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Refractory Glaucomas. Types and Management

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ABSTRACT

Certain types of glaucomas do not respond to conventional trabeculectomy; they are named refractory glaucomas. They are notorious and often recurrent. Examples include: childhood, neovascular, uveitic, traumatic, glaucomas with wide conjunctival scars, post-vitrectomy, post-keratoprosthesis, post-keratoplasty, ciliary block, recurrent and glaucoma in aphakic and pseudophakic eyes. Some of those glaucomas require specific medical management like uveitic glaucoma. However, surgical intervention is ultimately needed in most of cases. Different surgical strategies include: antimetabolites-assisted trabeculectomy, drainage implants, cyclodestructive surgeries and other approaches. This review article will discuss the current management strategies for refractory glaucomas and the application of those treatment modalities to the specific glaucoma types.

Keywords: Glaucoma; refractory; valves; cyclodestructive procedures, trabeculectomy

Certain glaucomas do not expect to respond well to conventional trabeculectomy, they are collectively named Refractory glaucomas. Potential types are neovascular, uveitic, traumatic, glaucomas with wide conjunctival scars, childhood and juvenile, post-vitrectomy, post-keratoprosthesis, post-keratoplasty, ciliary block glaucoma, recurrent, glaucoma in aphakic and pseudophakic eyes[1,2].

Management options

Glaucoma drainage devices (GDD):

- Non-restrictive: Molteno & Barvaledlt's
- Restrictive: Ahmed glaucoma valve (AGV) & Krupin

Cyclodestructive procedures:

- Trans-scleral diode
- Trans-scleral micropulse diode cyclo G6
- Endoscopic
- High intensity focused ultrasound

Pharmacological

- Anti-glaucoma drugs
- Antimetabolites
- Anti-VGEF
- Amniotic membrane
- Ologen implant

Combined approaches

Glaucoma drainage devices (GDD)

Use of setons to "Wick" aqueous from the anterior chamber dates back to 1906, with the use of horse hair to drain aqueous through a paracentesis. Various materials, including suture, glass, metals, plastic, and biologic material were used and ultimately failed due to problems with inflammation, fibrosis, and infection[3]. In the 1970s, Molteno pioneered development of a shunt, with a plate implanted posterior to the limbus and connected to the anterior chamber by a long silicone tube[4,5]. Molteno variations are: 1. Polypropylene plates, including single-plate (133mm^2), double-plate and pediatric, 2. Molteno 3 is a flexible and larger implant[2,3]. Baerveldt implant was introduced in 1990; 250mm^2 and 350mm^2 silicone plates[6]. Flow-restrictive implants were developed in order to avoid problems associated with early postoperative hypotony. An implant with a pressure-sensitive slit opening was described in 1976 by Krupin (no longer available). AGV was introduced in 1993. The valve is comprised of 2 thin silicon elastomer membranes positioned in a venturi-shaped chamber. Different models include polypropylene plates (single-, double-plate, and pediatric), silicone plates (single-, double-plate, and pediatric), and a porous polyethylene plate. The silicone single-plate model (FP-7) has been popular among clinicians. AGV is the only available resistance glaucoma drainage device[7,8]. The indications for valve implantation are refractory glaucomas, and perhaps as a primary surgery[9,10].

Cyclodestructive procedures

Betti introduced cyclocryotherapy in 1950. Then it was the era of cyclophotocoagulation (CPC). In 1961, Weekers was the first to use light energy as a means of cyclodestruction. Trans-scleral xenon arc photo-coagulation over ciliary body lowered IOP. In 1985 Beckman used ruby laser for cyclo-ablation. Nd:YAG CPC is 1064nm in the infrared spectrum was then used. Nowadays, diode laser is the most commonly used laser for cyclophotocoagulation[11,12].

Trans - scleral cyclophotocoagulation (TSCPC)

Diode laser 810nm applied through the sclera targets and destroys the melanin-containing pigmented ciliary epithelium resulting in decrease aqueous production. Other postulated mechanisms of action include ciliary body ischemia and uveoscleral flow enhancement[13,14]. TSCPC is indicated in refractory glaucomas regardless the visual potential[14-18]. The G-probe is placed with its edge at the limbus. The initial settings are 1.500mW for 2 seconds with a total of 24 spots for the 360° treatment sparing the 3:00 and 9:00 clock positions. Some surgeons treat 270° sparing the upper nasal quadrant. Treatment is guided by the audible "pop" sound that indicates tissue explosion within the ciliary body. Increase the power by 100mW till the audible pop is reached, then reduce 100mW below that power setting[19]. After treatment, The IOP reduction is variable, 54% to 92% of treated eyes attain IOP below 21mmHg. Re-treatment rate is up to 30%[20,21]. Rotchford and co-workers[22] evaluated the effects of diode CPC in patients with good (≥ 20/60) visual acuity. The results showed that 73.5% of patients had a final IOP of 16mmHg or less and that only 30.6% lost 2 or more Snellen lines. To compare, in the Tube Versus Trabeculectomy (TVT) study, 63.9% of patients in the tube shunt group and 63.5% of patients in the trabeculectomy group had an IOP of 14mmHg or less. Forty-six (46%) of the tube shunt patients and 43% of the trabeculectomy patients lost 2 or more lines of Snellen visual acuity[23]. Complications include surface burns, uveitis, atonic pupil, hyphema and vitreous hemorrhage in eyes with neovascular glaucoma (NVG), hypotony and phthisis bulbi[19,24].

Endoscopic cyclophotocoagulation (ECP)

In this technique, the secretory ciliary epithelium is coagulated under direct

visualization using a Xenon-illuminated microscope. It is desirable that the patient is pseudophakic or aphakic; either pre-existing or achieved at the time of surgery (Phaco-ECP). ECP is performed using the Uram E2 ophthalmic endoscopic laser (Endo Optics, Little Silver, N,J). This consists of a 20-guage endoscopic probe containing four elements: (1) 175 W Xenon light source, (2) Helium-Neon laser aiming beam, (3) Finer optic cable for imaging, and (4) 810 nm diode thermal laser. ECP is performed through a clear cornea or pars plana approach. In the former, anterior vitrectomy is not required. A pars plana approach may be useful in eyes that have previous vitrectomy or at the time of vitrectomy. Treatment is applied in a "painting" technique, starting at the top of the ciliary processes and progressing toward their bottoms[25]. Laser settings: treat 180 to 360 degrees, continuous settings, about 3 seconds for slow whitening, 250-900mW (up to a maximum of 2.0W)[11]. Encouraging results have been reported with refractory glaucomas and combined with cataract surgery as a primary surgical treatment, however re-treatments are occasionally needed[26-32]. ECP has apparent advantages including a relatively short learning curve, quick, well-tolerated, and repeatability[25]. Fibrinous uveitis is the main complication after ECT (up to 51%). Other complications include, hyphema, IOP spikes, choroidal detachment, retinal detachment, reduced vision, corneal decompensation, and cystoid macular edema (CME)[33,34]. In comparison to TSCPC, ECP is an invasive procedure, though it is a disadvantage, it allows for direct visualization of the ciliary processes with titration of treatment and much less tissue destruction compared to TSCPC[35]. Both achieved a desired IOP reduction (21mmHg with or without medications) in 67.6% of the ECP group and 30.8% of the TSCPC group after 6 months in penetrating keratoplasty glaucoma. In comparison to tube surgery, in a prospective study performed on pseudophakic eyes, at 24 months, 70.59 % and 73.53% achieved the desired IOP for AGV and ECP groups, respectively[36].

Micropulse trans - scleral cyclophotocoagulation (MP-TSCPC)

The cyclo G6 with the MP3 probe, (figure 1), applies a series of short (microsecond), repetitive bursts of energy that effectively confines the thermal effect to the absorbing tissue. The micropulse delivery mode includes on and off cycles, allowing energy to build up in the targeted pigmented tissues, eventually reaching the coagulative threshold.

Figure 1. MicroPulse® P3 glaucoma laser probe.

The micropulse duty cycle on the laser is set to 31.3% and the power is set to 2W[37], (figure 2).

Figure 2. The Cyclo G6 diode micropulse system set to 31.3% duty cycle and 2W power.

In a prospective interventional case series of 40 eyes of 38 consecutive patients with refractory glaucoma, the mean age of patients was 63.2 +/- 16.0 years. The mean follow-up period was 16.3 +/- 4.5 months. The mean preoperative IOP was 39.3 +/- 12.6 mmHg that decreased to 31.1 +/- 13.4 mmHg at 1 day, 28.0 +/- 12.0 mmHg at 1 week, 27.4 +/- 12.7 mmHg at 1 month, 27.1 +/- 13.6 mmHg at 3 months, 25.8 +/- 14.5 mmHg at 6 months, 26.6 +/- 14.7 mmHg at 12 months and 26.2 +/- 14.3 mmHg at 18 months, p value was statistically significant (P<0.001) at all time points. No patient had hypotony or loss of best-corrected visual acuity. The overall success rate after a mean of 1.3 treatment sessions was 72.7%[38]. Numerous studies have then demonstrated the efficacy and high safety profile of MP-TSCPC in refractory glaucomas[39-45.]

High intensity focused ultrasound (HIFU)

The EyeOP1 is a portable device that consists of a control module and a probe that uses an HIFU technology at 21MHz. The rationale of the device is to perform circular ultrasound cyclocoagulation (UC3) in a single step. A ring containing six active piezoelectric elements is inserted in a coupling cone[46,47]. The first clinical pilot study using miniaturized HIFU in refractory glaucoma was conducted by Aptel and co-workers[47] in 2011. They documented a surgical success rate of 83.3%, a significant reduction in IOP from a mean pre-operative value of 37.9 +/- 10.7mmHg to 26.3 +/ 5.1mmHg at 3-month follow-up. The EyeMUST1 Study was a 12-month open-label multicenter prospective study conducted to determine the efficacy and safety of UC3[48]. Primary outcome was IOP reduction at 12 months. This was achieved in 57.1% of the patients. Success was lower in patients with secondary glaucoma compared to patients with primary open-angle glaucoma (45.0 vs 78.6%). Mean IOP reduction at 6 months was 30.2%, and at 1 year was 36.0%. However, this study found no reduction in IOP-lowering medications. Other studies have been conducted to evaluate the clinical outcomes of UC3 in refractory glaucoma[48,49]. Overall, it seems that UC3 tends to have lasting efficacy in controlling the IOP during the first year, with a success rate ranging from 48% to 83.3%[50,51].

Pharmacological - assisted surgeries

Antimetabolites

Both 5-fluorouracil (5-FU) and mitomycin C (MMC) are used to inhibit fibroblast proliferation and enhance surgical success. Their use has become a standard clinical practice, particularly in complex high-risk cases[52,53].

5-Fluorouracil

Intraoperative: 25 or 50mg/mL undiluted solution on a filter paper or a sponge and left for 5 minutes. Postoperative: 0.1ml injection of 50mg/ml undiluted solution adjacent to the bleb. Repeat injections are often necessary.

Mitomycin-C

Intraoperative: diluted solution 0.1-0.5mg/ml for 1-5 minutes on a filter paper or a sponge. Postoperative injection of 0.1ml of 0.02mg/ml solution adjacent to but not into the bleb. A meta- analysis comparing intraoperative MMC to 5FU showed greater percentage of IOP reduction achieved with MMC[54]. Adjunctive MMC to tube surgery proved beneficial[52,55]

Anti-vascular endothelial growth factor (VEGF)

The role of the vascular endothelial growth factor in rubeotic glaucoma is well documented. Additionally, it plays an important role in wound conjunctival healing. Conjunctival VEGF is upregulated in presence of inflammatory cytokines such as TGF-B1, interleukin 1ß, and interleukin-4[56]. Subconjunctival injection of bevacizumab after trabeculectomy in a rabbit model improved bleb morphology, and reduced vascularity and scarring[57]. Human studies have shown that MMC is superior to anti-VEGF in terms of IOP control[58,59]. Methods of administration of anti-VEGF include subconjunctival, intracameral, and intravitreal injections[60].

Ologen TM implant
Ologen is a biodegradable lyophilized porcine matrix that aims to provide a scaffold for random fibroblast growth. This reduced the subconjunctival scarring severity. When inserted under the conjunctiva at the time of trabeculectomy, it acts as a spacer. Encouraging results are reported with primary trabeculectomy[61]. However, comparative studies revealed a lower success rate compared to MMC[52]. Other studies reported similar efficacy[62,63] A recent study evaluated Ologen both subconjunctival and subscleral together with MMC (0.1mg/ml for 1 min) in cases of advanced primary glaucoma[64]. Another study documented good results with Ologen implant in refractory glaucoma following failed trabeculectomy[65].

Amniotic membrane Human amniotic membrane is an antifibrotic, anti-inflammatory agent. It was known for its beneficial effect in preventing subconjunctival fibrosis in glaucoma filtering surgery[66]. Low-quality evidence from nine studies suggests that use of amniotic membrane with trabeculectomy may be associated with lower IOP at one year compared with trabeculectomy alone[67]. The amniotic membrane has been used successfully with AGV[68] and in failed trabeculectomy[69].

Specific forms of refractory glaucomas
Childhood glaucomas
Childhood glaucomas include a wide variety of conditions which result in elevated intraocular pressure and optic nerve damage. They are classified into: (1) Primary congenital glaucoma (newborn and infantile), when an isolated idiopathic developmental abnormality of the anterior chamber angle exists. (B) Glaucomas associated with congenital anomalies; aqueous outflow is reduced due to congenital ocular or systemic disorder, and (C) Acquired glaucoma; the outflow impairment is the result of acquired ocular disease or systemic abnormality[53]. Medical treatment is frequently needed as a temporary measure to lower the IOP before surgery or as an adjunct therapy after partially successful surgical procedures. Medications are occasionally the first-line for some cases (e.g. uveitis-related, glaucoma after cataract removal). Brimonidine should be avoided in young children[70]. Surgery by a trained surgeon is the ultimate management in the majority of cases. The first operation is usually the best chance. Options include: (1) Angle surgery; goniotomy, trabeculotomy (conventional or circumferential) is the procedure of choice. (2) Trabeculectomy with adjunctive antimetabolites. (3) Combined trabeculotomy and trabeculectomy, (figure 3).

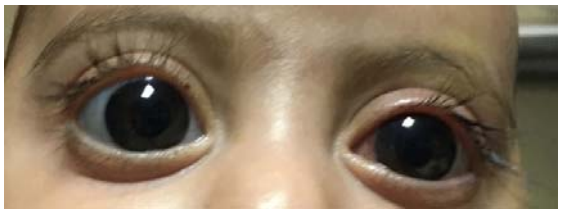

Figure 3. A 3-month old baby with advanced PCG where bilateral combined trabeculotomy/trabeculectomy were performed.

(4) Glaucoma drainage devices with questionable results of additional anti-metabolites in cases refractory to angle surgery and trabeculectomy, (figure 4).

Figure 4. Encapsulation around the plate of AGV.

(5) Cyclodestructive procedures with limited long-term success and often requires re-treatment and continuation of medications[70-72].

Deep sclerectomy has been proposed by some as an alternative to other procedures in high risk pediatric glaucoma cases such as Sturge-Weber syndrome, where it is desirable to minimize sudden hypotony and the resultant possibility of massive choroidal serous or hemorrhagic detachments[73]. In conclusion, primary congenital glaucoma (PCG) in the mild and moderate forms responds well to angle surgery, whereas, recurrent PCG, advanced disease, and secondary forms are classified as refractory glaucomas with consideration of other surgical options, guided by the literature reports and surgeon's experience.

Neovascular Glaucoma

Neovascular glaucoma (NVG) is a potentially blinding secondary glaucoma, characterized by the development of neovascularization of the iris, and elevated intraocular pressure. The underlying pathogenesis in most cases is posterior segment ischemia, which is most commonly secondary to proliferative diabetic retinopathy or central vein retinal occlusion[74]. VEGF plays a major part in mediating active intraocular neovascularization in patients with ischemic retinal diseases[75]. VEGF and insulin growth-1 factors are produced locally in the human eye by a variety of cells including Mueller cells, retinal pigment epithelial cells, retinal capillary pericytes, endothelial cells and ganglion cells[76]. The non-pigmented ciliary epithelium is an important site of VEGF synthesis in patients with NVG. In fact, a recent study considered the ciliary epithelium as an additional focus of treatment in the management of NVG, especially in eyes that were not responsive to pan-retinal photocoagulation (PRP)[77]. Initial medical treatment is considered to lower the high IOP levels and alleviate the pain. Topical β-adrenergic antagonists, α-2 agonists and topical or oral carbonic anhydrase inhibitors are the preferred drugs. Topical atropine and corticosteroids reduce the inflammation. Prostaglandins and pilocarpine are avoided[78]. PRP is the mainstay in controlling NVG[79]. PRP induces complete regression of retinal neovascularization in 67–77 % of cases, visual loss can be prevented in 59–73 % and IOP reduction can be achieved in 42% of the cases[80]. Intravitreal anti-VEGF (bevacizumab, ranibizumab, and aflibercept) injections can lead to regression of both iris and angle neovascularization, and intraocular pressure control when the angle remains open[81]. They are considered alone or as a pre-treatment with glaucoma surgeries. A debate still exists about the real effectiveness of anti-VEGF in the management of NVG, evidence showing that a pre-treatment with anti-VEGF before definitive IOP lowering glaucoma surgeries can significantly lower the frequency of hyphema[82-89]. Interestingly, continuous intravitreal anti-VEGF injections may cause both transient and sustained elevation in IOP[90]. Surgical options include antimetabolites-augmented trabeculectomy with high failure rate, particularly when hyphema develops[91,92]. AGV surgery with variable success rates (20.6%-70%)[93,94]. AGV has been combined with intravitreal bevacizumab injection with encouraging results[95], and has been implanted at the time of pars plana vitrectomy[96-98]. TSCPC with and without the use of anti-VEGF has been shown to be effective in lowering IOP and relieving pain in advanced cases of NVG[99,100]. When compared to AGV implantation in a randomized controlled trial, no significant difference was found in the success rate at 24 months between the diode cyclophotocoagulation (61.18 %) and AGV valve implantation (59.26 %) in NVG treatment[101].

Glaucoma after silicone oil injection 5.9% to 56% of cases got IOP elevation after silicone oil injection, it may be transient or permanent. In the early postoperative phase, it may be related to pupillary block, inflammation, preexisting glaucoma, and silicone oil migration into the anterior chamber. In the intermediate and late phases, it may be due to infiltration of the trabecular meshwork by emulsified silicone oil, steer response,

synechial closure, and rubeosis[102,103]. Inferior peripheral iridotomy at the time of surgery prevent pupillary block in aphakic and pseudophakic eyes[104]. Cases refractory to medical treatment benefit from silicone oil removal with or without glaucoma surgery[105,106]. Trabeculectomy with antimetabolites has a high rate of failure. Aqueous shunts are more likely to succeed. The implant can be positioned superiorly or inferiorly to avoid silicone oil migration. Pars plana insertion of the tube is another option. Cyclodestructive procedures are another option[107,108]. Selective laser trabeculoplasty (SLT) has been used with encouraging results in eyes with persistent IOP elevation after silicone oil evacuation[109].

Uveitic glaucoma (UG)

Glaucoma occurs in around 20% of all patients with chronic uveitis. Higher rates are reported in those with rheumatoid arthritis-associated iridocyclitis, Fuchs heterochromic iridocyclitis (27%), sarcoidosis (34%), herpes simplex keratouveitis (54%), zoster uveitis (38%), Lyme-associated uveitis, cancer-associated uveitis[13], juvenile idiopathic arthritis (12–35%), Behçet's disease, pars planitis, sympathetic ophthalmia, and syphilis[110]. About 30% of eyes with UG may require surgery after initial medical treatment[111-113]. There is a consensus that the surgical success rate of filtering surgery is lower for eyes with UG compared with POAG. As a rule, suppression of inflammation in the peri-operative period significantly improves outcomes[114]. Regardless of the surgical modality chosen, all patients require meticulous control of inflammation preoperatively and vigilant monitoring for reactivation postoperatively. Surgical options for uveitic glaucoma include: trabeculectomy with success rates from 50% to 100%[115], Ex-PRESS Mini-Glaucoma shunt[116], non-perforating deep sclerectomy (NPDS) [117], canaloplasty[118], glaucoma drainage devices[119], iStent[120], trabectome surgery[114], goniotomy[121], cyclophotocoagulation[122,123], and iridotomy[124].

CONCLUSIONS

Refractory glaucomas constitute a group of disorders with pathologically elevated IOP causing optic nerve damage in which conventional trabeculectomy is less successful or even ineffective. 1- The common forms are: childhood, NVG, post-PPV, post-keratoplasty, uveitic, glaucoma in aphakic and pseudophakic eyes. 2- Medical treatment is effective in some cases, in conjunction with specific therapy. 3- The common surgical options are antimetabolites-assisted trabeculectomy, glaucoma drainage implants and cyclodestructive procedures. 4- There are tremendous improvements in the cyclodestructive techniques in the last few years with better outcomes.

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