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Editorial

New therapeutic avenues in glaucoma surgery

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Glaucoma filtration surgery (GFS) can be divided into penetrating and non-penetrating glaucoma surgery. Non-penetrating glaucoma surgeries (comprising deep sclerostomy and viscocanuloplasty) may have a more favourable risk profile in terms of hypotony related complications¹ and infections². However, due to its long learning curve and lower efficacy at reducing intraocular pressure (IOP) trabeculectomy remains the gold standard and the most commonly performed GFS¹. Aqueous shunts have traditionally been used in cases of refractory glaucoma following unsuccessful GFS surgery, or in patients at high risk of GFS failure. Over the past decade there has been marked increase in the development of new glaucoma drainage devices (GDDs). Emerging stents in the context of minimally invasive glaucoma surgery (MIGS) aim to improve the safety of glaucoma surgery without compromising efficacy and promote earlier surgical intervention. MIGS can have an *ab interno* or *ab externo* approaches some of which do not require a filtering bleb. Regardless of the type of filtration surgery or placement of devices draining into the subconjunctival or suprachoroidal space, scarring is the predominant cause of surgical failure. MIGS encompass a wide range of procedures utilising endolasers, electrocautery devices, microcatheters and stent implants with minimum or no scleral dissection. This editorial will focus on approved GDDs, stents and anti-scarring therapies in glaucoma surgery.

1. New advances in glaucoma drainage device surgery

GDDs are increasingly used due to their improved efficacy and continued concerns over bleb-related complications in GFS, despite the improved bleb appearance with modified methods of antimetabolite application³. Recent modifications to optimise surgical results include changes to the surface area and modifications to end plate materials, with the aim of optimising surgical success rates, improving IOP reduction and reducing post-operative complications.

The Ahmed Baerveldt Comparison Study recently published their five-year outcomes, comparing the Ahmed FP7 Glaucoma Valve (AGV) (New World Medical, Cucamonga, CA, USA) and the 350 mm² Baerveldt glaucoma implant (BGI) (Abbot Medical Optics, Santa ANA, CA, USA)⁴. The results showed that mean IOP was 14.7±4.4 and 12.7±4.5 mmHg in the AGV and BGI groups respectively⁴. Cumulative probability of failure during 5 years of follow up was 44.7% in the AGV group and 39.4% in the BGI group. Complications including persistent hypotony, implant explantation or loss of light perception occurred in 11/143 in the AGV group and 22/133 in the BGI group.

While GDDs offer the potential for reasonably effective IOP control, a new group of surgical procedures commonly known as Minimally Invasive Glaucoma Surgery (MIGS) have been developed

that aim to have an improved safety profile compared to traditional GDDs. MIGS can be divided into procedures that either bypass or eliminate the trabecular meshwork (TM) or offer an alternative drainage route into the suprachoroidal or subconjunctival space ⁵.

The iStent (Glaukos, Laguna Hills, CA, USA), was one of the first drainage devices used for MIGS to receive CE marking in 2008 followed by FDA approval in 2012. The iStent is a heparin-coated titanium implant, 1 mm in length and 0.33 mm high, which is inserted through the TM into Schlemm's canal. Craven et al. demonstrated that 66% of patients who underwent combined surgery achieved a 20% reduction in pressure without concurrent IOP-lowering medication, compared with 48% of patients who underwent cataract surgery alone ⁶. Further studies have demonstrated that the implantation of more than one iStent device may result in improved IOP reduction, compared to a single device with the second generation iStent Inject allowing for implantation of two devices that are pre-loaded on the insertion tool ⁷. A recent case series reported safe IOP control when two iStents, one iStent Supra and postoperative travoprost were used in combination in refractory glaucoma cases ⁸. However, multicentre, randomised control trials are warranted to compare MIGS procedures with established glaucoma filtering surgeries in refractory cases ⁹.

The Hydrus Microstent (Ivantis Inc, Irvine, CA, USA) is a 8 mm long crescent-shaped TM bypass device, composed of nitinol (a nickel and titanium alloy) that dilates and stents Schlemm's canal by 166 μ m along the length of the device and up to 241 μ m at the device inlet, allowing aqueous humour drainage via multiple collector channels ¹⁰. Pfeiffer et al. showed implantation of the device lowered postoperative IOP to 16.9 ± 3.3 compared to 19.2 ± 4.7 mmHg with cataract surgery alone and a greater proportion of patients were medication free at 2 years (73% versus 38%) ¹¹.

The CyPass shunt (Transcend Medical, Menlo Park, CA, USA), is a single lumen device composed of polyimide that drains into the suprachoroidal space. It has a lumen of 310 μ m in diameter and 6.35 mm in length and is inserted via an *ab interno* approach. The COMPASS trial two-year results showed implantation of the device decreased IOP from 24.4 ± 2.8 at baseline by 7.4 mmHg at two years with 85% of patients being medication free at 2 years ¹². While studies with these shunts have demonstrated early IOP reduction, long-term efficacy may still be limited due to fibrosis around the device, that has occurred with other devices in the suprachoroidal space.

The XEN Gel Stent (Aquesys Inc, Aliso Viejo, CA, USA) is a single lumen tube composed of porcine gelatin crosslinked with glutaraldehyde. It is 6mm in length, with a lumen size of 45 μ m ¹³. Grover et al. showed implantation of the device decreased IOP from 25.1 ± 3.7 at baseline by 9.1 mmHg at twelve months ¹⁴. While observed post-operative complications were mild or moderate

and transient, it is worthwhile noting that the needling rate was 32.3%. A comparative case series of Xen + Mitomycin-c versus trabeculectomy + Mitomycin-c in medically uncontrolled glaucoma showed no difference in risk of failure¹⁵. However, this study had a relatively higher rate of trabeculectomy failure and bleb needling compared with other studies with similar patient cohorts^{16,17}.

The InnFocus microshunt is based on a similar principle to the XEN gel stent, but the InnFocus has a 70 µm internal diameter and is placed following a conjunctival incision (InnFocus Inc, Miami, FL USA). Batlle et al. showed decreased IOP from 23.8±5.3 at baseline to 10.7±3.5 mmHg at three years¹⁸. Anti-scarring therapies with appropriate application technique (Moorfields Safer Surgery System) are critical as, despite the gain in ease of use and safety, the failure rate of these devices is significant without the appropriate use of antimetabolites.

2. New advances in scarring modulation post glaucoma filtration surgery

Scarring after glaucoma surgery is a critical determinant of long-term outcomes. Anti-metabolites such as mitomycin-c (MMC) and Fluorouracil (5-FU) are used to modulate conjunctival scarring after trabeculectomy and significantly protect against surgical failure. MMC is shown to reduce IOP by further 5mmHg when compared to placebo in primary trabeculectomies as well as in high risk groups¹⁹. Early iterations of the InnFocus microshunt showed that subconjunctival use of low dose MMC intra-operatively during insertion has a greater surgical success rate at 1 year of 67% (Bordeaux II study) versus 42% (Bordeaux I study) without MMC in advanced glaucoma cases²⁰. Surgical success was defined as IOP <21mmHg with a reduction from baseline of ≥20% with or without glaucoma medications and with no further incisional procedure. A Phase 3 randomised controlled trial (RCT) comparing InnFocus + MMC and trabeculectomy + MMC is underway with an expected completion by July 2019. Anti-metabolites continue to have a critical role in GDD surgeries.

Although antimetabolites have improved the survival of blebs after glaucoma surgery, concerns remain regarding post-operative complications, such as but not limited to, ischaemic blebs, corneal and scleral toxicity. Hypotony is more common at higher doses and prolonged exposure times of MMC. As such more targeted antimetabolite delivery systems are being developed such as hydrogels, liposomes and LDL-chitosan nanoparticles to decrease toxicity to healthy cells²¹⁻²³.

Small molecules identified to decrease scar formation during wound healing include antibodies against vascular endothelial growth factor (VEGF) and transforming growth factor beta 2 (TGF-β2). A Cochrane meta-analysis found there was not enough evidence to support the use of anti-VEGF by subconjunctival injection for control of wound healing in glaucoma surgery when compared to control or MMC in patients with refractory glaucoma²⁴. Anti-VEGF may have adjunctive

role with GFS for neovascular glaucoma, however, well designed RCTs are needed to prove this. Phase III studies investigating the efficacy subconjunctival administration of antibody TGF- β 2 (CAT 152) showed no difference between CAT 152 with placebo in preventing failure of primary trabeculectomy²⁵. The outcome of this trial may have resulted from the lack of antagonist affinity to different TGF isomers and also the extremely short half-life of subconjunctivally administered antibodies. More recently, a phase I, first in human trial showed intravitreal injection of anti-sense oligonucleotide (ASO) targeting TGF- β 2, delivered immediately post trabeculectomy surgery with MMC, in patients with POAG was found to be safe²⁶. This ASO has a longer half-life than that of CAT 152, with pharmacodynamic effects lasting up to 8 weeks in preclinical testing and repeat dosing is planned for phase II clinical trials. It will be interesting to see if this proves to be a useful adjunct to GFS in maintaining an anti-fibrotic effect post-operatively.

Continued progress has been made with Ilomastat, a broad-spectrum matrix metalloproteinases (MMP) inhibitor shown to reduce inflammation and extracellular matrix remodelling when injected subconjunctival in preclinical testing²⁷. Ilomastat can now be formulated as an eye drop for topical administration after GFS. Preliminary results demonstrate adequate conjunctival tissue penetration and therapeutic concentrations within sclera and conjunctiva and aqueous humour²⁸. *In vivo* testing is still required to assess its efficacy in reducing scar formation.

Beta radiation is known to reduce scarring response in glaucoma patients by modulating fibroblast activity and by causing cell cycle arrest. Beta radiation can be delivered as a single, inexpensive and timely controlled dose. A meta-analysis pooling 4 RCTs, showed that patients who received trabeculectomy with beta radiation had a lower risk of surgical failure versus trabeculectomy alone²⁹. More recently, Dhalla et al conducted a RCT directly comparing beta radiation with 5-FU as adjuncts to phacotrabeculectomy, which found no difference between the two arms in an African cohort³⁰, and there are studies underway comparing beta-radiation to MMC in trabeculectomy. There is a potential application for adjunctive beta radiation in high risk groups, particularly with new probes that can deliver equivalent doses in less than 30 seconds, but further studies are warranted.

3. Summary

The challenges of glaucoma filtration surgery (GFS) are best tackled with a combined approach. Essential to the enhanced efficacy of GFS are improved surgical techniques, optimal anti-scarring therapies, and surgical devices that minimise hypotony, scarring and ocular toxicity. While we still do not know the long-term success rates of MIGS devices, future developments may allow us to control

IOP at levels at which disease progression is halted with improved quality of life and cost effectiveness.

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