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REVIEW

The New Era of Glaucoma Micro-stent Surgery

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ABSTRACT

Minimally invasive glaucoma surgery (MIGS) has been gaining popularity over the last decade. Although there is no strict definition for MIGS, all the new procedures share the common theme of intraocular pressure reduction with minimal tissue destruction, short surgical time, simple instrumentation and fast postoperative recovery. The use of glaucoma drainage implants has long been the traditional treatment for complex glaucoma, but a new wave of glaucoma micro-stents are now being manufactured with various materials designed to increase aqueous outflow via different channels. This review summarises the current published literature on these devices, including Sclemm's canal stents (iStent, Hydrus), Suprachoroidal stents (CyPass, iStent supra), and subconjunctival stents (Xen, Innfocus).

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INTRODUCTION

Over the last decade there has been significant activity in developing novel surgical treatments for glaucoma. These techniques and devices embrace the common theme of not only being effective in reducing intraocular pressure (IOP) and medication burden but also in causing as little trauma as possible to the target tissue, and most importantly they are safe. There is interest in finding surgical options that reduce surgical time, have an easily reproducible technique, and which are accessible to all ophthalmologists who manage glaucoma patients, rather than being the preserve of glaucoma specialists.

The term "minimally invasive glaucoma surgery" (MIGS) has arisen to describe such procedures; however, there is no widely accepted definition of MIGS, and thus no consensus on which specific procedures the term encompasses.

There has been particular interest recently in developing tubular stents, comprised of various materials, which can lower pressure in a similar

manner to existing glaucoma drainage devices, but without the associated risks or the time-consuming and involved surgical procedure. Such new aqueous drainage devices can be classified on the basis of the targeted aqueous outflow pathway: via Schlemm's canal, via the suprachoroidal space, or via the subconjunctival space.

In this article we will describe the principle current glaucoma micro-implants, the currently available evidence underpinning their use, and how they may fit into future practice.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

TRABECULAR MESHWORK BYPASS

Aqueous outflow resistance largely determines IOP, and the majority of this resistance is generated between the juxtacanalicular connective tissue and the inner wall of Schlemm's canal. Bypassing this region is, therefore, a viable method of decreasing IOP.

iStent

The iStent (Glaukos Corporation, Laguna Hills, CA, USA) is a heparin-coated non-ferromagnetic titanium device (Fig. 1). It is placed ab interno through the trabecular meshwork into Schlemm's canal under gonioscopic view using a single-use injector. In the 15 years since its initial development, a substantial number of publications have looked at its efficacy as a single and multiple standalone device, and in combination with cataract surgery.

The randomised controlled trial (RCT) carried out by the iStent study group is the largest RCT to date. This compared the results of cataract surgery combined with a single iStent to those of cataract surgery alone in 240 patients. A statistically significant 72% of participants that received combination surgery maintained an IOP $\leq$21 mmHg at 12 months [1], and 61% at 24 months [2], compared to 50% at both time points in the control group that only underwent cataract surgery. The secondary outcome of a $\geq$20% reduction in IOP was achieved by 66% of the experimental group at 12 months and 53% at 24 months, compared to 48 and 44% in the control group. The mean IOP reduction was 8.4 ± 3.6 mmHg in the treatment group at 12 and 24 months post op.

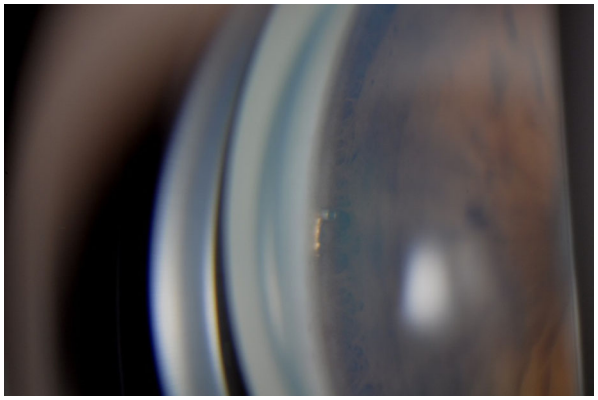

Fig. 1 Clinical picture of an iStent implanted in the angle

Medication reduction is another benefit of this procedure. The mean decrease in medications compared to screening in this trial was greater in the treatment group (1.4 ± 0.8 mmHg) versus the control group (1.0 ± 0.8) at 12 months ($P = 0.005$). This is significant not only for the patients' convenience and compliance, but importantly for the protection of their ocular surface and for the potential success of future drainage surgery. The reduction in ocular hypotensives was still numerically larger at 24 months in favour of the stent group, although no longer statistically significant. In the stent group, 15% were receiving medications at month 12, compared to 35% of the cataract only group ($P = 0.001$).

A smaller independent RCT by Fea et al. produced similar results with longer follow up [3]. After medication washout at 16 months, the mean IOP in the combined stent and cataract surgery group was significantly lower than in the cataract-only group (16.6 ± 3.1 vs 19.2 ± 3.5 mmHg, $P = 0.042$). This supports the hypothesis that the reduction in pressure seen with iStent implantation at the time of cataract surgery is not the result of the cataract surgery alone. This significant difference persisted at 48 months [4] (17.5 ± 2.3 vs 20.4 ± 3.2 mmHg, $P = 0.02$), demonstrating the prolonged effect of the stent. There was also a significant mediation reduction in both groups, but the difference between the two treatment groups did not reach statistical significance.

The use of iStents has not been limited to ocular hypertension and mild open-angle glaucoma [5]. Neuhann [6] published a case series of 62 eyes that included moderate to advanced glaucoma, and also patients with previous glaucoma surgery in that eye. The outcomes in the previous surgery group were good, although the lower target pressure needed for their more advanced glaucoma resulted in a higher medication burden than the group having no previous surgery. At month 36, mean IOP in the group with prior glaucoma surgery was 14.2 ± 2.3 mm Hg, with 44% of eyes on medications. In the group with no prior glaucoma surgery, mean IOP at month 36 was 15.4 ± 2.2 mmHg, with only 13% of eyes receiving medications.

Anatomical studies have shown that Schlemm's canal anatomy changes at higher pressures in normal eyes, with areas of partial collapse, and that this is exaggerated in primary open-angle glaucoma (POAG) eyes [7]. It is therefore possible that even if an iStent is correctly positioned in Schlemm's canal, the flow of aqueous humor to a collector channel may be restricted. Several studies have looked at the insertion of multiple iStents, which would both increase the flow of aqueous humor into Schlemm's canal by bypassing the trabecular meshwork in more regions, and increase the likelihood of ingress near a collector channel [8].

Belovay et al. published a case series of 53 eyes with two or three iStents inserted at the time of cataract surgery. They did not show a difference in IOP reduction between the two groups, but did show a significant difference in the mean number of postoperative medications [9]. A recent study by Katz et al. published a prospective study of 119 patients randomized to one, two, or three iStents. All but one of these patients was phakic, and the procedure was not combined with cataract surgery. At 18 months, mean unmedicated IOP was 15.9 ± 0.9 mmHg in one-stent subjects, 14.1 ± 1.0 mmHg in two-stent subjects, and 12.2 ± 1.1 mmHg in three-stent subjects. Intraocular pressure reduction was significantly greater with implantation of each additional stent ($P < 0.001$) [10].

With the view that multiple stents appear to be superior, Glaukos have manufactured a second-generation iStent, termed the iStent *Inject*. The single-use injector is designed to be used left- or right-handed, and comes pre-loaded with two stents. The stents are designed to be "bullet" rather than L-shaped. Initial laboratory studies confirmed that this device increased outflow facility [11]. In clinical use, insertion of two iStent Injects alone had the same efficacy as adding a second-line medication in patients uncontrolled on one medication [12]. Voskanyan et al. further demonstrated that in patients with IOP not controlled on two medications, two iStent Injects alone produced an IOP $\leq$18 mmHg

without medications in 66% of subjects at 12 months [13].

The safety profile with this procedure appears to be excellent, with no major complications reported in the literature.

Hydrus

The Hydrus Microstent (Ivantis Inc, Irvine, CA, USA) is a trabecular bypass device and Schlemm's canal scaffold (Fig. 2). It is manufactured from nitinol, an alloy of nickel and titanium. It is an 8-mm-long crescent with an open posterior surface and three windows in the anterior surface, designed to be inserted through trabecular meshwork and to follow the curve of Schlemm's canal. The length, being larger than the iStent, is such that three clock hours of Schlemm's canal can be cannulated, increasing the likelihood of accessing multiple collector channels, as well as dilating the canal and preventing canal compression. Increased outflow facility was demonstrated ex vivo and was twice as much as with double iStents [14]. Electron microscopy demonstrated no visible damage to the trabecular meshwork despite the size of the device [15].

Fig. 2 Clinical picture of Hydrus stent implanted into Schlemm's canal

Clinical results were published in 2012 by Pfeiffer et al. where 100 eyes were randomised to cataract surgery alone or cataract surgery plus Hydrus. At 24 months the proportion of patients using no hypotensive medications was significantly higher in the Hydrus plus cataract surgery group [16] (73 vs. 38%; $P = 0.0008$). The primary endpoint of a 20% reduction in washed-out diurnal IOP compared to baseline was achieved in a significantly higher proportion of Hydrus patients than with cataract surgery alone (80 vs. 46%; $P = 0.0008$). The washed-out diurnal IOP at 24 months was also significantly lower in the Hydrus patients (16.9 ± 3.3 vs. 19.2 ± 4.7 mmHg; $P = 0.0093$). Other studies directly comparing Hydrus with iStents are currently underway and results will likely be available in 1–2 years [17, 18].

SUPRACHOROIDAL SPACE

The suprachoroidal space is an intriguing target for the development of new procedures. There are several reasons to suppose that targeting this pathway might be successful. Firstly, the most effective topical hypotensive medications, the prostaglandins, exert their effect via this pathway [19]. Secondly, it is known that there is a negative pressure gradient that drives aqueous humor in the direction of the suprachoroidal space [20]. Thirdly, it has long been known that producing a cyclodialysis cleft lowers the pressure [21]. Consequently, there have been numerous attempts to develop a surgical technique to exploit this possibility. It had previously proven difficult to find a safe and accessible surgical technique that produces stable long-term results without the hypotony and rebound high pressure associated with cyclodialysis.

Cypass

The Cypass (Transcend Medical, Menlo Park, CA, USA) is a fenestrated polyamide tube 6.35 mm in length, with a 300-mm lumen. It is designed to be implanted ab interno and inserted between the ciliary body and the sclera. It provides a direct communication between the anterior chamber and suprachoroidal space.

The first published study on Cypass looked at its efficacy when combined with cataract surgery in two groups of patients [22]. Cohort 1 had uncontrolled open-angle glaucoma (IOP $\geq$ 21 mmHg). Cohort 2 consisted of patients whose glaucoma was controlled, but who wished to reduce their drop dependence. Two-year data showed a 37% reduction in IOP in the uncontrolled glaucoma group with a mean number of medications decreasing from 2.2 at baseline to 1.0 [23]. Similarly, the controlled glaucoma group showed a reduction in medications from 2.2 to 1.0. No sight-threatening adverse events occurred. Transient hypotony occurred in 15.4% of eyes and micro-stent obstruction due to iris tissue overgrowth in 8.8% [24]. Fifteen subjects (11%) required secondary incisional glaucoma surgery.

When a Cypass stent was inserted alone in patients who were not controlled on glaucoma medications, 83% of them avoided further glaucoma surgery [25]. Mean IOP was reduced by 35% to 16.4 $\pm$ 5.5 mmHg at 12 months ($P < 0.0001$) and mean medication usage decreased by 36% ($P = 0.002$). There were no serious adverse events. Seven patients were reported as having pressure rises >30 mmHg. There was no hypotony lasting more than 4 weeks postoperatively and no hypotonous maculopathy.

The COMPASS study is a prospective, multicentre, randomised controlled trial conducted at 27 sites in the United States. The patients have been randomised to receive either the Cypass Micro-Stent during cataract surgery or to undergo cataract surgery alone. More than 500 patients have been randomised so far, but no results have been published to date.

The iStent Supra

iStent Supra (Glaukos Corporation, Laguna Hills, CA, USA) is a 4-mm tube made of polyethersulfone and titanium (Fig. 3). The concept and mode of delivery is almost identical to the Cypass. There are currently no published studies on surgical outcomes, although preliminary results presented in scientific meetings have demonstrated promising results.

SUBCONJUNCTIVAL SPACE

The subconjunctival space is the traditional outflow pathway for glaucoma drainage surgery. Successful surgery depends on the continued patency of a pathway for aqueous humor, and on the scarring response in the conjunctiva (Fig. 4).

XEN GEL Implant

The XEN GEL Implant (AqueSys Inc., Aliso Viejo, CA, USA) is a 6-mm cylinder of

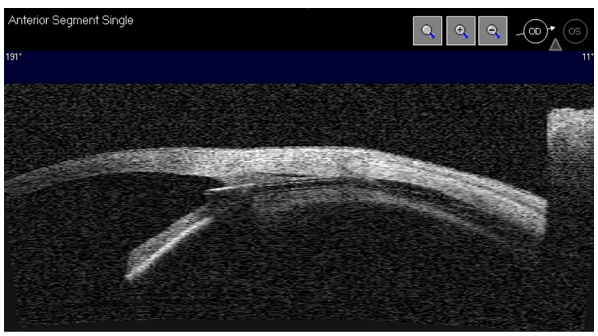

Fig. 3 Anterior segment OCT image of an iStent Supra in situ with fluid in the suprachoroidal space

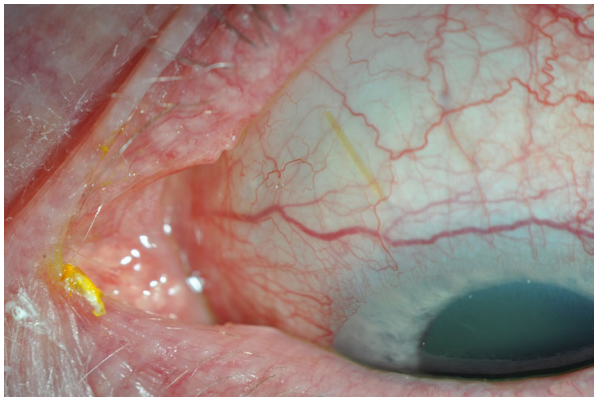

Fig. 4 Colour photo showing a Xen implant subconjunctivally in the superior nasal quadrant

collagen-derived gelatin cross-linked with glutaraldehyde, making it permanent and non-degrading, with no foreign body reaction. It comes pre-loaded in the injector and is implanted ab interno, creating a drainage pathway between the anterior chamber and subconjunctival space. The procedure is often augmented with subconjunctival injection of mitomycin-C. Long-term animal studies have shown the Xen implant structure to be stable over several years [26]. It softens on contact with water within 1–2 min, meaning that it can bend and conform to tissue, reducing the risk of erosion. Microforce testing has shown the XEN 45 to be more than 100 times as flexible as a typical silicone shunt tube [27].

Although initially produced with three different lumen diameters, the tube with the 45-nm lumen size is the only device now recommended for implantation by the manufacturer. This lumen size was chosen in an effort to design a device with the necessary dimensions to prevent postoperative hypotony by the primary flow resistance of the tube itself [28]. The tube length of 6 mm was identified as the ideal length for passage ab interno from the trabecular meshwork to the subconjunctival space at an optimal distance from the limbus. The Hagen-Poiseuille equation was then used to calculate the required internal dimensions of a tube that would prevent hypotony at average aqueous humour production of 2–3 μL/min by providing a steady-state pressure of approximately 6–8 mmHg. Implants of larger lumen size rely on conjunctival resistance to prevent hypotony, and as conjunctival resistance is low in the immediate postoperative period, the risk of hypotony with larger lumen tube stents is greatest at that time.

Little published data exists so far on the XEN 45 implant. A pilot study published in 2015 on cataract surgery combined with a XEN 63 (63 nm lumen) or XEN 140 (140 nm lumen) [29] showed a reduction of IOP from 22.4 (±4.2) mmHg to 15.4 (±3.0) mmHg at 12 months postoperatively ($P < 0.0001$). The number of medication classes reduced from 2.5 ± 1.4 to 0.9 ± 1.0.

In another pilot study on XEN 140 insertion as a standalone procedure [30] in 49 eyes, 40% of patients had an outcome classified as an unqualified success at 12 months, achieving an IOP $\leq$18 mmHg and $\geq$20% reduction in IOP, with 89% being successful when those on medications were included, despite a high proportion of patients having had a previous failed trabeculectomy.

These studies are not directly comparable to the currently recommended device and technique, however. As well as having larger lumen size, neither study used subconjunctival mitomycin C at the time of implant insertion. This is likely to have affected the degree of scarring, and therefore the outcome in terms of pressure, due to increased conjunctival resistance, and also the number of postoperative needling interventions required.

There were no serious adverse events attributed to the device in either study. At

12 months there were no cases of device erosion, despite the implants used having greater stiffness than the XEN 45. There were no cases of prolonged hypotony, although several patients in both studies required injection of ophthalmic viscoelastic device in the anterior chamber, more so with the 140-nm lumen tube.

The current Xen 45 is undergoing its phase 4 trial, and results should be available in 1–2 years time. Data was presented at ASCRS in 2015 on 31 patients with open-angle glaucoma, who required surgical treatment for glaucoma and cataracts, and who underwent implantation of the XEN 45 with MMC combined with phacoemulsification. The mean preoperative IOP was 20.8 ± 4.6 mmHg. The mean postoperative IOPs were 13.1 ± 3.6 mmHg at 12 months ($p < 0.001$) [31]. Mean number of preoperative medications was 2.7 ± 1, and this reduced to 0.9 ± 1.1 ($p < 0.001$) at 12 months. There were no complications.

InnFocus

The InnFocus Microshunt (InnFocus Inc, Miami, FL, USA), formerly known as the MIDI Arrow, is an aqueous drainage shunt designed to be implanted ab externo. As a fornix-based conjunctival flap and dissection of a shallow scleral pocket is required, unlike the other devices covered in this review, it resembles conventional trabeculectomy more than MIGS. Of interest, however is the product's material construction. The Microshunt is constructed from a material (Poly Styrene-block-IsoButylene-block-Styrene or SIBS) developed by the device's inventors specifically for medical implants. It is a biostable thermoplastic elastomer with some of the properties of silicone rubber and polyurethane [32]. It has enhanced biocompatibility and long-term stability with less inflammatory reaction than with traditional materials, which will hopefully lead

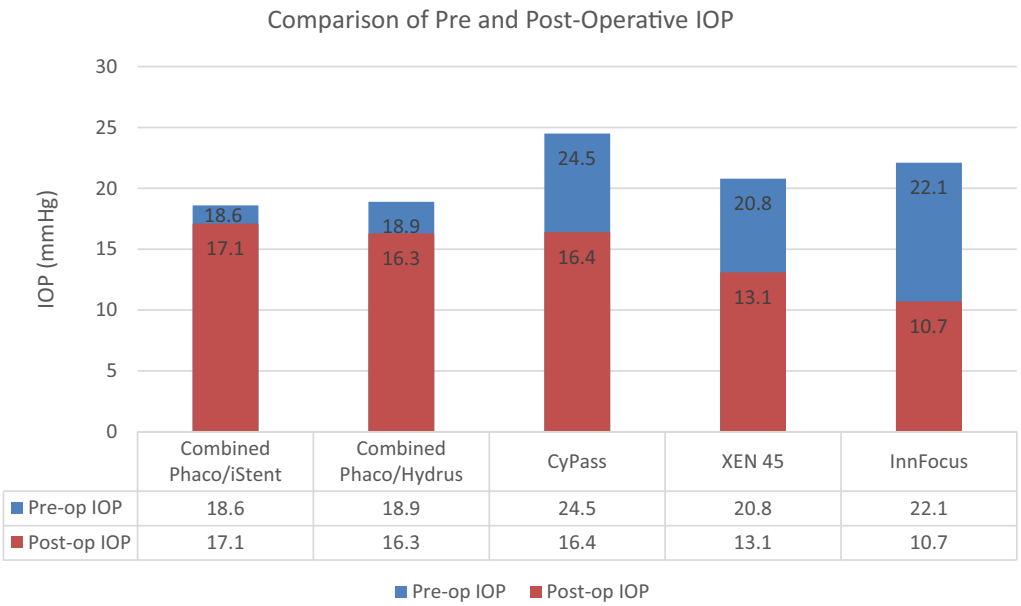

Fig. 5 Comparison of the pressure-lowering effect of (1) combined phacoemulsification and iStent [2], (2) combined phacoemulsification and Hydrus [16], (3) CyPass alone [25], (4) XEN 45 alone [31], and (5) InnFocus alone [33]

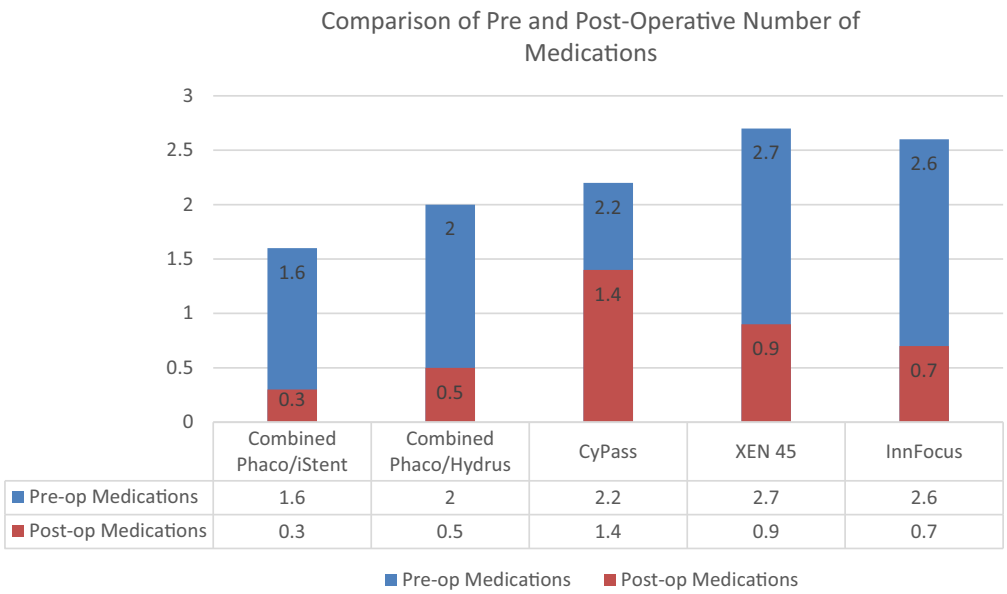

Fig. 6 Comparison of the reduction in number of medications following (1) combined phacoemulsification and iStent [2], (2) combined phacoemulsification and Hydrus [16], (3) CyPass alone [25], (4) XEN 45 alone [31], and (5) InnFocus alone [33]

to less postoperative conjunctival fibrosis. During development, however, it was found that the fins designed to prevent tube migration could erode through the conjunctiva—hence, the need for a scleral pocket.

A study of 23 eyes with Microshunt insertion, some with and some without cataract surgery, showed that over 80% of the patients had had an IOP ≤14 mmHg at 3 years [33]. At 3 years, the number of medications had fallen from 2.6 ± 0.9 to 0.8 ± 1.2 in the eyes with Microshunt alone, and from 2.0 ± 0.9 to 0.4 ± 0.1 in the eyes that underwent a combined procedure. In the group as a whole, the mean IOP at 3 years was 10.7 ± 3.5 mmHg and the qualified success rate (IOP ≤14 mmHg and IOP reduction ≥20%) was 95%. The most common complications were transient hypotony (13%) and transient choroidal effusion (8.7%), which all resolved spontaneously. There were no leaks, infections, migrations, erosions, persistent corneal oedema, or serious long-term adverse events.

Figures 5 and 6 summarise the pre and postoperative IOP and medications for each device using the most representative series.

DISCUSSION

The large number of new glaucoma drainage devices emerging in recent years is a testament to both the desire to find a safe and simple surgical procedure to treat mild to moderate glaucoma, and also to the inability of any one procedure to establish itself as filling this need.

Studies comparing a single iStent inserted at the time of cataract surgery to cataract surgery alone showed statistically significant but relatively modest additional reductions in pressure. The reduction in the number of medications is beneficial, however, and is more promising for the iStent finding a place in clinical practice given the ease of application. There are also new roles found for iStent use in other ways than as simply an adjunct to cataract surgery. There are several studies supporting its

use as a standalone device, as well as in cases of secondary glaucoma and following failed drainage surgery.

Multiple stents show more encouraging results in lowering pressure, and the new-generation device with multiple pre-loaded stents makes this easier. This would increase the cost of the procedure, however, and there is a real lack of data currently regarding the cost effectiveness of all these new devices.

The Hydrus Microstent theoretically has a better probability of improving the anatomical outflow pathway than the iStent, being larger and longer, and this appears to be borne out by laboratory results. So far the published clinical results look similar to those of the iStents, with a potentially better outcome at 2 years. The outcome of the Hydrus vs iStent studies should answer whether the results of laboratory studies suggesting greater efficacy than two iStents can be replicated in vivo.

Currently, there is particular interest in the XEN Gel Implant due to the potentially greater pressure lowering effect compared to other outflow pathways. There is, however, a correspondingly greater degree of postoperative management required compared to an "insert and forget" trabecular meshwork or supracilliary stent. It remains to be seen whether this additional workload is made worthwhile by its efficacy, and whether the greater simplicity and safety profile outbalances the established efficacy of traditional drainage surgery.

As efficacy and safety data emerges, before judging procedures against current practice, care must be taken in deciding which treatments to compare against one another. A modest treatment effect may be sufficient to justify a procedure if the risk profile is low enough. The treatment effect of selective laser trabeculoplasty is comparable to monotherapy with a prostaglandin analogue [34], and that is not considered an impediment to its use as an intervention. In many cases a modest additional effect is all that is needed to reduce a patient's risk to what we deem to be acceptable for their circumstances, and we regularly use this as a justification for adding a third or fourth medication to a patient's regimen.

A CyPass stent is unlikely to match the pressure-lowering effect of a trabeculectomy, but it may prove to be the equivalent of more than one drop. Given the widely recognised dissatisfaction and disadvantages with long-term drop therapy, the benefit from this should not be underestimated. These disadvantages are tolerated, by ophthalmologists at least, because of the relative safety of drops, but in many cases a patient might decide to accept a slightly higher risk profile to reduce or eliminate their drops. Further work will need to be done on patient-reported outcomes as well as on clinical effectiveness.

Similarly, subconjunctival drainage microstents should not be considered a direct replacement for traditional drainage surgery, as they do not appear to be able to achieve the lower target pressures needed for some patients, but the safety profile may prove to be such that a XEN implant is justifiable in a patient for whom a trabeculectomy was not, and not all patients need a pressure of 10 mmHg.

Another consideration that will certainly influence the uptake of new procedures is their economic benefit. In an economic analysis of iStent use in the Canadian medical system [35], cost savings of Can$20.77, Can$1,272.55, and Can$2,124.71 per patient were estimated over 6 years, when comparing two iStents versus mono-, bi-, and triple therapy, respectively. Two stents plus one medication still showed savings over two or three drops. In the CyPass

study described above, 83% of uncontrolled patients did not require trabeculectomy after CyPass insertion as a standalone procedure. This is likely to be associated with significant savings in theatre time and follow-up appointments, and similar savings have been discussed with the use of subconjunctival space stents. Nonetheless data to support the above does not currently exist in the literature.

CONCLUSION

The rapid influx of new devices onto the market in recent years has caused some to wonder whether we are entering a new era of microstent surgery in glaucoma management. The results of large prospective randomised studies are still awaited for many of the most promising devices. It will be interesting to see whether the "trabeculectomy holiday" that followed the introduction of prostaglandin analogues is repeated. It is more likely that, rather than replacing older treatments, new treatments will find their own niche depending on their respective risks and benefits. This has always been the case and the process of technological advance is on-going, bringing new treatments to challenge those discussed above. Future developments, such as the anticipated drug-eluting implants, will rekindle the debate.

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REFERENCES

1. Samuelson TW, Katz LJ, Wells JM, Duh Y-J, Giamporcaro JE, US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011;118(3):459–67.

2. Craven ER, Katz LJ, Wells JM, Giamporcaro JE, iStent Study Group. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. J Cataract Refract Surg. 2012;38(8):1339–45.

3. Fea AM. Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary open-angle glaucoma: randomized double-masked clinical trial. J Cataract Refract Surg. 2010;36(3):407–12.

4. Fea AM, Consolandi G, Zola M, et al. Micro-bypass implantation for primary open-angle glaucoma combined with phacoemulsification: 4-year follow-up. J Ophthalmol. 2015;2015:795357.

5. Arriola-Villalobos P, Martínez-de-la-Casa JM, Díaz-Valle D, et al. Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract. Br J Ophthalmol. 2013;97(10):1250–5.

6. Neuhann TH. Trabecular micro-bypass stent implantation during small-incision cataract surgery for open-angle glaucoma or ocular hypertension: long-term results. J Cataract Refract Surg. 2015;41(12):2664–71.

7. Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP. Anatomic changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures. Investig Opthalmol Vis Sci. 2014;55(9):5834.

8. Bahler CK, Smedley GT, Zhou J, Johnson DH. Trabecular bypass stents decrease intraocular pressure in cultured human anterior segments. Am J Ophthalmol. 2004;138(6):988–94.

9. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed IIK. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. J Cataract Refract Surg. 2012;38(11):1911–7.

10. Katz LJ, Erb C, Carceller GA, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. Clin Ophthalmol Auckl NZ. 2015;9:2313–20.

11. Bahler CK, Hann CR, Fjield T, Haffner D, Heitzmann H, Fautsch MP. Second-generation trabecular meshwork bypass stent (iStent inject) increases outflow facility in cultured human anterior segments. Am J Ophthalmol. 2012;153(6):1206–13.

12. Fea AM, Belda JI, Rękas M, et al. Prospective unmasked randomized evaluation of the iStent inject (®) versus two ocular hypotensive agents in patients with primary open-angle glaucoma. Clin Ophthalmol Auckl NZ. 2014;8:875–82.

13. Voskanyan L, García-Feijoó J, Belda JI, Fea A, Jünemann A, Baudouin C. Prospective, unmasked evaluation of the iStent® inject system for open-angle glaucoma: synergy trial. Adv Ther. 2014;31(2):189–201.

14. Hays CL, Gulati V, Fan S, Samuelson TW, Ahmed IIK, Toris CB. Improvement in outflow facility by two novel microinvasive glaucoma surgery implants. Invest Ophthalmol Vis Sci. 2014;55(3):1893–900.

15. Camras LJ, Yuan F, Fan S, et al. A novel Schlemm's Canal scaffold increases outflow facility in a human anterior segment perfusion model. Invest Ophthalmol Vis Sci. 2012;53(10):6115–21.

16. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, et al. A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma. Ophthalmology. 2015;122(7):1283–93.

17. Compare the Hydrus Microstent (TM) to the iStent for lowering IOP in glaucoma patients having cataract surgery (Hydrus III). https://clinicaltrials.gov/ct2/show/NCT02024464 [Internet].

18. Comparing effectiveness of the hydrus microstent (TM) to two iStents to lower IOP in Phakic eyes (Hydrus V). https://clinicaltrials.gov/ct2/show/NCT02023242 [Internet].

19. Weinreb RN, Toris CB, Gabelt BT, Lindsey JD, Kaufman PL. Effects of prostaglandins on the aqueous humor outflow pathways. Surv Ophthalmol. 2002;47(Suppl 1):S53–64.

20. Emi K, Pederson JE, Toris CB. Hydrostatic pressure of the suprachoroidal space. Invest Ophthalmol Vis Sci. 1989;30(2):233–8.

21. Razeghinejad MR, Spaeth GL. A history of the surgical management of glaucoma. Optom Vis Sci. 2011;88(1):E39–47.

22. Hoeh H, Ahmed IIK, Grisanti S, et al. Early postoperative safety and surgical outcomes after implantation of a suprachoroidal micro-stent for the treatment of open-angle glaucoma concomitant with cataract surgery. J Cataract Refract Surg. 2013;39(3):431–7.

23. Höh H, Grisanti S, Grisanti S, Rau M, Ianchulev S. Two-year clinical experience with the CyPass micro-stent: safety and surgical outcomes of a novel supraciliary micro-stent. Klin Monatsblätter Für Augenheilkd. 2014;231(4):377–81.

24. Grisanti S, Margolina E, Hoeh H, et al. Supraciliary microstent for open-angle glaucoma: clinical results of a prospective multicenter study. Ophthalmol Z Dtsch Ophthalmol Ges. 2014;111(6):548–52.

25. García-Feijoo J, Rau M, Grisanti S, et al. Supraciliary micro-stent implantation for open-angle glaucoma failing topical therapy: 1-year results of a Multicenter Study. Am J Ophthalmol. 2015;159(6):1075–1081.e1.

26. Yu D-Y, Morgan WH, Sun X, et al. The critical role of the conjunctiva in glaucoma filtration surgery. Prog Retin Eye Res. 2009;28(5):303–28.

27. Lewis RA. Ab interno approach to the subconjunctival space using a collagen

glaucoma stent. J Cataract Refract Surg. 2014;40(8):1301–6.

28. Sheybani A, Reitsamer H, Ahmed IIK. Fluid dynamics of a novel micro-fistula implant for the surgical treatment of glaucoma. Invest Ophthalmol Vis Sci. 2015;56(8):4789–95.

29. Sheybani A, Lenzhofer M, Hohensinn M, Reitsamer H, Ahmed IIK. Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: pilot study. J Cataract Refract Surg. 2015;41(9):1905–9.

30. Sheybani A, Dick B, Ahmed IIK. Early clinical results of a novel ab interno gel stent for the surgical treatment of open-angle glaucoma. J Glaucoma. 2015. doi:10.1097/IJG.0000000000000352

31. Sheybani A, Ahmed IK. Ab interno gelatin stent with mitomycin-C combined with cataract surgery for treatment of open-angle glaucoma: 1-year results. In: Presented at ASCRS 2015.

32. Pinchuk L, Wilson GJ, Barry JJ, Schoephoerster RT, Parel J-M, Kennedy JP. Medical applications of poly(styrene-block-isobutylene-block-styrene) ("SIBS"). Biomaterials. 2008;29(4):448–60.

33. Batlle JF, Fantes F, Riss I, et al. Three-year follow-up of a novel aqueous humor microshunt. J Glaucoma. 2016;25(2):e58–65.

34. Nagar M, Ogunyomade A, O'Brart DPS, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br J Ophthalmol. 2005;89(11):1413–7.

35. Iordanous Y, Kent JS, Hutnik CML, Malvankar-Mehta MS. Projected cost comparison of trabectome, iStent, and endoscopic cyclophotocoagulation versus glaucoma medication in the Ontario Health Insurance Plan. J Glaucoma. 2014;23(2):e112–8.