results of two iStent trabecular microbypass stents as a solo procedure in Japanese patients with medically uncontrolled POAG. The 6-month results are similarly modest, possibly attributable to reasons mentioned above, with a 23.2% reduction in IOP on the same number of glaucoma medications. With the globalization of MIGS, the use of these devices is likely to extend into other subtypes of glaucoma, including angle closure glaucoma [1] and uveitic glaucoma [2].

Microinvasive glaucoma surgery has largely been confined to eyes with mild to moderate glaucoma and moderately elevated IOP. However, in experienced hands, it can potentially achieve more remarkable efficacy in eyes with markedly raised IOP. In this special issue, H. Akil et al. reported impressive results with the Trabectome in patients with preoperative...
IOP of 30 mmHg or higher. The IOP was reduced from 35.6 ± 6.3 mmHg at baseline to 16.8 ± 3.8 mmHg at 12 months, with a reduction in medications from 3.1 ± 1.3 to 1.8 ± 1.4. It is likely that the Schlemm’s canal is more consistently assessed when trabeculectomy bypass procedures are performed by experienced surgeons. Hopefully, advancements in ocular imaging would allow us to detect these changes in aqueous venous flow in successful surgeries [3].

Data on subconjunctival and suprachoroidal MIGS devices are currently inadequate. In this special issue, A. Galal et al. reported one of the first results on the clinical efficacy of the XEN-45 implant. Subconjunctival drainage associated with the implant was able to achieve IOP in the low teens, though only 42% of the eyes achieved ≥20% decrease in IOP without medications at 12 months. New modalities of cycloablation, such as ultrasonic circular cyclocoagulation by high-intensity focused ultrasound (HIFU), in their attempt to “re-brand” as MIGS procedures, claim good safety records and no reports of serious complications such as persistent hypotony or phthisis. Hence, HIFU has been performed on patients with early glaucoma naïve to filtration surgery, though detractors may argue that the resultant scleral architecture remodelling is a concern if subsequent filtration surgery is required.

The studies in this special issue highlight that more MIGS surgeons are venturing beyond the context of mild to moderate POAG. With increased access to these devices globally, the glaucoma surgeon is spoilt for choice and is faced with the exciting prospect of tailoring glaucoma surgery to the needs of each patient. Comparative studies are required to evaluate the relative efficacy of different MIGS devices and to ascertain their cost-effectiveness.

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Review Article

High-Intensity Focused Ultrasound Circular Cyclocoagulation in Glaucoma: A Step Forward for Cyclodestruction?

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The ciliary body ablation is still considered as a last resort treatment to reduce the intraocular pressure (IOP) in uncontrolled glaucoma. Several ablation techniques have been proposed over the years, all presenting a high rate of complications, nonselectivity for the target organ, and unpredictable dose-effect relationship. These drawbacks limited the application of cyclodestructive procedures almost exclusively to refractory glaucoma. High-intensity focused ultrasound (HIFU), proposed in the early 1980s and later abandoned because of the complexity and side effects of the procedure, was recently reconsidered in a new approach to destroy the ciliary body. Ultrasound circular cyclocoagulation (UC³), by using miniaturized transducers embedded in a dedicated circular-shaped device, permits to selectively treat the ciliary body in a one-step, computer-assisted, and non-operator-dependent procedure. UC³ shows a high level of safety along with a predictable and sustained IOP reduction in patients with refractory glaucoma. Because of this, the indication of UC³ was recently extended also to naïve-to-surgery patients, thus reconsidering the role and timing of ciliary body ablation in the surgical management of glaucoma. This article provides a review of the most used cycloablative techniques with particular attention to UC³, summarizing the current knowledge about this procedure and future possible developments.

1. Introduction

Lowering intraocular pressure (IOP) is the only proven approach to reduce the rate of retinal ganglion cell loss and the rate of progression in patients with glaucoma [1]. Nevertheless, in many cases, medical and surgical approaches do not reach the required target IOP [2].

Refractory glaucoma comprises all forms of glaucoma in which the IOP remained uncontrolled despite maximum-tolerated medical therapy and previous laser or surgical procedures. In this case, the IOP remains uncontrolled also after repeated standard filtration surgeries. Surgical approaches for refractory glaucoma include techniques increasing the aqueous humor (AH) outflow (filtrating procedures, drainage devices) and techniques reducing the AH inflow, by destroying portions of the ciliary body [3].

Several cycloablative methods have been proposed over the years, such as cryotherapy, microwave heating, endoscopic laser coagulation, and transscleral diode laser photocoagulation, which remain the most used ablative procedure [4–7]. Given the occurrence of potential vision-threatening complications, unpredictable dose-effect relationship, significant variability in the final IOP lowering, and poor reproducibility, the ciliary body ablation is still considered as a last resort treatment, recommended only in patients with refractory glaucoma [8].

The high-intensity focused ultrasound (HIFU) technology was proposed as a safer alternative of ciliary body destruction in the 1980s and 1990s (Therapeutic Ultrasound System; Sonocare Inc., Ridgewood, NJ) [9–15]. This technique permits a selective thermic effect on the target organ, limits damage to neighbouring tissues, and allows treating nonoptically...
transparent structures [9]. Nevertheless, because of the excessive complexity and duration of the treatment, the technique was progressively abandoned despite evidence of good efficacy and safety [14, 15]. In the last years, HIFU has been reconsidered after critical technical modifications and significant improvements in all steps of the procedure.

The ultrasonic circular cyclocoagulation (UC3) is an automated, computer-assisted, non-operator-dependent cycloablative procedure that utilizes a circular-shaped probe matching the three-dimensional anatomy of the ciliary body. The particular geometry of the probe permits correctly focusing the target organ. Recent studies in patients with refractory glaucoma report encouraging results after UC3 in terms of both IOP reduction and safety of the procedure [16–21].

This article provides a review of all cycloablative techniques proposed over the years, giving particular attention to mechanisms of action, efficacy, safety, and possible future developments of UC3.

2. Methods

PubMed searches were performed on June 20, 2016, using the following phrases: cyclo-ablation and refractory glaucoma or open angle glaucoma; cyclo-destruction and refractory glaucoma or open angle glaucoma; high-intensity focused ultrasound cyclo-ablation and refractory glaucoma or open angle glaucoma; ultrasonic circular cyclo-coagulation and refractory glaucoma or open angle glaucoma. The searches identified 86 unique publications in English, which were considered for the present review. Publications that were not in English were included only if they provided enough information in the English abstract. All studies considered in the present review met the following inclusion criteria: patients get and signed an informed consent after explanation of the nature and possible consequences of the study and were approved by an Ethics Committee and/or Institutional Review Board.

3. Cyclodestructive Techniques

Several cyclodestructive procedures have been proposed during the past 70 years.

The first report was the surgical excision of the ciliary body, named as cyclectomy, which required a full thickness scleral flap to expose the ciliary body, with a following up to one-quarter removal of the organ [22]. Despite a substantial good efficacy, the procedure was rapidly abandoned because of serious complications such as phthisis bulbi and vitreous and expulsive hemorrhages [23].

The following procedures proposed to ablate the ciliary body avoided the excision and aimed at ablating-selected portions of the ciliary processes, by using different physical approaches. Generally, the epithelial cell destruction is considered as the major mechanism for the reduction of the AH secretion and, thus, the IOP.

In cyclodiathermy, heat was transsclerally delivered by using a round-tipped probe attached to a cautery unit in order to destroy selective portions of the ciliary body epithelium [24]. Vogt subsequently modified the technique proposing the penetrating cyclodiathermy; in this procedure, the probe penetrates the sclera and directly treats the ciliary body [25]. Initial reports were encouraging, but studies with longer follow-up produced very poor results since only the 5% of the treated eyes presented a well-controlled IOP [26]. Moreover, serious postoperative complications similar to those described in cyclectomy were frequently described [27]. Therefore, with the diffusion of newer and safer cryodestructive techniques, the use of cyclodiathermy was progressively abandoned.

Cyclocryotherapy allowed treating the ciliary body in a less destructive and more predictable way than cyclodiathermy, exploiting the effects of freezing. This approach was found to reduce the mean IOP from 7.9 to 24.3 mmHg in refractory open- or closed-angle glaucoma [28]. The IOP was better controlled in angle closure or primary open-angle glaucoma (POAG) (66.7% of cases) compared to that in secondary open-angle glaucoma (0%), with the success rate ranging from 57% to 76% [4, 29].

Despite good efficacy, cyclocryotherapy presents several postoperative complications, both mild (pain, anterior chamber inflammation, or a transient hyphema in neovascular glaucoma) and severe or vision threatening (persistent hypotony, choroidal detachment, visual acuity loss, and phthisis bulbi) (Table 1). The significant risk for vision-threatening adverse events limits the spectrum of application of this procedure, except for neovascular glaucoma where it is still considered as a valid therapeutic option [3, 28, 30–42].

In other cases, the use of cyclocryotherapy is indicated in end-stage glaucoma and in patients with a poor visual acuity, because of the high risk of visual loss [29].

To date, cyclophotocoagulation still represents the most widely used cycloablative procedure. The transscleral cyclocoagulation, which utilizes argon laser, has the advantage to directly treat the ciliary body without the need to pass through the sclera. However, the procedure presents a poor efficacy in terms of IOP reduction [42–44]. The transscleral cyclophotocoagulation uses lasers with shorter wavelengths, with the neodymium-yttrium aluminum garnet (Nd:YAG) being the most diffuse. This kind of laser allows penetrating the sclera more effectively and with less backscatter than other kinds of short-wavelength lasers [45]. Histopathology studies showed atrophy of the ciliary processes 1–2 months after Nd:YAG cyclophotocoagulation, with ablations of the secretive epithelium and vasculature necrosis, leading to significant IOP lowering [46–48]. Several studies documented a good efficacy of this technique in reducing the IOP in patients with refractive glaucoma [49–51].

Nd:YAG cyclophotocoagulation can be performed in a noncontact or a contact way. However, though noncontact Nd:YAG cyclophotocoagulation showed encouraging results, the high rate of complications related to the procedure (anterior chamber inflammation, choroidal detachment, transient hypotony, sympathetic ophthalmia, and scleral thinning) led the transscleral contact approach to become the most commonly used cyclophotocoagulative technique [52, 53].

The contact treatment induces damage to the pigmented and nonpigmented epithelia and the stroma of ciliary
processes, without a secondary effect to the overlying sclera [54]. The advantage of the contact procedure is to reduce the IOP using the same amount of energy than the that of the noncontact Nd:YAG procedure, but with an ability to deliver the energy sixty times lower, this leads to less tissue destruction and fewer postoperative complications. One of the most important studies on the efficacy of contact Nd:YAG cyclophotocoagulation was conducted by Schuman et al. (mean follow-up, 3.2 months) [55]. In this short-term follow-up study, 62% of patients reduced IOP under 22 mmHg and 49% under 19 mmHg. The preoperative IOP was 36.7 mmHg and decreased to 21.2 mmHg, with a mean IOP reduction of 15.5 mmHg; notably, the final IOP reduction was achieved soon after surgery, or within one week of treatment.

Afterwards, Brancato et al. used lower energy levels and fewer applications achieving similar results, even though IOP dropped under 20 mmHg in a limited number of cases [56]. In long-term follow-up studies conducted on contact cyclophotocoagulation in refractory glaucoma (2 to 10 years), the success rate of the procedure was reported to range from 37% to 92% [55, 57–64]. In these studies, mean preoperative IOP ranged from 29.9 to 40 mmHg and reduced from 15 to 21.8 mmHg. The most common postoperative complications described after contact Nd:YAG cyclophotocoagulation are reported in Table 2 [38, 65–69].

In 1992, Uram [70] reported the initial results of a novel ciliary body photocoagulation delivered under direct visualization through endoscopy, in patients with neovascular glaucoma. With respect to transscleral cyclophotocoagulation, which is reserved to intractable and advanced glaucoma, the endoscopic cyclophotocoagulation (ECP) is used also in non-refractory cases, without absolute contraindications [71–73]. ECP has numerous advantages over transscleral cyclophotocoagulation, since the target tissue is directly visualized and, therefore, overtreatment is usually avoided.

Because of this, ECP was used in both mild POAG and advanced secondary glaucoma, also in combination with cataract surgery. In POAG, the IOP reduction was found to range from 18% to 47% (3.9 to 10.9 mmHg), with a mean IOP decrease of 31% (7 mmHg). In advanced secondary glaucoma, the IOP reduction ranged from 26% to 68% (7 to 28 mmHg) or yielded a mean IOP decrease of 50% (18 mmHg) [70, 71, 74–76]. In the largest retrospective study on ECP (7.4 years of follow-up), Lima et al. reported a postoperative IOP ranging between 6 and 21 mmHg in 79% of patients, with a mean number of medications of 1.9 [75].

### Table 1: Complications after cyclocryotherapy.

| Complications | Incidence | Reference |
|---------------|-----------|-----------|
| Mild          |           |           |
| AC flare/uveitis | 17.6%–100% | [3], [28], [32], [40] |
| Hyphema       | 4%–17.6%  | [4], [29], [30], [40] |
| Sterile hypopyon | 1.5%     | [28]      |
| Lens dislocation | 1 case reported | [31]    |
| VA loss       | 5.3%–58%  | [3], [28], [29], [32], [36] |
| VA decrease*  | 32.3–45.1% | [28], [32] |
| Hypotony      | 3.33%–32% | [33–35]   |
| Severe/vision threatening |           |           |
| Phthisis bulb | 3.3%–40%  | [3], [29], [32], [37], [40] |
| Choroidal detachment | 2%   | [3], [4] |
| Retinal detachment | 1.6% | [3], [29] |
| Sympathetic ophthalmia | ? | [41] |

VA: visual acuity; ?: unsolved question.

* ≥2 Snellen lines.

### Table 2: Complications after transscleral contact cyclophotocoagulation.

| Complications | Incidence | Reference |
|---------------|-----------|-----------|
| Mild          |           |           |
| AC flare/uveitis | 9%–28%    | [57], [58], [64], [65] |
| Hyphema       | 0%–2%     | [55], [58], [59] |
| Pain          | 9%–21%    | [55], [58], [64] |
| Pupillary changes | 0.8%–50% | [57], [61] |
| VA loss       | 8.8%–47%  | [38], [54], [56], [64], [68] |
| VA decrease*  | 38.5%–62.5% | [56], [57], [59] |
| Hypotony      | 0%–26%    | [3], [43], [56], [58], [61], [66] |
| Phthisis bulb | 0%–10.7%  | [39], [54], [55], [61], [67] |
| Retinal detachment | 1% | [55] |
| Sympathetic ophthalmia | ? | [3], [41] |

VA: visual acuity; ?: unsolved question.

* ≥2 Snellen lines.
Usually, ECP presents transient complications such as anterior chamber inflammation (22%), hyphema (11%), or cystoid macular edema (10%). The serious and potentially vision-threatening complications are less frequent in external cyclophotocoagulation and are represented by persistent hypotony (1–9%), phthisis (15 case reports), retinal detachment (1–6%), and vision loss or reduction (3–24%), especially in more advanced stages [71].

In closing, ECP is an effective and relatively safe procedure in recalcitrant glaucoma, which can be considered as a surgical option also in very selected cases of nonrefractive glaucoma.

4. High-Intensity Focused Ultrasounds (HIFU)

The HIFU technology, which is based on the favourable effects of high-frequency ultrasounds, is used in many fields of medicine. HIFU was initially proposed to treat different central nervous system diseases [77, 78]. Afterwards, in 1970s, its application was extended also in oncology, to induce a prolonged hyperthermia (elevation of tissue temperature to 43°C for one hour) in the entire tumor volume [79].

In ophthalmology, the HIFU technology was tested to treat retinal diseases, crystalline lens diseases, and choroid plexus diseases and to partially destroy the ciliary body. Baum and Greenwood showed that an ultrasound beam could disperse the ocular blood [80]; Purnell et al. published early results on cataract development and treatment of chorioretinal lesions [81]; Coleman et al. produced cataracts in rabbit lenses, observing the thermal mechanism underlying the final effect of high-intensity ultrasounds [11]. They also obtained the first in vivo threshold curves to induce chorioretinal lesions in albino rabbits, for the treatment of retinal detachment.

In the 1980s, the device was investigated for treatment of glaucoma. Coleman et al. conducted the first studies to evaluate the efficacy and safety of high-intensity focused ultrasounds (HIFU) in patients with uncontrolled IOP and advanced glaucoma [11, 12]. The strategy produced a commercially available device called as Sonocare Therapeutic Ultrasound System Model (Sonocare Inc., Ridgewood, New Jersey, USA) [82]. In the Sonocare system, the transducer was a single-spherical piezoceramic with 80 mm of diameter, working with a 4.6 MHz frequency. The system, which was attached to an articulated arm, required a 37° bath of saline solution to couple the eye with the transducer. The procedure was repeated to produce six pinpoint lesions of the ciliary body.

In the study of Coleman et al. at the third month of follow-up, IOP was less than 25 mmHg or 18 mmHg in 83% and 62% of patients, respectively [12]. In a larger case series, Burgess et al. reported similar results, reporting IOP values less than 25 mmHg in 90% of patients three months after the procedure [13]. At one year of follow-up, IOP was ≤25 mmHg in 65% of patients. The authors also documented the same efficacy of the procedure in retreating failing or unresponsive cases. Sterk et al. reported a 42.2% of IOP reduction after three months of follow-up in the 44 eyes with uncontrolled refractory glaucoma [15].

Several mechanisms of action were proposed to explain the final IOP lowering after HIFU, such as localized destruction of the ciliary-pigmented and nonpigmented epithelium, atrophy of the ciliary muscle, cyclodialysis cleft, and scleral thinning [11–13, 83]. Despite encouraging initial evidence, the ultrasound cyclodestruction was used only in advanced and refractory glaucoma, because of the significant risk of complications (scleral staphycoma, corneal thinning, persistent hypotony, phthisis bulbi, and loss of the visual acuity). Moreover, the particular complexity and duration of insufflation with the Sonocare system led to progressively abandon the procedure in the middle of 1990s.

By refining the transducer design, the modes of energy delivery and the real-time imaging of the HIFU technology was rediscovered in oncology in the 1990s as an additional effective strategy to treat cancer. Currently, this technology is particularly used for primary solid tumors and metastatic diseases and to enhance the drug delivery through tissues. Uterine fibroids, prostate cancer, pancreatic cancer, liver tumors, and thyroid tumors are the main solid tumors accessible to the ultrasound energy benefit [84–87].

The availability of advanced imaging technologies such as the magnetic resonance thermometry and particular ultrasound imaging techniques permits the real-time monitoring of treatment effects induced by HIFU.

5. Miniaturized High-Intensity Focused Ultrasounds for Cyclodestruction in Glaucoma

In the last years, a miniaturized HIFU device assembled to precisely match with the ocular globe geometry was developed to insonify the ciliary body in uncontrolled refractory glaucoma. The device consists of a disposable therapeutic circular probe, a coupling cone, and a touch screen console; the coupling cone and the probe are connected to the console by means of a tube and an electric cable, respectively, and a foot pedal allows the activation of the treatment. The procedure was named as ultrasonic circular cyclocoagulation (UC3).

The device (Figure 1) allows a sequential, computer-assisted treatment of the cylinder-shaped regions of the ciliary body, in a quick one-step circular procedure, thus eliminating the need to move the probe during the treatment. The circular shape of the probe, reproducing the macroscopic anatomy of the ciliary body, allows a high-precision coupling with the target organ (thus sparing the neighbouring structures) and permits a nonoperator-dependent treatment with highly reproducible lesions of the target organ [19]. To selectively impact with the ciliary body, the ultrasound beam is focused at a depth of 2 mm below the sclera, corresponding to the spatial position of the ciliary body.

In order to be safe and efficient, the system respects four anatomical constraints: (i) avoiding insonification of the cornea and the lens (obtained by a transducer aperture of 36°), (ii) avoiding the nasal and temporal zones during treatment, in order to preserve a sufficient aqueous humor production (the angle between the two transducers in the nasal and temporal sectors is 70°), (iii) minimizing the propagation
distance through tissues, with the aim to reduce the attenuation of the energy, and (iv) avoiding a retinal overexposure (obtained by choosing a cylindrically shaped transducer).

The probe, which is 30 mm in diameter and a 15 mm high ring, is divided in six cylindrical piezoceramic transducers generating six ultrasound beams that allow treating up to 30% of the ciliary body. Transducers were operated at 21 MHz of frequency with an acoustic power of 2 watts; ultrasounds rapidly increase the local temperature of the ciliary body (up to 90° to avoid tissue boiling). The transducers are elliptic cylinder-shaped segments of a 10.2 mm radius, with a 4.5 mm width and a 7 mm length, generating an active surface area of 35 mm². The result is a highly precise focusing of the target zone, not exceeding 0.1 mm × 1 mm in size. Transducers are equidistant between them, distributed three in the superior and three in the inferior regions. The focal volume of transducers presents an elliptic cylinder shape, which finally coagulates the same volume of the ciliary body.

The probe is inserted into a truncated polymer-made coupling cone and placed in direct contact with the eye; this allows the optimal positioning of the probe in terms of centering and distance and a stable alignment to the optical axis. The coupling cone is connected to a suction ring, which allows the application of a low-level vacuum to maintain the cone in contact with the ocular surface during the procedure, without movement and misalignment. A one dual-function foot pedal allows activating the suction and the firing phases directly by the surgeon or the second operator. Probes are commercialized in three different ring diameters (11, 12, and 13 mm), which allow them to fit most ocular sizes, except in cases of nanophthalmos or primary or secondary megaphthalmos. The probe size is determined before surgery by using ultrasound biomicroscopy (UBM), which permits to simulate the locations of the focal zones; the model that best targets the ciliary body is then chosen [16]. For UBM assessment, radial and transverse scans are obtained at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° meridians.

The main module of the HIFU device is constituted by the following components: (i) a signal generator producing an electrical voltage, (ii) an amplifier that enhances the electric voltage and allows transducers to be excited and produce ultrasounds, (iii) a watt meter that measures the incident and reflected electric power during the insonification, (iv) an electronic switch controller, which enables the electric voltage to be sent to transducers, and (v) a computer that controls the electronic switch and the signal generator and permits to set up the treatment parameters (frequency, power, duration, and number of sectors to treat). The computer sequentially activated sectors during treatment.

According to patient and physician preferences the procedure can be performed under topical, peribulbar, or general anaesthesia; nevertheless, anaesthesia is locally administered in most parts of cases.

5.1. UC3 Procedure. After registration of the surgeon name and the patient demographic data, the operator connects the probe to the console and selects the eye. The device automatically recognizes the probe and the suction test starts after clumping of the suction tube. In the next step, the surgeon puts in contact the coupling cone with the ocular surface and gently moves the cone to obtain a correct positioning and centering (a homogeneous white scleral ring surrounding the cornea should appear). The surgeon activates a 70 mmHg suction from the foot pedal, and when the optimal suction has been obtained (green bar on the screen), the probe is inserted into the cone and the position is maintained throughout the treatment. To facilitate the ultrasounds transmission, the cone is finally filled with balanced saline solution. At this stage, the device is ready to use and the treatment can start by selecting the firing button of the foot pedal. Transducers are sequentially activated clockwise, starting from the superior sectors both in the right and in the left eyes. Each transducer is activated for 4 or 6 seconds, with 20 seconds of interval between each sector, and the passage between sectors is completely automatic without the need to release the foot pedal. The particular interval between the activation of adjacent sectors allows the heat to be
completely evacuated. The entire treatment, according to the selected regimen of insonification, lasts 2 minutes and 4 seconds (in the 4-second regimen) or 2 minutes and 16 seconds (in the 6-second regimen).

In the 4-second regimen, the volume of the destroyed ciliary process corresponds to 4.8 mm$^3$, while in the 6-second regimen, 7.8 mm$^3$; the regimen dose selection generally depends on the preoperative clinical status of the patient, in order to produce a lower or higher AH inflow reduction.

The console screen allows controlling the successful sequential activation of transducers during the whole procedure.

In the last year, a new-generation probe (Figures 1(a)–1(d)) with a modified coupling cone was commercialized, and it replaced the first-generation probe. The objectives of the technical modifications were to make the UC$^3$ procedure even more intuitive and surgeon-friendly and to further boost clinical efficacy without compromising the favourable safety profile. The device was successfully redesigned to make the intraoperative handling simpler and smoother. The treatment probe was modified to treat up to an average 45% of the entire circumference of the ciliary body, increasing the active surface of the transducers from 2.5 to 4 mm in width. In this way, the active surface now covers almost the entire area of the transducer. Different from the original procedure, where the surgeon can select the desired time dose regimen (4 or 6 seconds), the novel probe offers a unique 8-second dose exposure for each of the six transducers, maintaining the same interval between sectors. Therefore, the procedure currently lasts 2 minutes and 32 seconds.

At the end of the treatment, patients receive topical antibiotics and steroids three times a day for 1 week, according to surgeon preferences and the postoperative course, and cyclopentolate twice daily for 4 days. In the first weeks after surgery, the IOP-lowering medications are generally maintained.

5.2. Efficacy and Safety of the Procedure. Clinical studies, conducted with the first-generation probe in patients with refractory glaucoma, reported encouraging results, especially in the early postoperative period. Mastropasqua et al. reported an overall success rate of 63.6% at month 1, with a higher success rate in the 6-second dose regimen (80%) compared to that in the 4-second dose regimen (41.6%) (UC$^3$ was considered successful when at least a 30% reduction from preoperative IOP was obtained at one-month follow-up) [88]. These results were in line with the 66.7% reported by Denis et al. in both groups of treatment at month 1 [17].

Considering the percentage IOP reduction, Mastropasqua et al. reported values of 30.1 and 38.7% in the 4-second and 6-second dose regimens, respectively, which were almost in line with literature that reported percentage reduction ranging from 22.8 to 26.4% in the 4-second regimen and from 28.2 to 38.2% in the 6-second regimen at month 1 [17]. The mild differences could probably depend on the different stages of disease and the typology of refractory glaucoma enrolled in the studies. The same studies produced partially conflicting results when considering longer follow-up. At 12 months, Aptel et al. reported an overall success rate of 83.3%; successful procedures were complete in 50% of cases and qualified in 68% of cases [16, 18]. Denis et al. reported a success rate ranging from 48% to 57% (Groups 2 and 1, respectively), and Melamed et al. reported a success rate of 65% [17, 21].

In these studies, preoperative IOP ranged from 27.5 to 39.1 mmHg, whereas postoperative IOP ranged from 17.1 to 23 mmHg at the last follow-up [16–18, 21, 88, 89].

Overall, based on these results, it seems that the procedure tends to maintain the IOP-lowering efficacy in the first year, with a success rate ranging from 48% to 83.3%, without reduction of the topical IOP-lowering medications. The mean number of the UC$^3$ procedure in the first 12 months ranged from 1.05 to 1.13 in the study of Aptel et al., while Denis et al. reported percentages of retreatment from 17.6 to 29.4% in the 6- and 4-second dose regimens, respectively [17, 89]. Finally, all these studies did not report a significant reduction of the mean number of medications after the procedure, especially in the long-term studies. On this basis, the UC$^3$ usually produces a qualified surgical success. Though the new probes have been introduced to increase the efficacy of the procedure, to date, no direct comparative study has been published.

In all studies, the procedure was reported to be safe without serious intra- or postoperative complications. The most frequent complications were described in the early postoperative period (1 week) and were represented by conjunctival hyperaemia, punctate keratitis, subconjunctival hemorrhage, anterior chamber inflammation, and a transient IOP increase (more than 10 mmHg from baseline) (Table 3).

The introduction of the new probe allowed maintaining a high level of safety, even though in our initial case series, we

| Complications | Incidence |
|---------------|-----------|
| Intraoperative pain | 4.1%–10.7% |
| Conjunctival hyperaemia | 37.5%–75% |
| Subconjunctival hemorrhage | 4%–16.6% |
| Mild | |
| Superficial punctate keratitis | 10.7%–40% |
| Anterior chamber reaction | 16.6%–40% |
| IOP spikes * | 6.6%–20.8% |
| Focal scleral thinning | 3.3% |
| Severe/vision threatening | |
| Transient VA decrease ** | 10.7% |
| Transient hypotony | 1.6%–5% |
| Corneal edema | 7.1%–8.3% |
| Corneal ulceration * | 8.3%–16.6% |
| Transient macular edema | 3.3%–3.6% |

UC$^3$: ultrasonic circular cyclocoagulation; VA: visual acuity.

* IOP increase higher than 5 versus baseline, in the first week.
** ≥2 Snellen lines, transient.
§ Patients with preexisting corneal disorders.

References [16–21, 88, 89].
noted a slight higher incidence of anterior chamber inflammation (cellularity and proteins determined by a slit lamp examination and graded according to the Likert scale).

A transient IOP increase occurs also during the procedure, because of the suction needed to couple the device with the ocular surface; this should be carefully considered in relation to the visual field of the treated eye. Though the occurrence of optic nerve and retinal vascular changes after UC3 has been not documented, studies on subjects undergoing LASIK (that similarly requires suction) reported cases of optic neuropathy and visual field loss related to the suction process [90, 91]. Considering these potential

Figure 2: Anterior segment-optical coherence tomography of the sclera before insonification. Preoperative normal sclera presenting a relatively homogeneous stroma, with some scattered linear- (asterisk) or oval- (arrowhead) shaped hyporeflective spaces interspersed between the collagen fibres.

Figure 3: Anterior segment optical coherence tomography of scleral modifications after successful UCCC. (a–c) Second-generation probes (8-second treatment; 4 mm wide active area); (d–f) first-generation probes (6-second treatment; 2.5 mm wide active area). Intrasceral hyporeflective spaces (arrows and asterisks), with a different degree of internal reflectivity, are clearly recognizable within the stroma. These spaces are prominent after seven days from the treatment (a), and persist, even though reduced, after one (b) and three (c) months. No significant macroscopic differences are detectable between the two generation probes, even though the current probes seem to induce a greater scleral delamination. Scans were taken at the superior-temporal quadrants, 3 mm from the site of previous filtration surgery.
complications, UC$^3$ was not recommended in advanced/end-stage glaucoma.

Serious complications such as persistent hypotony or phthisis, which were relatively common in other cycloablative techniques (occurring 6 to 30 months after surgery), were never described after UC$^3$. Given the high rate of safety demonstrated in refractory glaucoma [16–21, 88], Aptel et al. recently conducted a study to evaluate the efficacy and safety of UC$^3$ in patients with early glaucoma, naïve of any previous filtering surgery [89]. The authors reported a complete and qualified success of 46.7% and 63%, respectively, with a mean IOP reduction of 37% at 12 months, using the 6-second regimen.

Based on these encouraging results, the indication for the procedure has been extended also to patients with primary or secondary open-angle glaucoma naïve to filtration surgery.

5.3. Mechanisms of Action of UC$^3$. The AH inflow reduction following the thermic necrosis of the ciliary epithelium seems to play the main role in the final IOP lowering after UC$^3$. In the pilot histopathology studies conducted on rabbits, Aptel et al. found that the distal and intermediate parts of the ciliary processes presented necrotic changes of the stroma and epithelium, ranging from oedema to vascular congestion; conversely, the basal parts of the ciliary processes and the rest of the ciliary body appeared normal [19, 92]. Focal interr uptions and disruptions of the ciliary processes and pars plana microvasculature were also observed with light and scanning electron microscopy.

On the other hand, the evenly delivered ultrasound dose did not induce significant inflammatory reactions in the treated portions and permitted a good preservation of the blood aqueous barrier. The adjacent untreated areas presented normal ciliary epithelium and stroma, no signs of inflammation, and a complete preservation of the 3D vasculature. These anatomical aspects confirm that high-frequency ultrasounds are precisely focused on the target volume, producing histological lesions strictly limited to the site of sonication. These findings also represent the basis for the higher clinical safety of UC$^3$ compared to those of standard cyclo-destructive procedures, which do not spare the neighbouring tissues during the energy delivery.

Besides the effects on the ciliary body, an increase of the suprachoroidal and transscleral AH outflow has been also documented [16–19]. A hypoechogenic suprachoroidal space was observed in 67% patients one month after the ciliary body insonification; this indicated an increased uveoscleral outflow through the supraciliary and suprachoroidal space, in line with histological findings.

In a recent study, our group observed significant modifications of the scleral and conjunctival anatomy one month after UC$^3$, in patients insonified with either 4- or 6-second regimen [88]. Anterior segment optical coherence tomography documented the formation of new (or the enlargement of preexisting) intrascleral hyporeflective spaces (HSs) 1 month after the procedure. HSs were defined as intrasomal cavities presenting a lower degree of reflectivity compared to those of the surrounding sclera. Intrascral HSs markedly increased from two to three times with respect to baseline.
Figure 5: In vivo confocal microscopy of the superior temporal conjunctiva in the same patient scheduled to undergo a 4-second dose UCCE (Group 1). (a) The baseline planar reconstruction shows small roundish microcysts, located at different levels within the epithelium, scattered, and sometimes clustered (arrowhead). (b) Microcysts increased density and area (arrow) thirty days after insonification. Bar represents 100 μm (from [88], with permission of the publisher).
Figures 2 and 3) only at the site of transducer contact, without involvement of the surrounding sclera. We hypothesized that the HS increase was a consequence of a thermic-induced scleral fibre delamination; in fact, a heating of the suprachoroid, sclera, and conjunctiva during the procedure may occur, given that the transducer produces a thermic halo (1.89 mm³) with a temperature gradient from the ciliary body to the ocular surface. The preliminary results of an ongoing thermal infrared imaging study seem to support this hypothesis, since we observed a significant increase in the ocular surface temperature at the site of insonification, immediately after the UC³ (Figure 4). This thermic effect may also account for the higher HS increase in patients treated with the 6-second dose regimen, which received a prolonged duration of the insonification. The increase of such HSs leads to an enhancement of the scleral hydraulic conductivity and, therefore, of the AH transscleral outflow.

In vivo confocal microscopy confirmed the transscleral outflow enhancement one month after the procedure by documenting a significant increase of conjunctival microcysts at site of insonification (Figures 5 and 6). These microcysts were proposed as an in vivo hallmark of the AH passage through the sclera and finally the conjunctiva [93–100].
The scleral architecture remodelling observed after UC3 may pose concerns in patients candidate to further filtration surgery, since the (intra- and postoperative) resistance of the sclera and the AH permeability of collagen fibres could be significantly altered, especially after repeated sonications. At this moment, there are no studies that addressed this point; therefore, these aspects must be considered and carefully pondered before proposing filtration surgery after HIFU, either in refractory or (even more) in nonrefractory cases. In addition, there are no long-term studies that evaluated the risk of hypotony after repeated insonifications or the risk of hypotony whether patients receive further filtration surgery. Despite no comparative randomized clinical trials have been performed, an overview of literature leads to a hypothesis that UC3 might have a little lower efficacy (also in terms of reduction of number of medications) and provide a shorter duration of the IOP-lowering effect compared to that of the other cyclodestructive approaches, though with a greater safety profile [16–19, 42, 43, 54–69, 88]. On the other hand, the new probes seem to increase the IOP-lowering efficacy of the technique, maintaining the same level of safety.

In closing, even though promising and safe, the ultrasonic cyclocoagulation still requires correct positioning in terms of indication and timing, in the management of glaucoma.

6. Summary and Conclusions

Currently, cyclodestructive procedures are exclusively limited to refractory/end-stage glaucoma, because of the high incidence of vision-threatening complications. All proposed procedures are noncompletely selective for the target organ, have an unpredictable dose-effect relationship, are operator dependent, and are poorly reproducible. UC3 is an emerging and encouraging technique, which utilizes the HIFU technology to induce a one-step, automated, computer-assisted, non-operator-dependent, and highly reproducible thermal coagulation of the ciliary epithelium. This procedure allows a selective destruction of the limited and predefined portions of the ciliary body, thus reducing the AH inflow in a controlled way. UC3 presents several advantages over traditional cyclodestructive techniques since it minimizes the intra- and postoperative complications, preserves neighbouring organs from undesired treatment, allows a faster postoperative recovery, and permits retreatments (by rotating transducers) because there is no dose limit.

Besides the reduction of the AH inflow, which is the main mechanism that reduces IOP, UC3 increases also the AH outflow, by favourably remodelling the anatomical architecture of suprachoroid, sclera, and conjunctiva. This indicates that UC3 may influence the entire hydrodynamic system, exploiting different mechanisms to finally reduce the IOP. The promising results, along with the high level of safety reported in refractory glaucoma, allowed extending the indication for UC3 also in glaucomatous patients naïve to surgery, thus reconsidering the role and the timing of cyclodestruction in the management of glaucoma.

However, to date, no comparative study between UC3 and other cyclodestructive procedures has been published. Therefore, whether UC3 represents a better solution for refractory glaucoma with respect to standardized cycloablative techniques needs to be addressed.

The described effects of high-frequency ultrasounds on the sclera and conjunctiva might open future strategies to lower IOP in glaucoma. In fact, the development of modified HIFU probes that will focus the ultrasonic beam just within the sclera avoiding the ciliary body could stimulate the uveoscleral outflow pathway by increasing the transscleral AH resorption. This may have the great advantages to reduce the IOP by stimulating the physiological AH outflow routes and reduce the postoperative complications by preserving the ciliary body, which plays a critical role in the global health of the eye.

Conflicts of Interest

There are no competing interests.

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Review Article
Safety and Efficacy of Microinvasive Glaucoma Surgery

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Microinvasive glaucoma surgery (MIGS) is emerging as a new therapeutic option for glaucoma patients who wish to reduce their medication burden and avoid the postoperative complications of conventional glaucoma filtration surgery. These devices differ in terms of their efficacy and safety profile. Schlemm’s canal devices have the most favorable safety profile at the compromise of modest efficacy, while subconjunctival and suprachoroidal devices are potentially more effective at lowering the intraocular pressure at the expense of a higher rate of complications. This review consolidates the latest evidence on the efficacy and safety of the MIGS devices in clinical use and provides an overview on upcoming devices which would likely also become viable treatment options in the near future. These clinical data would assist a glaucoma surgeon in selecting the most appropriate MIGS device for each patient based on the glaucoma severity and patient expectations.

1. Introduction

The management of glaucoma revolves around control over intraocular pressure (IOP). Traditionally, this has been achieved through both nonsurgical (topical medications [1] or laser therapy [2, 3]) and surgical (trabeculectomy, glaucoma drainage devices) means [4–6]. Neither methods are ideal—compliance with medications being an issue for the former while surgical complications are common in the latter.

More recently, microinvasive glaucoma surgery has emerged as a new treatment for open-angle glaucoma (OAG) including pseudoxfoliative glaucoma (PXF) and pigmentary glaucoma (PG). MIGS typically utilizes an ab interno approach, often through a clear corneal incision familiar to most ophthalmic surgeons, thus allowing for minimal tissue disruption, a more favorable risk profile, and faster recovery as compared to conventional trabeculectomy or glaucoma drainage device implantation. Currently, it is most commonly indicated for mild-to-moderate glaucoma in patients with poor tolerance or compliance to antiglaucomatous medications. However, critics question the poorer IOP-lowering effect of MIGS. At the point of writing, there are a multitude of MIGS devices, with several different mechanisms of action, and varying efficacy and safety profiles. In this review article, we attempt to review current understanding on MIGS and consolidate the safety and efficacy of these devices.

2. Material and Methods

A PubMed search using a combination of keywords and Medical Subject Headings on the following keywords was made on 29th December 2016: “safety”, “complication”, “efficacy”, “outcome”, “minimally invasive glaucoma surgery”, “micro-invasive glaucoma surgery”, “MIGS”, “trabectome”, “iStent”, “iStent inject”, “Hydrus”, “excimer laser trabeculectomy”, “ELT”, “CyPass”, “XEN”, “Aquesys”, “Innfocus”. Results were classified according to the types of device (Schlemm’s canal, suprachoroidal, and subconjunctival devices). All randomized controlled trials (RCTs) and case series in English-published articles either online or in print prior to the date of search were considered. Prospective articles were given higher priority. Review articles were...
excluded from the search, but relevant referenced primary articles were included in this literature review. For articles where full texts were unavailable, we requested for a full article from the corresponding author; failing which, relevant data was extracted from the abstract itself.

The primary outcome measures for efficacy included preoperative and postoperative IOP, as well as the number of medications required. Success and failure rates were defined heterogeneously across studies, and only selected results from RCTs were included as a secondary outcome measure for efficacy. Primary outcome measures for safety included a qualitative description of intraoperative and postoperative complications, as well as the need for repeat surgeries.

3. Results

A total of 317 articles were included from the search result. After review and exclusion by a single reviewer, 65 articles were included (Figure 1). The following sections summarize the findings. Table 1 summarizes the physical properties of these devices and their approved usage in the US as well as in Europe.

### 3.1. Schlemm’s Canal

Schlemm’s canal devices are performed through an ab interno method through the assistance of a gonioscopy lens, with an aim to increase aqueous outflow through the conventional pathway. Therefore, the potential effect on aqueous outflow is influenced by episcleral venous pressure. The commonest procedures involving the Schlemm’s canal include the removal of trabecular tissue (ab interno trabeculotomy, excimer laser trabeculotomy) or the implantation of a small device (e.g., iStent, iStent inject®, and Hydrus MicroShunt). The following sections would highlight the different methods in detail.

#### 3.1.1. iStent

The iStent (Glaukos Corporation, CA, USA) is a heparin-coated titanium microbypass device. This L-shaped device is 1.0 mm long and 0.33 mm wide and comes preloaded in a single-use sterile inserter. The short side (inlet) faces the anterior chamber, while the lumen (foot) resides in the Schlemm’s canal, and could be inserted either right or left handedly. In 2012, this device was approved in the US for use in patients with mild-to-moderate glaucoma who are undergoing cataract surgery. It was the first MIGS device to be approved for use in the US. In Europe, this

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**Figure 1: Literature search and included articles.**

**Table 1: Physical properties of MIGS devices and approved indications for use.**

| Instrument           | Length (mm) | Luminal diameter (μm) | FDA approval | CE mark |
|----------------------|-------------|-----------------------|--------------|---------|
| Schlemm’s canal      |             |                       |              |         |
| Trabectome           | NA*         | NA*                   | 2004         | 2004    |
| ELT                  | NA*         | NA*                   | Pending 1998 | 1998    |
| iStent               | 1           | 120                   | 2012         | 2004    |
| iStent inject        | 0.36        | 230                   | US IDE 2010  | 2010    |
| Hydrus               | 8           | 185–292               | US IDE 2011  |         |
| Suprachoroidal devices |           |                       |              |         |
| CyPass               | 6.35        | 300 (inner) 510 (outer)| 2016         | 2009    |
| iStent Supra         | 4           | 160                   | US IDE 2010  | 2010    |
| InnFocus             | 8.5         | 45 (inner) 150 (outer)| 2016         | 2011    |

*ELT: excimer laser trabeculotomy; NA: not available; US IDE: US investigational device exception. *No device implantation required.
device is approved for use either as a stand-alone surgery or as a surgery combined with cataract surgery.

Several authors have independently reviewed the efficacy of iStent devices (Table 2). When performed as a stand-alone procedure, the implantation of a single iStent reduced IOP by 4.2 mmHg after 18 months as compared with medicated baseline IOP in a RCT performed by Katz et al. [7]. In a retrospective analysis of 42 pseudophakic eyes by Ferguson et al., the implantation of a single iStent reduced IOP from 20.26 ± 6.00 mmHg preoperatively to 13.62 ± 4.55 mmHg at two years postoperatively (p < 0.01) [8]. However, there was no significant decrease in the number of medications (1.95 ± 1.01 versus 1.33, p > 0.05), and there was a high dropout rate of 50% (21 of 42 patients). Buchaca et al. demonstrated an absolute IOP reduction of 9.5 mmHg from baseline (relative reduction of 36%) in a small group of 10 subjects with secondary OAG [9], but this finding might be limited by the small sample size and relatively short follow-up period of one year.

The placement of more iStents in the same eye appears to have an additive effect on IOP lowering; Katz et al. demonstrated a progressively higher absolute IOP reduction from 4.2 mmHg with one iStent to 8.3 mmHg with three iStents at 18 months postoperatively. Other studies which placed two iStents in the same eye reported an absolute IOP reduction of between 5 and 8 mmHg [7, 10–16]. Vold et al. reported an IOP reduction of 11 mmHg when subjects with newly diagnosed open-angle glaucoma were implanted with two iStents [10, 11, 15].

iStent is also commonly performed with cataract surgery. A large RCT performed by Craven et al. demonstrated modest IOP reduction of 1.5 mmHg from preoperative medicated IOP levels with a corresponding decrease in medications from 1.6 ± 0.8 to 0.3 ± 0.6 [17], while another large RCT by Samuelson found an equally modest IOP reduction of 1.5 mmHg after 1 year with a decrease in medication from 1.5 ± 0.6 to 0.2 ± 0.6 [18]. Two other smaller RCTs by Fea et al. found similar IOP reductions and medication reduction to 0.5 medication or less [19, 20] (Table 2). In some RCTs, there was a specified medication washout period postoperatively and the authors found postoperative IOP to be around 17 mmHg [10, 16]. In contrast, other prospective and retrospective case series have found inconsistent IOP reductions from the medicated baseline, ranging from as low as 1.6 mmHg at 6 months to as high as 9.2 mmHg at 3 years postoperatively [14, 21–27]. This suggests that while combined cataract surgery and iStent may have synergistic effects in lowering IOP, their effects are not necessarily additive.

Intraoperative and postoperative complications are listed in Table 3. In general, iStent implantation is associated with a good safety profile that is comparable with cataract surgery alone, with the commonest complication being transient (and commonly self-limiting) hyphema. Stent obstruction and stent malposition also occur and often do not require intervention, though sometimes they may require laser or surgical intervention [17, 18, 27] (Table 3). Reoperation rates were understandably rare as the subjects who underwent iStent implantation usually had mild or moderate glaucoma. 3.1.2. iStent Inject. The iStent inject, the second generation version of the iStent, is a single-piece heparin-coated, gamma-sterilized titanium device. It is symmetrically designed, and up to two iStents can be injected with a single injector device using the G2-M-IS injector system. This allows for the availability for the surgeon to inject two iStents while entering the eye only once, thus reducing the risks of adverse events even further.

Fea et al. compared the efficacy of two iStent inject implantations with fixed combination of latanoprost/timolol medication administration in a randomized unmasked study [28]. At one year postoperatively, the medicated IOP of the iStent inject group has decreased from 21.1 ± 1.7 mmHg (postwashout baseline IOP 25.2 ± 1.4 mmHg) to 13.0 ± 2.3 mmHg and concluded that the effect of two iStent injects is at least as effective as two medications while reducing medication burden. Two other independent prospective studies by Voskanyan et al. [29] and Arriola-Villalobos et al. [30] found similar results (Table 2).

Gonnermann et al. evaluated the only comparative study available between Trabectome and iStent inject [31]. In a retrospective intra-individual comparative study, the authors performed Trabectome and cataract surgeries in one eye and two iStent inject implantations with cataract surgery in the contralateral eye. At one year postoperatively, the authors found similar IOP-lowering effects in both groups and concluded that both were effective in lowering IOP (Table 2). The safety profiles of both groups were also similar.

3.1.3. Hydrus Microstent. The Hydrus® (Irvine, CA, USA) is a relatively new Schlemm’s canal device. Using a custom preloaded hand-held injector, the 8 mm long crescent-shaped device is implanted ab interno; its curvature shaped to match that of the Schlemm’s canal. It dilates the canal up to 3 clock hours and allows direct communication between the anterior chamber and the Schlemm’s canal.

A recent randomized controlled trial, HYDRUS II [32], recruited 50 subjects to compare the safety and efficacy of the Hydrus microstent (Hydrus) in a combined Hydrus and phacoemulsification procedure with a control population of 50 subjects with OAG who underwent only phacoemulsification, and they were followed up for two years postoperatively. For the combined group, postwashout IOP levels decreased from 26.3 ± 4.4 mmHg preoperatively (medicated IOP 18.9 ± 3.3 mmHg) to 16.9 ± 3.3 mmHg postoperatively (Table 2), and the number of medications required also reduced from 2 ± 1 to 0.5 ± 1. While the mean postoperative IOP was lower than baseline IOP for both groups at 12 and 25 months postoperatively, the postoperative IOP of the combined group was significantly lower than that of the control group at 24 months (16.9 ± 3.3 mmHg versus 19.2 ± 4.7 mmHg, p = 0.0093). Postoperatively, the proportion of subjects with a 20% or greater reduction in washed out diurnal IOP compared with baseline was significantly higher in the study group than in the control group (80% versus 46%, p = 0.0008).

Fea et al. conducted a nonrandomized prospective interventional case series between 31 subjects who underwent Hydrus implantation and 25 subjects who underwent
| Author                          | Year | Operation                        | Number of eyes | Follow-up (months) | Preop IOP (mmHg) | Postop IOP (mmHg) | IOP reduction (mmHg, %)* | Preop meds | Postop meds | Medication reduction (n, %)* |
|--------------------------------|------|----------------------------------|----------------|--------------------|------------------|-------------------|--------------------------|------------|-------------|----------------------------|
| **Schlemm’s canal devices**    |      |                                  |                |                    |                  |                   |                          |            |             |                            |
| *Trabectome*                   |      |                                  |                |                    |                  |                   |                          |            |             |                            |
| Wecker et al. [39]             | 2016 | Trabectome ± CS                  | 60             | 12                 | 24.5 ± 3.5       | 15.7 ± 3.4        | 8.8 (35.9)               | 2.1 ± 1.3  | 1.8 ± 1.2   | 0.3 (14.3)                |
| Lee et al. [38]                | 2016 | Trabectome                       | 17             | 6                  | 24.4 ± 4.4       | 16.9 ± 5.1        | 7.5 (30.7)               | 3.9 ± 0.8  | 2.8 ± 1.6   | 1.1 (28.2)                |
| Jordan et al. [40]             | 2013 | Trabectome ± CS                  | 261            | 6                  | 24.2 ± 5.5       | 18.2 ± 6.1        | 6 (24.8)                 | 2.1 ± 1.3  | 1.2 ± 1.1   | 0.9 (42.9)                |
| Bussel et al. [37]             | 2015 | Trabectome                       | 58             | 12                 | 23.7 ± 5.5       | 16.2 ± 3.9        | 7.5 (31.6)               | 2.8 ± 1.2  | 2.0 ± 1.3   | 0.8 (28.6)                |
| Maeda et al. [64]              | 2013 | Trabectome                       | 80             | 6                  | 26.6 ± 8.1       | 17.4 ± 3.4        | 9.2 (34.6)               | 4.0 ± 1.4  | 2.3 ± 1.2   | 1.7 (42.5)                |
| Maeda et al. [64]              | 2013 | Trabectome                       | 450            | 12                 | 25.5 ± 7.9       | 16.8 ± 3.9        | 8.7 (34.1)               | 2.7 ± 1.3  | 2.2 ± 1.3   | 0.5 (20.9)                |
| Ting et al. [36]               | 2012 | Trabectome                       | 67             | 12                 | 29 ± 7.5         | 16.1 ± 4.0        | 12.9 (44.5)              | 3.1 ± 1.2  | 2.2 ± 1.4   | 0.8 (28.5)                |
| Francis et al. [42]            | 2008 | Trabectome ± CS                  | 6.3            | 12                 | 19.7 ± 5.4       | 15.6 ± 3.2        | 4.3 (21.6)               | 2.4 ± 1.1  | 1.7 ± 1.3   | 0.8 (31.3)                |
| Minckler et al. [35]           | 2005 | Trabectome                       | 37             | 12                 | 28.2 ± 4.4†      | 16.3 ± 2.0        | 11.9 (42.2)              | 1.2 ± 0.6  | 0.4 ± 0.6   | 0.8 (66.7)                |
| **ELT**                        |      |                                  |                |                    |                  |                   |                          |            |             |                            |
| Babighian et al. [49]          | 2010 | ELT                              | 15             | 24                 | 25.0 ± 1.9       | 17.6 ± 2.2        | 7.4 (29.6)               | 2.2 ± 0.6  | 0.7 ± 0.8   | 1.5 (66.8)                |
| Wilmsmeyer et al. [48]         | 2006 | ELT                              | 75             | 12                 | 23.3 ± 0.6       | 18.8 ± 0.8        | 4.5 (19.3)               | 1.9 ± 0.1  | 1.8 ± 0.2   | 0.1 (5.3)                 |
| **iStent**                     |      |                                  |                |                    |                  |                   |                          |            |             |                            |
| Vold et al. [15]               | 2016 | 2 iStents                        | 54             | 36                 | 25.5 ± 2.5       | 14.6              | 10.9 (42.7)              | 0          | 0.1         | -0.1                      |
| Katz et al. [7]                | 2015 | 2 iStents                        | 41             | 18                 | 20.1 ± 1.6       | 13.8 ± 1.3        | 6.3 (31.3)               | 1.8 ± 0.5  | 0.12        | 1.6 (93.2)                |
| Craven et al. [17]             | 2012 | 1 iStent + CS                    | 116            | 24                 | 18.6 ± 3.4       | 17.1 ± 2.9        | 1.5 (81)                 | 1.6 ± 0.8  | 0.3 ± 0.6   | 1.3 (81.3)                |
| Fea [19]                       | 2010 | 1 iStent + CS                    | 12             | 16                 | 17.9 ± 2.6       | 16.6 ± 3.1        | 1.3 (73)                 | 2 ± 0.9    | 0           | 2 (100)                   |
| Fernandez-Barrientos et al. [13]| 2010| 2 iStents + CS                   | 17             | 12                 | 24.2 ± 1.8†      | 17.6 ± 2.8        | 6.6 (27.3)               | 1.1 ± 0.5  | 0           | 1.1 (100)                 |
| Lindstrom et al. [16]          | 2016 | 2 iStents                        | 57             | 18                 | 19.5 ± 1.5       | 14.4 ± 2.1        | 5.1 (26.2)               | 1          | 0.02        | 0.98 (98.0)               |
| Tan and Au [23]                | 2016 | 1 iStent + CS                    | 41             | 36                 | 21.2 ± 4.7       | 17.1 ± 2.4        | 4.1 (19.3)               | 2.1 ± 1.0  | 1.3 ± 1.2   | 0.8 (38.1)                |
| Donnenfeld et al. [10]         | 2015 | 2 iStents                        | 39             | 36                 | 20.6 ± 2.0       | 14.2 ± 2.1        | 6.4 (31.1)               | 1          | 0.05        | 0.95 (95.0)               |
| Fea et al. [20]                | 2015 | 1 iStent + CS                    | 10             | 48                 | 17.8 ± 2.7       | 15.9 ± 2.3        | 1.9 (10.7)               | 1.9 ± 0.9  | 0.5 ± 0.8   | 1.4 (74.7)                |
| Neuhann [22]                   | 2015 | 1 iStent + CS                    | 62             | 36                 | 24.1 ± 6.9       | 14.9 ± 2.3        | 9.2 (38.2)               | 1.8 ± 0.9  | 0.3 ± 0.5   | 1.5 (83.3)                |
| Ahmed et al. [11]              | 2014 | 2 iStents                        | 39             | 12                 | 22.2 ± 2.0       | 17.1 ± 2.2        | 5.1 (23.0)               | 2          | 1           | 1 (50.0)                  |
| Arriola-Villalobos et al. [12] | 2013 | 2 iStents + CS                   | 20             | 12                 | 20.0 ± 3.7       | 16.8 ± 2.2        | 3.2 (16.0)               | 1.3 ± 0.7  | 0.3 ± 0.6   | 1 (76.9)                  |
| Author                      | Year | Operation        | Number of eyes | Follow-up (months) | Preop IOP (mmHg) | Postop IOP (mmHg) | IOP reduction (mmHg, %) | Preop meds | Postop meds | Medication reduction (n, %)* |
|-----------------------------|------|------------------|---------------|-------------------|------------------|-------------------|------------------------|------------|-------------|----------------------------|
| Patel et al. [26]           | 2013 | 1 iStent ± CS    | 44            | 6                 | 21.5             | 16.7              | 4.8 (22.3)             | 2.3        | 0.6         | 1.7 (73.9)               |
| Arriola-Villalobos et al. [25] | 2012 | 1 iStent + CS    | 19            | 36                | 19.4 ± 1.9       | 16.3 ± 4.2        | 3.2 (16.3)             | 1.3 ± 0.5  | 0.8 ± 0.9    | 0.48 (36.4)              |
| Buchacra et al. [9]         | 2011 | 1 iStent         | 10            | 12                | 26.5 ± 7.9       | 17.0 ± 2.5        | 9.5 (35.8)             | 2.9 ± 0.7  | 1.1 ± 0.6    | 1.8 (62.1)               |
| Samuelson et al. [18]       | 2011 | 1 iStent + CS    | 111           | 12                | 18.4 ± 3.2       | 16.9 ± 3.0        | 1.5 (8.2)              | 1.5 ± 0.6  | 0.2 ± 0.6    | 1.3 (86.7)               |
| Vandevalle et al. [24]      | 2009 | 1 iStent ± CS    | 10            | 12                | 19.6             | 15.8              | 3.8 (19.4)             | 2.7        | 1.7         | 1 (37.0)                  |
| Spiegel et al. [27]         | 2009 | 1 iStent ± CS    | 47            | 12                | 21.5 ± 3.7       | 16.9              | 4.6 (21.4)             | 1.6 ± 0.8  | 0.4         | 1.2 (75.0)               |
| **iStent inject**           |      |                  |               |                   |                  |                   |                        |            |             |                            |
| Fea et al. [28]             | 2014 | 2 iStent injects | 94            | 12                | 21.1 ± 1.7       | 13.0 ± 2.3        | 8.1 (38.4)             | 1          | 0.1         | 0.9 (91.5)               |
| Arriola-Villalobos et al. [30] | 2016 | 1 iStent inject + CS | 11          | 60                | 20.4 ± 4.5       | 16.2 ± 2.3        | 4.2 (20.5)             | 1.2 ± 0.8  | 1.1 ± 0.8    | 0.1 (7.6)                |
| Voskanyan et al. [29]       | 2014 | 2 iStent injects | 99            | 12                | 22.1 ± 3.3       | 15.7 ± 3.7        | 6.4 (29.0)             | 2.2 ± 0.4  | 0.3         | 1.9 (87.3)               |
| Gonnermann et al. [31]      | 2016 | 2 iStent injects + CS | 25          | 12                | 21.3 ± 4.1       | 14.0 ± 2.3        | 7.3 (34.0)             | 2.0 ± 0.9  | 1.3 ± 1.2    | 0.7 (36.0)               |
| Klamann et al. [65]         | 2015 | 1 iStent inject†† | 17            | 6                 | 21.2 ± 2.6       | 14.2 ± 1.4        | 7.1 (33.4)             | 2.2 ± 0.9  | 0.9 ± 0.6    | 1.3 (59.8)               |
| **Hydrus**                  |      |                  |               |                   |                  |                   |                        |            |             |                            |
| Pfeiffer et al. [32]        | 2015 | Hydrus + CS      | 50            | 24                | 18.9 ± 3.3       | 16.9 ± 3.3        | 2.0 (10.6)             | 2.0 ± 1.0  | 0.5 ± 1.0    | 1.5 (75.0)               |
| Fea et al. [33]             | 2016 | Hydrus           | 31            | 12                | 23.1 ± 5.1       | 16.5 ± 2.6        | 6.6 (28.5)             | 2.3 ± 0.8  | 0.9 ± 1.0    | 1.4 (60.7)               |
| Gandolfi et al. [34]        | 2016 | Hydrus           | 21            | 24                | 26.0 ± 4.0       | 16.0 ± 2.0        | 10.0 (38.5)            | 2.7        | 0.9 ± 1.0    | 1.8 (66.9)               |
| **Suprachoroidal devices**  |      |                  |               |                   |                  |                   |                        |            |             |                            |
| CyPass                      |      |                  |               |                   |                  |                   |                        |            |             |                            |
| Vold et al. [15]            | 2016 | CyPass + CS      | 374           | 24                | 24.4 ± 2.8 †     | 17.0 ± 3.4        | 7.4 (30.3)             | 1.4 ± 0.9  | 0.2 ± 0.6    | 1.2 (85.7)               |
| Hoeh et al. [53]            | 2016 | CyPass + CS      | 142           | 12                | 20.2 ± 6.0       | 15.9 ± 3.1        | 4.3 (21.3)             | 2.0 ± 1.1  | 1.1         | 0.9 (45.0)               |
| Garcia-Feijoo et al. [54]   | 2015 | CyPass           | 65            | 12                | 24.5 ± 2.8       | 16.4 ± 5.5        | 8.1 (33.1)             | 2.2 ± 1.1  | 1.4 ± 1.3    | 0.8 (36.4)               |
| Hoeh et al. [52]            | 2013 | CyPass + CS      | 184           | 6                 | 21.1 ± 5.9       | 15.6 ± 0.5        | 5.5 (26.1)             | 2.1 ± 1.1  | 0.8         | 1.35 (64.3)              |
| **Subconjunctival devices** |      |                  |               |                   |                  |                   |                        |            |             |                            |
| XEN-45                      |      |                  |               |                   |                  |                   |                        |            |             |                            |
| Perez-Torregrosa et al. [55] | 2016 | XEN-45 + CS     | 30            | 12                | 21.2 ± 3.4       | 15.0 ± 2.5        | 6.2 (29.1)             | 3.1 ± 0.7  | 0.2 ± 0.7    | 2.9 (94.5)               |
| **InnFocus**                |      |                  |               |                   |                  |                   |                        |            |             |                            |
| Battie et al. [63]          | 2016 | InnFocus + CS    | 23            | 36                | 23.8 ± 5.3       | 10.7 ± 3.5        | 13.1 (55.0)            | 2.4 ± 1.0  | 0.7 ± 1.1    | 1.7 (70.8)               |

CS: cataract surgery; ELT: excimer laser trabeculotomy; IOP: intraocular pressure; * represents unpaired results; ** represents only prospective case series and randomized controlled trials are included; † represents postwashout IOP; †† represents study was split into three groups: phakic open-angle glaucoma, phakic pseudoexfoliation glaucoma, and pseudophakic subjects, respectively.
### Table 3: Safety of MIGS devices.

| Author                         | Year | Postoperative complications ($n$, %) | Reoperations ($n$, %) |
|-------------------------------|------|--------------------------------------|-----------------------|
| Sclemm’s canal devices*       |      |                                      |                       |
| **Trabectome**                |      |                                      |                       |
| Lee et al. [38]               | 2016 | Herpetic keratitis reactivation = 1 (5.3) | AC washout = 1 (5.3) |
|                              |      | IOP > 21 mmHg = 5 (26.3)             | Repeat glaucoma surgery = 2 (10.5) |
| Bussel et al. [37]            | 2014 | Transient hypotony = 5 (6.8)         |                       |
|                              |      |                                      | Tube surgery = 6 (8.2) |
| Jordan et al. [40]            | 2013 | Reflux bleeding = 512 (91.9)         |                       |
|                              |      | IOP > 30 mmHg = 44 (7.8)             | Cyclophotocoagulation = 2 (2.7) |
|                              |      | Cystoid macular edema = 3 (0.5)      | Repeat Trabectome = 1 (1.4) |
| Maeda et al. [64]             | 2013 | Reflux bleeding = 80 (100)           |                       |
|                              |      | Reoperation (glaucoma surgery) = 13 (16.3) | Repeat glaucoma surgery = 13 (16.3) |
| Ting et al. [36]              | 2012 | Transient hypotony = 4 (1.3)         |                       |
|                              |      | IOP > 10 mmHg from baseline = 32 (10.5) |                       |
|                              |      | Reflux bleeding = 238 (78.3)         | Tube surgery = 1 (0.3) |
| Francis et al. [42]           | 2008 | Reflux bleeding = 37 (100)           |                       |
|                              |      | Persistent minimal DM injury = 1 (2.7) |                       |
|                              |      | Peripheral anterior synaechiae = 9 (24.3) |                       |
|                              |      | Goniosynechiae = 5 (13.5)            |                       |
| Minckler et al. [66]          | 2005 | IOP > 5 mmHg from baseline = 2 (5.4) |                       |
| Babighian et al. [49]         | 2010 | IOP > 5 mmHg from baseline = 3 (20)  |                       |
| Wilmsmeyer et al. [48]        | 2006 | Iris adhesion to corneal tunnel = 2 (1.5) |                       |
| iStent                        |      |                                      |                       |
| Tan and Au [23]               | 2016 | Transient hyphema = 1 (2.4)          |                       |
| Neuhann [22]                  | 2015 | Stent not visible = 1 (1.6)          | Cyclophotocoagulation = 3 (4.8) |
| Katz et al. [7]               | 2015 | 0                                    | Shunt surgery = 2 (3.2) |
| Vold et al. [15]              | 2016 | Intraoperative stent malposition = 2 (3.7) |                       |
| Lindstrom et al. [16]         | 2016 | 0                                    |                       |
| Fiea et al. [20]              | 2015 | 0                                    |                       |
| Donnenfeld et al. [10]        | 2015 | Hyphema = 2 (5.1)                    | AC paracentesis = 1 (2.6) |
| Ahmed et al. [11]             | 2014 | Transient hypotony = 1 (2.6)         |                       |
| Arriola-Villalobos et al. [12]| 2013 | 0                                    |                       |
| Craven et al. [17]            | 2012 | Stent obstruction = 5 (4.3)          | Trabeculoplasty = 1 (0.9) |
|                              |      | Stent malposition = 3 (2.6)          | Stent repositioning = 3 (2.6) |
|                              |      | YAG laser for stent obstruction = 1 (0.9) | Stent replacement = 1 (0.9) |
| Patel et al. [26]             | 2013 | Hyphema = 1 (2.3)                    | 0                     |
| Author                          | Year | Postoperative complications (n, %)                                      | Reoperations (n, %) |
|--------------------------------|------|-----------------------------------------------------------------------|--------------------|
| Arriola-Villalobos et al. [25] | 2012 | Stent malposition = 1 (10.0)                                          | 0                  |
|                                |      | Mild hyphema = 7 (70.0)                                               |                    |
|                                |      | IOP ≥ 30 mmHg = 1 (10.0)                                              |                    |
|                                |      | Corneal edema = 2 (20.0)                                              |                    |
|                                |      | Stent obstruction by blood clot = 3 (30.0)                            |                    |
| Buchacra et al. [9]            | 2011 |                                                                        |                    |
|                                |      | Stent obstruction = 4 (4.0)                                            |                    |
|                                |      | Stent malposition = 3 (3.0)                                           |                    |
|                                |      | Elevated IOP = 2 (2.0)                                                |                    |
|                                |      | Elevated IOP requiring treatment = 1 (1.0)                            |                    |
|                                |      | YAG laser for stent obstruction = 1 (1.0)                             |                    |
| Samuelson et al. [18]          | 2011 | Stent obstruction = 4 (4.0)                                            | Stent repositioning = 3 (3.0) |
|                                |      | Stent malposition = 3 (3.0)                                           |                    |
|                                |      | Elevated IOP = 2 (2.0)                                                |                    |
|                                |      | Elevated IOP requiring treatment = 1 (1.0)                            |                    |
|                                |      | YAG laser for stent obstruction = 1 (1.0)                             |                    |
| Fernandez-Barrientos et al. [13]| 2010| Stent malposition = 6 of 34 stents (17.6)                             | 0                  |
|                                |      | Stent fall out = 1 of 34 stents (2.9)                                  |                    |
|                                |      |                                                                        |                    |
| Spiegel et al. [27]            | 2009 | Stent malposition (no repositioning) = 6 (10.3)                       | Trabeculectomy = 2 (3.4) |
|                                |      | Stent obstruction = 7 (12.1)                                           | Stent repositioning = 1 (1.7) |
|                                |      | Argon laser = 1 (1.7)                                                 | Stent replacement = 2 (3.4) |
|                                |      |                                                                      | Corneal paracentesis = 1 (1.7) |
| Vandewalle et al. [24]         | 2009 | Stent malposition = 1 (10.0)                                          | 0                  |
|                                |      | Corneal edema = 2 (20.0)                                              |                    |
|                                |      | Blood reflux into angle = 5 (50.5)                                    |                    |
|                                |      | Elevated IOP requiring medications = 10 (10.1)                       |                    |
|                                |      | YAG laser for stent obstruction = 2 (2.0)                             | Phacotrabeculectomy = 1 (1.0) |
|                                |      | Argon laser for stent obstruction = 1 (1.0)                           | Goniotrephination = 1 (1.0) |
|                                |      | Stent obstruction = 3 (3.0)                                           |                    |
|                                |      | Stent malposition = 1 (1.0)                                           |                    |
|                                |      | Goniosynechiae (without treatment) = 1 (1.0)                          | Deep sclerectomy = 1 (1.0) |
|                                |      | Lens-iris synechiae (laser treatment) = 1 (1.0)                       |                    |
|                                |      | Stent not visible upon gonioscopy = 13 (13.1)                         |                    |
| Arriola-Villalobos et al. [30] | 2016 | 0                                                                     | 0                  |
| Hydrus                         |      |                                                                      |                    |
| Fea et al. [33]                | 2016 | Transient IOP spike = 2 (6.5)                                         | 0                  |
|                                |      | BCVA < 2 lines from baseline = 3 (9.7)                                |                    |
| Gandolfi et al. [34]           | 2016 | Transient hyphema = 4 (19.0)                                          | 0                  |
|                                |      | IO ≥ 30 mmHg within 48 hrs = 1 (4.8)                                   |                    |
|                                |      | YAG lysis of PAS = 4 (19.0)                                           |                    |
| Pfeiffer et al. [32]           | 2015 | IOP > 10 mmHg from baseline = 2 (4.0)                                 | Repeat glaucoma surgery = 1 (2.1) |
|                                |      | Focal PAS = 9 (18.8)                                                  |                    |
| Suprachoroidal devices CyPass  |      |                                                                      |                    |
| Vold et al. [51]               | 2016 | Corneal abrasion = 7 (1.9)                                            | Secondary ocular surgical intervention = 20 (5.5) |
|                                |      | Corneal edema = 13 (3.5)                                              |                    |
|                                |      | Cyclodialysis cleft > 2 mm circumference = 7 (1.9)                    |                    |
|                                |      | Iritis = 32 (8.6)                                                     |                    |
|                                |      | Hypotony = 11 (29.9)                                                  |                    |
|                                |      | IOP ≥ 10 mmHg above baseline = 16 (4.3)                               |                    |
|                                |      | Cystoid macular edema = 6 (1.3)                                       |                    |
|                                |      | Stent obstruction = 8 (2.1)                                           |                    |
|                                |      | Conjunctivitis = 4 (1.0)                                              |                    |
selective laser trabeculoplasty (SLT) to compare the IOP-lowering effects between the two groups [33]. At one year postoperatively, mean IOP decreased from 23.1 ± 5.08 to 16.5 ± 2.6 mmHg for the Hydrus group, and a similar decrease was found for the SLT group (from 23.2 ± 2.15 mmHg to 15.9 ± 2.49 mmHg). However, subjects in the Hydrus group had significantly greater medication reduction when compared to those in the SLT group (−1.4 ± 0.97 versus −0.5 ± 1.05, p = 0.001).

The Hydrus implant is generally safe, and complications are infrequent. Several studies have shown the Hydrus to have a transient early IOP spike from baseline in less than 10% of patients [32–34], of which one of the authors attributed to retain viscoelastic material at the end of operation [33]. Gandolﬁ reported transient hyphema in 4 subjects (19.0%) in a retrospective cohort of subjects, and this resolved without treatment [34]. The HYDRUS II study found focal peripheral anterior synechiae in 9 subjects (18.8%), which did not require further intervention [32].

### 3.1.4. Ab Interno Trabeculotomy

**Ab interno trabeculotomy** is performed most commonly using the Trabectome device (NeoMedix, Tustin, USA). Using high frequency electrocautery energy, the Trabectome ablates part of the nasal trabecular meshwork and inner walls of the Schlemm’s canal over a 90° to 120° arc through a single temporal incision [35]. This procedure may be performed with or without phacoemulsification in the same setting.

Numerous studies have been conducted to identify the IOP-lowering effect of Trabectome, either as a stand-alone procedure or as a procedure combined with phacoemulsification. However, results from prospective RCTs are lacking. The first prospective case series was performed by

**Table 3: Continued.**

| Author            | Year | Postoperative complications (n, %)          | Reoperations (n, %)          |
|-------------------|------|-------------------------------------------|-----------------------------|
| Garcia-Feijoo et al. [54] | 2015 | IOP > 30 mmHg = 7 (10.8)                  | Trabeculectomy = 9 (13.8)   |
|                   |      | Transient hyphema = 4 (6.2)               |                             |
|                   |      | BCVA reduced by ≥2 lines = 2 (3.1)        | Additional CyPass = 2 (3.1)  |
|                   |      | Laser trabeculoplasty = 1 (1.6)          |                             |
| Hoeh et al. [53]  | 2016 | Early postoperative IOP elevation = 2 (1.2)| Repeat glaucoma surgery = 10 (6.0) |
|                   |      | Late postoperative IOP elevation = 3 (1.8)| Implant reposition = 1 (0.6) |
|                   |      | Mild transient hyphema = 2 (1.2)          |                             |
|                   |      | Hypotony = 23 (13.8)                      |                             |
|                   |      | Endothelial touch = 2 (1.2)               |                             |
|                   |      | Implant obstruction = 9 (5.4)             |                             |
|                   |      | Macular edema = 1 (0.6)                   |                             |
| Hoeh et al. [52]  | 2013 | AC reaction > 1 month = 8 (4.4)           | Device repositioning = 1 (0.6) |
|                   |      | Early hyptony (<1 month) = 25 (13.8)      |                             |
|                   |      | Hypotony > 1 month = 1 (0.5)              |                             |
|                   |      | Shallow AC without central touch = 1 (0.5)| Repeat glaucoma surgery = 9 (5.0) |
|                   |      | IOP > 10 mmHg from baseline = 19 (10.5)   |                             |
|                   |      | Postoperative hyphema = 2 (1.1)           |                             |
| Perez-Torregrosa et al. [55] | 2016 | Encapsulation of filtration bleb = 1 (3.3) | 0                           |
| **InnFocus**      |      | Tube-iris touch = 3 (13.0)                | Repeat glaucoma surgery = 1 (4.3) |
|                   |      | Transient hyptony < 3 months = 3 (13.0)   |                             |
|                   |      | Shallow or flat AC = 3 (13.0)             |                             |
|                   |      | Hyphema = 2 (8.7)                         |                             |
| Batlle et al. [63] | 2016 | Choroidal effusion/detachment = 2 (8.7)   | AC paracentesis = 1 (4.3)   |
|                   |      | Elevated IOP requiring bleb needling = 1 (4.3)|                             |
|                   |      | Tube obstruction = 1 (4.3)                |                             |
|                   |      | Vitreous hemorrhage = 1 (4.3)             |                             |
|                   |      | Bleb leak = 1 (4.3)                       |                             |

AC: anterior chamber; BCVA: best corrected visual acuity; CRVO: central retinal vein occlusion; IOP: intraocular pressure; PAS: peripheral anterior synechiae; SLT: selective laser trabeculoplasty. *Only prospective case series and randomized controlled trials are included.
Minckler et al. in 2005 [35], who recruited 37 subjects for stand-alone Trabectome procedure and followed them up for one year postoperatively. They found postoperative-mediated IOP to be 16.3 ± 2.0 mmHg, down from a baseline postwashout IOP of 28.2 ± 4.4 mmHg. There was a corresponding decrease in medication usage from 1.2 ± 0.6 at baseline to an average of 0.3 medications through the postoperative period.

Subsequent studies have found similar IOP-lowering effects between 4 mmHg and 10 mmHg up to one year postoperatively [36–40] (Table 2). The effect appears to be more significant in patients with exfoliative glaucoma. In a large prospective cohort study done by Ting et al. [36], subjects with exfoliative glaucoma experienced a greater IOP reduction postoperatively compared to subjects with open-angle glaucoma one year after Trabectome incision with or without phacoemulsification (Table 2). The authors postulated that the mechanical effect of trabecular meshwork removal facilitates the washout of exfoliative material thus contributing to a great decrease in IOP.

Being a minimally invasive procedure, the safety profile of Trabectome is impressive (Table 3). A prominent observation of using the Trabectome is blood reflux into the anterior chamber. Almost all patients experience some degree of blood reflux upon the withdrawal of the instrument from the eye, although the effects are almost always self-limiting [35, 40–43]. Intraoperative blood reflux is often considered to be a positive sign which indicates patency of the Schlemm’s canal and the downstream collector channels and aqueous veins [42], although inadvertent damage to anterior chamber structures may also occur, resulting in the formation of peripheral anterior synechiae or goniosynechiae [35]. Overall, the complication rates of Trabectome surgery are much lower than those of traditional glaucoma filtration surgeries.

3.1.5. Gonioscopy-Assisted Transluminal Trabeculectomy, Kahook Dual Blade, and Trab360. The following devices are similar to the Trabectome and increase outflow through the Schlemm’s canal through directly removing a part of the trabecular meshwork. As such, some may argue that they may not qualify as MIGS because there is significant tissue destruction. The Kahook Dual Blade (DKB) (New World Medical, CA, USA) is a novel dual-blade device that elevates and removes the trabecular meshwork, allowing for cleaner removal of the tissue, thus minimizing damage to adjacent structures [44]. There is limited clinical data on the efficacy of this FDA-approved device. Gonioscopy-assisted transluminal trabeculotomy (GATT) (Glucoma Associates of Texas, TX, USA) and Trab360 are devices that allow circumferential 360-degree removal of the trabecular meshwork. Studies suggest that the efficacy of these procedures is superior to that of Trabectome, but with a higher rate of hyphema [45–47].

3.1.6. Excimer Laser Trabeculotomy. Unlike the Trabectome, excimer laser trabeculotomy (ELT) utilizes an endoscopically guided excimer laser (AIDA, Tuilaser, Munich, Germany) to induce microperforations within the trabecular meshwork [48]. The photoablative effects of the XeCl 308 nm laser open the trabecular meshwork without thermal effects which may induce scarring. This procedure may be performed with or without phacoemulsification.

In 2006, Wilsmeyer et al. published a retrospective review on a group of 135 patients with open-angle glaucoma [48]. 75 patients underwent ELT alone (group 1), while another 60 patients with concurrent visually significant cataracts underwent combined phacoemulsification and ELT (group 2). At one year postoperatively, there was a reduction of IOP from 23.3 ± 0.6 mmHg to 18.8 ± 0.8 mmHg for group 1 and a corresponding reduction of IOP from 22.4 ± 0.8 mmHg to 16.4 ± 0.4 mmHg for group 2 (Table 2). The number of medications required was not significantly different pre- and postoperatively for both groups. The authors concluded that phacoemulsification with ELT is more efficacious than ELT alone. Babighian et al. conducted a prospective RCT comparing ELT with selective laser trabeculoplasty (SLT) in 15 patients with refractory open-angle glaucoma for two years postoperatively [49]. In the ELT group, there was a significant decrease in IOP from 25.0 ± 1.9 mmHg preoperatively to 17.6 ± 2.2 mmHg at two years postoperatively, with a corresponding decrease in medications from 2.27 ± 0.6 to 0.73 ± 0.8 (Table 2). These results were similar to those of SLT, and the authors also found no significant difference in the success rates between the two groups. Another similar study by Bagighian et al. in 2006 found similar findings [50].

Complications from ELT are mostly self-limited. In Babighian’s study, 80% of patients had transient intraoperative anterior chamber bleeding and 20% of patients had IOP increase of more than 5 mmHg which resolved spontaneously without treatment (Table 3). No reoperations were reported. In contrast, Wilsmeyer et al. reported reoperation in 19% of their patients, most of them due to treatment failure (Table 3). Two patients had iris adhesion to corneal tunnel, and one patient had central retinal vein occlusion five months postoperatively, which the authors deemed to be unrelated to the procedure [48].

3.2. Suprachoroidal Space. In contrast to Schlemm’s canal devices, several other devices have attempted to utilize the alternative uveoscleral outflow pathway as a means to reduce intraocular pressure. Unlike the Schlemm’s canal in which aqueous outflow could be affected by episcleral venous pressure, the suprachoroidal space is a potential space that confers minimal resistance to aqueous outflow. It allows aqueous to traverse the sclera directly via the intercellular spaces between ciliary muscle fibres and loose connective tissues of the suprachoroidal space. The CyPass MicroStent (Transcend Medical, Menlo Park, CA, USA) and the iStent Supra (Glaukos Corporation, CA, USA) are MIGS devices that drain to the suprachoroidal space. Other devices that utilize this drainage pathway include the Gold Micro Shunt (SOLX Inc., Waltham, MA, USA) and the Aquashunt, but these require ab externo implantation requiring conjunctival dissection and scleral incision, hence are not typically regarded as MIGS devices and are beyond the scope of this review.
3.2.1. CyPass. The CyPass MicroStent (CyPass) is a flexible fenestrated microstent made of polyimide material, which follows the curvature of the sclera as it is threaded through a guidewire and applicator into the suprachoroidal space. This is performed through a single corneal incision and blunt dissection through gonioscopic guidance.

Vold et al. published the only RCT to date for the CyPass, the COMPASS II study [51]. This large RCT included 374 subjects with OAG who underwent combined phacoemulsification and CyPass implantation, compared with 131 control subjects who underwent standard phacoemulsification alone. Subjects were followed up for two years postoperatively with less than 5% dropout rate. IOP reduced from preoperative washout levels of 24.4 ± 2.8 mmHg to 17 ± 3.4 mmHg at two years postoperatively. Medication requirement was reduced from an average of 1.4 ± 0.9 to 0.2 ± 0.6 mmHg (Table 2). Compared with the control group which had only phacoemulsification, there was a significantly greater IOP-lowering effect as well as threefold reduction of IOP-lowering medications in the group which underwent combined phacoemulsification and CyPass implantation. The authors concluded that CyPass with phacoemulsification had sustained 2-year efficacy benefit for the IOP control. This comprehensive study corroborated the efficacy findings in previous prospective case series and interventional studies by other authors [52–54] (Table 2).

Compared to Schlemm’s canal devices, the CyPass is associated with a higher incidence of early IOP fluctuations (both transient hypotony and transient ocular hypertension) in the immediate postoperative period [51–54]. Transient hypotony is hypothesized to be due to the creation of a cycloidalysis cleft which might extend beyond the external diameter of the CyPass [52]. Unlike in subconjunctival procedures, transient hypotony does not cause anterior chamber shallowing as aqueous outflow is contained internally and ocular tissue integrity is maintained. On the other hand, transient IOP spikes could potentially be dangerous for patients with advanced glaucoma; unlike in subconjunctival drainage devices where outflow could be modulated with mitomycin C (MMC) or bleb manipulation procedures such as needling, there is no way of preventing or reversing scarring in the suprachoroidal space. Overall, however, reported adverse event rates of CyPass with phacoemulsification were not significantly higher than those of phacoemulsification alone (39% versus 36%, resp., COMPASS II study) [51]. Being an ab interno procedure, the CyPass also eliminates concerns about bleb-related and conjunctival complications.

3.2.2. iStent Supra. The iStent Supra is an investigational device similar to the CyPass. It is made of polyethersulfone and titanium and implanted ab interno; it may be implanted after cataract surgery. Studies are underway to evaluate the efficacy and safety of this device, though there is no published literature at the point of writing.

3.3. Subconjunctival Space. The subconjunctival space is a potential space under the Tenon’s capsule which is not part of the physiological outflow pathway. However, it is the drainage pathway most familiar to glaucoma surgeons as it is utilized in conventional glaucoma surgery, including trabeculectomy and tube implant surgery. Just like the suprachoroidal space, this area is not limited by the episcleral venous pressure but aqueous drainage can be compromised by fibrosis and scarring. The XEN-45® implant (Allergan, Dublin, Ireland) is the first MIGS device that drains to the subconjunctival space. Though the Innfocus MicroShunt (Santen Pharmaceutical Co. Ltd., Osaka, Japan) is implanted through an ab externo approach requiring conjunctival dissection, the US Food and Drug Administration (FDA) has classified it as a MIGS device; hence, it is included in this review.

3.3.1. XEN-45 Gel Stent. The XEN-45 Gel Stent (XEN-45) is a hydrophilic collagen tube made with gelatin and glutaraldehyde. Its physical composition makes the device harder when dry, but softer and more flexible when hydrated. It is preloaded in an injector which allows controlled ab interno insertion into the subconjunctival space, emerging 3 mm posterior to the limbus. Bleb formation is confirmed at the end of surgery, and XEN-45 implantation may be performed together with cataract extraction surgery. The implant was recently approved by FDA for use in medically and surgically refractory open-angle glaucoma.

Recently, Perez-Torregrosa et al. published a prospective nonrandomized case series of 30 phakic subjects with OAG who underwent combined phacoemulsification and XEN-45 implantation [55]. One year after the surgery, IOP was reduced from 21.2 ± 3.4 mmHg preoperatively to 15.0 ± 2.47 mmHg postoperatively, with a corresponding reduction in medications from 3.07 ± 0.69 to 0.17 ± 0.65 (Table 2). The success rate was 90% (27 out of 30 eyes), with success being defined as IOP ≤ 18 mmHg without medications.

The XEN-45 also demonstrated good safety profile in the same study above, with intraoperative hemorrhage (both intracameral and at scleral exit point) being the most common (Table 2). Importantly, postoperative encapsulation of filtration bleb was found in only one eye (3.3%), although a longer follow-up period may be required to identify the prevalence of late fibrosis of subconjunctival space. The authors also recommended that the optimal placement of the 6 mm device would be 2 mm subconjunctival, 3 mm intrascleral, and 1 mm intracameral to balance implant coverage and aqueous outflow. With an internal lumen diameter of 45 μm and a length of 6 mm, the XEN-45 implant confers protection against hypotony as it has an intrinsic outflow resistance of 6–8 mmHg according to the Hagen-Poiseuille equation [56]. This is achieved through designing specific lengths and internal diameters of the tube, which has been demonstrated through flow testing by Sheybani et al. [57].

Aside from isolated case reports [58, 59] and a single pilot study on combined XEN implant with the Baerveldt tube (Abbott Inc., Lake Bluff, IL, USA) [60], there is currently a lack of other published literature on the XEN-45. A study by Sheybani et al. reported promising clinical results in 37 patients who underwent combined XEN-140 (140 μm internal diameter) and XEN-63 (63 μm internal diameter);
implantation and cataract surgery, albeit with 9% of patients developing transient hypotony, require intracameral viscoelastic injections within the first postoperative week [61]. More randomized and controlled studies are required to determine whether the XEN-45 implant is as effective as its predecessors (XEN-140 and XEN-63) with a lower rate of hypotony.

3.3.2. InnFocus MicroShunt. The InnFocus MicroShunt (MicroShunt) is an experimental device which is a trial product awaiting FDA approval. It is purported to act as a flow resistor to maintain the long-term transscleral pressure above 5 mmHg. As with all subconjunctival procedures, there exists a risk of subsequent conjunctival fibrosis limiting aqueous outflow [62]. For this reason, MicroShunt surgery may be performed with intraoperative MMC, as with XEN-45.

Batlle et al. studied the efficacy of the MicroShunt with MMC over a period of three years in a nonrandomized prospective case series of 23 eyes with OAG [63]. 14 subjects underwent isolated InnFocus insertion while another 9 had it implanted with concurrent cataract surgery. At the end of 36 months, there was a significant reduction in IOP from a preoperative level of 23.8 ± 5.3 mmHg to 10.7 ± 3.5 mmHg. The authors quote a qualified success rate of up to 95% up to three years (IOP ≤ 14 mmHg and IOP reduction ≥ 20%). In the same study, the authors found the complications to be transient and self-limiting (Table 3). Specifically, there were no cases of bleb leaks, infections, migrations, erosions, or other serious bleb-related complications known to conventional trabeculectomy.

However, the small and nonrandomized sample size of this study make their findings hard to generalize and more clinical studies would be required to support these preliminary findings. Our literature search did not reveal any other published articles on InnFocus MicroShunt; a multicenter clinical trial comparing MicroShunt to primary trabeculectomy is currently underway.

4. Conclusion

Currently, the glaucoma surgeon is spoilt for choice where MIGS devices are concerned. However, aside from the Trabectome and iStent, high quality evidence on the efficacy of MIGS devices is still lacking. The overall modest IOP reduction effect and generally favorable safety profile of Schlemm’s canal devices make it a welcome option for patients with mild or moderate glaucoma who would like to reduce their medication burden. Suprachoroidal and subconjunctival devices offer the potential of greater IOP reduction, but suprachoroidal devices such as CyPass are potentially associated with unpredictable IOP spikes and hypotony while subconjunctival devices may fail as a consequence of subconjunctival fibrosis or result in bleb-related complications. More prospective randomized trials with longer follow-up periods are required to further evaluate the efficacy and safety of this rapidly evolving field of glaucoma treatment. Further comparative studies would also be helpful to evaluate the relative efficacy of different MIGS devices.

Conflicts of Interest

David Z. Chen has no conflict of interest regarding the publication of this paper. Chelvin C. A. Sng is a consultant for Allergan and Glaukos and has received research funding from Glaukos.

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Clinical Study

Short-Term Clinical Results of Ab Interno Trabeculotomy Using the Trabectome with or without Cataract Surgery for Open-Angle Glaucoma Patients of High Intraocular Pressure

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Purpose. To assess the safety and efficacy of Trabectome procedure in patients with preoperative intraocular pressure (IOP) of 30 mmHg or higher.

Methods. All patients who had undergone Trabectome stand-alone or Trabectome combined with phacoemulsification were included. Survival analysis was performed by using Kaplan-Meier, and success was defined as IOP ≤ 21 mmHg, 20% or more IOP reduction from baseline for any two consecutive visits after 3 months, and no secondary glaucoma surgery. Results. A total of 49 cases were included with an average age of 66 (range: 13–91). 28 cases had Trabectome stand-alone and 21 cases had Trabectome combined with phacoemulsification. Mean IOP was reduced from a baseline of 35.6 ± 6.3 mmHg to 16.8 ± 3.8 mmHg at 12 months (p < 0.01∗), while the number of medications was reduced from 3.1 ± 1.3 to 1.8 ± 1.4 (p < 0.01∗). Survival rate at 12 months was 80%. 9 cases required secondary glaucoma surgery, and 1 case was reported with hypotony at day one, but resolved within one week. Conclusion. Trabectome seems to be safe and effective in patients with preoperative IOP of 30 mmHg or greater. Even in this cohort with high preoperative IOP, the end result is a mean IOP in the physiologic range.

1. Introduction

Glaucoma is a progressive disease which causes irreversible damage to the optic nerve [1]. The main goal of treatment is to lower intraocular pressure (IOP) to a level which is safe for the optic nerve head. Although trabeculectomy or episcleral aqueous drainage implants demonstrated a permanent IOP reduction, they may have a high risk profile regarding the intraoperative and postoperative complications [2]. This has influenced the development of a less invasive surgical technique, trabeculotomy by internal approach with the Trabectome (NeoMedix Corp., Tustin, CA), which works on the trabecular meshwork and inner wall of Schlemm’s canal to reduce outflow resistance [3, 4]. This surgical approach provides a postoperatively stable eye without damaging the conjunctiva and can be further combined with cataract surgery easily with low incidence of intraoperative and postoperative complications.

Results of Trabectome in various types of open-angle glaucoma patients with preoperative IOP of less than 30 mmHg have been shown to be favorable with fewer rates of complication compared to those of traditional trabeculectomy, giving the surgeons hope of an effective and safe treatment option for patients with higher preoperative IOPs [2–4].

The study was conducted to report the success rate of ab interno trabeculotomy within a single-surgeon, single-
center cohort of patients with a preoperative IOP of 30 mmHg or higher.

2. Patient and Methods

This is a nonrandomized prospective analysis of patients treated by a single experienced surgeon (BAF). The study followed the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act and had the Institutional Review Board approval. Cohort comparison was studied between patients with open-angle glaucoma-receiving Trabectome combined with phacoemulsification cataract extraction and intraocular lens (IOL) and patients receiving Trabectome alone.

The inclusion criteria for both the combined Trabectome group and Trabectome-alone group were as follows: open-angle glaucoma (as defined by glaucomatous optic nerve appearance with or without glaucomatous visual field damage)—an unobstructed view of the angle, age greater than or equal to 18, a visually significant cataract, and follow-up of at least 2 years. The severity of visual fields was graded according to the Hodapp-Anderson-Parrish (HAP) classification and visual field index (VFI) score [5]. Exclusion criteria were as follows: angle closure, uveitic or neovascular glaucoma, previous glaucoma surgery, and no clear view of the nasal angle.

A total number of 49 eyes of 49 patients were included in the study. Twenty-one eyes underwent combined Trabectome surgery and 28 eyes underwent Trabectome-alone surgery. In each group, patient demographics, preoperative cup-to-disc ratio, preoperative and postoperative visual acuity, IOP, and medications were recorded. Postoperative data at day one and months 1, 3, 6, and 12 were collected.

The surgical procedure has been described in detail elsewhere [2–4]. Briefly, the surgery was performed with the Trabectome® system, including the single-use handpiece with an irrigation-aspiration (I/A) system (Neomedix Inc., Tustin, USA). In combined surgery, the Trabectome surgery was performed prior to phacoemulsification. The head and microscope were tilted to give a gonioscopic view of the angle. The goniosurgical lens (a modified Swann-Jacob lens)
was placed on the cornea to visualize the angle structures. A 1.7 mm keratome was used to create a temporal corneal incision. An ophthalmic viscosurgical device (OVD) was injected to form the anterior chamber. The Trabectome handpiece was inserted and advanced along the meshwork, ablating and removing between 90 and 150 degrees of the nasal trabecular meshwork and inner wall of Schlemm’s canal. The power was adjusted up or down depending on the desire to ablate a wider strip of trabecular meshwork or to minimize burning of tissue, respectively. Irrigation and aspiration were then used to remove any remaining blood, viscoelastic, or cellular material.

Postoperative care is varied according to clinical presentation but routinely includes topical steroids four times per day tapered over 8 weeks, topical antibiotics four times per day for 7 days, and pilocarpine 1% three to four times per day tapering over two to eight weeks. Typically, the patients were advised to continue preoperative glaucoma medications after surgery if needed.

The estimated cumulative success rate was obtained by Kaplan-Meier life-table analyses using the following criteria: Kaplan-Meier survival curve of the success of the procedure defined as a decrease in IOP of 20% or more or a decrease in glaucoma medications with no need for additional medications or glaucoma procedures.

3. Statistical Analysis

One-way repeated-measures analysis of variance (ANOVA) test was used for the baseline and postoperative values for each group. The difference in IOP and number of antiglaucoma medications between groups were assessed by an unpaired t-test. Pearson’s χ² test was used for subgroup comparison of sex and lens status before surgery. We estimated the cumulative percentages of success as well as the failure rates over time with the Kaplan-Meier method. Statistical significance was assumed for p ≤ 0.05.

4. Results

Demographic data and descriptive statistics of 49 cases were included into the study (Table 1). The mean age of the study population was 66 ± 18 and 39% were females. The proportion of Caucasians was higher (63%) and the proportion of
African American patients was lower (4%) in the study group. The mean preoperative IOP was 35.6 ± 6.3 mmHg. By postoperative month 12, the average IOP was 16.8 ± 3.8 (55.3% decrease) \((p < 0.01)\). The average number of glaucoma medication use was significantly decreased from 3.1 ± 1.3 to 1.8 ± 1.3 at month 12 \((p < 0.01)\). Primary open-angle glaucoma (POAG) was the major diagnosis (49%) in the study group and it was followed by pseudoexfoliation glaucoma (24%). Nine patients (18%) needed secondary surgery one year after the surgery and 1 case was reported with hypotony at postoperative 1st day but resolved within one week. The overall survival rate was 80% by postoperative month 12. Figure 1 shows the IOP and glaucoma medication trend with the survival rate of the procedure during the postoperative follow-up.

Twenty-eight cases had Trabectome-alone surgery and 21 cases had combined Trabectome phacoemulsification surgery. There were some statistically significant differences found between the two groups. The preoperative IOP was significantly lower in the combined Trabectome group \((33.0 ± 4.9 \text{ mmHg})\) compared to that in the Trabectome-alone group \((37.6 ± 6.6 \text{ mmHg})\) \((p = 0.01)\). The Trabectome only group had a better preoperative visual acuity, which reflects the presence of the cataract in the combined Trabectome group. The mean age of the combined Trabectome group was 72 ± 17 and 57% were female. However, the mean age of the Trabectome-alone group was 62 ± 18 and 75% were male \((p = 0.06)\). The study reported a higher proportion of Caucasians and lower proportion of Asian patients in both groups. The Trabectome-alone group showed a higher proportion of severe visual field defects compared to the combined Trabectome group. Tables 2 and 3 give the demographic data of each group.

### 5. Combined Trabectome Group

The mean preoperative IOP was 33.0 ± 4.9 mmHg (Figure 2) and by postoperative month 1, it has dropped to 18.5 ± 6.4 (44.2% decrease). By postoperative month 12, the average IOP was even lower at 16.6 ± 4.8 (51.8% decrease) \((p < 0.01)\). Figure 2 shows the IOP and glaucoma medication trend with the survival rate during the postoperative follow-up. The average number of glaucoma medications use in the group was 2.7 ± 1.1. By postoperative month 12, it has significantly decreased to 1.8 ± 1.5 \((p < 0.01)\). Survival rate at 12 months of follow-up was 86%. One eye (5%) needed secondary surgery to control IOP one year after the surgery. Hypotony, aqueous misdirection, wound leak, and postoperative infection were not reported in any of the patients. There was no clinically significant bleeding which may require intervention.

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### Table 2: Demographics and descriptive statistics of the patients with IOP ≥ 30 mmHg and having undergone combined Trabectome surgery.

|                                | n = 21 |
|--------------------------------|--------|
| **Age**                        |        |
| Mean ± SD                      | 72 ± 17|
| Range                          | 23–88  |
| **Gender**                     |        |
| Female                         | 12 (57%)|
| Male                           | 9 (43%) |
| **Race**                       |        |
| African American               | 1 (5%)  |
| Asian                          | 3 (14%) |
| Caucasian                      | 12 (57%)|
| Hispanics                      | 5 (24%) |
| **Diagnosis**                  |        |
| POAG                           | 6 (29%) |
| Pseudoexfoliation glaucoma     | 9 (43%) |
| ACG                            | 2 (10%) |
| Ocular hypertension            | 1 (5%)  |
| Secondary glaucoma             | 1 (5%)  |
| Others                         | 2 (10%) |
| **Preop Snellen acuity**       |        |
| 20/20–20/40                    | 5 (24%) |
| 20/50–20/70                    | 6 (29%) |
| 20/80–20/100                   | 3 (14%) |
| 20/200–20/400                  | 6 (29%) |
| <20/400                        | 0 (0%)  |
| NR                             | 1 (5%)  |
| **VF**                         |        |
| Mild                           | 1 (5%)  |
| Moderate                       | 4 (19%) |
| Advanced                       | 0 (0%)  |
| MD/others                      | 16 (76%)|
| **Disc C/D**                   |        |
| <0.7                           | 5 (24%) |
| 0.7 to 0.8                     | 9 (43%) |
| >0.8                           | 5 (24%) |
| NR                             | 2 (10%) |
| **Lens status**                |        |
| Phakic                         | 20 (95%)|
| Pseudophakic                   | 0 (0%)  |
| Aphakic                        | 0 (0%)  |
| NR                             | 1 (5%)  |
| **Shaffer grade**              |        |
| I                              | 0 (0%)  |
| II                             | 1 (5%)  |
| III                            | 4 (19%) |
| IV                             | 1 (5%)  |
| NR                             | 15 (71%)|

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### Table 2: Continued.

|                                | n = 21 |
|--------------------------------|--------|
| Prior surgeries                |        |
| SLT                            | 9 (43%) |
| ALT                            | 1 (5%)  |
| Trabeculectomy                 | 1 (5%)  |

African American patients was lower (4%) in the study group. The mean preoperative IOP was 35.6 ± 6.3 mmHg. By postoperative month 12, the average IOP was 16.8 ± 3.8 (55.3% decrease) \((p < 0.01)\). The average number of glaucoma medication use was significantly decreased from 3.1 ± 1.3 to 1.8 ± 1.3 at month 12 \((p < 0.01)\). Primary open-angle glaucoma (POAG) was the major diagnosis (49%) in the study group and it was followed by pseudoexfoliation glaucoma (24%). Nine patients (18%) needed secondary surgery one year after the surgery and 1 case was reported with hypotony at postoperative 1st day but resolved within one week. The overall survival rate was 80% by postoperative month 12. Figure 1 shows the IOP and glaucoma medication trend with the survival rate of the procedure during the postoperative follow-up.
6. Trabectome-Alone Group

The mean preoperative IOP was 37.6 ± 6.6 mmHg (Figure 3) and on postoperative day 1, it has decreased to 14.3 ± 5.6 mmHg (61.7% decrease). But by postoperative month 1, IOP increased to 19.9 ± 7.8 (47.1% decrease). By postoperative month 12, the IOP was stable at 16.9 ± 2.4 (56.9% decrease). The average number of glaucoma medications used in the group was 3.4 ± 1.3. By postoperative month 12, it has significantly decreased to 1.8 ± 1.3 (p < 0.01). Figure 3 shows the IOP and glaucoma medication trend with the survival rate during the postoperative follow-up. Eight cases required secondary surgery. Hypotony (IOP < 5 mmHg) at postoperative day one was observed in one patient (4%) and resolved later.

7. Discussion

The Trabectome seems to be a favorable method of minimal invasive glaucoma surgery with or without cataract surgery in patients with preoperative IOP of 30 mmHg or greater. The current data also suggests the effectiveness of Trabectome-alone surgery in reducing IOP and postoperative number of medications compared to combined Trabectome surgery.

The baseline IOP in our study was 33.0 ± 4.9 mmHg in the combined Trabectome group and 37.6 ± 6.6 in the Trabectome-alone group which is higher than the values in the studies by Francis [3] (22 mmHg), Minckler et al. [4] (25.7 mmHg), Jea et al. [6] (28.1 mmHg), or Trabectome-alone surgery significantly reduced the postoperative IOP in our study patients as well as combined Trabectome surgery. The IOPs at 1 year after surgery were significantly reduced from baseline to mid teens (16.9 ± 2.4 mmHg and 16.6 ± 4.8 mmHg, resp.) which is similar to those previously reported [2–6]. These results suggest that Trabectome surgery with or without cataract extraction may offer a clinically useful control on IOP levels. Some studies reported IOPs as 16.1 mmHg [4], 17.4 mmHg [6], and 16.6 mmHg [7] after 1 year of Trabectome surgery. Moreover, in this study, the number of medications were significantly reduced after both surgeries similar to other studies [3, 4, 8]. The success rate after Trabectome surgery has been reported to be about 30%–50% in the literature [2–4, 6–8]. In our study, the success rate for IOP decrease was 55% in the overall study population, 51.8% in the combined group, and 56.8% in the Trabectome-alone group. Mizoguchi et al. [9] reported that their Trabectome failure rate was higher in the eyes with a preoperative IOP <18 mmHg and lower in those with a preoperative IOP of 18–22 mmHg, and they concluded that the
results of Trabectome surgery may differ according to baseline IOP. Although the relationship of the surgical success and preoperative IOP level has not been established yet, our study showed that Trabectome surgery can be effective and safe at baseline IOP levels around 35.6 (±6.3) mmHg. Markedly high and low baseline IOPs have been reported as risk factors for poor surgical outcomes [6, 7].

The current study had a control group of glaucoma patients having Trabectome surgery alone; therefore, it was possible to determine to what extent Trabectome trabeculotomy or cataract extraction contributed to the lowering of IOP and medications. The IOP was lowered by 17.7 ± 7.7 mmHg (51.8% decrease) in the combined Trabectome group and 21.2 ± 7.9 mmHg (56.9% decrease) in the Trabectome-alone group by postoperative month 12. It has been generally suggested that phacoemulsification cataract extraction alone may lower IOP in glaucoma patients as well as in nonglaucomatous individuals, with the amount of 2–4 mmHg [10, 11]. Our study showed that there is a decrease to the normal physiologic level in IOP after a Trabectome procedure. Although a higher proportion of IOP decrease was reported in the Trabectome-alone group, it may be caused by higher baseline IOP levels compared to that in the combined Trabectome group.

In a prospective interventional study [12], patients with open-angle glaucoma underwent combined Trabectome surgery. Mean preoperative IOP was 20.0 ± 6.3 mmHg, and mean postoperative IOP was 15.5 ± 2.9 mmHg, with a 1.4 ± 1.3 mean number of glaucoma medications after one year of follow-up. Nine patients needed additional glaucoma procedures.

Another study with a large number of case series evaluated the outcomes of Trabectome-alone versus combined procedures with phacoemulsification [4]. At 24 months, IOP decreased by 40% from 25.7 ± 7.7 mmHg preoperatively to 16.6 ± 4.0 mmHg in the Trabectome-alone group compared to 30% from 20.0 ± 6.2 mmHg to 14.9 ± 3.1 mmHg in the combined Trabectome group. Mean number of medications decreased from 2.9 to 1.2 in the Trabectome group and from 2.6 to 1.5 in the combined group. A total of 14% of patients were considered failure cases from the Trabectome-alone group.
A prospective nonrandomized study grouped open-angle glaucoma patients who underwent Trabectome procedures according to baseline IOP levels [13]. In the group with preoperative IOP levels ≤ 17 mmHg, the IOP mean reduction was 7% mmHg with a 35% reduction in IOP-lowering medications. However, patients having IOP ≥ 30 mmHg showed IOP reduction as 48% with a 25% reduction in IOP-lowering medications.

Maeda et al. [14] also reported a decrease from mean preoperative IOP of 26.6 ± 8.1 mmHg to 17.4 ± 3.4 mmHg after surgery. The number of IOP-lowering medications decreased from 4.0 ± 1.4 to 2.3 ± 1.2 at 6 months.

In our study, Trabectome surgery with or without cataract surgery achieved fairly good IOP levels from the values of 30 mmHg or higher to mid teens (16.8 ± 3.8). The number of IOP-lowering medications also decreased from 3.1 ± 1.3 to 1.8 ± 1.4 at 12 months.

The strengths of our study include having the Trabectome-alone group as controls to determine the IOP-lowering effect of procedures accurately and close monitoring of IOP, medications, and complications in a prospective fashion. Results are presented by differences in mean IOP and glaucoma medications as well as by a Kaplan-Meier survival curve. Our study covers high IOP cases with short-term follow-up; so, it might be valuable to compare the results with the long-term follow-up studies (Figure 4) [4, 6–8, 12, 14–16]. Severe complications like expulsive hemorrhage which may be caused by sudden drop of IOP after the surgery have not been reported yet; therefore, ab interno trabeculotomy using Trabectome might be safer compared to filtration procedures regarding the pressure changes. One of the major limitations of this study is the inclusion of the patients with a high initial IOP (presumably above the mean baseline of all patients undergoing Trabectome). One would anticipate that repeated IOP measurements in this group (even without Trabectome) would be closer to the mean (i.e., lower) on subsequent readings. The other limitations include the nonrandomized design of the study, with the inherent selection bias and drop-out issues. Although IOP and a number of medications were found to be lower during follow-up after the surgery, it cannot be claimed that the surgery itself lowered the pressure without a comparison group. Additionally, the patients who maintained a one-year follow-up may have a selection bias. In our study, we did not have a wash-out time interval for
glaucoma medications before or after surgery; so, we cannot be certain as to the efficacy or necessity of the number of medications either pre- or posttreatment. We included a comparison group of glaucoma patients who had Trabectome-alone surgery. We encountered some differences between the groups in ethnicity, type of glaucoma, amount of visual field loss, prior surgeries, and degree of angle opening. However, these differences can be expected given the pathogenesis and epidemiology of cataract and glaucoma. The next step would be the establishment of randomized trials to determine the efficacy of Trabectome surgery compared with newer IOP-lowering surgeries for OAG, with one another, and with phacoemulsification alone (in the case of combined procedures).

In conclusion, the risk-to-benefit profile of trabeculotomy by internal approach in patients with high IOP levels has not been studied yet. The results of our study showed that the Trabectome, as a minimally invasive glaucoma surgery, might be considered as an alternative to standard filtration surgery in the surgical treatment of the open-angle glaucoma patients with higher IOP levels because of its internal approach, giving a good option for the combined cataract-glaucoma surgery, the low-risk profile, and the remaining of the future option for filtration surgery.

Disclosure

An earlier version of this work was presented as a poster at the 25th Annual Meeting of the American Glaucoma Society, 2015.

Conflicts of Interest

Dr. Brian A. Francis reports consulting agreements with Neomedix company (Trabectome). No other author has a financial or proprietary interest in any material or method mentioned.

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Clinical Study

XEN Glaucoma Implant with Mitomycin C 1-Year Follow-Up: Result and Complications

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Purpose. To evaluate gel microstent (XEN, Aquesys, Inc) for treatment of primary open angle glaucoma (POAG).

Methods. In this prospective interventional study, 13 eyes with POAG underwent XEN implantation with subconjunctival mitomycin-C. Of those eyes, 3 were pseudophakic and 10 underwent simultaneous phacoemulsification and XEN. Patients had uncontrolled IOP, had intolerance to therapy, or had maximal therapy but undergoing cataract extraction. Follow-up visits included IOP, number of medications, vision, and complications and lasted for 1 year. Complete success was defined as IOP reduction ≥20% from preoperative baseline at 1 year without any glaucoma medications while partial success as IOP reduction of ≥20% at 1 year with medications.

Results. IOP dropped from 16 ± 4 mmHg pre-op to 9 ± 5, 11 ± 6, 12 ± 5, 12 ± 4, and 12 ± 3 mmHg at 1 week, 1, 3, 6, and 12 months (p = 0.004, 0.026, 0.034, 0.01, and 0.01, Wilcoxon Signed Ranks) consecutively. BCVA (LogMAR) was 0.33 ± 0.34 and improved to 0.13 ± 0.11 at 1 year. Mean number of medications dropped from 1.9 ± 1 preoperatively to 0.3 ± 0.49 (p = 0.003) at 1 year. 42% of eyes achieved complete success and 66% qualified success. Complications included choroidal detachment in 2 eyes, and implant extrusion in 1 eye, and 2 eyes underwent trabeculectomy. Conclusion. XEN implant is an effective surgical treatment for POAG, with significant reduction in IOP and glaucoma medications at 1 year follow-up.

1. Background

Glaucoma is one of the blinding diseases affecting 60 million worldwide; treatment is comprised of medications, lasers, and surgeries [1]. The most common glaucoma surgeries are trabeculectomy and tube shunt drainage devices, lower intraocular pressure (IOP) by diverting aqueous humor (AH) from the anterior chamber (AC) to the subconjunctival space; these surgeries are performed through a de externo approach [2]. Both trabeculectomy and shunt surgery come with a range of complications like hypotony, leakage, shallowing of the anterior chamber, choroidal effusion, and valve-related complications as in encapsulation, tube blockage, erosion, and endothelial cell loss [2]. A novel technique of creating an alternative route through an ab interno approach via implantation of a collagen implant XEN® (AqueSys, CA, USA) has been described in an attempt to overcome the different complications which are seen in both trabeculectomy and shunt operations [3].

XEN implant depends on the Hagen-Poiseuille equation, which allows us to calculate the resistance to flow through a cylindrical tube. Assuming laminar flow of a noncompressible fluid, the outflow resistance and therefore pressure differential increase linearly in relation to the length of the tube and decrease to the fourth power of the lumen radius. A longer thinner tube will provide more resistance to flow than a shorter and wider tube. This equation was used as the principle of XEN implant [4].

This work aims at assessing the results of XEN implants in regard to IOP-lowering effect, number of medications used after surgery, if ever, visual acuity, and possible complications.
2. Patients and Methods

This prospective interventional study was conducted in Alpha Vision Augenzentrum, Bremerhaven, Germany. This study included 13 eyes of 10 patients; 6 males and 4 females. All the patients signed an informed consent concerning the procedure, and the study followed the tenants of the Declaration of Helsinki.

The study included 13 eyes with primary open-angle glaucoma (POAG). Glaucoma was previously diagnosed by measured elevated IOP with associated optic nerve head changes detected clinically and confirmed by visual field and HRT.

Three eyes were pseudophakic, and they underwent XEN implantation with subconjunctival mitomycin C. 10 eyes had simultaneous cataract so they underwent phacoemulsification and XEN implantation with subconjunctival mitomycin C.

Inclusion criteria for this study were patients with primary open-angle glaucoma (POAG) with or without cataract already diagnosed and being followed up in our clinic for at least 5 years or those eyes not reaching the target IOP pressure with maximal therapy. Inclusion criteria also included medication intolerance or patients with lack of compliance.

Exclusion criteria included previous trabeculectomy surgery, any possible allergic reaction with the material of the implant, controlled IOP by less than 3 different medications, single-eyed patients, pseudoxefoliation, shallow anterior chamber, and angle closure glaucoma.

Primary open-angle glaucoma was reached in all patients after extensive ocular examination including slit lamp examination, gonioscopy, and IOP measurement by the Goldmann Applanation Tonometry in addition to visual field and HRT.

Ocular examination in the preoperative visit included best corrected visual acuity (BCVA), slit lamp examination, gonioscopy, and IOP measurement by the Goldmann Applanation Tonometry, visual field, and HRT. Postoperative visits were conducted for all patients at 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months after surgery. All patients had to discontinue any prostaglandin topical medications 1 week before surgery.

A minimum follow-up period of 1 year was required from all eyes. In each postoperative visit following examination was performed, visual acuity, IOP measurement, and possible complications were reported. Visual field and HRT tests were performed at 6 and 12 months after surgery. Surgery was performed for all patients under general anesthesia, and the procedure included mitomycin C 0.01% (MMC) subconjunctival injection and insertion of XEN implant with or without cataract extraction.

All prostaglandin analogue medications were discontinued at least for 1 week before surgery.

The XEN implant (AqueSys, CA, USA) is derived from collagen and made of gelatin. The implant is made from cross-linked porcine collagen. The XEN45 implant used in this study has a lumen diameter of 45 microns and a length of 6 mm that would provide aqueous filtration around resistance to flow and is designed to rely on subconjunctival resistance alone. A handheld disposable injector is designed specifically for the surgical implantation of the implant. The inserter has a 27-gauge needle preloaded with the implant.

All surgeries were done by the same surgeon. After skin disinfection, proper field dressing, and speculum insertion, superior nasal conjunctiva was marked 2 and 3 mm from the limbus. Intraoperative 0.1 ml MMC 0.01% was injected subconjunctivally using a 27G hypodermic needle under tenon and spread with microsponge applied to conjunctiva in the superior nasal quadrant where the implant would be inserted, and it remained for 10 minutes before the implant was injected or in case of cataract extraction before phacoemulsification starts. The MMC was not washed out.

Using an ab interno approach, the preloaded injector needle was inserted through a 1.2 mm corneal paracentesis incision opposite the site of desired implantation after the AC was filled with highly cohesive viscoelastic device. An intraoperative goniolens was used to verify placement through the angle to avoid iris and iris root trauma in all cases. The needle was then directed across the AC and implanted in the target quadrant (usually superonasal). The implant is ideally placed through the scleral spur and tracked 3.0 mm posterior to the limbus exiting through the sclera into the subconjunctival space. Approximately, 2 mm of the implant is left in the AC to provide a connection from the AC to the subconjunctival space which was confirmed by the goniolens. Viscoelastic device was removed from the AC. No further sutures were applied, and at that point, the surgery is terminated.

In cases where cataract extraction was indicated, a main incision was performed at the steepest corneal axis and the paracentesis incisions were performed one nasal and one temporal-inferior at 7 o’clock position and 5 o’clock position for the right and left eyes, respectively. The latest incision was done 2-3 mm central to the limbus and used for the insertion of the XEN45 into the superior nasal area.

After phacoemulsification was finished, no viscoelastic material was used to implant the intraocular lens (IOL) and was implanted only under BSS being our standard technique in phacoemulsification procedures. After the IOL was properly placed in the bag, the AC was filled with cohesive viscoelastic device and a corneal suture was used to secure the principle 2.4 mm incision. XEN implantation followed as previously indicated. Viscoelastic was promptly removed from AC to prevent XEN implant potential blockage or partial closure after surgery.

Patients were prescribed Isoptomax® (dexamethasone 0.1%, neomycin sulfate, and polymyxin B sulfate, Alcon USA) 4 times a day which was tapered by one drop each week, Predforte® (prednisolone acetate 1%, Allergan USA) twice daily for one month then once for another month, and Ketovision® (Ketolactrometamol Omnivision, Germany) 3 times a day for 3 weeks postoperatively. The follow-up visits were conducted at 1 day, 1 week, and 1, 3, 6, and 12 months postoperatively.

Outcome measured in each visit included BCVA, IOP, medications, possible complications, and management. At 6 and 12 month visits, visual field and HRT tests were done.
Complete success was defined as a postoperative IOP drop of ≥20% from preoperative baseline at 12 months without any glaucoma medications. Partial success was defined as a postoperative IOP reduction of ≥20% at 12 months with medications. Failure was defined as vision loss of light perception or worse, need for additional glaucoma surgery, or <20% reduction of IOP from baseline at 1 year.

In case needling was required, after anesthesia drops were instilled in the eyes together with 2 drops of povidone-iodine 5%; a sterile speculum was inserted. The patient was positioned at the slit lamp, and a sterile 27-gauge insulin syringe was advanced into subconjunctival space adjacent towards the bleb temporally and moved into the subconjunctival space at the same time advancing it toward the scleral flap. The needle was advanced till reaching sclera flap (which was not lifted), and the episcleral adhesions were released. Procedure ended by high bleb formation after aqueous was introduced to the subconjunctival space. No MMC was used during the needling procedure.

2.1. Statistical Analysis. Data were statistically described in terms of mean ± standard deviation (±SD) and percentages when appropriate. Comparisons of numerical variables were done using Wilcoxon signed-ranks test, Friedman’s two-way analysis test, and Kaplan-Meier survival. All statistical calculations were done using the computer program IBM® SPSS® Statistics 21 (Statistical Package for the Social Science). p values less than 0.05 were considered significant.

3. Results
Thirteen eyes of ten patients were included in this study. The mean age of the patients was 73.1 ± 10 (58–87) years. All patients had POAG, 10 eyes had XEN implant and cataract extraction on same session, and 3 eyes were pseudophakic.

Mean preoperative IOP was 16 ± 4 (10–24) mmHg which dropped significantly to 9 ± 5 (2–20) mmHg, 11 ± 6 (4–28) mmHg, 12 ± 5 (6–25) mmHg, 12 ± 4 (6–21) mmHg, and 12 ± 3 (6–18) mmHg at 1 week, 1 month, and 3, 6, and 12 months of follow-up (p = 0.004, 0.026, 0.034, 0.01, and 0.01—Wilcoxon signed-rank test) consecutively (Figure 1).

There was significant drop of IOP throughout the study (p = 0.003—Friedman’s two-way analysis). The percent of drop of IOP was 42% at 1 week postoperatively, 30%, 21%, 21%, and 23% at one, 3, 6, and 12 months of follow-up.

Mean number of medications dropped from 1.9 ± 1 (1–3) preoperatively to 0.3 ± 0.49 (0–1) (p = 0.003) at 12 months of follow-up.

Preoperative visual acuity was 0.33 LogMAR ± 0.34 (0.0–1.0), which improved significantly to 0.13 ± 0.11 (0.0–0.4) at 12-month follow-up (p = 0.0001—Wilcoxon rank test) (Figure 2).

From the patients included in this study, 41.7% of eyes achieved complete success and 66.7% achieved qualified success by Kaplan-Meier survival curve analysis (Figure 3).

Four eyes (30.7%) required needling during postoperative follow-up, and the needling was done using slit lamp without mitomycin C at 1 month postoperatively in 3 eyes and 3 month postoperatively in the other eye.

Two eyes suffered choroidal detachment and hypotony which were transient and responded to medical treatment in the form of systemic steroids and atropine eye drops.
IOP without the presence of a valve. Utilizes the Hagen-Poiseuille equation to achieve the targeted intraocular approach sparing the conjunctiva. The implant XEN implant as a new modality shunt device with an ab @glaucoma surgeries [5].

The implant utilizes subconjunctival microimplant could not be included as a member of the intraocular manipulation for its insertion; however, this and the formation of a corneal incision. XEN implant requires mitomycin injection implants although its insertion is done through minimum is highly debatable whether to include XEN in the MIGS tional surgery and to reduce dependency on medications. It vide a safer, less invasive means of reducing IOP than traditi-

4. Discussion

Minimally invasive glaucoma surgery (MIGS) aims to provide a safer, less invasive means of reducing IOP than traditional surgery and to reduce dependency on medications. It is highly debatable whether to include XEN in the MIGS implants although its insertion is done through minimum corneal incision. XEN implant requires mitomycin injection and the formation of a filtering bleb beside the necessary intraocular manipulation for its insertion; however, this microimplant could not be included as a member of the MIGS. The implant utilizes subconjunctival filtration creating a nonphysiologic route for aqueous outflow which is the basis of the traditional trabeculectomy and aqueous shunt glaucoma surgeries [5].

In this prospective interventional study, we evaluated XEN implant as a new modality shunt device with an ab interno approach sparing the conjunctiva. The implant utilizes the Hagen-Poiseuille equation to achieve the targeted IOP without the presence of a valve.

To our knowledge, there are very few articles in the literature regarding XEN implant in humans.

In this study, there were some social and psychological limitations that prevented us from obtaining the uncon-
trolled IOP that required the elimination of all the therapeu-
tic lines and left the patients without therapy for several weeks and this somehow was not possible to achieve. All prostaglandin analogue drops were discontinued in all patients for a minimum of 1 week before surgery to decrease the risk of failure and inflammation postoperatively. Surgery was performed for all patients under general anesthesia as indicated by the anesthesia department in our clinic, but we believe it could be done using local anesthesia.

There was a significant drop of IOP from 16 mmHg (±4) to 12 mmHg (±3) at 12 months of follow-up; this was com-
pared to the study by Sheybani et al. [4]. They had preoperative IOP of 23 mmHg (±4.1) and 12 month IOP of 14 mmHg (±3.7). Our mean preoperative IOP was much lower than that of the other study, as some of our cases were initially well controlled on treatment but with intolerance to medications. In our study, 2 eyes had advanced glaucomatous optic nerve damage and they needed lower target IOP.

Preoperative medications decreased significantly from 1.9 ± 1 (1–3) preoperatively to 0.3 ± 0.49 (0-1) (p = 0.003) at 12 months of follow-up, which compare to the decrease from 3.0 at baseline to 1.3 at 12 months (p < 0.001) achieved by Sheybani et al. [4].

Our patients achieved a mean IOP reduction of 29.4% at the end of follow-up which was slightly lower than the 36.4% achieved by Sheybani et al.; our cumulative success rate was 41.7% for patients on no medications achieving complete success and 66.7% achieving success on medication, and this again was lower than the partial success rate of 88.9% yet similar to complete success rate of 40.0% achieved by Sheybani et al. [4].

Our procedure differs from that described by Sheybani et al. as we injected 0.01% MMC subconjunctivally without the need to wash it in all our cases; this decreased the rate of nee-
dling in our series to 30.7% compared to 47% in their series.

In the tube versus trabeculectomy (TVT) study [6], the mean IOP of the tube arm dropped from 25 ± (5.3) to 12 ± (3.9) at one year of follow-up and dropped from 25 ± (5.3) to 12 ± (5.8) in the trabeculectomy arm. Similar drop was achieved in other studies comparing Ahmed valve to trabeculectomy [7], whereas, in our study, the drop was less from 16 mmHg (±4) to 12 mmHg (±3) at 12 months.

Pérez-Torregrosa et al. performed phacoemulsification combined with XEN45 implant surgery in 30 eyes, and they followed them up to 1 year. Phacoemulsification surgery was performed through 2 temporal incisions, separated by 90°, using the inferior to insert the XEN45 and to implant it in the superior nasal region. The preoperative IOP was 21 ± 3.4 mmHg, with 3 medications and decreased by 29.34% at 12 months. At the end of the study, the number of medications decreased by 94.57%. Complications occurred in 3 eyes, 2 eyes had XEN implantation aborted due to surgical difficulties (subconjunctival hemorrhage and XEN extrusion during preparations), while one eye had filtration bleb failure due to encapsulation 5 months after surgery [8].
Early postoperative complications reported with both tubes and trabeculectomies such as shallow AC, wound leak, aqueous misdirection, suprachoroidal, and vitreous hemorrhage [2, 7] were not encountered in our study yet we encountered two cases of early postoperative hypotony due to choroidal effusion that persisted for less than a month and were treated conservatively using systemic steroids and atropine drops. Late complications such as bleb leak, endophthalmitis, and cystoid macular edema [9] were also not recorded. Complications related to the XEN implant such as exposure of the implant [10] were seen in one case and were managed by applying conjunctival sutures and relocation of the implant in the subconjunctival space. The explanation for this could be that this eye would have had previously scarring and thinning of conjunctiva related to previous nonreported glaucoma procedure. The conjunctival scarring was minimal and was not detected. After implant exposure occurred and was successfully repositioned, the 77-year-old patient recognized that 20 years ago he underwent a nonspecified glaucoma procedure. Although previous failed glaucoma procedure is an exclusion factor for implanting XEN, we did exclude this case to show the potential risk of implanting XEN implant in such a case.

5. Conclusion

XEN implant is a recent microshunt device that is implanted through an ab interno approach, thus sparing the conjunctiva for further interference that maybe needed later. This new implant is easy to insert and can achieve reasonable IOP lowering, with minimal complications. Yet, this new technique needs further assessment for longer follow-up survival.

Conflicts of Interest

The authors have no financial or proprietary interest in a product, method, or material described herein.

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Clinical Study

Safety and Efficacy of Two Trabecular Micro-Bypass Stents as the Sole Procedure in Japanese Patients with Medically Uncontrolled Primary Open-Angle Glaucoma: A Pilot Case Series

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Purpose. To evaluate efficacy and safety of a trabecular micro-bypass stent system when used as the sole procedure in Japanese patients with medically uncontrolled primary open-angle glaucoma (POAG).

Design. Prospective nonrandomized interventional pilot study.

Methods. Ten eyes of 10 Japanese patients with medically uncontrolled POAG taking three ocular hypotensive medications were treated using only the implantation of two iStent trabecular micro-bypass stents. Each patient continued to take the same ocular hypotensive medications used preoperatively throughout the study. Intraocular pressure (IOP) and endothelial cell density (ECD) were determined at baseline and at 1, 3, and 6 months postoperatively. Best-corrected visual acuity (BCVA) was measured at baseline and 6 months after surgery. Results. Mean IOP was 22.0 ± 3.0 mmHg at baseline and 16.9 ± 3.6 mmHg at 6 months, which represented a mean reduction of 5.1 mmHg or 23.2%. No significant changes were observed in the ECD and BCVA. Complications that occurred during the early postoperative period included hyphema, peripheral anterior synechiae, and occlusion of the stent by the iris. Conclusion. Implantation of two trabecular micro-bypass stents as the sole procedure in Japanese POAG patients effectively reduced IOP and exhibited a favorable safety profile. Clinical Trials Registration number is UMIN000004002.

1. Introduction

The goal of glaucoma therapy is to halt the progression of the disease through reduction of the intraocular pressure (IOP) in the safest manner possible. In some glaucoma patients, however, combination therapy using antiglaucoma medications cannot sufficiently achieve the target pressure. In such cases, while laser trabeculoplasty is considered safe, the procedure may have a limited efficacy and durability, and it can also be associated with pain and inflammation [1]. We consider laser trabeculoplasty as an adjunctive to medical treatment, not a replacement of the incisional surgery. However, while glaucoma filtration surgery does provide a significant reduction in the IOP, this procedure is generally reserved for more serious cases due to potential risks such as endophthalmitis, suprachoroidal hemorrhage, and hypotony maculopathy [2–4].

Microinvasive glaucoma surgeries (MIGS) were developed to address the need for a less invasive surgical approach to lowering IOP. The iStent trabecular micro-bypass procedure (Glaukos Corp.) is the first of this class of new ab interno devices that may significantly reduce the IOP while maintaining a high safety profile [5]. The first generation of the iStents was the titanium, L-shaped stent (GTS100), which was designed to create a patent bypass through the trabecular meshwork in order to facilitate the natural outflow of the aqueous humor, thereby lowering the IOP [6]. Although the iStent has been investigated in a number of worldwide studies over the past several years [7–16], only a few have reported on the efficacy of a single iStent (GTS100) or two stents when used as the sole procedure [13, 16, 17]. The present study was designed to assess the IOP-lowering effect and safety when using two iStents (GTS100) as the sole procedure in medically uncontrolled primary open-angle glaucoma (POAG).
2. Subjects and Methods

2.1. Patients and Study Design. This was a prospective, noncomparative, nonrandomized, single-center consecutive case series involving 10 eyes from 10 patients with medically uncontrolled POAG. In this case series, patients were defined as being "medically uncontrolled" if they had both a progressive visual field disturbance and an intraocular pressure of 18 mmHg or higher while on a regimen of three or more hypotensive eye drops that included a prostaglandin analogue, beta-blocker, and carbonic anhydrase inhibitor. At the time of this study, these regimens were considered to be the maximal tolerable topical glaucoma therapy in Japan. Based on our experience of conventional trabeculotomy, bibliographic information, and our unpublished work on trabecular micro-bypass stents, we believed that there was no reason to include any exclusion criteria regarding visual field loss. However, we did not include any patient that had any risk of the loss of useful central vision due to poor postoperative IOP control. In addition, individuals were excluded if they had previous argon laser trabeculoplasty, selective laser trabeculoplasty, or intraocular surgery (with the exception of cataract surgery).

This study was approved by the Keio University School of Medicine Ethics Committee and written informed consent was obtained from each patient. This clinical trial is registered with the University Hospital Medical Information Network (UMIN000004002).

Patient demographics, IOP, corneal endothelial cell density (ECD), and best-corrected visual acuity (BCVA) were recorded preoperatively. ECD was measured with noncontact specular microscopy (FA-3509, Konan Medical) and the IOP was measured with Goldmann application tonometry (Haag-Streit).

2.2. Surgical Technique. All surgical procedures were performed by DS. A 1 mm clear corneal incision was made in the temporal quadrant. The anterior chamber was then filled with viscoelastic agent (OPEGAN Hi, Santen Pharmaceutical Co., Ltd.) to improve visualization of the angle. With the operator positioned at the temporal side of the patient, an inserter with the first stent was introduced in the anterior chamber via a clear corneal incision. Angle view was obtained with a surgical gonioscopy (Ocular Hill Surgical Gonioscopy, Ocular Instruments). If the right eye was operated on, the leading edge was gently slid downwardly through the lower nasal region of the trabecular meshwork into Schlemm’s canal. If the left eye was operated on, the leading edge was gently slid upwardly through the upper nasal region of the trabecular meshwork into Schlemm’s canal. The first stent was inserted using a clockwise rotation, with the GTS100R stent used for the insertions in either the right or left eye. If the right eye was used, a second stent was inserted upwardly (counterclockwise rotation) through a second incision made at the inferior temporal cornea into the upper nasal region of the trabecular meshwork. After inserting the stent facing upwards, it was then released from the inserter followed by removal of the inserter. The second anticlockwise insertion used the GTS100L stent. The clock positions of the stents were 2 and 4 when used in the right eye and 8 and 10 when used in the left eye. The viscoelastic agent was then removed and the anterior chamber inflated with saline solution to achieve physiologic pressure.

2.3. Follow-Up. Postoperative care included 0.5% levofloxacin drops (Cravit, Santen Pharmaceutical Co., Ltd.) and 0.1% betamethasone sodium phosphate eye drops (Sanbetason, Santen Pharmaceutical Co., Ltd.) 3 times a day for 1 month. Patients were instructed to restart the same preoperatively used glaucoma medications 1 day postoperatively. Thus, the patient’s preoperative ocular hypotensive eye drop regimen was maintained throughout the study period.

Follow-up visits occurred at 1 day, 1 week, and at 1, 2, 3, and 6 months. Examinations performed at each of these follow-up visits included slit-lamp examination, gonioscopy, and measurement of the IOP. In addition, specular microscopy was performed at 1, 3, and 6 months, while the BCVA was checked at 1 day, 1 week, and 1 and 6 months.

2.4. Data Analysis. Statistical analyses were carried out using the IBM SPSS Statistics 20 software. The paired t-test was adapted to a single comparison between the preoperative BCVA and the BCVA at 6 months. In patient exited from the study before the 6 months’ visit, the last available BCVA was used by last observation carried forward method. Dunnett’s procedure was used as a multiple comparison procedure for the analysis of the IOP and ECD before surgery versus at each postoperative visit. P value of <0.05 was considered significant.

3. Results

This study investigated 10 eyes (including 3 pseudophakic eyes) of 10 patients (7 male, 3 female), all of whom were Japanese. The mean age was 64.6 ± 10.7 years. Three ocular hypotensive topical medications were prescribed for each of the included eyes. While taking these medications, the mean preoperative IOP was 22.0 ± 3.0 mmHg. Mean preoperative ECD was 2506 ± 570 cells/mm² and mean preoperative BCVA was −0.014 logMAR. The Shaffer grades determined for the preoperative ocular angle opening were 3 in 1 phakic eye and 4 in the other 9 eyes. The average of the mean deviation values for the Humphrey field analyzer 30-2 was −15.4 ± 8.1 dB. Three patients that exhibited severe visual field disturbance had already lost their useful central visual field. The surgery was uneventful in all eyes, with all of the stents successfully implanted upon the first or second attempt. Eight patients completed 6 months of follow-up. One pseudophakic patient was lost to follow-up at 3 months due to other health problems. As 1 pseudophakic patient underwent a trabeculectomy at 4 months after the stent implantation, our analysis included the data from before but not after the trabeculectomy. Although patient exhibited an IOP reduction for a month, his IOP at 1 month postoperatively was 18. In addition, even though the stents were implanted correctly and were not obstructed by the iris or anything else, there was...
Table 1: Postoperative complications.

| Complication                  | N  |
|-------------------------------|----|
| Hyphema                       | 4  |
| Microhyphema*                 | 3  |
| Hyphema                       | 1  |
| IOP ≥ 30 mmHg                 | 1  |
| Peripheral anterior synechiae | 4  |
| Occlusion by iris             | 3  |

*Microhyphema only observed by gonioscopy.

reelevation of his IOP to 26 and 24 mmHg at 2 and 3 months postoperatively.

Mean IOP dropped to 16.1 ± 3.5 mmHg at 1 month postoperatively. The reduction in pressure was maintained at 6 months, with a mean IOP of 16.9 ± 3.6 mmHg (Figure 1, Supplementary Table 1 in Supplementary Material available online at https://doi.org/10.1155/2017/9605461). This represents a clinically and statistically significant reduction in the IOP of 5.1 mmHg from the preoperative mean IOP (P < 0.05). At 6 months, the IOP reduction rate was 23.2%. No significant changes were observed for either the ECD (Figure 2) or the BCVA. Mean ECD at 6 months was 2556 ± 577 cells/mm² compared to 2506 ± 570 cells/mm² at baseline. At last observation, the mean BCVA was −0.0059 ± 0.11 logMAR, compared to −0.0014 ± 0.11 logMAR at baseline (n = 10, P = 0.34). No stent malposition was observed throughout the study period (Figure 3(a)).

Postoperative complications included microhyphema (only observed by gonioscopy) in 3 eyes and mild hyphema in 1 eye, all of which resolved without intervention by the 1-month visit; transient IOP elevation of 32 mmHg on the next day following the surgery in 1 eye, which resolved spontaneously; peripheral anterior synechiae (PAS) in 4 eyes, which was treated with argon laser gonioplasty (LGP); and occlusion by the iris, which occurred in 2 eyes of the LGP-treated eyes with PAS by the 1-month visit and in 1 eye of the LGP-treated eyes with PAS at the 2-month visit (Table 1, Figure 3(b)). These occlusions were observed only in phakic eyes. Blood reflux from the stent was often observed in a few eyes for a week postoperatively (Figure 3(c)). There was no evidence of hypotony, flat anterior chamber, choroidal detachment, or endophthalmitis in any of the eyes.

4. Discussion and Conclusion

Starting in 1960, attempts have been made to reduce the resistance of the trabecular outflow pathway. Trabeculotomy ab externo was one of such attempts and is one of the more representative procedures [18, 19]. The IOP-lowering effect of trabeculotomy in adult patients was first reported in a study by Tanihara et al. [20]. Recently, Chin et al. reported finding a much better IOP-lowering effect of modified 360-degree suture trabeculotomy using 5-0 nylon suture [21]. Even though trabeculotomy has been considered to be a safe and effective surgical method, its invasiveness to the conjunctiva and sclera has prevented the method from becoming globally widespread. The trabecular micro-bypass stent system theoretically provides the same IOP-lowering mechanism as trabeculotomy, with the advantage of having a much smaller invasiveness than that for trabeculotomy. Out of the current MIGS, we found that implantation of two trabecular micro-bypass stents clinically and significantly reduced the IOP even when used as the sole procedure over 6 months postoperatively.

Several previous studies have also published surgical results for the trabecular micro-bypass procedure. However, since most of these compared trabecular micro-bypass
surgery combined with cataract extraction to cataract extraction solo surgery, this made it difficult to determine the outcomes and the genuine effect of the trabecular micro-bypass because of the variable ocular hypotensive medications and the IOP reduction associated with cataract extraction itself. Samuelson et al. reported on the use of single trabecular micro-bypass stent surgery combined with cataract surgery [8]. In their report, single trabecular micro-bypass stent implantation induced a 20% increase in patients free of medication as compared to the cataract surgery group. Also, patients in the iStent group reported a mean reduction of 1.4 hypotensive medications versus 1.0 medication in the cataract surgery only group, representing a difference in medication reduction of 0.4 medications. On the other hand, Fernández-Barrientos et al. utilized the two trabecular micro-bypass stents’ surgery approach combined with cataract surgery [9]. Their findings showed that the implantation of two iStents resulted in an additional 4.0-mmHg reduction in the IOP and an additional 0.4 decrease in the glaucoma eye drops compared with the cataract surgery group at 6 months. Comparable to their results, our present study that used two stents also showed a 5.1-mmHg decline in the IOP without any medication change.

Prospective studies on the use of the second generation of iStent (iStent inject: GTS400) as a solo procedure have been reported by two researchers [22, 23]. Although the GTS400 was designed to enhance trabecular outflow in the same way as for the GTS100, it has been modified in order to make it easier to implant and achieve an enhanced IOP reduction when performing a surgery with two stents. Since one GTS400 applicator contains two stents, we expect the results for the GTS400 will be similar to that found for the present study that also implanted two stents. These previous studies also reported washout IOP decreases of 13.0 mmHg and 10.6 mmHg from the baseline washout IOPs of 25.2 mmHg [22] and 26.3 mmHg [23], respectively. A retrospective study of the iStent inject (GTS400) when used as a solo procedure additionally reported similar outcomes in POAG or pseudoexfoliation glaucoma eyes [24]. The different design of the iStent inject (GTS400) from the iStent (GTS100) might result in a different outcome profile from iStent. Further studies that address the generation difference of iStent will need to be undertaken. More recently, a comparative study of one, two, or three trabecular micro-bypass stents (GTS100) in POAG eyes was published by Katz et al. [17]. In this report, when two-stent implantation surgery was used as a solo procedure, the mean IOP decreased by 6.6 mmHg from the preoperative 20.1 mmHg on 1.76 medications at 6 months. Out of 41 eyes in the two-stent group, only 4 eyes required the addition of medications postoperatively. Compared to these previous studies, the 5.1 mmHg IOP reduction noted in our current study when using the same medications seems to be slightly smaller. We speculate that there are two reasons for this discrepancy. First, as our patients had a mean preoperative IOP of 22.0 mmHg under three medications, they should have had a much higher baseline washout IOP and more severe dysfunction in the aqueous outflow pathway. Second, our study included 3 phakic cases that exhibited stent occlusion due to the iris in one of the two stents. Due to this occlusion, the enhancement of the aqueous outflow was thought to have deteriorated to some extent. Thus, if we only take the 7 phakic eyes into consideration, this results in nearly half of the eyes implanted with two stents undergoing occlusion due to the iris. The reason for this is most likely related to having performed the surgery in phakic eyes of Asian patients. Buchacra et al. reported
finding no incident of stent occlusion due to the iris in 10 eyes, which included 7 phakic eyes [16]. However, there was no description of the race of the patients included in their study. Moreover, in a study of Caucasian phakic eyes in a clinical setting that was similar to ours, there was no mention of any occlusion due to the iris [17]. Far East Asians have been reported to have a narrower ocular angle in general [25]. Thus, it is rational to expect that there would be more occlusions due to the iris in Japanese eyes versus Caucasian eyes. Although the prophylactic use of LGPs to target the adhesions associated with PAS was performed in order to prevent occlusion of the stents after PAS had arisen, these treatments could not effectively preclude the occlusions of the stent, thereby resulting in PAS enlargement. The management of PAS or stent occlusion will need to be examined in a future study.

Originally, the trabecular micro-bypass stent system was designed to be used in combined surgery with cataract extraction. Nonetheless, some surgeons showed an interest in the solo use of the system, and some studies, including the present study, have reported finding significant IOP reductions. Although our study only included a small group of patients, our findings indicate that care should be taken when performing trabecular micro-bypass stenting surgery in the phakic eye, especially in patients of the Asian race.

Based on the results of our current study, we speculate that the implantation of two stents was able to relieve the unfavorable effect of the obstruction by the iris. A multiple stents surgery can reduce the probability of obstructions in all of the stents. Consequently, surgeries using multiple stents or combined surgeries with cataract extraction might be advisable in cases with shallow angled eye.

Since any artificial object in the anterior chamber could potentially cause damage to the corneal endothelium such as the anterior chamber intraocular lens, confirmation on whether trabecular micro-bypass stents impair the corneal endothelium needs to be determined [26]. At the present time, there has been no published data on the safety of using trabecular micro-bypass stenting with regard to the corneal endothelium. However, when the Hydrus stent procedure was combined with cataract extraction, Fea et al. reported finding no additional damage to the corneal endothelium as compared to cataract alone [27]. In the present study, the mean ECD was maintained throughout the study. While the number of cases in the present study was too small to demonstrate our proposed thesis, our results do reinforce the safety of the corneal endothelium after the trabecular micro-bypass stent implantation procedure.

There were some limitations for the current study, especially regarding the small number of patients and the short duration of the follow-up due to the fact that this was a pilot study. Thus, due to the small patient number and short study duration, we cannot definitively determine whether trabecular micro-bypass stenting solo surgery should be adopted for routine glaucoma management based on the current results. However, there have been a few previous studies that have reported finding a long-term stability for the IOP reduction when using the trabecular micro-bypass stent [12, 14]. Based on the results of these prior studies in conjunction with our pilot study, a future study with a larger number of patients and longer follow-up will need to be undertaken in order to confirm our present results.

The current study is the first assessment of the iStent (GTS100) when used as a sole procedure in Asian POAG eyes. The current efficacy and safety results are moderately consistent with several earlier published studies on solo surgery or combined surgery with cataract extraction. Based on these findings, we conclude that the iStent (GTS100) is effective in providing significant IOP reduction while maintaining a favorable safety profile, even if used as the sole procedure.

**Ethical Approval**

This study followed the tenets of the Declaration of Helsinki and was approved by the Keio University School of Medicine Ethics Committee.

**Consent**

Written informed consent was obtained from each patient.

**Competing Interests**

The stents used in the present study were provided by Glaukos Corp., Laguna Hills, CA, USA. No other funding or sponsorship was received for the publication of this article.

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Clinical Study

Glaukos iStent inject® Trabecular Micro-Bypass Implantation Associated with Cataract Surgery in Patients with Coexisting Cataract and Open-Angle Glaucoma or Ocular Hypertension: A Long-Term Study

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Purpose. To evaluate the long-term efficacy and safety of the iStent inject device (Glaukos Corporation, Laguna Hills, CA) combined with phacoemulsification in patients with coexistent cataract and open-angle glaucoma or ocular hypertension (OHT). Methods. A prospective, uncontrolled, nonrandomized, interventional case series study was conducted in patients with both mild or moderate open-angle glaucoma or OHT and cataract. Patients underwent cataract surgery along with the implant of two iStent inject devices. Outcome measures were intraocular pressure (IOP), topical hypotensive medications required, and best-corrected visual acuity (BCVA). Results. 20 patients were enrolled. Mean follow-up was 47.4 ± 18.46 months. Mean baseline IOP was 19.95 ± 3.71 mmHg with medication and 26 ± 3.11 mmHg after washout. Mean end-follow-up IOP was 16.25 ± 3.14 mmHg, representing an IOP decrease of 36.92%, 9.74 ± 3.14 mmHg (P < 0.001), from baseline washout IOP. The mean number of medications was significantly reduced from 1.3 ± 0.66 to 0.75 ± 0.79 (P = 0.017). 45% of patients were medication-free by the end of follow-up. Mean logMAR BCVA improved significantly from 0.42 ± 0.16 to 0.18 ± 0.16 (P < 0.001). No complications of surgery were observed. Conclusion. The iStent inject device combined with cataract surgery served to significantly reduce both IOP and medication use in the long term in patients with coexistent open-angle glaucoma or ocular hypertension (OHT) and cataract.

1. Introduction

Glaucoma is the leading cause of irreversible blindness worldwide and is estimated to currently affect more than 60 million people [1]. Elevated intraocular pressure (IOP) is the main risk factor for the onset and advance of glaucoma. In effect, reducing IOP is the accepted consensus strategy to delay or even avoid the development of glaucoma and to manage its progression [2]. Thus, the ideal treatment for glaucoma should offer continuous IOP management along with a favourable safety profile.

Filtration surgery is usually performed in moderate or advanced cases but is linked to complications [3] including visual loss, bleb leak, inflammation, hypotony, and endophthalmitis [4]. Microinvasive glaucoma surgery tries to preserve conjunctival tissue of scarring through an ab
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After phacoemulsification and IOL placement, two GTS-400 iStent devices were implanted through the clear corneal incision (approximately 2.85 mm) placed for phacoemulsification. First-generation prototype G2-0 injectors were used to deliver the stents. Antiglaucoma topical therapy was introduced postoperatively if the desired target IOP range, as judged by the investigator, was not achieved.

Postoperative visits were scheduled for 1 day, 1 week, 1, 3, and 6 months, and 1, 2, 3, 4, 5, and 6 years after surgery. Every visit included slit-lamp biomicroscopy, applanation tonometer (Clement Clarke Perkins MK2 Tonometer) IOP measurement, number of glaucoma medications, and BCVA. Preoperatively and one month, three months, and every year postoperatively, the nasal angle was examined by gonioscopy.

2.1. Data Analysis. Efficacy outcome measures were IOP and topical ocular hypotensive medications used pre- and postoperatively. Successful treatment was defined as an IOP reduction ≥20% regardless of medication. We also defined “complete success” as an IOP ≤18 mmHg without postoperative medication and “qualified success” as an IOP ≤18 mmHg with medication [18]. These outcomes were determined by proportional analysis. Kaplan-Meier graphs were constructed to estimate surgical success according to those success criteria.

Failure rate included those patients who did not meet success criteria, required further glaucoma surgery, or had severe visual loss secondary to surgery itself.

Safety outcome measures were complications and log MAR BCVA.

For a descriptive statistical analysis, we used Excel 2007 (Microsoft Corp.) with SPSS software (version 15.0, SPSS Inc.). Results are provided as the mean ± standard deviation (SD).

The Kolmogorov-Smirnov test was used to check the normal distribution of data. A paired-sample t-test was used to compare outcomes in the study group. Significance was set at P ≤ 0.05.

3. Results

Combined surgery was uneventful in all the participating patients and the iStent was successfully implanted in all eyes, although three patients received just one iStent for logistic reasons. Postoperatively, gonioscopy revealed the presence of only one iStent in a further four patients (20%). So, in seven patients (35%), only one iStent was confirmed as functional. Both groups were comparable in baseline IOP and meds data, because no significant differences were obtained at that time point.

3.1. Patient Demographics. Twenty Caucasian subjects (11 women) were enrolled in the study, eight of whom had primary open-angle glaucoma, eight had OHT, and four had pseudoexfoliative glaucoma.

Mean follow-up was 47.4 ± 18.46 months (range 12–72 months) and median follow-up was 60 months. Eleven of the patients completed at least five years of follow-up, and two of them were followed six years (Table I). Nine patients did not

intermo microincisional approach, with efficacy, high safety profile, and fast recovery in mild-to-moderate glaucoma [5]. The iStent Trabecular Micro-Bypass (Glaukos Corporation, Laguna Hills, CA, USA) bypasses the trabecular meshwork (TM), which is the major source of resistance to outflow in open-angle glaucoma. iStent has been successfully employed to increase outflow in human anterior segments in vitro [6] and in glaucoma patients [7].

The first-generation iStent, Model GTS-100, is a titanium L-shaped stent that has proved safe and effective in lowering IOP in patients with mild-to-moderate glaucoma [7–10], even in the long term [11]. This device has also been described to achieve an IOP reduction to less than 15 mmHg if two or more iStent devices are implanted during cataract surgery [12].

A second-generation new microscale stent recently developed, the iStent inject Trabecular Micro-Bypass Model GTS-400, also increased outflow facility in cultured human anterior eye segments [13]. So far, three case series have revealed the safety and efficacy of the iStent inject device [14–16]. Another randomized study compared outcomes of two iStent inject devices versus two ocular hypertensive agents [17], showing that the use of iStent inject device is at least as effective as two medications. However, the follow-up of these studies was no longer than 12 months.

The purpose of our study was to assess the long-term efficacy and safety of implanting of two iStent inject Model GTS-400 stents combined with phacoemulsification in patients with coexistent cataract and open-angle glaucoma or ocular hypertension (OHT). This study is a continuation of our initial work [14], in which we reported outcomes one year after iStent inject device placement inserted via first-generation prototype G2-0 injectors.

2. Methods

Twenty patients with cataract and primary open-angle and pseudoexfoliative glaucoma or OHT were enrolled for this prospective, noncomparative, uncontrolled, nonrandomized, intervention study.

The study protocol adhered to the tenets of the Declaration of Helsinki and Spanish legislation and was approved by our Institutional Review Board. Before recruitment, written legally binding informed consent for Glaukos iStent implantation and cataract surgery was obtained from each patient.

Detailed subject inclusion criteria and surgical technique were previously described [14]. The main inclusion criteria were a previous diagnosis of mild-to-moderate open-angle glaucoma (including pseudoexfoliative glaucoma) or OHT and an IOP of 14–30 mmHg as measured at the last two con-
secutive visits if receiving ocular hypertensive medications, of 22–30 mmHg if not, or of 22–32 mmHg after hypertensive drops washout.

Before surgery, all the patients receiving ocular hypertensive medications were instructed to discontinue their use to obtain baseline IOP measurements. All surgical procedures were performed by two of the authors (JMJC and JGF), both with similar experience in MIGS surgery. Surgical technique is similar to that described for the GTS-100 device [13, 14].
Table 1: Postoperative follow-up of 20 patients (*n*: number of patients).

| Surgery | 1 year | 2 years | 3 years | 4 years | 5 years | 6 years |
|---------|--------|---------|---------|---------|---------|---------|
| n       | 20     | 20      | 19      | 15      | 12      | 11      | 2       |

| Preop | 24h | 1 month | 6 months | 1 year | 2 years | 3 years | 4 years | 5 years | 6 years |
|-------|-----|---------|-----------|--------|---------|---------|---------|---------|---------|
| 19.95 | 22.56 | 17.55 | 17.25 | 17 | 17.45 | 17.07 | 17 | 17.45 | 17.45 |

**FIGURE 1:** Mean intraocular pressure (IOP) (+standard error of the mean) recorded at each follow-up visit (baseline IOP is medicated IOP).

3.2. IOP Results. Mean IOP with medication at baseline was 19.95 ± 3.71 mmHg and after washout was 26 ± 3.11 mmHg (Figure 1). At the end of follow-up, mean IOP was 16.25 ± 1.99 mmHg. The IOP decrease from preoperative washout IOP was 9.74 ± 3.14 mmHg, representing a significant decrease of 36.92% (*P* < 0.001). The mean IOP drop relative to preoperative IOP with medication was 3.7 ± 3.7 mmHg, representing a 16.49% decrease (*P* < 0.001). Figure 2 shows preoperative IOP and final IOP without and with medication in each patient via scatter plot (Figure 2).

In the 11 patients completing at least five years of follow-up, mean IOP with medication at baseline was 20.36 ± 4.57 mmHg and after washout was 25.7 ± 3.06 mmHg. End-follow-up mean IOP was 16.18 ± 2.27 mmHg. Reductions in IOP from preoperative washout IOP and from preoperative IOP with meds (9.5 ± 3.1 mmHg and 4.18 ± 4.62 mmHg; 36.56% and 17.52%; *P* < 0.001 and *P* = 0.013, resp.) recorded in this subset of 11 eyes were similar to the reduction observed for the entire set of 20 eyes.

Subanalysis of IOP results depending on the number of functional iStent devices showed no significant differences in final IOP decrease between one and two functional iStent devices (*P* = 0.425). However, the group with two iStent devices had an IOP decrease of 10.42 ± 3.6 mmHg versus 8.57 ± 1.81 mmHg in the one functioning iStent group.

Three eyes (15%) showed transient IOP elevation to above 30 mmHg one day postoperatively. We previously attributed this to retained viscoelastic and observed its resolution by the one-week visit [14]. There were no additional reports of IOP elevation during the remaining course of long-term follow-up.

![Figure 2](image-url)  
**FIGURE 2:** Scatter plot representing preoperative intraocular pressure (IOP) after washout and postoperative IOP without and with meds. Continuous line represents regression line (*R*² = 0.098). Discontinuous line represents IOP of 18 mmHg, defined as success in the study.

Table 2: Number of antiglaucoma medications used at baseline and final follow-up.

| Follow-up time | None drops | One drop | Two drops |
|----------------|------------|----------|-----------|
| Baseline       | 2 (10%)    | 10 (50%) | 8 (40%)   |
| Final          | 9 (45%)    | 7 (35%)  | 4 (20%)   |

3.3. Antiglaucoma Medications. The majority of subjects reduced their medication burden during the course of follow-up. Before surgery, the mean number of glaucoma medications was 1.3 ± 0.66 (Figure 3). At the end of follow-up, the mean number of medications decreased to 0.75 ± 0.79, representing a significant mean reduction in glaucoma medications of 0.5 ± 0.89 (*P* = 0.017). Table 2 shows the proportion and number of patients receiving no, one, or two medications at baseline and at the final follow-up.

At one year, 15 patients (75%) required no topical therapy, while just one subject (5%) needed two antiglaucoma medications. At the 3-year visit, seven of the 13 patients (53.9%) who completed the three years of follow-up were using one or two medications, while six patients were medication-free (46.2%).

![Table 2](image-url)
Table 3: Success rates recorded during follow-up (w/o: without).

| Follow-up time | IOP reduction ≥ 20% | Complete success | Qualified success |
|----------------|---------------------|------------------|-------------------|
|                | w/o meds with or w/o meds |                  |                   |
| 1 month        | 63% 84%             | 55%              | 10%               |
| 3 months       | 84% 100%            | 65%              | 15%               |
| 6 months       | 73% 94%             | 50%              | 15%               |
| 1 year         | 73% 100%            | 50%              | 20%               |
| 2 years        | 25% 62%             | 35%              | 41%               |
| 3 years        | 33% 86%             | 31%              | 46%               |
| 4 years        | 30% 80%             | 28%              | 36%               |
| 5 years        | 20% 100%            | 28%              | 64%               |

At five years, three patients (27.3%) were medication-free; four patients (36.4%) were taking one medication, while four patients (36.4%) were using two antiglaucoma drops. In the 11 eyes with 5-year follow-up data, the number of subjects on two medications translated to a nonsignificant glaucoma medication reduction in that group of patients.

The mean number of medications administered preoperatively in the patients who completed five years of follow-up was 1.18 ± 0.75. At the end of follow-up, this figure fell to 1.09 ± 0.83 medications, representing a mean reduction of 0.09 ± 0.94 (P = 0.756). At five years, three of the 11 patients (27.3%) were free of medication.

Subanalysis of medication use results depending of the number of functional iStent devices showed no significant differences in the final mean number of glaucoma medications (P = 0.255). However, the group with two iStent devices had a mean reduction of 0.77 ± 0.93 meds versus 0.14 ± 0.9 meds in the one functional iStent group. Besides, the percentage of eyes not requiring antiglaucomatous medications at the end of follow-up was higher in the group with two functioning iStent devices (61.5%) than in the group with one functioning iStent (14.3%).

3.4. Success Rate. At three years of follow-up, 33% of patients achieved an unmedicated IOP reduction ≥ 20% versus baseline unmedicated IOP, and 86% experienced an IOP reduction ≥ 20% regardless of medication. At five years, the percentage of patients showing an unmedicated IOP reduction ≥ 20% versus baseline washout IOP was 20%, while 100% experienced an IOP reduction ≥ 20% regardless of medication. At this follow-up time, seven out of 11 patients (63.63%) showed an IOP ≤ 16 mmHg regardless of medication.

The cumulative probability of success defined as an IOP reduction ≥ 20% using Kaplan-Meier survival analysis was 72.4% at two years and 64.4% at three years (Figure 4).

Complete success at the end of follow-up was recorded in eight patients (40%) and qualified success in 10 of our 20 patients (50%). Similar rates were obtained for the subset of patients completing five years of follow-up, though the complete success rate was slightly lower and the qualified success higher (Table 3). The cumulative probability of complete and qualified success using Kaplan-Meier survival analysis at two years was 10% and 35%, respectively (Figures 5 and 6).

By the end of follow-up, 15 of the 20 subjects (75%) showed an IOP ≤ 16 mmHg regardless of medication, including six patients of the 20 (30%) requiring no medication.

No patient needed any further glaucoma surgery over the follow-up period.
Table 4: Outcome variables reported in the studies that have addressed the efficacy of iStent GTS-400 placement. The data provided for the present study are end-follow-up data for the 20 eyes enrolled and 5-year results for 11 eyes.

| Source                  | n  | Combined phaco | Follow-up (months) | Mean IOP reduction (mmHg) from preop | IOP ≤ 18 mmHg w/o meds | Mean reduction in meds |
|-------------------------|----|----------------|--------------------|-------------------------------------|------------------------|------------------------|
| Arriola-Villalobos et al. [14] | 20 | Yes            | 12                 | 3.2 ± 3.75                          | 50%                    | 1 ± 0.79               |
| Voskanyan et al. [15]   | 92 | No             | 12                 | 22.1 ± 3.3 versus 15.7 ± 3.7†        | 66%                    | NA                     |
| Klamann et al. [16]     | 17 | No             | 6                  | 21.19 ± 2.56 versus 14.19 ± 1.38†    | NA                     | 2.19 ± 0.91 versus 0.88 ± 0.62† |
| Fea et al. [17]         | 94 | No             | 12                 | 8.1 ± 2.6                           | 92.6%                  | NA                     |
| Present study*          | 11 | Yes            | 60                 | 4.18 ± 4.62                         | 28%                    | 0.09 ± 0.94            |

Preoperative IOP refers to medicated IOP. (n: number of patients; w/o: without; † data not available, mean preoperative versus mean postoperative data; * same set of patients; NA: not available.)

3.5. Safety Outcomes. No visual acuity loss was recorded; logMAR BCVA significantly improved from a mean of 0.42±0.16 preoperatively to 0.18 ± 0.16 at the end of follow-up (P < 0.001).

No adverse events related to iStent inject implantation were reported. During the long-term follow-up, five patients suffered an eye condition unrelated to iStent inject implantation. Three of these patients required Nd:YAG capsulotomy due to posterior capsule opacification (PCO). One patient (who had OHT and high myopia) suffered retinal detachment 40 months after the initial surgery, with excellent visual recovery after pars plana vitrectomy. The last of these patients developed epiretinal membrane three years after the initial procedure. However, no surgery was required due to the patients’ lack of symptoms and good visual acuity.

4. Discussion

In this series of 20 patients, the implant of two iStent inject devices using first-generation prototype G2-0 injectors combined with phacoemulsification led to a significant IOP reduction (P < 0.001) and a significant decrease in the number of antiglaucoma medications required (P = 0.017) after a mean follow-up of almost four years. The subset of 11 patients completing five years of follow-up showed a similar significant IOP decrease (P < 0.001) along with a nonsignificant decrease in the number of antiglaucoma medications required (P = 0.756).

In both the full set of 20 eyes and the subset of 11 eyes, the IOP reduction from medicated preoperative IOP was approximately 4 mmHg. This decrease is higher than the approximate 2 mmHg decrease reported after cataract surgery alone [19].

IOP reduction in this small patient cohort was not as pronounced as that reported in the larger studies that have addressed iStent inject implantation (Table 4) as a single procedure [15–17]. In all these studies, two iStent inject devices were implanted per eye. This difference in outcome may be attributed to shorter follow-up times. Our study outcomes may have been affected by the fact that the patients in this trial
were the first at our centre to receive an iStent inject device such that surgeons were at the start of their learning curve. Further, we used first-generation prototype G2-0 injectors in all 20 patients in this series although a second-generation injector (G2-M-IS) has since been introduced. This new model is able to hold two stents so that the clinician can insert two devices while entering the eye only once. This improved injector design reduces the number of surgical steps and thus raises the chances of more reliable surgery and improved outcomes. Further, in our prior study, in a large proportion of patients (7/20), only one functional stent was observed on post-surgery gonioscopy [14]. It is likely that these patients would have shown a greater IOP reduction if two stents had been confirmed as functioning, based on in vitro results indicating that that a second stent achieved a further increase in outflow facility [4]. In effect, Belovay et al. [12] observed the improved ability of multiple GTS-100 iStent devices to reduce IOP to below 15 mmHg and reduce topical ocular hypotensive medications. In fact, our subgroup analysis, although not significant, showed higher decrease in IOP and medication use at the end of the follow-up in the group of two functioning iStent devices. These differences could be significant with higher sample size.

In our patients, IOP was stable during follow-up (Figure 1). The number of medications used increased over time after the one-year visit (Figure 3). A slight increase in the number of medications beyond one year of follow-up was also reported in the long-term study in which one iStent GTS-100 was implanted during phacoemulsification [11]. Notwithstanding, a discrete reduction was produced in the number of antiglaucoma drops at five years, including three patients (27.3%) who were medication-free. A recent report has shown that the placement of two iStent GTS-400 devices as a sole procedure is at least as effective as two medications [17]. Reducing or eliminating the use of antiglaucoma drops is highly desirable because the chronic use of antiglaucoma drugs may lead to ocular surface damage and conjunctival inflammation [20] or even reduce the success of subsequent trabeculectomy [21].

Success in our study defined as an IOP reduction ≥ 20% regardless of medication was achieved in all the patients at the end of follow-up. At that time point, an IOP reduction ≥ 20% with no medications was achieved in nine out of 20 patients, to give a success rate of 45%. Beyond the one-year visit, success rates fell (Table 2), consistent with the increased use of antiglaucoma medications. We hypothesize that ultrastructural changes in the TM or Schlemm’s canal could be responsible for this increase in medications required. Our complete success rate at one year (50%) was lower than the other reported rates for two GTS-400 devices at one year. Fea et al. [17] reported a 92.6% of complete success, while Voskanyan et al. [15] reported 66%. Probable reasons for this discrepancy have been analysed above.

Our findings indicated a highly acceptable safety profile, with no adverse events or long-term complications related to stent implant. No subjects experienced hypotony, endophthalmitis, or sight-threatening complications associated with more invasive surgery procedures. Mean visual acuity was significantly improved at each follow-up visit. There was a mild decrease in mean visual acuity beyond the one-year visit, attributed mainly to PCO.

Our study has several limitations. The number of patients was low and, being a long-term study, several patients were lost to follow-up such that only slightly more than half of the patients completed 60 months of follow-up. Being uncontrolled, we could not determine the individual effects of phacoemulsification or iStent placement on IOP and the number of hypotensive drugs required. The cohort examined was a heterogeneous group of subjects, with mild-moderate primary open-angle or pseudoexfoliative glaucoma along with OHT patients. Moreover, as reported above, these patients were the first to receive the iStent GTS-400 at our centre, meaning that, despite experience with the GTS-100 model, the surgeons were at an early learning stage with the use of the new model, which could affect outcomes. Finally, in seven patients (35%), only one iStent was confirmed as functional [14]. This potential shortcoming could also affect the IOP and medication use results [7, 12], although nonsignificant differences were found.

5. Conclusions

To the best of our knowledge, this is the first study to assess combined GTS-400 iStent implantation and phacoemulsification surgery over a follow-up period longer than one year. Significant reductions were achieved in IOP and number of medications required after more than 47 months of follow-up. At the end of follow-up, 45% of the patients were medication-free and all patients showed good visual outcomes with no serious adverse events recorded. Our findings suggest that iStent GTS-400 placement added to phacoemulsification could be a long-term safe and effective treatment option alternative for patients with both cataract and mild-moderate open-angle glaucoma or OHT. These findings, nevertheless, require confirmation in randomized controlled studies conducted in large patient cohorts.

Competing Interests

The authors have no commercial or proprietary interest in any of the products or companies mentioned in this article. Julian Garcia-Feijoo is a consultant for the Glaukos Corporation.

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