3

CUTTING EDGE

Glaucoma

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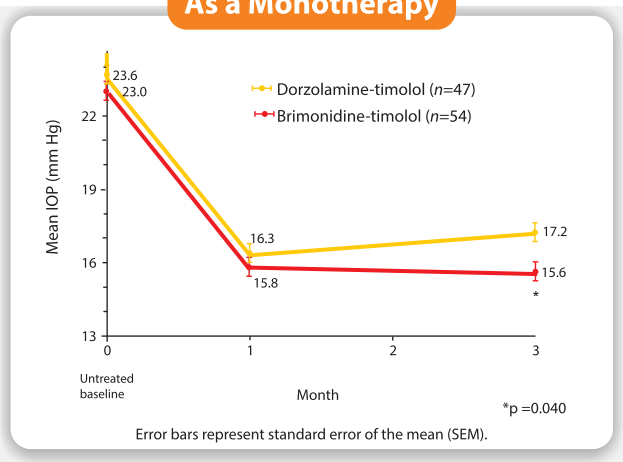
In Primary Open Angle Glaucoma & Ocular Hypertension

Rx BRIMOLOL

Brimonidine Tartrate 0.15% + Timolol Maleate 0.5%

Greater IOP Reduction Over Dorzolamide & Timolol Combination[1]

As a Monotherapy



- BTFC offer mean IOP reduction from baseline upto 32% as compared to 26% IOP reduction with DTFC[1]
- DTFC caused more ocular stinging upon Instillation than BTFC[2,3]

No Washout Effect#

Combined power, Greater benefits

1: Nixon etal, Current medical research and opinion Vol.25,iss,7,2009 2: Enyr etal, Current medical research and opinion,683-689
#Benefit of FDC's Anne J etal, clinical opthalmology 2008: 545-55 DTFC: Dorzolamide Timolol Fixed Combination.
BTFC: Brimonidine Timolol Fixed Combination 3: P = 0.027 , FDC : Fixed Dose Combination

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1. Pediatric trabeculectomy using the Moorfields Safer Surgery technique. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth)

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Pediatric Trabeculectomy

Maria Papadopoulos, Peng Tee Khaw

History

Trabeculectomy was first described by Cairns in 1968 in an attempt to replace full-thickness sclerostomy with a safer "guarded sclerostomy" associated with fewer complications [1]. With time trabeculectomy was to become, and still remains, the reference standard for filtering surgery worldwide. Following its introduction in adult glaucoma surgery, it was also adopted for use in children. Conventional techniques at the time such as Elliot trephining, iridencleisis, and cyclodialysis were associated with poor outcomes for refractory cases and significant complications in buphthalmic eyes, fuelling the search for alternative operations with better and safer outcomes [2, 3]. Furthermore, it gradually became evident that angle surgery even after multiple attempts was not always successful in primary congenital glaucoma (PCG), especially in older children [4], and even less so in secondary childhood glaucoma [5, 6].

Beauchamp and Park were the first in 1979 to publish trabeculectomy outcomes in children with advanced or refractory glaucoma. Most children in the series had previous surgery before trabeculectomy, and around 30% of eyes were aphakic at the time of surgery. Successful outcomes were low and complication rates high for which the authors cited numerous reasons, including "more rapid healing processes" [7]. Despite subsequent more encouraging reports of trabeculectomy in children without previous surgery (primary trabeculectomy) [8–10], excessive scarring in the region of the scleral flap remained a barrier to success in many cases. In the adult glaucoma literature, evidence was mounting that adjunctive therapy such as topical steroids [11] and 5-fluorouracil (5FU) [12] could improve outcomes by limiting the wound healing response and reducing fibrous tissue formation. However, the association of 5FU with complications such as corneal toxicity and the need for frequent postoperative subconjunctival injections made its use in children impractical. In 1991, Miller and Rice demonstrated the use of intraoperative beta radiation (750 cGy) to the surgical site improved trabeculectomy outcomes in children and was

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associated with diffuse elevated blebs with no increase in complications [13]. However, despite the simplicity of application, it never gained widespread use probably because of limited access to the strontium^{90} probes. The introduction in the late 1990s of mitomycin C (MMC), a potent inhibitor of fibroblast function, which could be applied at varying potencies and required only intraoperative exposure, offered major advantages over 5FU as an adjunct to trabeculectomy surgery in children. Although MMC was generally thought to improve trabeculectomy success, its association with significant, potentially blinding complications such as bleb-related infection led over the years to trabeculectomy falling out of favor in children and to alternative techniques to replace it, such as glaucoma drainage devices (GDD) [14–16].

However, the limited surgical armamentarium for childhood glaucoma and the fact that trabeculectomy was able to achieve lower mean intraocular pressure (IOP) and be less dependent on medication for IOP control than GDDs, led to a reevaluation of the technique in the late 1990s [17]. The resulting simple modifications to the surgical and antiscarring application technique have shown trabeculectomy in the twenty-first century to be associated with satisfactory outcomes in appropriate cases in children of all ages and with reduced complications [18, 19]. This is of particular relevance and importance to the developing world, where often the need is great but access to GDDs limited.

Indications and Contraindications

In PCG, the most common indication for trabeculectomy is failed angle surgery [20]. However, it can be considered as first-line surgery by surgeons unfamiliar with angle surgery, if angle surgery is not possible, or if the patient is unlikely to respond sufficiently to angle surgery (e.g., very early or late presentations). A further indication may be cases where very low target pressures are required (advanced optic disc damage or to improve corneal clarity) as the IOP can be potentially titrated. In juvenile open-angle glaucoma (JOAG), trabeculectomy is usually the procedure of choice [21], although 360° trabeculotomy may be effective in selected cases. For most phakic secondary glaucomas, trabeculectomy can be considered first-line due to the lower success rates of angle surgery compared to PCG. Possible exceptions include uveitic glaucoma [22], congenital rubella [5], and infantile presentations of Sturge-Weber syndrome (SWS) [23] when angle surgery may be attempted first.

Trabeculectomy is contraindicated in glaucoma secondary to malignant intraocular tumors to prevent the risk of tumor seeding. Relative contraindications to trabeculectomy surgery include aphakia or pseudophakia following congenital cataract surgery due to poor outcomes and Peters anomaly (moderate to severe forms) as it is our impression it's associated with an increased risk of trabeculectomy failure. The presence of a cataract requiring imminent surgery or corneal pathology that may require transplantation in the near future is also a relative contraindication because of the high risk of failure after pediatric anterior segment surgery. And, the inability to regularly review children in the postoperative period to assess bleb function and inflammation may compromise success.

Risk Factors for Failure

There are numerous risk factors for failure of trabeculectomy in children, which include age, severity of disease, previous surgery involving the conjunctiva, absence of a natural lens, and lack of cooperation with examination and with the administration of drops in the postoperative period.

Children have lower trabeculectomy success rates compared to adults [24]. It has been suggested that a thicker Tenon capsule in children acting as an impediment to filtration and as a large reservoir of fibroblasts results in an enhanced inflammatory and healing response in pediatric eyes [7, 25]. Infancy, especially less than the age of 1 year [26–29], has often been cited as a risk factor for failure; however, contemporary trabeculectomy results in infants suggest satisfactory long-term outcomes [19].

Conjunctival scarring [13, 24, 29–31], a legacy of previous surgeries, increases the risk of failure as does aphakia or pseudophakia following congenital cataract surgery [28, 32–34] and long-term drop use particularly when associated with conjunctival redness and inflammation [13].

Glaucoma filtering surgery, such as trabeculectomy, is unique in that the actual technique contributes only partially to success, with bleb management in the postoperative period being just as important. Failure tends to occur early in children, and so frequent postoperative examinations to assess the bleb and the ability to perform postoperative manipulations, such as suture removal, are crucial to trabeculectomy success. Regular and sometimes intensive steroid topical therapy is also often required to avoid failure from excessive inflammation. However, both these factors can be challenging for clinicians and parents due to difficulties with cooperation in infants and young children. Examinations under anesthesia (EUA) may be required possibly on a repeated basis to adequately monitor IOP and bleb progress. Although there are concerns related to multiple general anesthetics in children affecting development, they should be considered within the context of the high risk of blindness from glaucoma inadequately assessed or managed surgically.

Advantages and Disadvantages

For advantages and disadvantages of trabeculectomy with MMC, refer to Table 1 [20].

Preoperative Considerations and Preparation

Once the decision is made that trabeculectomy is the best surgical option, it is vital to discuss the details of the surgery with the parents including likely success, the need for regular follow-up, and intensive postoperative drops along with the possibility of unplanned surgery should there be a complication. A "quiet eye" is necessary to maximize the chances of success, for example, in children with uveitic glaucoma who may need additional topical and/or systemic immunosuppression preoperatively.

Preoperatively it is important to also give consideration to the MMC dose, which depends on multiple factors such as the type of glaucoma, age, race, inflammatory state of the eye, previous surgical history, corneal clarity, severity of optic nerve damage, and the state of the fellow eye. For

Table 1: Advantages and disadvantages of trabeculectomy with mitomycin C.

Advantages	• Titration of postoperative IOP possible with corneal buried releasable sutures • Lower IOP achievable compared to GDD and therefore indicated if low IOP required, e.g., to clear hazy cornea • Less medication for IOP control compared to GDD • Fewer postoperative surgical revisions compared to GDD • No tube-related complications, e.g., corneal decompensation or tube retraction/ exposure • May significantly clear cloudy corneas and avoid potential corneal surgery • Many surgeons worldwide have experience performing trabeculectomy
Disadvantages	• More invasive and higher complications than angle surgery • Need regular postoperative follow-up which may include examinations under anesthesia • Less likely to be successful if previous superior conjunctival surgery • Poor results in aphakic and pseudophakic patients even with MMC • Significant lifetime risk of endophthalmitis with thin, avascular bleb (more likely with small treatment areas of MMC and a limbal-based conjunctival flap)

Adapted from Papadopoulos *et al*. [20] with permission
IOP intraocular pressure, *GDD* glaucoma drainage device, *MMC* mitomycin C

example, you are more likely to use a higher concentration of MMC if a combination of high-risk factors exists or if a low IOP is required to maximize corneal clarity or to preserve a very damaged optic nerve's function in advanced glaucoma.

The surgical instruments required are as per trabeculectomy for adult glaucoma surgery. A small but adequate 500 μm sclerostomy can be created quickly with a Khaw Descemet membrane punch 7–101 (Duckworth & Kent, UK) and can be considered. An anterior chamber (AC) maintainer is mandatory for all cases. For MMC treatment, Merocel corneal shields (Beaver Visitec, UK) or pieces of a wick sponge can be used. In infants, consideration should be given to treating the undersurface of the scleral flap with a tear film strip (Clement Clarke, UK) soaked in MMC (Table 2).

Operation

Intraoperative Preparation

Following general anesthesia induction, a sterile field is prepared.

Surgical Technique

The aim of trabeculectomy surgery is to create a pathway for external drainage of aqueous from the AC to the subconjunctival space. Although there are many ways to successfully perform trabeculectomy surgery in children, contemporary trabeculectomy techniques have evolved with the aim of encouraging posterior aqueous flow and the development of diffuse drainage blebs to minimize complications while achieving satisfactory outcomes (Fig. 1). One such technique is the Moorfields Safer Surgery System [35], which emphasizes posterior aqueous flow through a

Table 2: Suggested instruments, suture, and consumables for pediatric trabeculectomy surgery.

Instruments and knives
Eye speculum (e.g., Khaw pediatric or standard glaucoma speculum)
Needle holder
Fine, notched/grooved forceps
Tying forceps
Westcott scissors
Tooke knife
Calipers
15° Feather® blade
Angled crescent blade
Descemet membrane punch (e.g., Khaw small Descemet membrane punch 0.5 mm)
Vannas scissors (straight or curved)
Sutures and consumables
7/0 Mersilk for corneal traction suture
10–0 Nylon on a spatulated needle
23G needle on 3 ml syringe
Anterior chamber maintainer (e.g., Lewicky)
Bipolar diathermy
Mitomycin C
Merocel corneal shields
Balanced salt solution
20 ml syringe with 20G Rycroft cannula
Sterile air
Apraclonidine 0.5% (for hemostasis)
± Tear film strip
± Viscoelastic (e.g., Provisc or similar)

fornix-based conjunctival flap, a large area of treatment with antiscarring agents, and short scleral flap radial incisions which discourage direct flow near the limbus (Fig. 2). Titration of postoperative IOP is possible with releasable or adjustable sutures. Buphthalmic eyes are especially prone to hypotony, flat anterior chambers, choroidal effusions, and suprachoroidal hemorrhage due to low scleral rigidity if aqueous flow is not well-controlled. The potential for these complications should never be underestimated. Measures to minimize hypotony are essential in trabeculectomy surgery especially in cases such as aniridia and SWS. In cases of SWS, some surgeons have suggested prophylactic measures such as sclerotomies with glaucoma surgery [36] to prevent suprachoroidal effusion and hemorrhage, but others have questioned the need [37]. We feel that the use of an AC

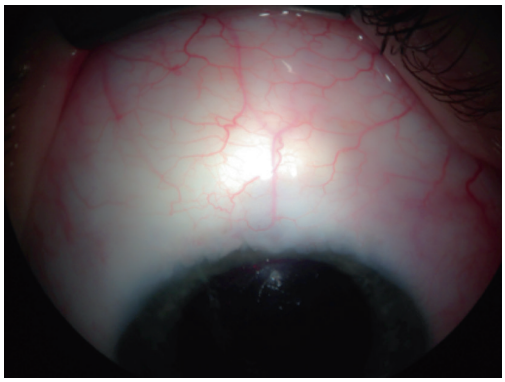

Fig. 1: Diffuse, elevated bleb using contemporary trabeculectomy surgery. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

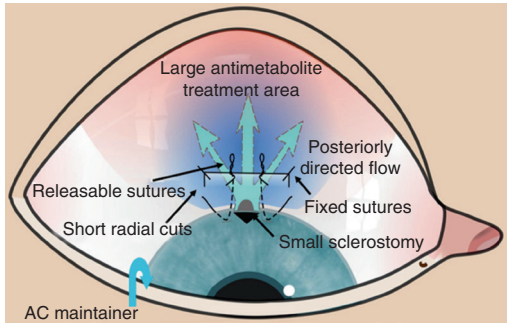

Fig. 2: Moorfields Safer Surgery System: a contemporary pediatric trabeculectomy technique for infants and children. (Courtesy of Peng Tee Khaw, PhD, FRCP, FRCS, FRCOphth, FRCPath, CBiol and Maria Papadopoulos, MBBS, FRCOphth).

maintainer and secure closure techniques significantly reduce the rate of choroidal effusions and the need for prophylactic sclerotomies in these cases.

Moorfields Safer Surgery System

Adequate exposure of the superior fornix is necessary and can be achieved with a 7/0 Mersilk (Ethicon, US) corneal traction suture (see Table 2). Apraclonidine 0.5% drops are applied to the superior conjunctiva before the conjunctival incision to minimize intraoperative bleeding from the conjunctiva. We prefer this to adrenaline as it produces better blanching and less pupil dilatation. A superior fornix-based conjunctival flap is created by incising the conjunctiva and accessing the Tenon layer at the limbus with fine, notched forceps and Westcott scissors. The peritomy is extended to allow adequate access to the superior sclera to fashion the scleral flap. This is followed by posterior blunt dissection of the subconjunctival space, around 8 mm from the limbus, to create a space for antiscarring treatment. Any bleeding vessels are cauterized before a wide area of approximately 3 clock hours is treated with MMC-soaked Merocel corneal shields (Beaver Visitec, UK) (Fig. 3). In infants MMC treatment occurs after the scleral flap is fashioned so that the undersurface of the scleral flap can also be treated with a tear film strip (Clement Clarke, UK) cut to size and soaked in MMC. MMC is applied at concentrations varying between 0.2 and 0.5 mg/ml for 3 min before irrigation with 20 ml of balanced salt solution.

Diathermy is applied to blanch the area of incision, and loose episcleral tissue is cleared with a Tooke knife. At the 12 o'clock position, a 15° Feather® blade (PFM Medical, UK) is used to create a 5 mm partial thickness tangential incision which forms the posterior edge of the flap about 4 mm from the limbus. A rectangular (5 mm × 4 mm), lamellar scleral tunnel is then fashioned with an angled crescent blade beginning at the posterior incision and advancing anteriorly to the superficial limbus for the width of the initial incision with care not to enter the AC (Fig. 4). In infants with buphthalmic eyes, the wide limbus mandates the correct positioning of the scleral

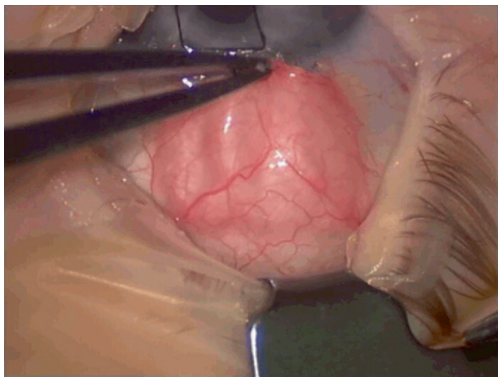

Fig. 3: Large treatment area with mitomycin C -soaked Merocel corneal shields. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

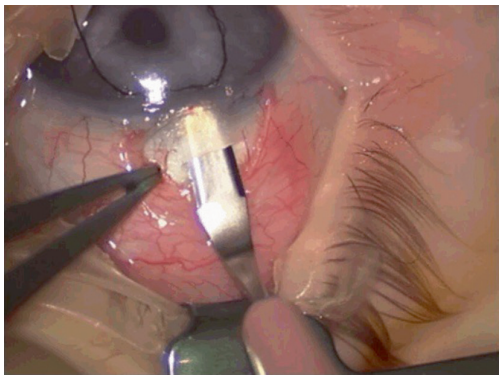

Fig. 4: Lamellar scleral tunnel fashioned with an angled crescent blade. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

flap. The posterior edge of the flap should not be at the edge of the limbus but within more robust sclera to minimize cheesewiring of sutures. The sides of the scleral tunnel are then opened toward the limbus with the Feather® blade to create the scleral flap. Due to the elastic nature of sclera in children, these radial cuts should be short to enable tight closure without the need to suture the radial edge of the flap and to also encourage posterior aqueous flow and a diffuse bleb (Fig. 5).

A 10-0 nylon (Alcon, UK) is used to preplace intralamellar scleral sutures, with a fixed suture at each corner and two releasable sutures at the posterior edge of the scleral flap (Fig. 6). We avoid passing the needle full thickness through the sclera to avoid aqueous seepage around the needle track. Releasable sutures are preferable as they can be loosened or removed while under EUA in infants and young children and on the slit lamp in older children. The releasable loop is buried in a corneal slit parallel to the limbus, so it can be left indefinitely without the risk of infection. Preplacement of the sutures with a formed globe is easier than after the sclerostomy, and it also reduces the duration of intraoperative hypotony after the sclerostomy and peripheral iridectomy have been performed. The paracentesis for the AC maintainer (Lewicky, Beaver Visitec, UK) is then created with a Feather® blade and 21G green needle and the AC maintainer inserted in the AC. An AC maintainer is used in all cases to rapidly reform the AC, maintain the IOP intraoperatively, minimize intraoperative hypotony-related complications (choroidal effusions, suprachoroidal hemorrhage, vitreous prolapse with peripheral iridectomy), and facilitate the accurate judgment of flow through the scleral flap to ensure adequate flap closure.

The AC is entered at the anterior edge of the scleral bed, and a 500 μm sclerostomy is created with a Khaw Descemet membrane punch 7-101 (Duckworth & Kent, UK) followed by a surgical iridectomy. The scleral flap is then sutured closed by tying the preplaced releasables first (four throws), followed by the fixed sutures in infants and children. The AC maintainer must be temporally turned off to soften the eye when tightening the sutures to prevent them from tearing the scleral flap. Further sutures are placed in the scleral flap as required with the aim of achieving minimal or slow aqueous flow through the flap at the end of procedure, e.g., gradual hydration of a sponge swab. A tenonectomy is not performed to minimize the theoretical risk of a thin

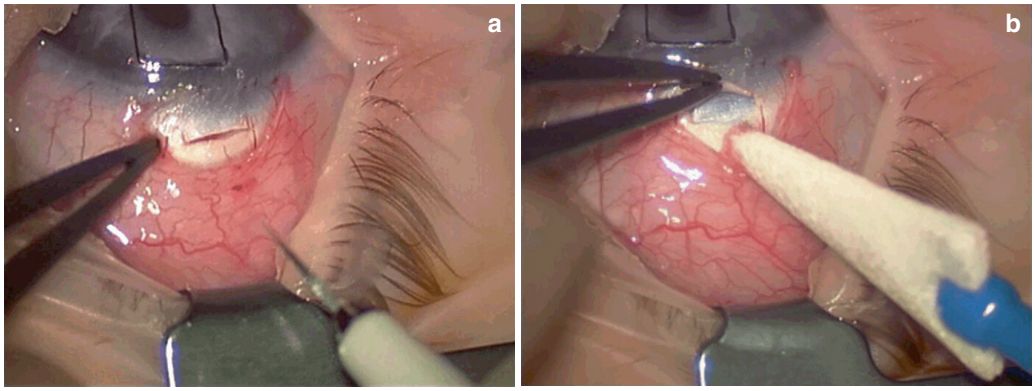

Fig. 5: Short radial cuts to encourage posterior aqueous flow and a diffuse bleb. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

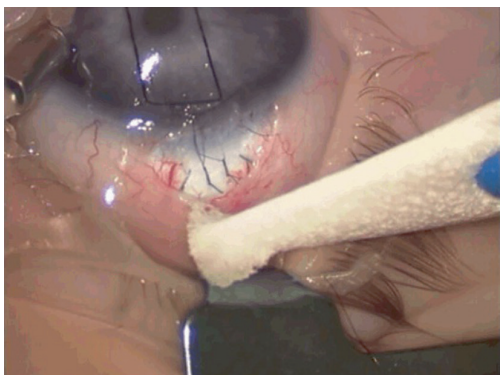

Fig. 6: Two fixed 10-0 nylon sutures at the edge of flap and two releasables with four throws at posterior edge of flap allowing minimal flow. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

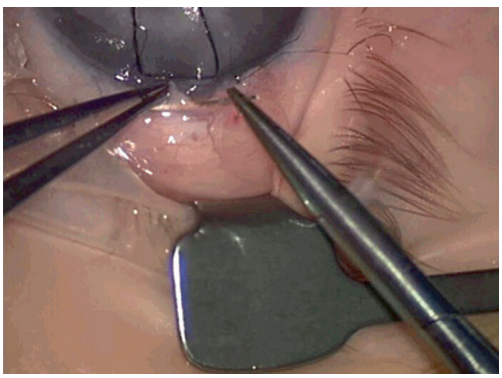

Fig. 7: Horizontal mattress suture for conjunctival closure. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

bleb developing. The removal of the AC maintainer with suturing of the paracentesis (required in buphthalmic eyes, unlike adults) is followed by conjunctival closure with 10-0 nylon sutures, all the while intermittently judging the depth of the AC and IOP. Purse-string sutures are used at the edges of the peritomy with either horizontal mattress sutures along the limbus (Fig. 7) or corneal buried, conjunctival sutures. Nylon suture ends are trimmed short to disappear in the corneal slit with corneal conjunctival closure, or cut short and covered well by a conjunctival frill with horizontal mattress suture closure along the limbus. This is to avoid discomfort and excessive eye rubbing which may lead to conjunctival wound dehiscence.

Viscoelastic (usually Provisc®, Alcon, UK) and air are occasionally left in the AC if the scleral flap cannot be secured by multiple sutures. Subconjunctival injections of steroid (betamethasone), antibiotic (cefuroxime), and often local anesthetic (Marcaine) to minimize postoperative pain and possibly reduce scarring by suppression of fibroblast activity are given at the end of the case. All eyes are patched overnight (Table 3) [20] (Video 1).

Table 3: Pediatric trabeculectomy technique aimed at encouraging posterior flow and formation of diffuse bleb: important surgical points.

Surgical steps	Surgical points/rationale
Corneal traction suture (7/0 Mersilk)	Allows adequate exposure Avoids hemorrhage from superior rectus muscle suture
Fornix-based conjunctival flap	Less likely to form a scar limiting posterior flow Allows better visualization of limbal anatomy
Wet field cautery	Hemostasis Avoids scleral shrinkage (important in thin sclera)
Antiscarring agents	Diffuse, large treatment to minimize risk of a focal, avascular bleb
Scleral flap	Consider fashioning scleral flap first before antiscarring treatment in infants to enable treatment under scleral flap Large scleral flap (4 × 5 mm) and as thick as possible Sutures less likely to cheesewire Greater resistance to aqueous outflow Posterior edge must be well beyond limbus to prevent cheesewiring of flap Dissection forward into cornea avoids iris, ciliary body, and vitreous incarceration Short radial cuts enough to allow reflection of scleral flap for the sclerostomy Greater the scleral elasticity (incision gap) the shorter the radial cuts Directs aqueous flow posteriorly to prevent cystic blebs
Preplaced scleral flap sutures before sclerostomy	Easier to place with formed globe Reduces duration of intraoperative hypotony after sclerostomy and PI performed Releasable sutures through posterior edge of scleral flap and fixed sutures at corners if scleral flap gapes, e.g., in infants Releasable loop buried in cornea so suture can be left indefinitely without risk of infection Can be adjusted or removed under anesthetic or slit lamp without laser
Paracentesis for anterior chamber (AC) maintainer	Oblique, peripheral, long tunnel with a 21G needle minimizes risk of inadvertent lens damage, avoids wound leak, and stabilizes infusion cannula Allows maintenance of intraoperative IOP preventing hypotony and potential choroidal effusions, suprachoroidal hemorrhage, and vitreous prolapse with PI Allows AC reformation Must turn off temporarily when tying scleral flap sutures tight to prevent cheesewiring Used to gauge flow through sclera flap and ensure adequate flap closure
Sclerostomy	Small sclerostomy punch (500 µm diameter) allows increased control of aqueous outflow both intra- and post-operatively and is quick to perform As anterior as possible prevents iris, ciliary body, and vitreous incarceration
Scleral flap closure	Tight closure vital with antiscarring agent use Add additional sutures as required to reduce flow
Fornix-based conjunctival closure	10–0 Nylon retains tension longer than dissolvable sutures with minimal inflammation Purse-string sutures at peritomy edges Corneal buried, conjunctival suture closure, or limbal horizontal mattress sutures
Prevention of postop hypotony	Appropriate concentration of MMC Short radial cuts direct flow posteriorly and minimizes anterior flow from scleral flap sides Tight scleral flap sutures with option to adjust or release at later stage Watertight conjunctival closure Suture paracentesis May leave viscoelastic in AC if high flow rate through scleral flap despite maximal suturing or if ciliary body shut down anticipated (uveitic cases)

Adapted from Papadopoulos *et al*. [20], with permission
IOP intraocular pressure, *AC* anterior chamber, *PI* peripheral iridotomy, *MMC* mitomycin C

Antiscarring Agents

The main cause of filtration ceasing and trabeculectomy failure is fibrous tissue formation in the region of the scleral flap, which necessitates the use of an antiscarring agent in children. This is usually MMC due to its greater antiproliferative potency than 5FU and the need for only intra-operative exposure. In a small prospective series of 12 eyes of primary and secondary childhood glaucoma comparing the use of MMC (0.2 mg/ml, 88%) and perioperative 5FU to perioperative 5FU alone (maximum 6 injections), 7/8 eyes of the MMC and 5FU group were controlled off medications as opposed to 0/4 eyes in the 5FU group alone [38].

The greatest advance in MMC therapy has been the understanding that a wider application of MMC treatment is more likely to be associated with a diffuse elevated bleb as opposed to a focal avascular bleb and therefore associated with a significantly reduced risk of complications such as bleb-related infection [18, 19, 39] (Fig. 8). However, we suggest adjunctive MMC for those experienced in its use. The most appropriate MMC application method (i.e., whether to also treat under the scleral flap), concentration, and duration of exposure for children are unclear from the literature. The MMC dose is usually determined by the number of risk factors for scarring and the surgeon's familiarity with specific concentrations, but most surgeons use between 0.2 and 0.5 mg/ml. The duration of MMC exposure is best kept constant, and only the dose varied to establish consistency of use, with our preference being for 3 min [40]. An approach when using MMC in infants following failed angle surgery is to use a low dose, e.g., 0.2 mg/ml, at the time of surgery which minimizes the risk and duration of early complications such as hypotony but then to "top up" with subconjunctival 5FU injections at the time of postoperative EUA, as indicated [19].

Potential Modifications

Trabeculectomy can be combined with trabeculotomy to theoretically provide two major outflow pathways and potentially better results than either operation performed alone, but there are no prospective comparisons of all three operations. Combined trabeculotomy-trabeculectomy (CTT) is advocated in some ethnic populations due to its higher incidence of successful IOP control retrospectively compared to these operations performed separately, for example, from the

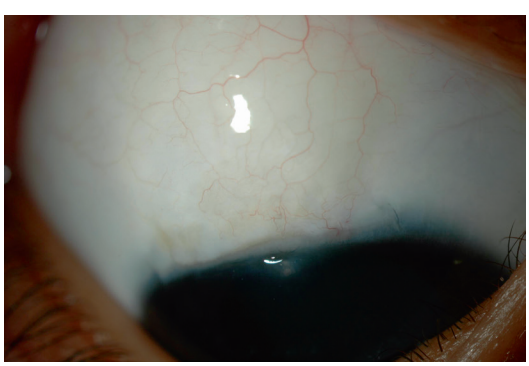

Fig. 8: Elevated, diffuse bleb following Moorfields Safer Surgery System trabeculectomy with a large treatment area of mitomycin C.

Middle East [41–43]. However, Dietlein *et al.* in a retrospective study comparing trabeculotomy, trabeculectomy, and CTT without antiscarring agents in PCG patients (Caucasian 71%, Turkish and Arabian 29%) demonstrated no statistical difference in success between the three operations after a median follow-up of 3 years [31]. The authors argued that success was determined more by the severity of the disease rather than the procedure. Conversely, Lawrence and Netland in a retrospective review of trabeculectomy versus CTT both with MMC (0.25 mg/ml, same average exposure time) in 40 eyes (mostly Caucasian and African-American) reported a lower success rate in the trabeculectomy group (70.6% versus 91.3%) at the last follow-up. Mean IOP was the same for both groups. Success was defined as IOP control (6–21 mm Hg) with or without glaucoma medications and without further glaucoma surgery or loss of light perception. However, there were significant differences between the two groups with regard to age (trabeculectomy group was older, 100 months versus 19 months), lens status (more aphakic/pseudophakic children in the trabeculectomy group), number of preoperative medications (higher in the trabeculectomy group), casemix (more PCG and anterior segment dysgenesis in the CTT group), and follow-up (longer for CTT group). Chronic hypotony was the cause of three of the five failures in the trabeculectomy group and one of the two in the CTT group [44].

With regard to CTT technique, once the trabeculotomy is performed, a block of sclera is removed at the limbus by scissors or punch by extending the initial Schlemm canal incision. As a result the sclerostomy is placed more posteriorly than is usual for trabeculectomy, which increases the likelihood of the iris incarceration. This can be avoided by making a separate more anterior incision under the hinge of the scleral flap for the sclerostomy.

Postoperative Management

Postoperatively, children receive intensive steroid drops (dexamethasone 0.1%) every 2–3 h and ointment at night (e.g., betamethasone ointment). Topical steroids are gradually weaned over 3–4 months or sooner as dictated by the degree of conjunctival inflammation and the IOP. Antibiotic drops (e.g., chloramphenicol) four times a day are usually stopped once exposed sutures are removed. Cycloplegics are not routinely administered but necessary when the AC is significantly shallow and/or choroidal effusions are present. A plastic shield over the operated eye at night time for the first month after surgery is advised.

An important consideration in the planning of a trabeculectomy in children concerns postoperative management. Failure tends to occur early in children, and so frequent monitoring in the early postoperative period is vital. Children should be examined the first postoperative day followed in cooperative older children and teenagers by weekly monitoring for the first month, as with adults, to examine for the presence of a bleb and the degree of bleb inflammation. Subsequent outpatient visits occur at greater intervals depending on bleb appearance and IOP control (Fig. 9). In infants, at least one EUA is often needed within the first month after surgery, preferably within the first 2 weeks. Jayaram *et al.* reported close postoperative monitoring of infants with EUAs at 1 week, 3 weeks, and 6 weeks following trabeculectomy surgery and average duration of postoperative topical steroids of around 3 months achieved satisfactory long-term outcomes off

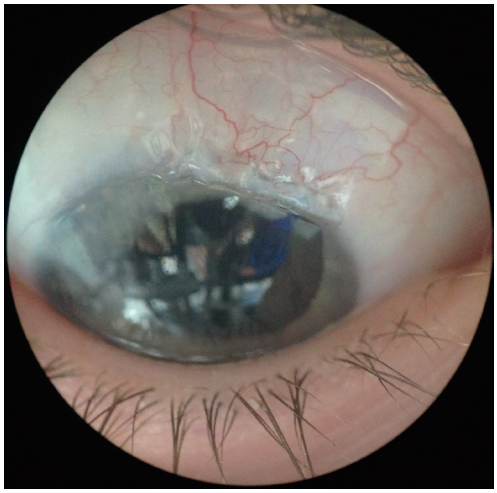

Fig. 9: A diffuse bleb with minimal inflammation 2 months post-trabeculectomy surgery. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

medications [19]. While under anesthesia, sutures can be loosened or removed, and subconjunctival 5FU (0.2–.3 ml of 5FU 50 mg/ml), steroids such as betamethasone, and local anesthetic can be injected adjacent to the bleb depending on the characteristics of the bleb and the degree of bleb inflammation. Monitoring for complications in the postoperative period is also important, and B-scan can be useful in uncooperative children to exclude choroidal effusions.

Complications

There are a many challenges to successful trabeculectomy surgery. These relate not only to surgical technique but also to anatomical factors of a buphthalmic eye, which must be respected to minimize complications. The potential for complications in children after trabeculectomy, especially with MMC, cannot be overstated. Trabeculectomy surgery in young children has been associated with significant surgical complications including early hypotony, flat anterior chambers, choroidal effusions, and suprachoroidal hemorrhage along with retinal detachments and phthisis [14, 26, 32]. Thin avascular, cystic blebs, which use to be common [26, 28], predispose to late complications of bleb-related infection such as endophthalmitis and chronic bleb leaks [14, 28, 32]. However, with contemporary pediatric trabeculectomy techniques, most of these are now avoidable and have significantly decreased [18, 19, 45]. The most common complications associated with trabeculectomy are discussed, along with management and prevention. It is worth emphasizing the point that the best way to manage complications is to avoid them.

Hypotony

Hypotony is a potentially major sight-threatening complication of surgery due to the risk of suprachoroidal hemorrhage in buphthalmic eyes which can occur intra- or post-operatively. The risk is significantly higher in buphthalmic versus normal adult eyes, so careful attention to

surgical technique is critical to avoid this potentially devastating complication. In addition to hemorrhage, hypotony can also result in a shallow or flat AC, which in phakic patients may precipitate or hasten cataract formation. Furthermore, lens-endothelial corneal touch can lead to endothelial decompensation and ultimately to corneal failure. Hypotony maculopathy and choroidal effusions can also develop.

Children with glaucoma are at high risk of hypotony with trabeculectomy surgery for many anatomical reasons. The thin sclera of buphthalmic eyes and the reduced scleral rigidity of pediatric eyes result in a tendency for the eye to collapse at low pressures. A sufficiently thick scleral flap is vital for the adequate closure of the flap to avoid hypotony and to prevent sutures cheesewiring the flap causing full-thickness holes and leaks. However, it is made challenging by the scleral thinness of buphthalmic eyes. Elastic sclera tends to gape when incised requiring increased suture tension to close the incision. Furthermore, if the sclera is very thin, other modalities such as GDD surgery might be more appropriate.

Children with SWS who have choroidal hemangiomas are especially prone to large serous choroidal effusions, even at relatively normal IOP, and also to suprachoroidal hemorrhage in the early postoperative period. In light of this, it could be argued that an alternative operation to trabeculectomy such as GDD (with the use of an AC maintainer, a tight tunnel with a 25 gauge needle, both an extraluminal ligature (6-0 Vicryl) and an intraluminal stent (3-0 Supramid) to restrict flow with a Baerveldt implant) should be considered in SWS patients with choroidal hemangiomas. Postoperative hypotony with this technique may be less likely compared to trabeculectomy in which early postoperative IOP may be less predictable despite efforts to avoid low IOP. Uveitic patients also carry an increased risk of hypotony and its consequences thought to be due to ciliary body shutdown from surgically induced inflammation, so inflammation must be suppressed pre- and post-operatively with topical and if necessary systemic immunosuppression. Children with aniridia are particularly vulnerable to lens-endothelial touch due to an absent iris to separate an anteriorly displaced lens and the cornea, and so hypotony should be avoided at all costs.

Early hypotony following trabeculectomy is potentially common and has been reported in almost 50% of cases [28]. However, more recent literature suggests a lower incidence of around 10% [19]. Choroidal effusions and flat anterior chambers associated with early hypotony following trabeculectomy surgery have been reported at a rate of 22% [32] and 10% [26], respectively, in the past. With recent modifications to the trabeculectomy technique, these complications have been significantly reduced to a choroidal effusion rate of 10% and no cases of flat anterior chambers [19]. Chronic hypotony associated with trabeculectomy can also occur but is much less common and has been reported at a rate of 0–8% [14, 15, 19].

The management of hypotony depends on the degree of hypotony and is targeted toward its cause. Buphthalmic eyes with significant hypotony should not be managed conservatively by observation for very long due to the real risk of suprachoroidal hemorrhage. Following trabeculectomy, early hypotony is often due to overfiltration rather than a limbal bleb leak with fornix-based conjunctival flaps, which is uncommon due to the new closure techniques. If the IOP is low but the AC is reasonably formed and there are no choroidal effusions, the patient can be observed with the frequency of topical steroids reduced to encourage healing and a cycloplegic, e.g., atropine, added. However, if the AC is very shallow or flat and/or there are significant

choroidal effusions, it is appropriate to consider injecting viscoelastic into the AC with a reduction in the frequency of topical steroids, or further surgery if the cause is excessive filtration through the scleral flap which can be resolved with the addition of further sutures. Dealing with the consequences of hypotony alone such as drainage of choroidal effusions should be avoided as these resolve once the cause of hypotony is addressed and the IOP rises.

To prevent hypotony and suprachoroidal hemorrhage during surgery, the use of an AC maintainer is advised. Furthermore, incisions such as paracentesis should be adequately sutured as they may not remain watertight with stromal hydration as they do in adults, due to reduced pediatric corneal rigidity. Postoperative hypotony following trabeculectomy can be minimized by using an appropriate concentration of MMC at the time of surgery to minimize prolonged early hypotony, fashioning as thick a scleral flap as possible with short radial cuts to minimize leakage through the scleral flap sides, tight scleral flap lamellar sutures to avoid cheesewiring and watertight conjunctival closure. Occasionally, the use of a small amount of cohesive viscoelastic can help maintain the AC and the IOP in the first 24–48 h after surgery if the flap allows slightly too much flow despite maximal suturing.

Bleb-related Infection

Infection can develop in a bleb usually as a late complication of trabeculectomy surgery and is very serious as it is potentially rapidly blinding. Bleb-related infection (BRI) refers to a spectrum of disease severity ranging from infection limited to the bleb (blebitis) to fulminant endophthalmitis (bleb-related endophthalmitis). Blebitis is generally regarded as an isolated bleb infection without clinically apparent vitreous involvement, whereas bleb-related endophthalmitis (BRE) is generally regarded as extension of the infection into the eye (in which case a vitreous biopsy and intraocular antibiotics are indicated) [46]. BRI can occur following any filtration surgery in which there is a bleb such as trabeculectomy and combined trabeculotomy-trabeculectomy. Studies from the adult literature report a more virulent spectrum of organisms responsible for BRI such as *Streptococcus* species, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [46, 47] than those causing acute post-cataract surgical endophthalmitis which are usually Gram-positive organisms introduced at the time of surgery. In the pediatric literature, the pathogens are often not reported. When they are reported, the organisms are consistent with those found in adults [28]. Generally, visual acuity outcomes in BRE are worse than in acute onset endophthalmitis after cataract surgery, but most cases of blebitis achieve vision back to or within one line of preinfection visual acuity [14, 47].

Numerous risk factors for BRI exist but by far the most important relates to bleb morphology, that is, an avascular, thin-walled, cystic bleb which results in compromised physical and immunological defenses against organisms (Fig. 10). The use of MMC has long been thought to cause thin avascular blebs, and although it may play a role, these types of blebs have been associated with glaucoma surgery well before the introduction of antiscarring agents [48]. Recent publications suggest that the development of these blebs is more likely related to application and surgical technique rather than the use of MMC *per se* [18, 19, 39]. Other risk factors for infection include chronic bleb leak [14, 49], interpalpebral or inferior placement of the trabeculectomy [50], contact lens use [51, 52], and bacterial conjunctivitis [52, 53].

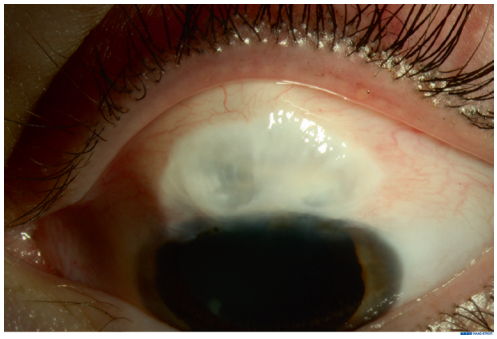

Fig. 10: An "at-risk" bleb: thin, avascular, cystic bleb at risk of infection. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

BRI is believed to occur more frequently in children compared to adults due to poor hygiene [54] with rates varying from none up to 17% in a study with a mean follow-up period of 28 months [14, 32]. Bleb-related endophthalmitis has been reported in up to 9% of pediatric MMC trabeculectomies [14, 32].

BRI is usually symptomatic and may present with foreign body sensation, photophobia, blurred vision, pain, conjunctival inflammation, or purulent discharge. A prodrome of a few days is characteristic of blebitis, whereas sudden onset and rapid progression suggests endophthalmitis. Children who present with a short prodrome of 24–48 h should be closely observed for progression of signs. In early blebitis there is intense conjunctival inflammation limited to the area immediately around the bleb, which helps distinguish it from generalized conjunctivitis, and this relative disparity alerts the clinician to the bleb as the source of the symptoms. The thin, cystic, avascular bleb is white against the hyperemic surrounding conjunctiva and is known as the "white-on-red" appearance (Fig. 11). This can progress to a mucopurulent infiltrate of the bleb and a purulent discharge. A thin slit lamp beam through the bleb may show a hypopyon within it. There may be an associated bleb leak. AC activity is variable and vitritis may be present indicating endophthalmitis. A B-scan is indicated if the presence of vitritis cannot be clinically assessed. Typically ultrasound shows low- to medium-density vitreal echoes with endophthalmitis. Conjunctival and eyelid cultures from BRE have been found to correlate poorly with intraocular cultures [47, 52].

BRI should be treated early and aggressively to maximize visual function as long-term visual prognosis depends on the extent of the infection, the virulence of the organism, and the timing of therapy. Blebitis, being a precursor of endophthalmitis, is more effectively treated at an earlier stage resulting in a better prognosis [46, 53]. Acute management is determined by the stage of disease, whether it is blebitis or endophthalmitis. There are no randomized, controlled trials which have established the optimum antibiotic regimen for the treatment of BRI. However, topical and systemic broad-spectrum antibiotics are indicated to cover the diverse spectrum of pathogens which may be responsible. The quinolones have a good broad-spectrum cover for Gram-positive and Gram-negative organisms. The 4th-generation quinolones (e.g., moxifloxacin, gatifloxacin, and besifloxacin) have better Gram-positive coverage including significant activity against *Strep. pneumoniae* and *Staphylococcus* species resistant to 2nd- and 3rd-generation quinolones.

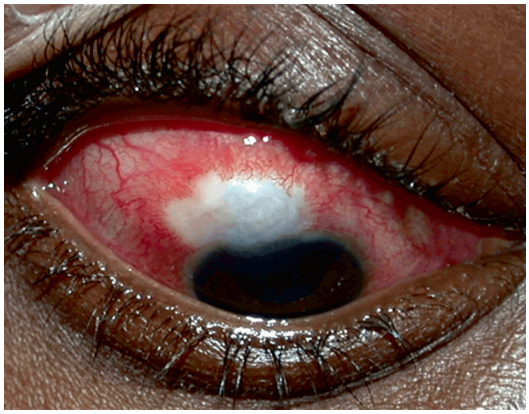

Fig. 11: "White-on-red" bleb appearance associated with bleb-related infection. (Courtesy of Maria Papadopoulos, MBBS, FRCOphth).

Systemic moxifloxacin is usually avoided in children because of the theoretical risk of arthropathy in weight-bearing joints, but ciprofloxacin and amoxicillin/clavulanic acid can be considered instead. Consideration should be given to the addition of polymyxin B for multidrug-resistant bacteria and Gram-negative bacteria and vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA). Later the antibiotic regimen can be refined according to the child's response to treatment and to the culture and sensitivity results. Children with BRI require frequent topical antibiotics (e.g., moxifloxacin hourly day and night). Cases of blebitis should be reevaluated within 4–6 h to check for signs of progression such as increasing symptoms, deterioration of vision, and/or cellular activity in the aqueous or vitreous. Hospital admission should be considered for clinical or social reasons when there are concerns that adequate treatment cannot be administered at home. BRE must also be treated with intravitreal antibiotics once aqueous and vitreous samples have been taken.

The value of intravitreal steroids in the treatment of BRE has also not been established although it may be associated with better visual outcomes [55]. The rationale is that the inflammatory response compounds the tissue destruction caused by the inciting infection. Topical steroids are recommended (e.g., dexamethasone 0.1%).

Clear guidelines for the role of vitrectomy versus vitreous tap and intravitreal antibiotics alone in BRE are lacking. In theory, vitrectomy decreases the bacterial load and associated toxins, helping to preserve retinal function. It is advisable to consider a vitrectomy if there is significant vitreous involvement or in culture-positive patients showing no improvement after vitreous tap and injection. Furthermore, in children, vitrectomy may be the best way to obtain a satisfactory sample for culture and diagnostic purposes.

Late management of an episode of BRI usually involves a decision about whether surgical intervention is indicated to minimize the risk of further infection. Bleb filtration function is usually maintained after infection and often not an issue [14, 32]. Multiple factors must be considered such as a bleb which extends into the interpalpebral fissure, poor contralateral vision, poor hygiene, persistent bleb leak, ability of the patient to follow advice and act on the symptoms or signs of infection, and the accessibility to ophthalmic care. This last factor would definitely lower

the threshold for surgical intervention. Bleb revision involving bleb excision and conjunctival advancement is the most definitive treatment. However, this alone will not prevent recurrence of a thin avascular bleb if scleral thinning or a full-thickness sclerostomy is evident at the time of the revision and is not also addressed with a simultaneous patch graft. Revising the bleb may lead to loss of IOP control. Bleb revision should be delayed until the infection has completely resolved which may be several weeks or months after the acute episode.

With regard to the prevention of infection of an "at-risk" bleb, the role of prophylactic antibiotics is controversial and has not been proven to decrease the incidence of infection. However, it may be appropriate in children with "at-risk" blebs who may be unable to reach an ophthalmologist urgently for assessment and treatment (e.g., while on vacation) to be given a broad-spectrum antibiotic to use if symptoms develop, until they can reach an ophthalmologist. If an avascular cystic bleb develops after surgery, parents should be informed about the risk and seriousness of bleb-related infection. They should be advised to report immediately to an ophthalmologist should symptoms or signs of bleb-related infection occur such as localized conjunctival injection, increasing pain, or an AC hypopyon. Children with filtering blebs, especially those which are "at risk," experiencing bacterial conjunctivitis should be treated with a topical bactericidal antibiotic and closely observed during and after treatment for the development of intraocular inflammation. Furthermore, a history of prior bleb infection should prompt even greater vigilance as this has been calculated to increase the risk of developing endophthalmitis approximately 12-fold [52].

The prevention of a "bleb at risk" is vital as it puts the child at a lifetime risk of infection and potential blindness. Wells *et al*., in a retrospective comparative study undertaken in children and young adults, demonstrated a significant reduction in the incidence of a thin avascular bleb and serious bleb-related complications with modifications such as a large area of antiscarring treatment, fornix-based conjunctival flap, and fashioning a scleral flap which encourages posterior flow [18]. Furthermore, antiscarring agents should be cautiously and appropriately selected according to the patient's risk factors for failure. Inferiorly placed blebs should be avoided, as should blebs with nasal and temporal extensions within the interpalpebral fissure. Releasable sutures should always be buried and antibiotics used when sutures are exposed.

Chronic Bleb Leak

Chronic bleb leaks tend to occur late in thin, avascular blebs which are fragile and easily traumatized especially by children, and may be intermittent. A leak should always be excluded in such blebs with fluorescein 2%. Reported rates of late bleb leaks from older pediatric trabeculectomy literature range from 3 to 23% [14, 28, 32]. However, in recent studies using contemporary surgical techniques when performing MMC trabeculectomies in children, there were no early or late bleb leaks [19, 45].

Chronic, late leaks are usually refractory to conservative measures such as a bandage contact lens due to poor tissue integrity. Often surgical revision is necessary with excision of the unhealthy conjunctival tissue and advancement of healthy conjunctiva with well-vascularized edges. To prevent the recurrence of a thin, avascular, cystic bleb, any scleral defects must be addressed with a patch graft. Repairing the bleb leak may lead to loss of IOP control.

The prevention of chronic bleb leaks is best achieved with contemporary pediatric trabeculectomy techniques which minimize the risk of a thin, avascular bleb developing as discussed above (see Fig. 2).

Outcomes

Criteria for success in published papers on trabeculectomy are largely based on IOP control either with (qualified success) or without (complete success) topical medications along with the absence of serious complications. Published studies of trabeculectomy for childhood glaucoma are all retrospective which makes comparison difficult as success is influenced potentially by a number of factors such as definition of success, patient's age and race, previous surgery, surgical technique, dose and duration of MMC, use of 5FU postoperatively, casemix (primary and secondary glaucomas), inclusion of non-phakic patients, and duration of follow-up. This makes the answering of questions regarding who are the best candidates for trabeculectomy and which is the most appropriate MMC dose or duration difficult to answer.

Early results of unenhanced trabeculectomy by Beauchamp and Parks in 25 eyes (44% PCG, 32% aphakic) were poor with only 50% success after a mean overall follow-up of 18 months and with a 20% complication rate. However, only 3 of the 25 eyes had a primary trabeculectomy (i.e., first operation on a virgin eye) [7]. Subsequent authors reported even lower success rates of 35% for trabeculectomy in childhood glaucoma after longer follow-up of around 3–5 years [24, 29]. These poor results were speculated to be due to multiple previous ocular surgery and age. In light of these findings, surgeons considered performing primary trabeculectomy. Fulcher *et al*. reported their findings in 20 Caucasian eyes (65% PCG) with primary, unenhanced trabeculectomy with a success rate (IOP of ≤ 18 mm Hg and clinical stability) of 92% in children with PCG and 86% in children with secondary childhood glaucoma (all phakic) and no serious complications, after a mean follow-up of almost 8 years [10]. These improved results likely reflected the fact that all patients were Caucasian and phakic and had no previous surgery. However, success of trabeculectomy as a primary procedure in certain populations was found to be lower at 54–72% [42, 56]. Elder reported results of unenhanced primary trabeculectomy in 44 eyes of Palestinian Arab children with PCG of 72% cumulative success (IOP of ≤ 21 mm Hg and no medication) with few complications, after a mean follow-up of only 2 years [42].

Despite encouraging reports of primary trabeculectomy in some groups, excessive scarring remained a barrier to success for many cases especially those cases refractory to previous glaucoma surgery. The introduction of MMC was thought to improve success in such cases [57]. Overall, the success of MMC trabeculectomy in children has been reported to be 59–95% with short follow-up of 2 years or less [14, 26, 27, 32, 57], reducing to 55–60% after 6–7 years mean follow-up [19, 58]. Publications suggest that the dose of MMC does not affect success or complication rates [27, 59]. Al Hazmi *et al*., in a large retrospective series of 150 PCG eyes undergoing trabeculectomy with variable MMC concentrations (0.2 or 0.4 mg/ml) and times of exposure (2–5 min), showed no significant difference in outcomes and complications [27].

Infancy (less than 2 years of age) has been reported to be a significant risk factor for MMC trabeculectomy failure. Outcomes in infants less than 1 year of age vary between 15 and 43% [26–28, 32] after less than 2 years of follow-up with the lower rates in series with aphakic patients [28, 32]. Beck *et al*. reported that being aged less than 1 year at the time of surgery was associated with almost a sixfold risk of failure [32]. For infants less than 2 years of age, Al Hazmi *et al*. described a success rate of 39% (IOP < 21 mmHg without topical medications) in 66 eyes (unreported follow-up) in a study population of PCG patients from the Middle East [27]. In a smaller series of 24 eyes with both primary and secondary childhood glaucoma (17% aphakic), Beck *et al*. reported a cumulative success rate of only 19% (IOP < 23 mmHg with topical medication) at 6 years in infants less than 2 years of age [15]. More recently, in a similar aged series of 40 eyes of phakic patients with primary and secondary childhood glaucoma, Jayaram *et al*. reported a cumulative probability of success of 60% at 7 years [19]. Almost all successful cases were not using topical IOP-lowering medications at final follow-up. For infants less than 1 year of age, 70% were successful at the end of follow-up.

A consistently reported risk factor for trabeculectomy failure, even with MMC, is glaucoma following congenital cataract surgery [28, 32–34]. In a study by Freedman *et al*. with a series of 21 eyes treated with MMC trabeculectomy (0.4 mg/ml, 3–5 min) and postoperative 5FU, the qualified success rates for phakic versus aphakic eyes (n = 7) were 64% to 29%, respectively, after 23 months [28]. Azuara-Blanco *et al*. further highlighted this point in a series of 21 eyes treated with MMC trabeculectomy (0.4 mg/ml, 1–5 min) who found 0% complete success after 18 months in aphakic eyes (n = 8) [33]. Beck *et al*. reported aphakia to carry an almost threefold risk of failure [32].

As the Tenon capsule is thought to be implicated in the higher failure rate of children, a recent 24-month prospective study by Awadein and El Sayed compared MMC trabeculectomy alone (0.4 mg/ml, 3 min) and MMC trabeculectomy with partial tenonectomy in 64 eyes of children with glaucoma [60]. A tenonectomy of about 8 mm in diameter to include the area over the scleral flap and expected bleb was performed from a fornix-based conjunctival flap leaving behind the "thinnest conjunctiva possible." There was no significant difference between the two groups with regard to age, lens status, diagnosis, and prior glaucoma surgeries. The mean postoperative IOP was significantly lower in the group who underwent tenonectomy throughout follow-up as were the number of medications from the third postoperative month. Complete success (IOP 5–21 mm Hg without medications and signs of glaucoma progression) and qualified success (with medications) were the same in both groups. More failures (uncontrolled IOP despite maximum tolerated medical treatment, further glaucoma surgery, or devastating complication) occurred in the non-tenonectomy group (30%) compared to the tenonectomy group (55%), but this was not significant. After multivariate analysis, only the number of prior glaucoma surgeries was a predictor of failure. With regard to bleb morphology, the authors report that the tenonectomy group had blebs with "thinner walls" and that encapsulation occurred significantly less frequently in the tenonectomy group (3% versus 25%). There was only one case of endophthalmitis that occurred in a child who did not have a tenonectomy, and there were no cases of chronic bleb leak. Furthermore, less needling and 5FU injections were necessary in the tenonectomy group

(3% versus 25%). Although this paper suggests a possible role for tenonectomy in pediatric trabeculectomy, the potential for the development of thin blebs at risk of infection and leaks in the longer term is a concern.

Another approach to improve trabeculectomy success was attempted by Mahdy *et al.*, through the use of intraoperative subconjunctival bevacizumab (Avastin), a recombinant humanized monoclonal vascular endothelial growth factor (VEGF) antibody to modulate the wound healing effects of VEGF. In a prospective paired-eye study design, they compared MMC (0.4 mg/ml, 3 min) trabeculectomy alone in one eye and MMC trabeculectomy with bevacizumab (2.5 mg in 0.2 mls) in the fellow eye of 12 children with refractory glaucoma [61]. Following limbal-based conjunctival flap closure, bevacizumab was injected subconjunctivally over the scleral flap area. Sham injections were performed in the fellow MMC trabeculectomy alone group. There were no significant differences between the two groups with regard to preoperative IOP, lens status, and diagnosis. The mean postoperative IOP was significantly lower in the group who had subconjunctival bevacizumab at 1-year follow-up. Complete success (IOP 5–21 mm Hg without medications and no further glaucoma surgery or visually devastating complications) and qualified success (with medication) were significantly better in the subconjunctival bevacizumab group (complete success 75% versus 58% and qualified success 92% versus 75%, respectively). Shallow AC was the most common complication in each group (17%). One case in MMC trabeculectomy group alone developed late bleb-related endophthalmitis after 3 months and resulted in phthisis bulbi (8.33%). Although off-label use of drugs is common in pediatric ophthalmology and bevacizumab as an adjunct may improve MMC trabeculectomy results, further study of anti-VEGF agents to assess the safety and efficacy of these drugs in this population is needed [62].

Despite the fact that the aim of surgery is to preserve vision in children, visual outcomes are rarely reported in the literature. In Beauchamp and Park's paper, visual acuity was assessed in 18 of the 26 eyes, and the best acuity was 20/200. Where trabeculectomy visual outcomes in children are described, the majority of eyes maintain visual acuity within two Snellen lines; however, in a study by Beck *et al.* from 1998, 11% of eyes were reported to have lost more than 2 lines of vision or progressed to no light perception attributable to devastating surgical complications [32]. More recently, Jayaram *et al.* reported final overall visual acuity outcomes of 34.2% seeing 20/40 or better, 89.5% seeing 20/200 or better, and no cases of loss of light perception [19]. Hopefully future studies will evaluate success not only in terms of IOP control and visual acuity but also with regard to functional vision and quality of life measures.

Comparison to Other Techniques

The accepted alternative to trabeculectomy following failed angle surgery is the insertion of a glaucoma drainage device (GDD). Success rates or success probabilities at last follow-up vary from 31 to 97% with variable follow-up from 1 to 7 years [63]. In infants, success of GDD at 1 year is reported at 74–87% [15, 64] with 53% survival at 6 years after surgery [15], comparable to the trabeculectomy outcomes of Jayaram *et al.* [19]. MMC trabeculectomy compared to GDDs may achieve lower mean IOP [32] and of significance be less dependent on medication for IOP control [19, 32, 63]. In one study, only 14% of infants undergoing GDD surgery achieved

IOP control without topical medications [64] compared to 62.5% (25/40) trabeculectomy cases [19]. However a major difference between trabeculectomy and GDD surgery is the significant burden of associated complications in the latter group often requiring surgical revision. Beck *et al.* reported 46% of eyes with a GDD required one or more operations due to a complication related to the implant (most commonly tube corneal touch and exposure), in contrast to 12.5% of eyes in trabeculectomy group [15]. Tube malposition, erosion, and endophthalmitis are consistently reported with greater frequency in the pediatric compared to adult population [63]. Tube malposition requiring further surgery has been reported in 26–35% of cases [15, 64]. Of concern is particularly the rate of corneal decompensation in the longer term for these children following GDD surgery.

Trabeculectomy has also been compared to deep sclerectomy both with MMC (0.2 mg/ml, 1 min) in a small series of children with uveitis as primary procedures and found to be more successful with regard to IOP control off medications (88% versus 50%) with all failed cases of deep sclerectomy requiring further glaucoma surgery [65].

Options After Failed Surgery

When trabeculectomy fails to control IOP, a popular option is to consider bleb needling with an antiscarring agent such as 5FU or MMC if the sclerostomy is patent. The MMC is best injected subconjunctivally posterior to the bleb and before needling while the intraocular pressure is still high, to prevent inadvertent intraocular entry after needling. Repeated needling may be necessary with early failure. Other options after failed trabeculectomy include repeating the trabeculectomy at an adjacent site with a higher dose of MMC or a GDD [20].

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Ab Interno Tube Ligation for Refractory Hypotony Following Non-Valved Glaucoma Drainage Device Implantation

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Abstract

Purpose To report the 2-year outcomes of a novel surgical technique allowing reduction of the intraluminal diameter of the tube without total tube occlusion in order to allow enough increase in outflow resistance to permit resolution of hypotony whilst also achieving adequate IOP control.
Methods This was a single-surgeon retrospective case note review of all non-valved GDD cases over an 8-year period (2008–2015) that underwent ab interno ligation of the drainage tube in order to manage post-operative hypotony (Baerveldt or Molteno). Twelve eyes of 12 patients (4.4%) developing refractory hypotony that did not respond to multiple intracameral ophthalmic viscoelastic device (OVD) injections were included in this retrospective case series and were treated with our ab interno tube ligation technique. The post-ligation management algorithm consisted of re-instating topical anti-glaucoma agents, laser suture lysis (LSL), or further ab interno ligation.
Results Mean IOP increased from 2.8 mmHg at baseline to 7.8 mmHg, 7.1 mmHg, 9.0 mmHg, 13.6 mmHg, 10.9 mmHg, 13.9 mmHg and 13.6 mmHg at day 1, week 1, month 1, month 3, month 6, year 1 and year 2 respectively, with or without additional topical anti-glaucoma medications. Although hypotony resolution following our technique was achieved in all eyes at 2 years, 8.3% of cases required reinstatement of topical medications to maintain IOP control within the target range.
Conclusions We propose ab interno partial tube tying as an effective surgical option to achieve an immediate, predictable and sustained IOP elevation either as a primary procedure or when traditional methods have failed to resolve hypotony in eyes with non-valved GDDs.

Keywords: Non-valved glaucoma drainage device, Hypotony, Glaucoma, Tube ligation

A. Vergados and A. A. Mohite contributed equally to this work.

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Introduction

Ocular hypotony following non-valved glaucoma drainage device (GDD) implantation can lead to sight-threatening hypotony-related complications (HRCs). The management can be challenging, requiring injections of ocular viscoelastic devices (OVDs) [1], total occlusion of the drainage tube using a ligating suture, or removal of the drainage tube from the anterior chamber [2].

Total ligation or removal of the tube may however cause excessive increase in intraocular pressure (IOP) and further jeopardize the already compromised optic nerve in these eyes. There is often a volatility in the fluctuation of IOP in these complex eyes, which are challenging to manage without causing serious permanent damage to vision. Restoring the fine balance between aqueous production and outflow is hence paramount in the successful treatment of refractory hypotony following non-valved GDD implantation.

We therefore developed a novel ab interno partial ligation technique that aims to reduce the intraluminal diameter of the tube without total tube occlusion, so that outflow resistance is increased enough to allow resolution of hypotony without causing a rebound spike in IOP. To the best of the authors' knowledge, this is the first study to describe such a technique and report its long-term outcomes in eyes with refractory hypotony following either Baerveldt or Molteno GDD implantation for complex glaucoma.

Methods

Patient Selection

This was a single-surgeon retrospective case note review of all non-valved GDD cases over an 8-year period (2008–2015) that underwent ab interno ligation of the drainage tube in order to manage post-operative hypotony. All cases were refractory to multiple fixed-volume intracameral injections of sodium hyaluronate 1.4% at the slit-lamp, our preferred initial intervention for early post-operative hypotony after non-valved GDDs [1]. Either a Baerveldt (Abbott Laboratories Inc., Abbott Park, IL, USA) or a Molteno (Molteno Ophthalmic Ltd., Dunedin, New Zealand) drainage device was used in all cases. Baerveldt implants were either 250 mm^2 or 350 mm^2 in size depending on the ocular history and risk of post-operative hypotony.

A standard surgical technique was performed for implantation of the GDD in all cases, as has been previously described [3]. In brief, all cases had placement of a full-length intraluminal occluding 3/0 polyamide stent suture (Supramid, S. Jackson Inc., Alexandria, VA, USA) as well as external tube ligation with a 6/0 polyglactin absorbable suture, to prevent excessive early post-operative filtration. All cases also had a 0.5-mm-long Sherwood tube fenestration slit made just anterior to the occlusive 6/0 ligature to allow some modulation of early post-operative IOP until dissolution of the ligature in about week 6.

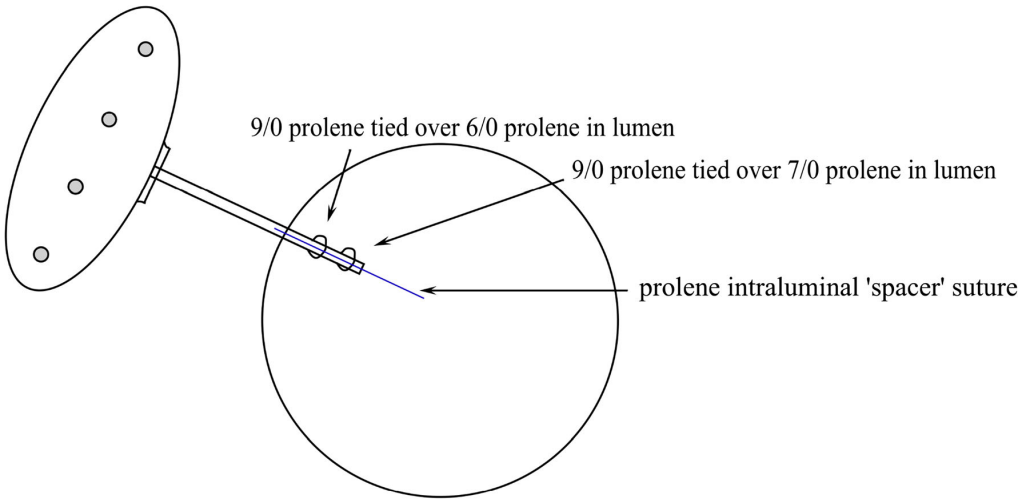

Fig. 1: Schematic of partial internal tube tying technique.

Ab Interno Tube Ligation Technique

Two 9/0 prolene sutures were tied around the intracameral portion of the tube using slip-knots. For the first tie a 6/0 prolene suture was placed within the tube lumen whilst tightening the knot, and then removed. The second tie was placed in the same way, but using a 7/0 prolene suture within the tube lumen, as illustrated in the schematic (Fig. 1). This was done under the operating microscope. Each intraluminal prolene suture acted as a 'spacer', allowing a consistent graduated reduction of the tube gauge, with the proximal portion of the tube becoming narrower than its distal portion. The aim was to achieve a graduated reduction in the intraluminal diameter of the tube without total tube occlusion.

The ties were placed intra-camerally without externalizing the tube, via two paracenteses on either side of the tube entry site (Fig. 2a). Another paracentesis was made at the limbus opposite to the tube position to allow the intraluminal prolene suture to pass straight into the lumen of the tube (Fig. 2a). A 9/0 prolene suture needle was passed through from one paracentesis to exit the second paracentesis by docking into a 25-gauge needle introduced via the second paracentesis. The 25-gauge needle then guided the prolene suture needle out of the second paracentesis, leaving the suture passing on the posterior side of the tube. Using an intraocular manipulator (Sung manipulator, Altomed Limited, Tyne and Wear, UK), the 9/0 prolene suture was then looped over the tube and brought out through the first paracentesis similar to the Siepser slip-knot technique [4]. A three-throw slip-knot was then fashioned outside the eye, slid inside the anterior chamber and tied tightly with 2 micro needle-holders on the posterior side of the tube. The tightness of the knot was tested by pulling the intra-luminal spacer suture gently to make sure that the knot was tight enough to narrow the lumen to the size of the spacer suture. Another double-throw knot was then tied to lock the knots in position. The threads of the suture were then cut

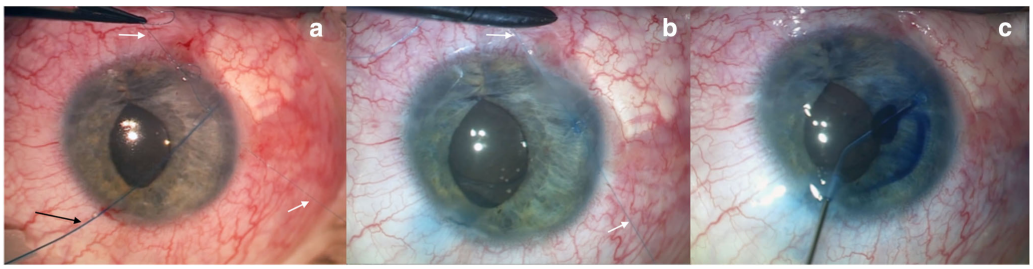

Fig. 2: Intra-operative images showing **a** the 6/0 prolene spacer suture, **b** a second tie with 9/0 prolene suture and **c** confirmation of total occlusion which was required in some cases, via injection of trypan blue dye. White arrows = tube ties. Black arrow = intraluminal spacer suture.

with 23-gauge intra-ocular scissors. The first 6/0 spacer suture was then removed from the tube lumen and replaced with a 7/0 prolene spacer suture. The whole procedure was then repeated with another 9/0 prolene suture tied more tightly and nearer to the proximal end of the tube (Fig. 2b). The 7/0 prolene spacer suture was then removed from the tube lumen. In some cases, a third total tie was placed at the most proximal end without an intra-luminal spacer suture to achieve total occlusion of the tube, depending on the extent of hypotony. Trypan blue dye was injected through the proximal tube opening using a 30-gauge cannula to check for total tube occlusion in cases where a third total occlusion tie was placed, and was confirmed when no dye was observed to pass beyond this tie (Fig. 2c).

Post-ligation Management

We followed a step-wise management strategy following this procedure. If IOP was deemed too high, pressure-lowering medications were then introduced back into the treatment regimen. If the IOP was still too high, the proximal tighter tie (nearer to the end of the tube in AC) was cut using neodymium-doped yttrium aluminium garnet laser suture lysis (LSL) in the outpatient clinic or surgically in theatre. If, however, the IOP did not increase following the procedure, a further totally occluding 9/0 prolene was tied around the tube without the use of an intra-luminal spacer suture as described earlier. This final tie could then also be released at a later date using LSL should the IOP then rebound too high.

Success was defined as resolution of hypotony with or without a rebound rise in IOP above 22 mmHg, and resolution of hypotony related complications. Complications of the procedure were recorded at each time point, including uncontrolled IOP rise requiring LSL, untying of one or more ligatures, or repeat ab interno tube ligation for unresolved hypotony. Persistent hypotony, choroidal or retinal detachments, endophthalmitis or phthisis, as well as development of visually significant cataracts, cystoid macular oedema (CMO) or epiretinal membrane (ERM) were recorded over a 2-year follow-up period.

The study was part of a larger retrospective study of the outcomes of glaucoma surgical intervention approved by the local Research Ethics Committee (reference: 12/WM/0158) and adhered

to the tenets of the Declaration of Helsinki. Descriptive statistical analyses were performed using IBM SPSS Statistics version 23.0.

Results

During the study period, 271 non-valved (Baerveldt or Molteno implants) GDD implant surgeries were performed by the authors' team (VS). Of these, 12 eyes of 12 patients (4.4%) developed refractory hypotony that did not respond to multiple intracameral OVD injections and were included in this retrospective case series. Four cases were in paediatric patients (< 18 years of age at the time of GDD surgery). Table 1 shows baseline patient demographics.

All eyes were on maximum tolerated medical therapy for their glaucoma prior to undergoing GDD implantation, with a mean of 4.3 (± 0.9) anti-glaucoma medications and a mean cup: disc ratio of 0.8 (± 0.1). Prior to tube-tying, 10 eyes (83.3%) had choroidal detachment or maculopathy due to refractory hypotony.

Mean IOP increased from 2.8 mmHg (± 2.3) prior to ab interno tube ligation to 7.8 mmHg (± 5.8) at day 1. This rise persisted long-term with resolution of hypotony in all cases (Fig. 3), with mean IOP measuring 7.1 mmHg (± 6.4), 9.0 mmHg (± 7.8), 13.6 mmHg (± 5.8), 10.9 mmHg (± 9.4), 13.9 mmHg (± 6.7) and 13.6 mmHg (± 6.5) at week 1, month 1, month 3, month 6, year 1 and year 2 respectively, with or without additional topical anti-glaucoma medications. Hypotony

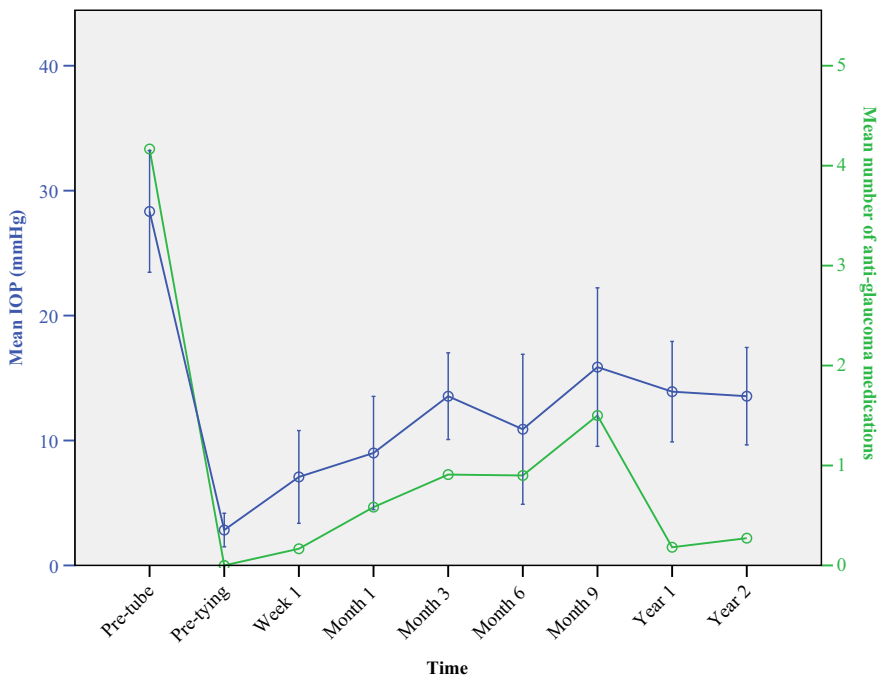

Fig. 3: Mean IOP and number of anti-glaucoma medications before tube surgery, prior to partial tying of tube, and at various time points after partial tying of tube. Error bars represent 95% confidence intervals.

Table 1: Patient demographics and clinical characteristics.

General	
Eyes, *n*	12
Males/females, *n* (%)	7 (58)/5 (42)
Mean age, years, (range)	33.9 (8.6–66.0)
Mean time to partial tube ligation, months, (± SD)	3.3 (± 3.7)
Primary glaucoma diagnosis, *n*, (%)	
Uveitic	5 (42)
JIA	2
Steroid induced	1
FHC	1
Sympathetic panuveitis	1
Neovascular (due to PDR)	2 (17)
Angle recession	2 (17)
Post-vitrectomy and oil	1 (8)
Pseudoexfoliation	1 (8)
Aphakic glaucoma/nanophthalmos	1 (8)
Previous incisional surgery, *n* (%)	
Trabeculectomy surgery	3 (25)
ECCE	1 (8)
Phacoemulsification	5 (42)
Pars plana vitrectomy	1 (8)
Previous TSCD treatment, *n* (%)	4 (33)
Of which 1 prior TSCD	2
Of which 2 prior TSCD	1
Of which 3 prior TSCD	1
In neovascular glaucoma	2
In angle recession	1
In pseudoexfoliation	1
In uveitic eyes	0
Type of GDD, *n* (%)	
Molteno	2 (17)
Baerveldt 350 mm^2	5 (42)
Baerveldt 250 mm^2	5 (42)
MMC not used, *n* (%)	2 (17)
MMC used, *n* (%)	10 (83)
0.2 mg/ml for 3 min	6
0.4 mg/ml for 3 min	3
0.4 mg/ml for 5 min	1

GDD, glaucoma drainage device; *PDR*, proliferative diabetic retinopathy; *JIA*, juvenile idiopathic arthritis; *FHC*, Fuch's heterochromic cyclitis; *TSCD*, trans-scleral ciliary body cyclodiode

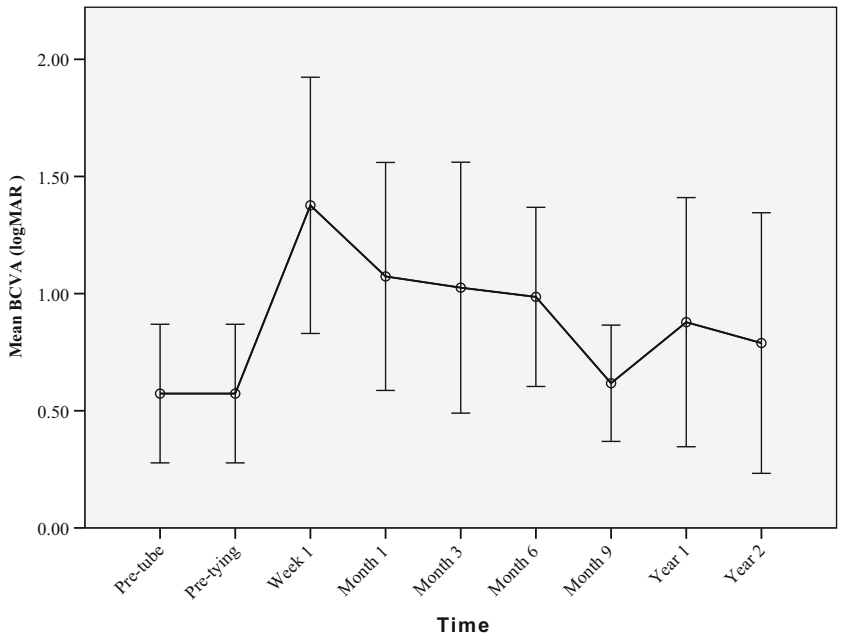

Fig. 4: Mean best-corrected logMAR visual acuity (BCVA) before tube surgery, prior to partial tying of tube, and at various time points after partial tying of tube. Error bars represent 95% confidence intervals.

resolution at 2 years was achieved in all eyes at 2 years, with no significant rebound IOP rise in 83.3% (10 eyes). Topical medications to maintain IOP control within target were reinstated in 16.7% (2 eyes). The change in BCVA over time is shown in Fig. 4.

Table 2 shows the number of additional interventions required over 2 years of follow-up following this technique. Only one case (8.3%) resolved without any further procedures. Five (41.6%) required further OVD injections into the AC. Two-thirds (66.7%) required further partial or total tying of tube with the same ab interno technique. Two-thirds (66.7%) required untying of one or more sutures either surgically or by LSL to lower the IOP. The hypotony resolved in all cases before the end of the 24-month follow-up period. One eye developed retinal detachment likely secondary to previous trauma, and there were no cases of phthisis or endophthalmitis. Of the five phakic eyes, four (80%) required cataract surgery after tube tying. Of these, two eyes were rendered aphakic whilst the other two had intraocular lens implantation. Visual acuity improved in all four eyes undergoing cataract extraction, with a mean pre- and post-phacoemulsification BCVA of 1.34 ± 0.6 and 0.49 ± 0.5 logMAR respectively.

Discussion

We achieved IOP control without the need to recommence any anti-glaucoma medications in 83.3% (10/12) of eyes. Two eyes required recommencement of medications. The first had a history

Table 2: Additional surgical interventions required per case after ab interno partial tying of tube.

Patient age (years)	Diagnosis	GDD implanted	Number of prior TSCD	Additional post-ligation interventions	Number of additional interventions
8.6	Uveitic (JIA related)	Molteno	0	Tube repositioning/Repeat partial tube ligation (month 21)	1
11.8	Uveitic (JIA related)	BVT 250	0	Untying of proximal tube tie (month 3) Repeat partial tube ligation (month 4) Repeat partial tube ligation (month 5) LSL of proximal tube tie (month 5)	4
13.1	Uveitic (sympathetic panuveitis)	BVT 250	0	Repeat partial tube ligation (month 3) Lensectomy/PPV/untying of distal tie (month 7)	2
36.5	Uveitic (FHC)	Molteno	0	Additional partial ligation with a 3rd proximal tie (week 3) LSL of 2 proximal tube ties (week 3) AC paracentesis × 8 (week 3) Repeat partial tube ligation of 2 distal tube ties (week 6)	4
59.1	Uveitic (steroid induced)	BVT 350	0	HGV into AC (week 1) Repeat partial tube ligation (week 2) AC paracentesis (week 2) LSL of proximal tube tie (week 4) HGV into AC (week 5)	5
14.5	Angle recession	BVT 250	1	HGV into AC (week 5) PPV/oil for exudative RD (month 7) ROSO as oil blocking tube (month 8) Untying of proximal tube tie (month 12)	4
66.0	Angle recession	BVT 350	0	HGV into AC (month 5) Repeat partial tube ligation with 3 × 9/0 (month 16) Re-insertion of supramid Repeat partial tube ligation (year 2)	3
18.1	Post-vitrectomy + oil	BVT 250	0	Untying of distal tube tie (month 7) LSL of proximal tube tie (month 10)	2
29.7	NVG	BVT 350	2	Nil	0
33.3	NVG	BVT 250	3	LSL of proximal tube tie (month 11) Repeat partial tube ligation (month 11) Lensectomy (month 9)	3

(cont'd...)

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53.7	Aphakic glaucoma	BVT? 350	0	HGV into AC (week 1, week 2, week 5) Phaco/IOL/GSL (month 4)	4
62.1	PXF/JOAG	BVT 350	1	HGV into AC (week 4, week 5, week 8, week 9, week 12) Total internal tube ligation (month 3) LSL of tube tie (month 5) Phaco/IOL/anterior vitrectomy (month 22)	8

JIA, juvenile idiopathic arthritis; *FHC*, Fuch's heterochromic uveitis; *NVG*, neovascular glaucoma; *PXF*, pseudoexfoliation glaucoma; *JOAG*, juvenile open angle glaucoma; *GDD*, glaucoma drainage device; *BVT*, Baerveldt tube; *TSCD*, trans-scleral cyclodiode; *LSL*, laser suture lysis; *AC*, anterior chamber; *HGV*, Healon GV; *PPV*, pars plana vitrectomy; *ROSO*, removal of silicone oil; *Phaco*, phacoemulsification

of juvenile glaucoma and was commenced back on glaucoma drops at year 2 (fixed combination of dorzolamide/timolol 0.5% and bimatoprost 0.01%), though this was still significantly fewer than the four topical agents plus oral acetazolamide that was required originally. This patient required total tube ligation due to persistent cystoid macular oedema. The second had a history of microphthalmos and vitrectomy with silicone oil tamponade in situ following retinal detachment, and required a fixed combination of brinzolamide/timolol to achieve target IOP having been on four topical agents plus oral acetazolamide prior to GDD implantation.

Visual acuities did not significantly improve despite resolution of hypotony in our series. In some cases, visual acuity actually worsened. This was due to the development of visually significant cataracts in 80% of the phakic eyes in our series (4 of 5 eyes) as well as retinal detachment requiring vitrectomy and oil in one eye. One pseudophakic eye required laser capsulotomy for posterior capsular opacification, two eyes developed significant ERM (of which one later underwent pars plana vitrectomy), and one eye developed early post-operative CMO treated successfully with orbital floor triamcinolone. This same eye developed corneal decompensation and later underwent endothelial lamellar keratoplasty 5 years after tube tying. There were no other cases of corneal decompensation in our series, and hypotony related maculopathy or choroidal detachments resolved in all cases. It is important to also note that all eyes had advanced glaucomatous optic neuropathy which would contribute to the gradual decline in BCVA over the post-operative follow-up period.

The Ahmed versus Baerveldt Study demonstrated that non-valved glaucoma tube shunts achieve a greater reduction in IOP and glaucoma medications at 5 years, as well as lower failure rates when compared to valved shunts [5]. However, non-valved shunts have a greater 5-year risk of hypotony and its related complications when compared to valved shunts [5, 6]. Although early hypotony following non-valved GDDs has been reported to occur in as much as 39% of eyes [3, 7], the incidence of persistent hypotony is far less common, with reports in the literature ranging from 0% to 13%, which is in keeping with our rate of 4.4% [6, 8–10]. The variation is likely to be due to a difference in case-mix between studies, with those studies having higher

proportions of complex eyes (chronic uveitis, trauma, prior cyclo-destructive procedures or neovascular glaucoma) being more likely to have greater rates of persistent hypotony.

Despite the well-known risk of persistent hypotony after GDD surgery, few studies have reported on the outcomes of surgical management of these cases. Common practice is to use intracameral injections of OVD or total ligation of the external portion of the drainage tube using non-absorbable sutures [8]. The former option may require multiple injections of OVD due to their short-lived effect, although more viscous devices such as reticulated hyaluronic acid have recently been used to prevent phthisis and maintain aesthetic appearance in pre-phthisical blind eyes with chronic hypotony [11]. One third of our cases had previous cyclo-destructive procedures, which may explain the poor resolution of hypotony in these eyes using fixed-volumes of repeated intracameral OVD injections.

Recent studies have described a controlled reduction of outflow restriction using LSL after Baerveldt tube surgery and graduated intraluminal stent removal to achieve low rates of hypotony-related complications [8]. Techniques used to treat eyes with HRC in this series included intracameral injections of OVD and re-insertion of the intraluminal Supramid stent. A recent case report describes the ab interno placement of two 5/0 nylon sutures to stent an Ahmed glaucoma valve without the need for intracameral tube tying in an eye with neovascular glaucoma [12], with good 6-month outcomes. Another paper describes the use of a 3/0 Supramid suture inserted ab interno for two cases of persistent hypotony, but with limited long-term data [13], whilst another study describes ab externo insertion of the Xen gel stent into the GDD tube lumen of two cases with chronic hypotony [14]. However, these techniques alone may not always resolve hypotony, particularly in very high-risk cases with volatile aqueous production rates [15].

In spite of our graduated technique of narrowing the tube diameter, it was still difficult to predict which eyes would recover immediately from the hypotony. We found that 40% still required further OVD injections and two-thirds required further ab interno tube tying, mostly with the addition of a total occlusion tie, to achieve early hypotony resolution. This would suggest that a total occlusion tie is necessary in the majority of cases to completely stop aqueous drainage, allowing ciliary body function and thus the IOP to recover. Conversely when the hypotony did recover, two-thirds of eyes required subsequent LSL or untying of one or more suture ties over the following months because of raised IOP. We believe this is to be expected because of the nature of such complex eyes, in which there is a fine, individualized, and volatile balance between the degree of ciliary body dysfunction, aqueous production, and outflow resistance.

Having a clear step-wise management strategy with close patient follow-up allowed us to respond to changes in IOP in a methodical manner whilst avoiding serious complications. Our LSL technique allows selective and stepwise release of the ties to minimize the risk of recurrent hypotony in these eyes. The delicate balance in these eyes is further reflected by the fact that despite our stepwise strategy, three cases (25%) required repeat ab interno tying of the tube.

Although some surgical techniques to deal with refractory hypotony have been described in academic meetings, to the best of our knowledge there have been no publications on their medium to long-term outcomes. Those described either require conjunctival dissection prior to ligation of the external portion of the tube, or externalization of the intracameral portion of the

tube via a full-thickness corneal incision over the tube opening. The former technique carries the risk of inciting further conjunctival inflammation and scarring, and makes later adjustment of this ligating suture difficult if the IOP then elevates excessively. The latter technique can potentially alter the tube position causing tube adhesion to the cornea and subsequent corneal endothelial damage, given that studies have shown accelerated rates of endothelial cell loss when the tube is positioned close to the endothelium [16]. In addition, a short corneal wound to gain access to the tube makes water-tight wound closure difficult, increasing the risk of leakage and its associated complications including epithelial ingrowth.

We used Mitomycin C (MMC) during GDD implantation in 83% of eyes in this series, based on a previous study that demonstrated that intraoperative use of MMC was not significantly associated with hypotony or low IOP at 3 and 5 years [3]. Our experience is that early hypotony within the first 3 months is due to over-drainage rather than MMC use.

The main weakness of this study is its retrospective nature and the relatively small number of the cases. However, it would take a long time to accumulate a substantially larger sample size given the low reported rates of persistent hypotony and our considerable experience in developing a safe GDD implantation technique aimed at keeping hypotony rates to a minimum.

Conclusions

We developed a novel-graduated ab interno tube ligation technique and post-ligation management strategy to manage refractory hypotony in high-risk eyes fitted with non-valved GDDs without the need for conjunctival incisions or externalization of the tube. Our series demonstrates high safety and efficacy at medium-term follow-up and we therefore propose our technique as an effective option to achieve immediate and sustained IOP elevation either as a primary procedure or when traditional methods (intracameral viscoelastic injections or re-insertion of intraluminal stents) have failed to resolve hypotony in eyes with non-valved GDDs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of retrospective study, formal consent was not required. All procedures performed were in accordance with the ethical standards of the local research committee and with the 1964 Helsinki declaration and its later amendments.

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"Minimally Invasive Glaucoma Surgery (MIGS) Is a Poor Substitute for Trabeculectomy"—The Great Debate

Philip Bloom, Leon Au

Abstract

Surgical treatment for glaucoma has undergone a dramatic change over the last decade. Trabeculectomy has been the main surgical procedure worldwide for almost 50 years. However, there is a growth in development of novel devices and surgical techniques designed to lower intraocular pressure in a less invasive fashion. The term minimally invasive glaucoma surgery (MIGS) has been coined and is the subject of investment, debate and, increasingly, research. The position of MIGS in the glaucoma treatment paradigm is yet to be clearly defined and its ability to replace conventional filtration surgery remains debatable. In this paper two glaucoma specialists were invited to debate the motion that "MIGS is a poor substitute for trabeculectomy".

Keywords: Glaucoma surgery, MIGS, Minimally invasive glaucoma surgery, Trabeculectomy

Introduction

Surgical treatment for glaucoma has undergone a dramatic change over the last decade. Trabeculectomy has been the main surgical procedure worldwide for almost 50 years. However, there is a growth in development of novel devices and surgical techniques designed to lower intraocular pressure (IOP) in a less invasive fashion. The term minimally invasive glaucoma surgery (MIGS) has been coined and is the subject of investment, debate and, increasingly,

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research. The position of MIGS in the glaucoma treatment paradigm is yet to be clearly defined and its ability to replace conventional filtration surgery remains debatable. In this paper two consultant glaucoma specialists were invited to debate the motion that "MIGS is a poor substitute for trabeculectomy".

For the Motion—Philip Bloom, Western Eye Hospital, London, UK

I write in favour of the motion 'MIGS is a poor substitute for trabeculectomy', a statement with which my learned colleague Leon Au disagrees; he professes to believe that MIGS can replace trabeculectomy as the gold-standard in sight-preserving glaucoma surgery. Debates like this can descend to semantics, but that is not the case here—I will argue that the operations are fundamentally different. Each should be offered in different situations, for different indications, in patients with different clinical pictures, in order to achieve different outcomes.

MIGS is a broad term, the definition of which merits discussion for the purpose of this debate. Non-incisional therapies such as selective laser trabeculoplasty (SLT) and all forms of trans-scleral cyclo-modulation (laser and ultrasound) are not traditionally regarded as MIGS so will not be considered, nor will cataract surgery alone when performed to treat angle closure.

I restrict the term MIGS to ab interno drainage procedures that do not require conjunctival incision; included therefore are Endoscopic Cyclo-Photocoagulation (ECP), Goniosynechialysis, Trabectome, iStent, Cypass, Hydrus, Kahook Dual Blade (KDB), ab interno Canaloplasty and Xen (though the need for regular conjunctival and incisional manipulation with Xen makes its inclusion contentious). Excluded are ab externo glaucoma drainage devices including all traditional tubes such as Baerveldt and Ahmed, 'non-penetrating' glaucoma surgery such as Deep Sclerectomy, viscocanalostomy or ab externo canaloplasty, Ex-Press Shunts and Innfocus devices.

What is the reason for the enduring success of trabeculectomy as the 'go-to' surgical glaucoma procedure, and why is it only now that we have started to actively explore high-volume alternatives? The glass half-full (rose-tinted) opinion of trabeculectomy sees it as a cheap, proven, effective, potentially long-lasting and acceptably safe incisional option [1]; at best a perfect, permanent, biological valve. The contrary view is that there is an attrition rate, complications are not infrequent and that the results of the procedure are frustratingly variable—even 2 eyes of the same patient with the same surgeon and same basic technique may turn out very differently.

But at its core the longevity and enduring popularity of trabeculectomy as an effective surgical option cannot be ignored, evidenced by the huge volume of evidence in the peer review literature supporting its use. Moreover, despite the keen interest in surgical modifications designed to refine the operation and to make it work better, more reliably, consistently and safely [2], it remains a reasonably cheap and simple operation, moderately independent of individual skill and technique. By contrast, the 'young pretender', MIGS, is expensive and as yet unproven. MIGS shows promise but experience is limited and long-term results are not known, hence the dearth of scientific publications (and evidence-based references) in the field.

To consider the relative merits of trabeculectomy vs MIGS in perspective, it is worth looking at the whole context of glaucoma treatment. All current glaucoma treatments work via reduction

of intra-ocular pressure, a dose-related protective effect correlated to lowering not only in the average pressure but also its diurnal variation. In this regard, all successful laser and surgical treatments should logically be more effective than medicines, the efficacy of which has to be reinforced daily by regular application related to a short, finite duration of action.

However, a traditional advantage of medical treatment has been that different medications may be combined to benefit from three distinct strategies for IOP reduction, namely reduction in aqueous inflow and increase in either conventional (trabecular) outflow or non-conventional outflow. Furthermore, logical application of basic principles has allowed a step-wise approach to medical treatment escalation, leading to logical and refined medical strategies such as switching medications for reasons of non-response or compliance, adding and combining medications.

When trabeculectomy was the only viable surgical option it was a blunt tool in our treatment armamentarium, its main benefit being its reliable and enduring efficacy. Dissatisfaction, principally with side effects and complications of trabeculectomy, led to the advent of glaucoma drainage devices and non-penetrating surgery; clearly these were not the answer as their use in the routine surgical control of glaucoma did not become widespread.

The advent of a variety of MIGS options represents a further attempt to refine the safety and efficacy of surgical intervention; furthermore, they allow a more logical and step-wise approach to surgery. ECP reduces aqueous inflow; conventional outflow can be restored/enhanced with iStent/Hydrus, bypassed with Trabectome/Xen/KDB; non-conventional outflow can be augmented with Cypass. Escalation of invasiveness and combination of treatment modalities now allow the new and real possibility of a sequential and additive approach to combining surgical interventions in away analogous to our use of medications. In this way MIGS offers the prospect of much greater efficacy than provided by the mere restoration of physiological outflow, one of the original aspirations for the procedure.

Of these treatments, perhaps use of ECP and Cypass offer the easiest and potentially most effective additional treatment options, as they utilise the less commonly employed inflow and non-conventional outflow pathways. In addition, inflow and outflow procedures can be amalgamated—ECP can be performed with iStent, either concurrently or at an interval; or different forms of outflow procedures may be combined—Cypass can be performed after failed or sub-optimal iStent or 'conventional' drainage surgery in an attempt to avoid riskier, more invasive surgery. A further advantage of MIGS is the ability to combine surgery with phacoemulsification; phaco-trabeculectomy is no longer widely performed but then again, combined surgery is not the subject of the debate at hand.

A potential limitation of trabecular restoration in patients with glaucoma is that, in the presence of normal aqueous inflow, Schlemm's canal drainage routes seem to have a physiological 'floor' of around 16 mmHg due to downstream resistance to flow [3]. Further lowering would require additional aqueous suppression treatment, a real disadvantage if low IOP is needed or medication use is to be avoided. By contrast, both conventional and non-conventional outflow procedures potentially bypass this 'choke-point', leading to lower IOPs but also raising the possibility of hypotony from overdrainage.

MIGS devices are unarguably expensive, largely due to development costs being recouped by the commercial entities that developed them. Proponents argue that the extra cost is defrayed by reduced need for intensive follow ups, but this is yet to be proven. Whilst this may be the case for a device such as the iStent, successful use of devices such as Xen still requires intensive follow up due to the common need for post-operative manipulations, over 50% in one series reported by Leon Au [4]. The same may be true for devices such as Cypass, early personal experience of which has demonstrated high effect magnitude in some patients which therefore may require close monitoring.

Devices that have a small unit effect may need to be implanted in costly multiples. Furthermore, if the effect is sub-optimal or if the device later fails, the health economics alter and may well ultimately favour conventional drainage surgery, as the true price comparator then is not drainage surgery but only the relatively cheap medications that MIGS spares. Assessment of quality of life (QoL) and cost/benefit differences between different treatments will require reasonable follow up for meaningful analysis—follow up should be for perhaps 5–10 years as long-term effect is important; if MIGS devices fail and trabeculectomy is still needed, this will greatly alter results. Finally, many QoL 'instruments' do not include assessment of drop use so may not be an appropriate tool for a MIGS/trabeculectomy comparison.

But is trabeculectomy really such a bad option? Can the enormous cost of, say, 1–2 MIGS procedures that may need to be performed in order to prevent (say) 50% of trabeculectomies be justified in fiscally responsible health economical terms, especially in the context of a model of healthcare for which the British public pay relatively little—as a proportion of gross domestic product—compared with other developed nations?

Ultimately the widespread adoption of MIGS will probably come down to assessment of safety vs efficacy. MIGS procedures that are inferior to trabeculectomy in efficacy will only be widely adopted if they have significant safety benefits, so it is appropriate to consider the individual efficacy vs safety profile for the most commonly performed MIGS procedures. For procedures performed in combination with cataract surgery it is always challenging to isolate the effect of the MIGS procedure from that of cataract surgery alone.

ECP may be considered the original MIGS procedure, as it has been performed for almost 30 years. Ultimately its wide adoption has not been limited by the original concerns over of safety, but by the extent and duration of the overall IOP effect. Its place should probably continue to be early in the treatment paradigm in combination with cataract surgery or in later cases, following failed or sub-optimal response to drainage/tube surgery.

Xen showed initial efficacy promise but has not fulfilled early safety and simplicity hopes, largely due to the frequent need for post-operative manipulations such as needlings, and continued incidence of bleb-related complications. iStent is probably still the safest MIGS procedure, but one of the least effective and most expensive. Cypass utilises a novel pathway whose longevity is unknown; it has been described as converting a 'potential space into to a space with potential' [5]. The word potential feels accurate—it is promising but as yet unproven. The most enduring and successful MIGS will work for long periods, but their later failure will not compromise future alternative surgical treatments.

In contrast to MIGS [4], trabeculectomy continues to be our best single 'fit & forget' option. The natural comparator for trabeculectomy is still other forms of 'conventional' drainage such as glaucoma drainage tubes and maybe the forthcoming Innfocus device, but to date trabeculectomy has yet to be bettered; twenty-first century trabeculectomy is an increasingly safe and effective procedure [1].

In the absence of widespread evidence about new procedures, my side of this debate has of necessity been somewhat of a personal, common-sense opinion based on the clinical perspective afforded by many years of practical experience. However, proof clearly needs to be gathered to examine and challenge these views.

Surely the best advice when faced with a challenging clinical scenario is, as ever, to 'treat the patient in front of you'. Consider individual clinical parameters and try to understand your patients' own perception of risk and benefit. In early disease, there are many options and often time to try a variety of treatment options. In a patient with advanced glaucoma, it cannot be appropriate to offer a treatment of unproven efficacy or longevity. Sadly, the decision to intervene surgically is put off repeatedly, leading to surgery being performed too late, which is why patients are older; we should be intervening earlier.

It is apparent from the foregoing that the existence of MIGS raises the level of sophistication and complexity in glaucoma surgical management, making it more 'granular', titratable and refined. It is simplistic to regard the choice between MIGS and Trabeculectomy as binary; the motion of this debate is clearly correct, as in reality the two options under consideration are rarely considered in clinical scenarios that make them competing surgical strategies, rather they are entirely complimentary therapies. In other words, MIGS is a poor substitute for trabeculectomy because it is no substitute at all; its existence reflects a completely different and new approach to surgical management.

There is an interesting corollary consideration; it has been suggested that the simplicity of MIGS procedures makes them appropriate for use by non-glaucoma specialists. In fact, although the procedures are simple, the decision-making around their selection is anything but, so in my opinion the selection and application of MIGS in the glaucoma treatment paradigm should remain solidly within the purview of glaucoma sub-specialists.

Gus Gazzard has asked: 'Whither MIGS' [6]? He writes 'I foresee a stepwise approach for mild to moderate disease … (that) leads on to true ab interno MIGS procedures, with or without lens surgery. More invasive conjunctiva-involving stents might then be used for more severe disease or those who fail initial efforts. Alongside this, traditional mitomycin or anti-VEGF augmented trabeculectomies will still be necessary for those needing near—10 or below—10 mmHg IOPs or presenting with advanced disease, while Tube surgery will likely remain the mainstay of surgical intervention for complex, secondary glaucomas and failed previous surgery'.

Ike Ahmed, a keen proponent of MIGS, has stated: "A common misperception of MIGS is that it needs to be compared with the gold standard of MMC-trabeculectomy to show its effectiveness; this inappropriate interpretation is based on the idea that MIGS procedures are designed to replace conventional filtering surgery. In fact, MIGS devices are designed to address the treatment gap that exists between medical therapy and more aggressive traditional surgical options" [7].

The statement 'MIGS is a Poor Substitute for Trabeculectomy' is therefore clearly a 'no-brainer'; we are nowhere near the point of accepting Leon Au's enthusiastic assertion that there exists a new gold standard for the surgical management of glaucoma; that remains trabeculectomy.

Against the Motion—Leon Au, Manchester Royal Eye Hospital, UK

As we look forward to celebrating the 50th anniversary of trabeculectomy, one cannot ignore the recent explosion of new surgical glaucoma treatments on the scene [8]. Never before have we seen such an intense level of clinical and financial investment in developing the "perfect" glaucoma treatment for our patients. Although the recipe for perfection has yet to be agreed, the ultimate goals of lowering intraocular pressure (IOP), preventing disease progression and sight loss are the desired ingredients. MIGS has been adopted by many glaucoma surgeons worldwide over the last decade and there is a growing body of evidence of its safety and efficacy. In this article I shall debate against the motion that "MIGS is a poor substitute for trabeculectomy". In fact by examining the evidence carefully and applying them to the right clinical context, MIGS most certainly can be a substitute for trabeculectomy.

Glaucoma is a multifactorial disease, but IOP remains the only modifiable factor currently available. In the majority of primary open angle and secondary glaucoma, IOP is raised leading to optic nerve damage and visual field loss. The surgical treatments of raised IOP mostly focus on improving aqueous outflow. For the past 50 years aqueous has been diverted into the subconjunctival space via trabeculectomy, while there's growing evidence that the obstruction lies within the trabecular meshwork and Schlemm's canal [8]. Over the last decade technologies have been developed to overcome some of these obstructions to restore physiological outflow. Trabecular meshwork could be removed using the Trabectome (NeoMedix, USA) or Kahook Dual Blade (New World Medical, USA), bypassed by inserting an iStent (Glaukos, USA) or Hydrus Microstent (Ivantis, USA); the Schlemm's canal can be dilated using ab-internal canaloplasty (Ellex, Australia). Aqueous can also be diverted into the suprachoroidal space via Cypass stent (Alcon, USA) and into the subconjunctival space via the Xen gelatin implant (Allergan, USA) [8].

We are practicing in the era of patient centered care. It is very important to involve our patients in the decision-making when choosing our surgical treatments. Glaucoma is mostly an asymptomatic condition and our treatment goal is to keep it that way. In spite of an understandable fear of sight loss, most of our patients would prefer the least invasive intervention. Ideally any surgery performed should have a low risk profile, short hospital stay, minimal postoperative hospital visits and short recovery period. Hence the concept of minimally invasive glaucoma surgery HAS to be the future; we may not have reached that goal with the current form of MIGS, but the principles need to be embraced.

Trabeculectomy has been shown to be an efficacious treatment in lowering IOP but its drawbacks have also been well reported [1, 9]. The National Survey of Trabeculectomy reported a high rate of complications including hyphaema, shallow anterior chamber, hypotony, cataract and visual loss [9]. These have mostly been reduced by modern trabeculectomy techniques, but the rate remains significantly higher than any of the MIGS procedure [1]. Moreover, trabeculectomy

requires an intensive follow up regime in the first 3 months and over half of patients require some form of bleb manipulation in the form of massage, suture adjustment or needling/5FU injections [10, 11].

MIGS cannot be a substitute for trabeculectomy if it is not efficacious in lowering IOP. Fortunately there is a growing body of evidence supporting MIGS efficacy. Schlemm's canal based procedures (Trabectome, iStent or Hydrus Microstent) have all been shown to lower IOP significantly to 16–17 mmHg while offering a significant reduction in medication [8]. Suprachoroidal stent (e.g. Cypass) has also demonstrated a similar level of pressure lowering [8]; this effect is often augmented by concurrent phacoemulsification, but standalone procedures have been shown to be efficacious, too [12]. For example, iStent injects have been shown to be more efficacious than double or triple medical therapy in patients with uncontrolled IOP [1], while Hydrus Microstent demonstrated superior IOP lowering and medication reduction when compared to selective laser trabeculoplasty [13]. In the Duette study where a standalone Cypass stent was inserted in patients who were medically uncontrolled awaiting filtration surgeries, a significant 35% reduction of IOP was observed at 12 months and 83% of patients did not proceed to formal filtration surgery [14]. For the purpose of this debate, that meant MIGS was the substitute for trabeculectomy in 83% of cases, at least for a year.

Most ab-internal MIGS procedures are an ideal solution to tackle concurrent cataract and glaucoma. RCTs have shown that combined phacoemulsification with iStent, Hydrus or Cypass offer extra IOP lowering with fewer medications then phacoemulsification alone [8]. Moreover, the visual recovery and safety profile are almost the same as phacoemulsification alone. On the contrary, combined phaco-trabeculectomy offers inferior IOP lowering results when compared to trabeculectomy alone, while the visual recovery is prolonged and the need for postoperative bleb management is increased [15]. Given the correct patient profile phaco-MIGS would actually be the preferred option over phaco-trab, especially when a low target IOP is not required.

When a lower target IOP is required, Xen implant can be considered both as a standalone procedure or combined with cataract surgery. Published results demonstrated the ability to achieve a lower teen IOP at 12 months, but with a higher level of postoperative care required than Schlemm's canal surgery [8, 16]. Nonetheless, the rate of complication and visual loss remained low and the postoperative journey is more favourable for our patients than trabeculectomy. In a retrospective multi-centre study the efficacy of Xen implant was shown to be almost identical to trabeculectomy [17]. While we cannot fully eliminate case selection bias in this retrospective study, it at least demonstrates the potential for MIGS procedures to be a substitute for trabeculectomy under the right circumstances.

Since open angle glaucoma is not a curable disease, the ability of any surgical procedure to offer lifelong pressure lowering is important. On the other hand, one must not forget the demographic of the patients we are treating. The majority of patients at diagnosis are elderly and their life expectancy needs to be taken into account. The current life expectancy in the UK is approximately 81 years, longer for females and shorter for males. Studies based in Oxford, UK, demonstrated that 30% of glaucoma patient died within 10 years of diagnosis, 44% died within 15 years [18]. In fact the average length of time from diagnosis to death was 7.54 years. The average age of

patients requiring glaucoma surgery is often high; the mean age is 70 years old for trabeculectomy while combined phaco-iStent or hydrus is around 75 years old [1, 8]. Considering the average life expectancy is 81 years, the desire for life-long efficacy needs to be put into context. In fact in a 10-year follow up series of phaco-deep sclerectomy, the authors found that half of the patients died during the study period [19]. Medium term results (over 5 years) of MIGS procedure are already emerging supporting a continuing lowering in IOP and medications [8]. With longer follow up we would no doubt observe increasing surgical failure, but the benefit these procedures offer in that all important 5–7 year period for this group of elderly patients is invaluable.

In many ways glaucoma treatment is a race against time, lowering IOP to slow down progression in order to preserve quality vision during our patient's lifetime. MIGS have been shown to lower IOP and medication burden in a patient-friendly, low-risk fashion. MIGS may not offer a very low target IOP or work well in more complicated secondary glaucoma. However, when applied to the right patient at the right time of the disease process, its efficacy is unquestionable. Just over a decade ago, the common glaucoma surgical question we asked ourselves in clinical practice would be the infamous: "to trab or not to trab….that is the question!" There is no doubt that thousands of glaucoma patients have had their sight saved by successful trabeculectomies, while the unfortunate minority have lost sight from their complications. Such a binary surgical option has in the past led to patients undergoing invasive procedure for mild disease (e.g. uncontrolled ocular hypertension), or worse, not getting the surgery they needed due to the fear of complications. The wait for the solution is over. We now have an array of surgical options for different patients at various stages of disease. For some (or maybe many), MIGS would be the right answer when medical therapy fails before visual threatening glaucomatous damage sets in. After all, not every patient requires a pressure of 10 mmHg for 10 years.

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Combined Trabeculotomy-Trabeculectomy Using the Modified Safer Surgery System Augmented with MMC: Its Long-Term Outcomes of Glaucoma Treatment in Asian Children

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Abstract

Background This study aimed to study the long-term surgical outcomes of combined trabeculotomy–trabeculectomy (CTT) using the modified Safer Surgery System in treating childhood glaucoma at a tertiary medical center in Taiwan.

Methods Retrospective, consecutive, noncomparative case series. We retrospectively reviewed medical records of 42 pediatric patients (age 0–18 years) who had CTT performed on their 65 eyes using the modified Safer Surgery System. The study period spanned 18 years (from January 1, 1997, to December 31, 2014). We evaluated the outcome in terms of postoperative intraocular pressure (IOP), axial length growth, disc cupping reversal, and use of antiglaucoma medications. The surgical success was rated using the Kaplan–Meier survival analysis and based on the incidence of complications.

Results The mean follow-up period was 85.05 ± 32.17 months (range 14–200). After operation, IOP dropped significantly from 35.76 ± 9.44 mmHg (mean ± SD) to 16.18 ± 7.20 mmHg together with a significant reversal of optic disc cupping. Similarly, the use of antiglaucoma medications was also significantly reduced in number from 1.26 ± 0.50 to 0.43 ± 0.70. Most of the axial lengths of the eyes measured at the last follow-up visit showed growths within the average ± 2 SDs in comparison with the healthy, age-matched population. After surgery, the qualified success rate was 90.77% at the end of the first year, 90.77% at the second year, 87.64% at the fifth year, 84.51% at the 10th year, and 81.38% at the 15th year. No serious intraoperative or postoperative complications were found.

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Conclusions For Taiwanese children, the combined trabeculotomy–trabeculectomy using the modified Safer Surgery System offered an efficient and safe surgical option for treating glaucoma with long-term satisfactory control of IOP.

Keywords: Combined trabeculotomy–trabeculectomy, Childhood glaucoma, Modified safer surgery system

Introduction

Childhood glaucoma presents with a wide variety of pathologies. It is basically a heterogeneous group of diseases leading to optic neuropathy and altered visual fields and even resulting in blindness (10% pediatric blindness) in the developing countries [1]. Glaucoma in children is not a common disorder, but it can have devastating visual consequences. The goal of treating childhood glaucoma is to minimize vision loss that can otherwise be expected from corneal edema or scarring, Haab's striae, amblyopia, and optic nerve damage leading to lifetime blindness. About 10% of childhood glaucoma is present at birth, and 80% is diagnosed during the first year of life [2].

Depending on the time of the glaucoma diagnosis and on the features as well as circumstances of its presentation, all aspects of the disorder should be carefully evaluated. Surgery is the main choice of treatment, while topical medication may be indicated for additional IOP control either following surgery or as a temporary treatment. Surgical intervention usually achieves an effective outcome if performed promptly and properly [3]. However, glaucoma surgery is challenging in children compared with adults, as it has a higher rate of failure and more complications. The postoperative complications such as hypotony or potentially blinding infections have led to low popularity of trabeculectomy applied to children. For trabeculectomy in adults, the Moorfields Safer Surgery System [4] has recently demonstrated satisfactory outcomes by simple modifications of the surgical procedures with suitable antiscarring medication potency and application techniques. Currently, there are several surgical options. While angle surgery (i.e., goniotomy or trabeculotomy) is widely used as the first-line treatment for childhood glaucoma, CTT (first reported by Maul *et al.*, in 1980) has been advocated for treating moderate to severe childhood glaucoma [5]. The rationale for combined trabeculectomy and trabeculotomy is to gain access to the dual outflow, through Schlemm's canal and/or the trabeculectomy fistula. In cases where Schlemm's canal cannot be identified (as it is the case in 11–15% of trabeculotomies), the trabeculectomy pathway can still be adopted.

Our aim is to retrospectively evaluate over a 15-year period this surgical approach on the long-term outcomes in terms of intraocular pressure (IOP) control, axial length growth, disc cupping reversal, the use of antiglaucoma medications, and surgical success rate of the combined trabeculotomy–trabeculectomy procedures.

Methods

In the present study, we used the modified surgical procedures of CCT in accordance with the Safer Surgery System. The modified Moorfields Safer Surgery System was used by a single surgeon, in one medical center cohort of patients in Taiwan.

Patient Selection

We retrospectively reviewed medical records of childhood glaucoma patients receiving combined trabeculotomy and trabeculectomy conducted by a single surgeon in the Tri-Service General Hospital. Data from patients aged 0–18 years were collected within an 18-year period (from January 1, 1997, and December 31, 2014). Patients all underwent surgery and received the postoperative follow-up for at least 1 year. We excluded those who underwent previous surgery for glaucoma, or with postoperative follow-up periods shorter than 1 year, or with older ages (> 18 years at the diagnosis of glaucoma), or whose Schlemm's canal was not identifiable during surgery. Glaucoma was defined according to the 9th Consensus Report of the World Glaucoma Association. Patients were diagnosed to have childhood glaucoma if they presented with an IOP > 21 mmHg (investigator discretion was required if IOP was to be taken in an examination under anesthesia), and in association with at least one sign of IOP-driven ocular anatomic changes. Such changes included optic disc cupping, Haab's striae or increased corneal diameter, and progressive myopia/myopic shift coupled with increased ocular dimensions in excess of normal growth. Patients with IOP < 21 mmHg under treatment using at least one antiglaucoma medication with the presence of increased corneal diameter with or without hazy cornea or Haab's striae were also considered for surgery. The study was conducted with the approval of Hospital Ethics Committee at Tri-Service General Hospital.

Examination, Data Collection, and Follow-Up

We collected the medical records which included gender of patient, age at diagnosis, laterality of glaucoma, all ophthalmic diagnoses, ocular parameters at glaucoma diagnosis including IOP, optic nerve status (cup-to-disc ratio: both horizontal and vertical dimensions), and the axial lengths of the eyeballs. We informed parents on their children's condition and obtained their consent for further investigation under chlorohydrate sedation (10%, 0.7–0.8 ml/kg body weight). The drug was applied via the rectal route for those less cooperative children.

The IOP was measured by one of the following methods: tonopen tonometer, air puff tonometer, or the Goldmann slit lamp applanation tonometer. Optic disc cupping and cup-to-disc ratios were assessed through an ophthalmoscope. The axial lengths were obtained via A-scan ultrasonography. The refraction was estimated with the use of refractometry or retinoscopy. These features were routinely recorded at the initial examination by an experienced ophthalmologist. During the follow-up period, the ocular biometry and the use of antiglaucoma medications were recorded.

Surgical Procedures

All CTT surgeries were performed by the same surgeon who specialized in treating glaucoma. Standard procedures were used on patients under general anesthesia. A surgical technique of combined trabeculotomy–trabeculectomy was performed in accordance at least in part with the Moorfields Safer Surgery System advocated by Professor PT Khaw in the late 1990s. First, a

corneal traction suture was placed at the 6 o'clock position and a fornix-based 8×6 mm^2 conjunctival flap was created, then Tenon's capsule was dissected to expose the sclera. Cautery was applied to the posterior edge of the wound throughout its depth. Mitomycin-C 0.04 mg/ml immersion of the large area was soaked into cut pieces of cellulose sponges and applied between the conjunctiva–Tenon's capsule and sclera for 5 min. The site of application was then washed with 30 ml of balanced salt solution (BSS). A limbus-based triangular scleral flap of 6×5 mm^2 was made without cutting the limbus (i.e., 1 mm posterior to the limbus remained intact). Mitomycin-C 0.4 mg/ml immersion under the scleral flap was applied by soaking into cellulose sponges for 1 min. A 2-mm incision was cut along the bottom of the scleral flap and slowly deepened until the outer wall of Schlemm's canal opened up, and a seeping of aqueous humor or pink liquid became visible. The outer wall incision was then extended by 1 mm. The McPherson trabeculotomy knife was further rotated into the anterior chamber, and the inner wall of Schlemm's canal and the trabecular meshwork were dissected 120° in both directions. An anterior chamber paracentesis was made. The scleral bed including the trabecular meshwork was further excised using a small sclerostomy punch. A peripheral iridectomy was done through the trapdoor. The triangular scleral flap was sutured with 10–0 nylon. The anterior chamber was reformed with BSS through the anterior paracentesis incision. The fornix-based conjunctival flap was subsequently closed with 8–0 vicryl interrupt sutures. Subconjunctival injection with Rinderon-A 0.5 ml and gentamicin 0.5 ml was finally performed.

Definition of Successful Surgical Intervention

Complete success was achieved when the patients showed a postoperative IOP of < 21 mmHg in the absence of medication. Qualified success was achieved for those who did not require additional glaucoma surgery and showed no evidence of disease progression (increased cup–disc ratio or uncontrolled IOP) with or without medications. The cup–disc ratio was assessed individually by the same ophthalmologist by indirect ophthalmoscopy and fundus photography in cooperative children. These criteria allowed the separation of patients into two groups: (1) the success group and (2) the failed group. The failed group had IOP > 21 mmHg, under maximal antiglaucoma medication and also requiring second operations. The occurrence of severe postoperative complications (such as hypotony, bleb-related endophthalmitis, or retinal detachment) was also considered as failure.

Statistical Analysis

Data were expressed as a mean ± standard deviation (SD). The SPSS analysis software (version 20.0, SPSS, Chicago, IL, USA) was used. For continuous parameters, we used Student's *t* test and Mann–Whitney *U* test for two independent samples. Preoperative and postoperative IOP, C/D ratio, and axial length (AL) were assessed with paired *t* tests. For categorical data, we used the chi-squared test (Fisher's exact test) for small samples. Fisher's exact test was applied to compare uses of antiglaucomatous drugs before and after operation. The cumulative success rate was evaluated by Kaplan–Meier survival analysis. p values < 0.05 were considered as statistically significant.

Results

Demographics and clinical characteristics of the subjects are presented in Table 1. A total of 42 patients with 65 eyes were analyzed. Twenty-six (42 eyes) patients were male and 16 (23 eyes) were female. Over half (64%) of the patients ($n = 27$) had primary glaucoma (PG), and the remaining patients (36%, $n = 15$) had secondary glaucoma (SG). The age at the first operation was 8.73 ± 11.74 months. More than half of the patients had bilateral glaucoma ($n = 27$), and the remaining patients ($n = 15$) had unilateral glaucoma. The 12 eyes of 7 patients were classified as having congenital glaucoma (existing before 2 months of age), 29 eyes of 16 patients were classified as having infantile glaucoma (diagnosed between 2 months to 2 years of age), and 4 eyes of 4 patients were classified as having juvenile glaucoma (diagnosed after 2 years of age). Coexisting systemic diseases included Axenfeld–Rieger syndrome in two eyes of one patient, Sturge–Weber syndrome in six eyes of six patients, and atopic dermatitis in four eyes of two patients. Another eight eyes of six patients were studied after pars plana lensectomy had been performed to treat congenital cataract.

Table 1: Clinical characteristics of all childhood glaucoma patients.

Characteristics	Primary glaucoma	Secondary glaucoma	*p* value	Overall cohort
Glaucoma patients, number (%)	27 (64%)	15 (36%)		42 (100)
Sex, number (%)				
Female	11 (69%)	5 (31%)	0.5148	16 (38)
Male	14 (54%)	12 (46%)		26 (62)
Age at glaucoma diagnosis (years)				
Mean (SD)	0.5452 (0.5339)	1.109 (1.492)	0.0287[a]	0.7274 (0.9787)
Median (range)	0.4167 (0.042–2)	0.5830 (0.0625–5)	0.2212	0.4167 (0.042–5)
Bilateral glaucoma, patient number (%)	22 (81%)	5 (33%)	0.1274	27 (64)
Unilateral glaucoma, patient number (%)	5 (19%)	10 (67%)		15 (36)
Coexisting systemic disease, number (%)	0	9		9 (21)
Sturge Weber syndrome	0	6		6 (67)
Axenfeld disease	0	1		1 (11)
Atopic dermatitis	0	2		2 (22)
Follow-up period after glaucoma diagnosis (months)				
Mean (SD)	80.12 (24.61)	91.78 (39.91)	0.2451	85.05 (32.17)
Median (range)	82.50 (14–126)	83.50 (42–200)	0.7410	83.50 (14–200)
Preoperative corneal clarity, number of eyes (%)				
Clear	33	16	0.9253	49 (75)
Edema	8	5		13 (20)
Haab's striae	2	1		3 (5)

[a]Significant *p* value ($p < 0.05$) for the given glaucoma characteristic being considered

IOP, Axial Length, and Cup–disc Ratio

Data on preoperative IOP, cup–disc ratio, and axial length as well as the use of postoperative medications at initial and follow-up are given in Table 2. Before the surgical intervention, IOP was 35.76 ± 9.44 mmHg. A significant reduction ($p < 0.001$) in the postoperative IOP was found at the final follow-up visits. Cup–disc ratios were evaluated in 49 eyes. A significant cupping reversal ($p = 0.0001$) was found postoperatively for both the horizontal and vertical diameters. At the final visit, optic discs revealed a glaucomatous excavation in six eyes. The cup–disc ratio in 43 eyes decreased after successful surgery. Axial length of 56 eyes was 20.95 ± 1.97 mm before operation, and this value increased significantly ($p = 0.0175$) to 23.33 ± 2.72 mm measured at the last visits. Compared with the AL of healthy, age-matched eyes, 48 eyes (86%) lay outside the range of ± 2 SDs of the mean before surgery. Out of 52 eyes we measured, 36 (69%) had growth within the ± 2 SDs range of the mean found in the age-matched controls, while AL growth of 16 became longer. The use of antiglaucoma medication was 1.26 ± 0.50 before surgery, and this number decreased significantly after operation ($p < 0.001$).

Complete success rate for 1 year was achieved in 53 eyes (81.5%), and qualified success in 59 eyes (90.8%). Within a year after the first combined trabeculotomy and trabeculectomy, we had to operate again for six patients (9.2%) who failed to have their IOP under control. In the group with successful surgery, their age at the first operation was older compared with the failed group ($p = 0.1596$) (Table 3). Of the patients who had received a second operation, four of the total seven patients (57.1%) were from very young subjects (age < 1 month old). In addition, between patients receiving surgical intervention at ages younger and older than 1 month, we found a significant difference in the success of their surgeries ($p = 0.009$). The mean IOP at the end of 1 year was 13.24 ± 4.45 mmHg. The number of antiglaucoma medications prescribed at 12 months was 0.39 ± 0.55. During the entire follow-up period, a total of 12 eyes (18.5%) showed signs of failure and required second operation. With regard to the surgical procedure, six received trabeculectomy and six received CTT. Meanwhile, the interval between the first and second operations was 4.53 ± 3.85 years. The age was 4.60 ± 4.51 years for those patients who had received second operations.

Table 2: Ocular features before and after surgery.

	Pre operation	Post operation	*p* value
Cup–disc ratio, mean ± SD			
Horizontal	0.77 ± 0.15	0.53 ± 0.12	0.0001
Vertical	0.76 ± 0.15	0.52 ± 0.10	0.0001
Axial length (mm), mean ± SD	20.95 ± 1.97	23.33 ± 2.72	0.0175
IOP (mmHg), mean ± SD	35.76 ± 9.44	16.18 ± 7.20	< 0.0001
Medication number at last follow-up	1.26 ± 0.50	0.43 ± 0.70	< 0.0001

Significant *p* value ($p < 0.05$) for the given ocular feature being considered. Data are presented as mean ± SD

Table 3: Characteristics of failed cases that needed second operation.

	Successful surgery group	Failure group that needs re-op	*p* value
Glaucomatous eyes, number (%)	53 (82%)	12 (18%)	
Age at first operation (years, mean ± SD)	0.79 ± 1.04	0.35 ± 0.56	0.1596
Age of operation < 1 month, patients, number	3	4	0.009
Age of operation > 1 month, patients, number	32	3	
Type of glaucoma patients, number			
Primary	22	5	1
Secondary	13	2	
IOP at final visits[a]	13.97 ± 3.30	32.25 ± 5.79	< 0.0001
Type of operation			
Trabeculectomy + trabeculotomy	53	6	
Time for receiving re-operation after 1st op (years, mean ± SD)	NA	4.53 ± 3.85	
Re-operation age, years (years, mean ± SD)	NA	4.60 ± 4.51	

Significant *p* value ($p < 0.05$) for the two groups being considered
IOP intraocular pressure
[a]IOP at final visits for the failed cases that required re-operation refers to the IOP measured at the visit just before secondary operation was performed

Postoperative IOP Change in 5 Years

IOP after initial CTT in the success group decreased significantly at the follow-up visits compared with their preoperative values ($p < 0.0001$), as measured during the first 5 years (Fig. 1).

Life-table Analysis

The Kaplan–Meier survival analysis for success (Fig. 2) in the eyes of 42 patients at the end of 1 year was 90.77%. The qualified success at different years was 90.77% (2 years), 87.64% (5 years), 84.51% (10 years), and 81.38% (15 years). At the final visit, 75% (three out of four patients) had reached qualified success with IOP < 21 mmHg on antiglaucoma medications, and one patient received a trabeculectomy surgery 185 months after the first operation.

The refractive status of children at operation was evaluated in 21 eyes. Nine were found with high myopia (> − 6D), and 12 with low myopia (> − 1D to < − 6D). The age at operation was 8.51 ± 6.92 months for patients with high myopia and 3.02 ± 2.15 months for those with low myopia. The group difference was statistically significant ($p = 0.03$).

Complications

In general, we found no severe intraoperative or postoperative complications. Hyphema, which had occurred in eight eyes during the first postoperative day, resolved spontaneously within the following week. No case of retinal detachment, choroidal effusion, or endophthalmitis occurred.

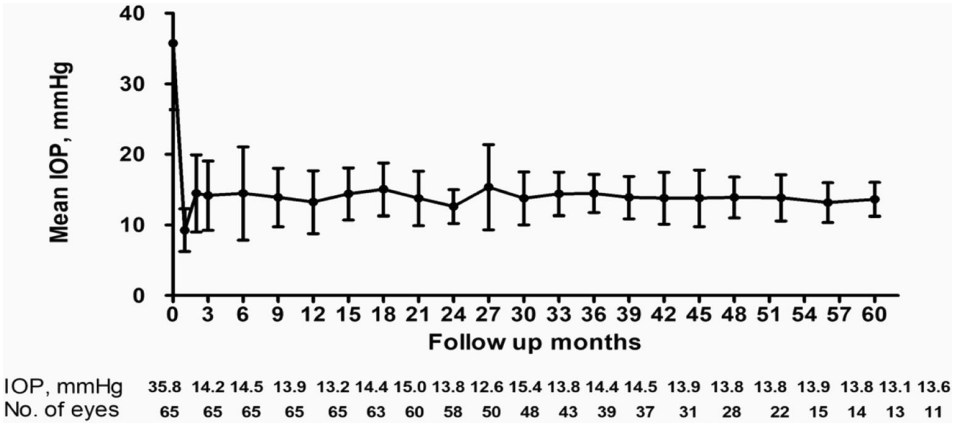

Fig. 1: Mean and standard deviation of IOP (mmHg) changing from baseline to 60 months of follow-up was represented as the curve. IOP: intraocular pressure.

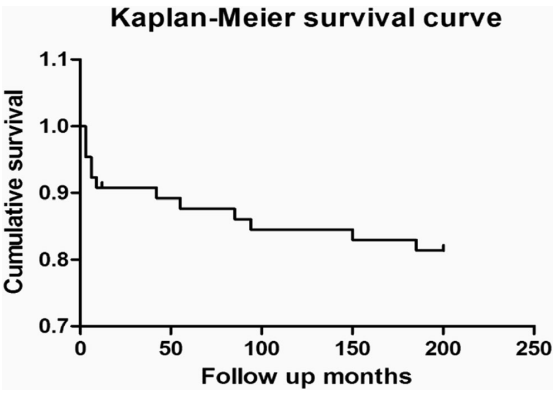

Fig. 2: Kaplan–Meier survival curve (for eyes with > 15 years of follow-ups). The cumulative success of CTT for the eyes of childhood glaucoma patients were evaluated by Kaplan–Meier survival analysis. Note that success probabilities declined over time.

Discussion

In this study, CTT surgery augmented with MMC showed good success without serious complications when evaluated a year later after operation. The surgical success rates were high (measured at 1, 2, 5, 10, and 15 years were 90.77, 90.77, 87.64, 84.51, and 81.38%, respectively). Other related studies with shorter follow-up periods also reported similar success rates (CTT between 75 and 93%). Surgery for IOP control is critical for the management of childhood glaucoma. While the intrinsic abnormality of childhood glaucoma lies in the angle, angle surgery (goniotomy and trabeculotomy) is the procedure of choice for childhood glaucoma with the exact procedures dependent on corneal clarity and the experience and preference of the attending surgeons [6]. Recently, CTT surgery has been reported to yield superior results compared with conventional single procedures, especially in Asian and Middle Eastern countries [7–10].

A number of studies on infants investigated the results of CTT with or without antifibrotic medication. In a series of 22 eyes from 14 patients with primary congenital glaucoma in Spain,

the cumulative probabilities of success for primary CTT without MMC were 95.5% after 1 year and 78.2% after 2 years [11]. Agarwal *et al.* from India reported the 1-year success rate of 93.2% for primary CTT without MMC in 41 eyes from 26 patients with congenital glaucoma [12]. Jalil *et al.* described 29 eyes of 21 patients who underwent CTT augmented with 5-FU. Their mean age was 11 months (range 7 days–108 months) with the mean follow-up period of 41.1 months (range 12–110 months). Their success rate was 79.3% (23 of 29 eyes) regardless of medications [13]. Zhang *et al.* [14] in China performed trabeculotomy as the primary preferred procedure, and the combined procedure with MMC (0.25 to 0.4 mg/ml) was performed in severe cases of glaucoma (age > 3 years, corneal diameter > 14 mm). Comparing the combined and the trabeculotomy-only groups, IOP was higher (33 versus 30 mmHg) in the combined group. For the combined group, surgical success (IOP < 21 mmHg with medications) was 92% at 1 year, 78% at 3 years, and 62% at 9 years. For the trabeculotomy-only group, the success rates were 91% at 1 year, 87% at 3 years, and 38% at 9 years. For CTT with MMC (0.2 mg/ml), Dubey *et al.* [15] reported postoperative success rates (in 137 eyes of 77 patients) of 90% measured at 6 months, 85% at 1 year, 82% at 2 years, 80% at 3 years, and 77% at 4 years. Compared with the previous studies, our results showed a higher success rate within a year, and satisfactory success rates in the longer follow-up period. The discrepancy in outcomes across different studies could be related to a number of factors, such as the concentration of MMC used and the variety of modifications used in the surgical procedures.

In addition, the mean age of our glaucoma patients at operation was younger than those in the previous studies. In older patients, the technical difficulty is greater when approaching the angle structures, and locating and identifying Schlemm's canal for the trabeculotome entry [16, 17]. Mandal *et al.* [18] studied the CTT surgical outcomes on very young children within their first month of birth (47 eyes from 25 patients with childhood glaucoma, 20 PCG, and 5 secondary developmental glaucoma). They reported a success rate of 89.4% at the first year, 83.6% at the second year, and 71.7% at the third year. Literature review suggests that the surgical prognosis is poor in very young patients with glaucoma present at birth [19]. In our study, 17% patients underwent surgery at age younger than 1 month. Of the re-operated patients, 57.1% belong to this very young age. Meanwhile, the significant difference found between the success group and re-operated group under and over 1 month of age ($p = 0.009$) indicated also that CTT surgery was less successful on very young subjects (age < 1 month old).

Regarding the antiscarring agent, the concentration of augmented MMC used in CTT fell between 0.25 and 0.5 mg/ml [20, 21]. The Moorfields Safer Surgery System applied MMC at a concentration of 0.2 or 0.5 mg/ml for 3 min. In our study, MMC was used in two stages, with 0.04 mg/ml in the subconjunctival space for 5 min and 0.4 mg/ml under the surface of the scleral flap for only 1 min. We have modified part of the surgical procedures of CTT to prevent thin, cystic blebs, and hypotony. During the operation, we left the surrounding flap area intact for 1 mm posterior to the limbus, in order to facilitate the flow of aqueous humor and to prevent excess leakage of aqueous humor. The better IOP control in our patients could be related to a few factors: (a) a higher intraoperative MMC concentration with a larger area of antimetabolite treatment, (b) a fornix-based flap for suppressing posterior scar formation, and (c) the posterior diversion of the aqueous humor by the construction of a scleral flap. The small single sclerostomy punch

prevented postoperative hypotony. Our present results in Asian children are in agreement with the Moorfields Safer Surgery System [22], an advanced safer surgical procedure with minimized complications for trabeculectomy, which has also improved surgical outcomes of CTT.

Optic disc cupping at the last visit showed significant reversal with decreased horizontal and vertical diameters. Previous studies [23, 24] showed that the cup–disc ratio is reversible after a successful surgery in congenital glaucoma. In our study, we confirmed that a decrease in the cup–disc ratio is an important indicator of successful IOP reduction. Postoperative axial length has been shown to correlate with postoperative IOP. Axial length measurements can therefore help to ascertain halting or progression of congenital glaucoma and thus are considered an important parameter in follow-up examinations [25]. The final axial length was 23.33 ± 2.72 mm. Most of the axial lengths (69%) had normal growth within ± 2 SDs around the mean of healthy, age-matched eyes. Among the total 65 eyes, the IOP measured at the last visit was 16.18 ± 7.20 mmHg, which was significantly decreased. The number of topical antiglaucoma medications (0.43 ± 0.70) was also significantly reduced. Medical therapy, apart from surgery, plays an essential ancillary role in the patient management. Beta-blockers, topical carbonic anhydrase inhibitors, or prostaglandin analogues were ineffective in the IOP control for our patients.

The desired outcome of glaucoma treatment in children is to preserve visual acuity and to prevent blindness. However, the precise assessment of visual acuity is technically challenging for very young subjects. For this reason, we measured instead their refractive errors, and limited the measurement to only those available on examination. Previous studies reported the occurrence of myopia in children with congenital glaucoma. In a study on CTT surgery by Mandal *et al.* [26], myopia was reported to be the commonest refractive error (80.5%) after operation. MacKinnon *et al.* [27] reported that myopia is frequently found in patients after treatment for primary infantile glaucoma. Their mean spherical equivalent was -3.25 D, with a maximum myopic refractive error of -19.00 D. Our present results are consistent with their findings, in that high myopia (> -6D) was found in older patients (8.51 ± 6.92 months) in contrast to low myopia in younger patients (3.02 ± 2.15 months). The group difference is statistically significant ($p = 0.03$). The pediatric population has thinner sclera, and the elevation of IOP presumably could induce axial elongation leading to myopia. With increasing ages (mostly by 3 years old), the elasticity of the eye decreases, and such scleral rigidity prevents the development of buphthalmos.

Glaucoma following congenital cataract surgery is the commonest secondary childhood glaucoma encountered in clinical practice. Other investigators found that the incidence of glaucoma is higher among aphakic patients than among pseudophakic ones. The younger the patient at cataract extraction, the higher the risk for developing glaucoma [28]. Secondary glaucoma in our cohort included seven eyes of aphakic glaucoma and one eye of pseudophakic glaucoma. For those who developed aphakic glaucoma, their age (3.21 ± 2.44 months) was lower compared to the pseudophakic subjects (8 months). However, our study failed to demonstrate results comparable with previous studies due to the limited number of subjects (only one pseudophakic glaucoma patient). Moreover, previous studies reported that children with primary congenital glaucoma have a better prognosis, better vision, and lower IOP with treatment than children who have associated systemic or ocular anomalies or secondary glaucoma [29, 30]. In our study, we found no

significant difference between patients with primary and secondary glaucoma regarding success or failure of their initial surgery.

Our patients showed no devastating intraoperative or postoperative complications. Neither thin avascular zones nor late bleb-related infections developed subsequently. Hyphema was observed in only eight eyes (12.31%) on postoperative day 1, which resolved spontaneously after 1 week without causing apparent IOP spikes. Tamcelik *et al.* [31] reported an incidence of 5% of hyphema after trabeculotomy with the use of viscoelastic materials compared to 31.4% without using such materials. In our study, a small amount of viscoelastic was left in the eyes to stabilize tissues after operation, and to control bleeding and to protect against undesired damage. In comparison, our incidence of hyphema was lower without permanent damage.

There are several limitations in the current study. First, the study has a non-randomized, retrospective design, with a relatively small sample of secondary glaucomas. Second, it has insufficient visual acuity data or analyses of visual fields. The explanation is the young age of patients and their noncompliance during examination. Third, due to the poor cooperation of the children, it is difficult to analyze the IOP lowering effect of the treatments by the same tonometer in patients of each visit. Finally, even though the study had a long period of postoperative follow-up (median 27.50 months, range 12–200 months), follow-up after the last glaucoma procedure was still short in some cases.

Conclusions

Our study demonstrated over a long term, the effectiveness and safety of augmented MMC in CTT with a modified Moorfields Safer Surgery System in treating Asian childhood glaucoma with excellent IOP control with no severe complications. Further investigations of visual function and optical correction of the refractive error and aggressive amblyopia therapy are warranted to evaluate surgical efficacy in the prevention of blindness.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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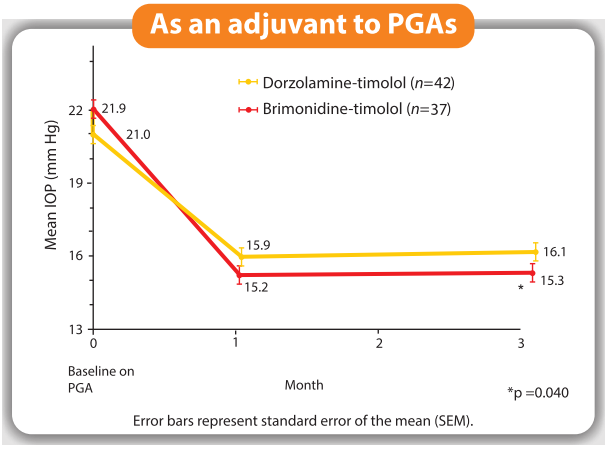

- BTFC offers 29.3% IOP reduction as Adjunct to PGA baseline compared to DTFC at 23.5%[1]
- Overall comfort scores were higher with brimonidine–timolol than with dorzolamide–timolol[1,#]

BTFC: Brimonidine Timolol Fixed combination

1: Nixon etal, Curr Med Res Opin. 2009 Jul;25(7):1645-53. DTFC: Dorzolamide Timolol Fixed combination #: P = 0.027 , PGA : PROSTAGLANDIN ANALOG