Penetrating Keratoplasty and Glaucoma
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Abstract. Glaucoma remains the leading cause of blindness after penetrating keratoplasty. Post-keratoplasty glaucoma was originally described in 1969, and its management is still controversial. Recent developments in management include newer classes of drugs, surgical procedures, such as trabeculectomy with mitomycin-C, implantation of glaucoma drainage devices, and cyclodestructive procedures with Nd: YAG and diode lasers. However, the risk of graft failure continues to be high with all surgical procedures. (Surv Ophthalmol 45:91–105, 2000. © 2000 by Elsevier Science Inc. All rights reserved.)

Key words. cyclodestructive procedures • glaucoma • glaucoma drainage devices • penetrating keratoplasty • post-keratoplasty glaucoma • mitomycin-C • trabeculectomy

Many complications can occur after penetrating keratoplasty. Allograft rejection leading to graft failure and severe graft astigmatism not amenable to contact lens fitting are major problems. These complications, however, do not limit the visual potential of the eye. On the other hand, glaucoma, one of the most problematic complications after penetrating keratoplasty, may be visually threatening because it causes irreversible optic nerve damage (as well as graft failure). The diagnosis and management of glaucoma after penetrating keratoplasty can be very challenging under the best of circumstances. This review addresses the etiology, diagnosis, and management of glaucoma after penetrating keratoplasty.

I. Incidence

The incidence of glaucoma after keratoplasty varies from 9% to 31% in the early postoperative period, and from 18% to 35% in the late postoperative period. Irvin and Kaufman reported the high incidence of increased intraocular pressure (IOP) following penetrating keratoplasty in 1969. They reported a mean maximum pressure in the immediate postoperative period of 40 mm Hg in eyes with aphakic transplants and 50 mm Hg in combined transplants and cataract extraction.

Important risk factors for glaucoma in patients undergoing penetrating keratoplasty are aphakic bullous keratopathy, combined penetrating keratoplasty and intracapsular cataract extraction, pre-existing glaucoma, perforation, and previous keratoplasty. Goldberg et al reported a 29% incidence of raised IOP in the early postoperative period and 30% in the late postoperative period in patients with aphakic bullous keratopathy. Goldberg found the incidence of raised IOP in repeat grafts to be higher (45% in the early postoperative phase and 52% in the late postoperative phase). Goldberg’s study found that 71% of patients with pre-existing glaucoma developed raised pressure in the early postoperative course.

Kirkness reported a higher incidence of glaucoma in patients undergoing keratoplasty after per-
foration, especially if the perforation followed suppurative keratitis.

It appears that the longer the period between perforation and the keratoplasty, the greater the likelihood of developing glaucoma. The most likely cause of this is inflammation leading to peripheral anterior synechiae and angle closure.

Other studies have found traumatized eyes and older patients to be at increased risk for developing glaucoma after penetrating keratoplasty.21,33,36,44,46,51,111

II. Pathogenesis

The etiology of glaucoma after penetrating keratoplasty is multifactorial and is probably related to distortion of the angle with collapse of the trabecular meshwork, suturing technique, postoperative inflammation, and peripheral anterior synechiae. Eyes may be subject to the usual causes of glaucoma such as postoperative inflammation, use of viscoelastic substances, and steroid-induced glaucoma.35 Olson and Kaufman72 tried to explain the high incidence of glaucoma in aphakic keratoplasty using a mathematical model. According to this model, the elevated IOP is the result of angle distortion secondary to a roll of excess compressed tissue in the angle. Because of edema and inflammation, trabecular meshwork function is compromised. Factors that aggravate angle distortion include tight suturing, long bites (more compressed tissue), larger trephine sizes, smaller recipient corneal diameter, and increased peripheral corneal thickness. Conversely, less-tight wounds, smaller trephine sizes, donor corneas larger than the recipient, thinner recipient corneas, and larger overall corneal diameter tend to alleviate the angle distortion.

Alternatively, Zimmerman et al119 proposed mechanical collapse of trabecular meshwork in aphakic grafts to be the key problem leading to glaucoma. They postulated that the trabeculum needs posterior fixation afforded by the ciliary body-lens support system and an anterior support afforded by Descemet’s membrane. In aphakia, the posterior support is relaxed, but not critically. With keratoplasty, this loose roll of tissue relaxes the anterior support and leads to partial trabecular collapse. This theory explains the high incidence of glaucoma in aphakic grafts as compared to phakic transplants. In perfusion studies of aphakic eyes, Zimmerman et al have shown that full-thickness sutures that approximate Descemet’s membrane were not associated with alterations of facility of outflow. On the other hand, midstromal bites were associated with a 37% reduction in the outflow facility.

Supporting this theory, Zimmerman et al117 have shown that oversized donor buttons (0.5 mm larger than the host bed) in aphakic patients reduced the incidence of glaucoma. The effect was more obvious when an 8-mm donor button was used in 7.5-mm host bed. Bourne119 also found that the grafts with oversized buttons were associated with better control of IOP in the early postoperative period (in eyes without pre-existing glaucoma). These results, however, were not reproduced in other studies. Perl et al25 showed that use of oversized grafts (0.5 mm) provided no protection against post-keratoplasty glaucoma in any study group (aphakics, pseudophakics, or phakics). Unfortunately, variables such as trephination technique, suturing technique, and corneal rigidity (which may lead to inconsistent button size), were not addressed in this study.

Lass25 proposed that post-keratoplasty glaucoma could be related to the development of fine peripheral anterior synechiae. A floppy, atrophic iris may lead to a higher incidence of peripheral anterior synechiae formation, which can be prevented by iris sutting or iridoplasty.23 The possible causes of glaucoma after penetrating keratoplasty are listed in Table 1.

III. Diagnosis

The diagnosis of glaucoma after penetrating keratoplasty is made based on IOP in the early postoperative period and on IOP, optic disk changes, and progressive visual field changes in the late postoperative period.

Accurate measurement of IOP in patients with keratoplasty can be difficult. IOP in the early postoperative period, when the corneal surface is irregular, can be measured with the Mackay–Marg electronic applanation tonometer,45 the pneumatic applanation tonometer,97 or the Tonopen.41 If the graft surface is smooth, the epithelium is intact, and the mires are regular, then Goldmann applanation tonometry can be used to measure IOP. Marked corneal astigmatism causes an elliptical fluorescein pattern. To obtain an accurate reading with the Goldmann applanation tonometer, the clinician should rotate the prism so that the red mark on the prism holder is set at the least curved meridian of the cornea (along the negative axis).83 Alternatively, two pressure readings taken 90° apart can be averaged.41 The accuracy of applanation tonometry is reduced in certain situations, such as corneal edema, scars, blood staining, or any condition that thickens or alters the cornea.26,58 Corneal epithelial edema27 and stromal edema41,58 predispose to inaccurately low readings, whereas pressure measurements taken over a corneal scar will be falsely high. Thin corneas result in underestimation and thick corneas result in overestimation.28 Tonometry per-
formed over a soft contact lens\textsuperscript{25} or after scleral buckling procedures gives falsely low values.

The pneumatic tonometer has a pressure-sensing device that consists of a gas-filled chamber covered by a silastic diaphragm. The gas in the chamber escapes through an exhaust vent. As the diaphragm touches the cornea, the gas vent is reduced in size and the pressure in the chamber rises. Because this instrument applanates only a small area of the cornea, it has the advantage of measuring the IOP in the presence of corneal scars or corneal edema, or when only a small portion of the cornea is visible (large tarsorrhaphy). In patients with neurotrophic keratopathy, it is possible to measure the IOP with minimal disturbance of the epithelium.

In cases with complete tarsorrhaphy an attempt must be made to measure the IOP by digital palpation.\textsuperscript{17,82} It is helpful to measure the IOP in the normal eye with use of one of the standard techniques (i.e., Goldmann applanation tonometry) and then perform digital palpation on both eyes.

IOP should be measured on every visit after penetrating keratoplasty. Optic disk changes should be monitored in all cases of elevated IOP. This can be done either by serial disk photography (where possible) or by same-observer serial optic disk diagrams.

Visual field testing may be difficult to perform in patients with a corneal graft, especially in the early postoperative period. In patients with reasonable vision, Humphrey visual fields or Goldmann visual fields should be tried and performed as indicated.

**IV. Management**

One of the major causes of graft failure is poor control of elevated IOP. Chronic elevation of IOP can potentially compromise the graft endothelial function. Acute and greatly elevated IOP has been shown to cause significant endothelial cell loss. The amount of cell loss appears to correlate with the duration of the IOP increase. Endothelial cell loss of 10\% to 33\% has been reported after acute angle-closure glaucoma.\textsuperscript{15,67,71,85,101} In eyes with acute angle-closure glaucoma lasting more than 12 days, 77\% cell loss has been reported.\textsuperscript{15} Morphological changes in the endothelial cells such as vacuolization, loosening of cell junctions, blebbing, disruption of the plasma membrane, exkaryotosis, and the loss of whole cells have been observed in experimentally induced acute glaucoma in the vervet monkey.\textsuperscript{101} Corneal sensation is also noted to be decreased in eyes with angle-closure glaucoma.\textsuperscript{75}

Thus, markedly elevated IOPs in the postoperative period could compromise the graft, both by causing endothelial cell damage and decreasing the corneal sensation. Therefore, any patient with elevated IOP after keratoplasty should be aggressively treated.

**A. PREVENTIVE MEASURES**

Pre-existing glaucoma is frequently more difficult to treat following keratoplasty in both aphakic and pseudophakic eyes.\textsuperscript{33,84,91} Pre-existing glaucoma is also noted to be a risk factor for graft failure.\textsuperscript{79,114} Reinhard et al.\textsuperscript{79} estimated the 3-year graft survival rate in patients with a preoperative history of glaucoma to be 71\%, in contrast to 89\% without such history. Some studies suggest a higher incidence of graft failure after a glaucoma operation performed after the penetrating keratoplasty.\textsuperscript{78} Hence, in this patient population, some studies suggest treating the glaucoma with mitomycin-C trabeculectomy\textsuperscript{30,63} or with a glaucoma drainage device\textsuperscript{32,78} combined with the penetrating keratoplasty surgery.

During keratoplasty, use of an oversized donor button (0.5 mm),\textsuperscript{19,56,117} deep bites,\textsuperscript{119} goniosynechiolysis in the presence of peripheral anterior synechiae,\textsuperscript{106} iridoplasty (iris tightening procedure) in cases of a floppy iris,\textsuperscript{23} removal of viscoelastic material at the end of the operation, and careful wound closure to prevent postoperative wound leaks help to reduce the incidence of postoperative glaucoma.

In the postoperative phase, judicious use of steroids controls the inflammation and prevents peripheral anterior synechiae. Cycloplegics (when indi-
cated) keep the pupil mobile and prevents pupillary block glaucoma.

B. MEDICAL MANAGEMENT

Medical management (topical drops or systemic pills) is still the first line of treatment in cases of glaucoma following keratoplasty. Currently available medications include beta-adrenergic blocking agents (timolol, betaxolol, etc.), adrenergic agents (epinephrine and dipivefrin), alpha-2 adrenergic agonists (brimonidine, apraclonidine hydrochloride), miotics (pilocarpine, echothiophate iodide, and carbachol), prostaglandin analog (latanoprost) and topical (dorzolamide, brinzolamide) and systemic carbonic anhydrase inhibitors (acetazolamide, methazolamide, dichlorphenamide).

Beta-adrenergic blocking agents have been the cornerstone of glaucoma management for the last 2 decades. They appear to act by decreasing the aqueous production and have no effect on the outflow pathways. Lass and Pavan-Langston demonstrated the efficacy of timolol in the treatment of glaucoma after keratoplasty, even in the presence of chronic angle closure. Side effects of beta-blockers include, but are not limited to, superficial punctate keratopathy, corneal anesthesia, and damage to the ocular surface. By decreasing the aqueous layer production rate and impairing the quantity and quality of the mucus layer of the tear film, these drops may lead to a dry eye state. All these side effects can have an adverse effect on the graft epithelium, which may compromise graft function.

Adrenergic agents can help lower the IOP, but should be used with caution in aphakic and pseudophakic patients, as they can produce cystoid macular edema.

Brimonidine tartrate 0.2% is a relatively selective alpha-2 adrenergic agonist, is better tolerated than apraclonidine hydrochloride and appears to be useful in controlling the IOP. Apraclonidine 0.5% is a potent anterior segment vasoconstrictor and is useful both to prevent anterior chamber bleeding during the operation and to control the pressure spike resulting from such a bleed. In cases with a high risk of bleeding, one drop of apraclonidine 0.5% is recommended 1 hour before surgery and 12 hours postoperatively. Long-term use of apraclonidine appears to be restricted because of a high incidence of allergic reactions (in up to 30–40% of patients) within 6 months of usage. Brimonidine on the other hand is better tolerated and may be used in the long term.

Miotics can be useful for controlling the IOP in patients with open angles, but may have very little effect in the presence of significant angle closure caused by peripheral anterior synechiae. Miotics can induce uveitis by breakdown of the blood-aqueous barrier, which may initiate graft rejection. In one report, three out of four grafts had graft rejection within 3 days to weeks after the start of the miotic agents. Three of these patients were on phospholine iodide, and one patient was on pilocarpine. Discontinuation of the miotics with intensive corticosteroid treatment reversed the rejection in one patient, whereas irreversible graft failure developed in the other two grafts. In aphakic eyes, miotics can increase the risk of a retinal detachment.

Dorzolamide was the first topical carbonic anhydrase inhibitor to be introduced to the market. The ocular hypotensive efficacy of dorzolamide 2% given three times a day is similar to that of betaxolol 0.5% given twice daily, and it is not associated with clinically significant electrolyte disturbances or systemic side effects, which are seen with systemic carbonic anhydrase inhibitors. In view of the recent report of irreversible corneal decompensation after use of topical dorzolamide in patients with compromised endothelial function, this drug should be used with caution in patients with post-keratoplasty glaucoma, especially in patients with a past history of graft rejection and/or with limited endothelial cell counts. Other side effects noted are a 1–10% incidence of allergic reaction and a 25% incidence of bitter taste. Brinzolamide 1% is a new topical carbonic anhydrase inhibitor that appears to be better tolerated than dorzolamide, as its pH at 7.5 is the same as the tear film.

Systemic carbonic anhydrase inhibitors have been prescribed for decades to treat glaucoma. They are very useful in the treatment of pressure spikes in the immediate postoperative period. However, long-term use of these drugs may be limited, as 30% to 50% of patients suffer from side effects, such as paresthesias, tinnitus, nausea, gastrointestinal disturbances, fatigue, depression, anorexia, and weight loss. Because of these side effects, oral carbonic anhydrase inhibitors should be used with great caution in elderly patients.

Newer drugs, such as the prostaglandin analog latanoprost, appear to be as effective as beta-blockers in the control of IOP. Prostaglandin analogs appear to decrease IOP by increasing the uveoscleral outflow and can be used with beta-blockers and carbonic anhydrase inhibitors. However, latanoprost should be used with caution in patients with a history of herpes simplex keratitis, as it has been recently reported to induce recurrent herpetic infection both in humans and in the rabbit model. In patients with aphakia and pseudophakia, latanoprost has been reported to cause cystoid macular edema, and in patients with a past history of uveitis, it should be used with caution.

Benzalkonium chloride (BAC [0.01% concentration]) is the preservative that is used in the majority
of the topical glaucoma medications. One drop of 0.02% BAC or several drops of 0.01% BAC can have toxic effects on the corneal epithelium (Fig. 1). These effects include cell wall damage and destruction of the corneal epithelial microvilli, leading to increased permeability of the corneal epithelium. Other preservatives used in glaucoma medications include benzododecinium bromide 0.012% (used in Timoptic XE [Merck & Co, West Point, PA]), whose effect on the corneal epithelium is less well studied. The acidic pH of some of the topical drops (e.g., Cosopt [Merck & Co] 5.8%, dorzolamide 5.6%), in addition to causing a burning sensation, may also be toxic to the corneal epithelium.

In patients who are allergic to the preservatives, preservative-free drugs, such as the Ocudose® (Merck & Co) form of timolol maleate should be used. Also, pilocarpine powder can be reconstituted with balanced salt solution locally by the pharmacy without any preservative.

In the case of a steroid-responsive glaucoma, the dose of steroid drops (prednisolone acetate 1%) may be tapered to the minimum required. Alternatively, stronger steroid drops, such as prednisolone acetate, can be replaced by steroids that have less tendency to increase the IOP, (e.g., topical fluorometholone, loteprednol etabonate 0.5% or 0.2%, and rimexolone 1%). Cyclosporin A 0.5% topical drops (in combination with topical glaucoma medications) may also help to control the pressure. Perry and coworkers have reported a mean reduction of IOP by 8.7 mm Hg after topical corticosteroids were replaced by topical cyclosporin A 0.5% (on a drop-to-drop basis) in 21 (84%) of their 25 patients. Graft clarity was maintained in all patients, with one allograft rejection episode that responded to hourly cyclosporin drops.

In summary, the practitioner should have a low threshold for treating glaucoma after keratoplasty. Topical carbonic anhydrase inhibitors, prostaglandin analogs, and miotics should be used with caution. As anti-glaucoma drops can cause superficial punctate keratopathy, the graft epithelium must be carefully examined in all cases for possible side effects and the offending drugs discontinued. Table 2 documents the disadvantages of using some of the...
topical glaucoma medications in patients with post-keratoplasty glaucoma.

C. SURGICAL MANAGEMENT

1. Argon Laser Trabeculoplasty

Argon laser trabeculoplasty (ALT) can result in a 10–40% reduction of the IOP in primary open-angle glaucoma in the short term. The efficacy of ALT depends on the clinical characteristics of the patients and the type of glaucoma treated. In general, older white patients with primary open-angle glaucoma have the best long-term results. Unfortunately, the IOP-lowering effect tends to diminish between 1.5 and 4 years postoperatively, with only a 40–50% success rate at 5 years. Patients with glaucoma secondary to uveitis, angle recession, and juvenile glaucoma uniformly have done poorly. Aphakic eyes with vitreous in the anterior chamber have less than a 50% probability of success. Pseudophakic eyes with primary open-angle glaucoma and intact posterior capsules seem to do as well as phakic eyes with ALT.

Van Meter and coworkers have reported successful control of IOP after ALT in 10 of 14 eyes after penetrating keratoplasty at 2 years (average follow-up of 22.8 months; range, 12 to 37 months). The average IOP was reduced from 30.6 mm Hg before treatment to 21.5 mm Hg after ALT, with an average decrease of 9.1 mm Hg (29.7% mean reduction). ALT was performed with a blue-green argon laser unit with a 50 micrometer spot size, 0.1 second duration and 300–1350 mWatts of power. Long-term results on these patients are not available.

Based on the data, ALT may be indicated in patients with open angles, clear grafts, and moderately elevated IOP (25–30 mm Hg) on glaucoma medications. If the IOP is greater than 30 mm Hg on maximum tolerable medications, literature seems to support surgical intervention over ALT, as, at best, the IOP reduction after ALT is 10 mm Hg and the IOP control seems short-lived.

2. Trabeculectomy

a. Conventional Trabeculectomy

The role of conventional trabeculectomy in the management of post-keratoplasty glaucoma is not well defined. The few published reports of trabeculectomy without antimetabolites (5-fluorouracil [5-FU]) and alkylating agents (mitomycin-C) in patients with post-keratoplasty glaucoma suggest a high failure rate. Several factors contribute to this high failure rate: limbal conjunctival scarring from previous surgery, extensive peripheral synchiae, aphakia, and extremely shallow anterior chamber. Gilvarry et al reported successful IOP control (off pressure lowering medications) with trabeculectomy in only 3 (9%) of 35 post-keratoplasty patients at the end of 3-year follow-up. An additional 15 patients (42%) were controlled with glaucoma medications. Seventeen eyes (50%) failed within 1 year of the operation and needed additional surgical procedures. Eighty-nine percent of the grafts remained clear in the successful group, as opposed to 41% in the failed group. Foulks reported five cases of conventional trabeculectomy in patients with post-keratoplasty glaucoma. Four patients had adequate IOP control. Three of the patients, however, had complications including graft failure, choroidal detachment, vitreous hemorrhage, and phthisis bulbi. Insler et al reported seven patients who underwent combined trabeculectomy with penetrating keratoplasty at the same surgery. Three patients had adequate IOP control with trabeculectomy alone, while the remaining patients required glaucoma medications to control the IOP. Two patients had complications: one graft failed and another patient developed retinal detachment. The average follow-up in this study was only 16.1 months.

b. 5-FU and Mitomycin-C Trabeculectomy

The introduction of 5-FU and mitomycin-C have increased the success rate of trabeculectomies, espe-
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The probability of IOP control was 55% at 1 year and 60% at 2 years. The cumulative probability of graft survival at 1 year and 60% at 2 years. They concluded that the bleb failure rate is higher when trabeculectomy was combined with additional surgical procedures, such as cataract surgery and vitrectomy.

In another study, Zalloum et al compared the rate of graft failure among three groups of patients with primary open-angle glaucoma. Group 1 consisted of 24 eyes of 24 patients treated with Molteno implant with penetrating keratoplasty. Group 2 consisted of 15 eyes of 14 patients who underwent multiple surgical procedures, including trabeculectomy. Group 3 included 28 eyes of 17 patients who underwent trabeculectomy alone with penetrating keratoplasty. The mean follow-up was 17.9 months in group 1, 22.4 months in group 2, and 19.6 months with group 3. The graft failure rate was 50% in group 1, 6.7% in group 2, and 0% in group 3.

It is clear from the above studies that the rate of graft failure is significantly less following mitomycin-C trabeculectomy as compared to Molteno implant and cyclodestructive procedures (Table 3), and that the success of mitomycin-C in controlling IOP is comparable to that of the other methods.

Overall, trabeculectomies, when successful, appear to be associated with fewer complications, especially decreased incidence of graft failure, as compared to other surgical options in the management of difficult to control glaucoma.

Results reported in the literature favor mitomycin-C trabeculectomy in eyes with post-keratoplasty glaucoma with freely mobile limbal conjunctiva and no peripheral anterior synechiae (especially in the superior quadrants). Mitomycin-C trabeculectomy appears to be more successful in controlling the IOP when performed alone, compared to being combined with additional surgical procedures.

If the operation is being performed in the presence of a clear graft, measures must be taken to prevent shallowing or flattening of the anterior chambers in the postoperative period. Endocylindrical cell loss after glaucoma surgery is 7% to 12% with iridocorneal touch and 40% to 50% with corneolenticular touch. Endocylindrical cell loss can potentially lead to graft decompensation. Relatively tight closure of the scleral flap followed by postoperative laser suture lysis where indicated may help to maintain the chamber depth.

The corneal surgeon should be aware of the relative contraindication of a contact lens in the presence of filtering blebs because of the increased risk of bleb related infections. The dellen effect on the cornea adjacent to the bleb could potentially lead to epithelial defects and stromal thinning.

In patients whose IOP is not adequately controlled following prior trabeculectomy with or without medications, trabeculectomy revision in the form of internal sclerostomy with the help of a cyclodial-
TABLE 3

Review of Results and Complications After Mitomycin-C Trabeculectomy, Glaucoma Drainage Devices, and YAG Cyclophotocoagulation in Patients with Post-Keratopathy Glaucoma

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Mean IOP</th>
<th>IOP controlled (%)</th>
<th>Graft Failure (%)</th>
<th>Graft Rejection (%)</th>
<th>Hypotony (%)</th>
<th>VA Worse by 1 or More Lines (%)</th>
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<tr>
<td>No. (months)</td>
<td>preop</td>
<td>last visit</td>
<td></td>
<td></td>
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<tr>
<td>Kirkness (without antimetabolites)</td>
<td>26</td>
<td>33.5</td>
<td>35</td>
<td>20</td>
<td>54</td>
<td>50</td>
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<td>Trabeculectomy before PKP</td>
<td></td>
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<td></td>
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<tr>
<td>Trabeculectomy with PKP</td>
<td>22</td>
<td>12</td>
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<td>14</td>
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<td>19</td>
<td>26</td>
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<td>Figuerido (Mitomycin trabeculectomy)</td>
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<td>23</td>
<td>36</td>
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<td>15.6</td>
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<td>10</td>
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<td>23</td>
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<td>12</td>
<td>96</td>
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<tr>
<td>Topouzis (Molteno single plate)</td>
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<td>16.8</td>
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</table>

PKP = penetrating keratoplasty

ACTSEB = Anterior chamber tube shunt to encircling band
ysis spatula can be done at the time of the corneal graft operation through the open-sky technique (Fig. 3). We had good long-term success with this technique in three patients.

3. Glaucoma Drainage Devices

Glaucoma drainage devices create alternate aqueous pathways by channeling aqueous humor from the anterior chamber through a long tube to an equatorial plate that promotes bleb formation. The concept of an implant in the management of glaucoma was conceived by Molteno. Kirkness et al was the first to report the use of glaucoma drainage devices in patients with post-keratoplasty glaucoma. Since then, many investigators have reported the use of these devices when post-keratoplasty glaucoma is resistant to conventional treatment. They appeared to control glaucoma in a high percentage of patients in all the published series (71–96%, with an average of 84.8%).

Unfortunately, implantation of a glaucoma drainage device appears to be associated with a high incidence of graft failure, in the range of 10–51% (average of 36.2%). The etiology is probably multifactorial. The presence of underlying chronic inflammation, extensive peripheral synechiae, and multiple previous surgeries may compromise the graft. The introduction of a glaucoma drainage implant into the anterior chamber may also be associated with increased inflammation and may compromise the graft further. Kirkness et al hypothesized that the glaucoma drainage implants could form an arc for aqueous humor to be in contact with circulating lymphocytes in the bleb and allow retrograde passage of the inflammatory cells into the anterior chamber. They have reported that a tidal flow of cells could be visualized in and out of the tube. Kirkness recommends the use of high-dose steroids (prednisolone acetate 1% 6–8 times a day) to minimize this complication.

The timing of glaucoma drainage implant surgery is another factor that can contribute to graft failure. In the series published by Beebe et al and Rapuano et al, there was a trend toward a higher incidence of graft failure when glaucoma drainage implant surgery was performed after penetrating keratoplasty. Rapuano et al reported the results in 13 patients who underwent glaucoma drainage implant surgery before penetrating keratoplasty (group A), 17 patients who received implants in combination with penetrating keratoplasty (group B), and 16 patients who received implants after penetrating keratoplasty (group C). IOP was lowered significantly in all three groups. The graft failure rate was 31% in group A, 29% in group B, and 44% in group C. Kaplan–Meier survival grafts demonstrated poorer graft survival in group C. The authors felt that this may have been related to surgical trauma to the corneal endothelium during glaucoma drainage implant surgery. This may also simply reflect the poor graft prognosis associated with any intraocular surgery. Lemp et al reported a graft failure rates of 30% when eyes with clear grafts underwent additional intraocular surgery. Prolonged exposure of the graft endothelium to uncontrolled IOP prior to the glaucoma surgery may also compromise the graft.

The drainage implant procedure itself is unlikely to contribute to endothelial cell loss and graft decompensation, as it is mostly an extraocular procedure. McDermott et al reported no clinically significant progressive trend in endothelial cell loss in patients undergoing uncomplicated Molteno drainage implants.

It has been shown that most corneal transplants undergo a 60% reduction in the central endothelial cell count during the first 2 postoperative years. It is possible that complications related to glaucoma drainage implant surgery, including inflammation, shallow anterior chamber with iris graft endothelial touch, and tube-endothelial touch could tip the balance and lead to graft failure. Meticulous surgery should avoid the complications of flat anterior chamber and tube-endothelial touch. The use of high-dose steroids for 3–6 months in the postoperative period may help to control and suppress inflammation.

In addition to graft rejection and failure, other reported complications following glaucoma drainage implant surgery in patients with post-keratoplasty glaucoma include conjunctival erosion, prolonged hypotony, tube-endothelial touch, tube obstruction, tube failure, retinal detachment, tube plate extrusion, epithelial down growth, and infection.

The choice of the glaucoma drainage implant in the treatment of post-keratopathy glaucoma depends upon the case and the surgeon. Currently, there are four main glaucoma drainage implants commercially available: the Ahmed and the Krupin implants, which offer resistance to the outflow in the form of a sheet valve and a slit valve, respectively, and the Molteno and the Baerveldt, which have no resistance to the outflow and, thus, may lead to hypotony. This problem can be avoided with the use of the tip-cord technique. The advantages of the valved implants, especially the Ahmed glaucoma valve, appear to be easy insertion following one quadrant dissection and low incidence of hypotony in the immediate postoperative phase. However, it is associated with a high incidence of hypertensive phase (up to 80%) 1 to 3 months after the operation that may need needling with 5-FU in-
The Ahmed glaucoma valve appears similar among all the glaucoma drainage implants, including corneal decompensation, appear to be similar among all the glaucoma drainage implants. The Ahmed glaucoma valve appears to function better in cases with mild to moderate glaucomatous optic nerve damage, and larger surface area implants, such as the double-plate Molteno and the Baerveldt implant with more significant pressure reduction, may be reserved for cases with more advanced optic nerve damage. The surgeon should take intraoperative precautions to decrease the incidence of postoperative hypotony and shallow anterior chambers. Topical steroids should be used liberally and for prolonged periods of time following the operation.

During the hypertensive phase in the postoperative period after glaucoma drainage implant surgery, antiglaucoma medications should be used initially when the level of IOP is considered a danger to the optic nerve. If the pressure does not decrease, the bleb can be needled. In patients with the Molteno and the Baerveldt implants, the hypertensive phase can be controlled by removal of the 4-0 Nylon stent (Ayyala unpublished data). Needling can be done if the IOP does not respond to the stent removal. When 5-FU is injected (5 mg/0.1 cc), it is best injected into the inferior fornix (and not into or adjacent to the bleb), especially in patients with Molteno or Baerveldt implants (non-valved) to prevent the risk of the 5-FU tracking into the anterior chamber and causing corneal endothelial damage. Needling can be repeated on multiple occasions. If the patient does not respond to the above measures, either a valve revision with excision of the Tenon’s cyst or a second valve can be used. Some surgeons may prefer to use cyclodestructive procedures, such as diode or Nd:YAG cyclophotocoagulation, at this stage or later.

The advantage of using mitomycin-C at the time of the glaucoma drainage device implantation remains unclear. In one study, 21 patients underwent double-plate Molteno with mitomycin-C application (0.5 mg/ml for 5 minutes) at the time of the operation. These patients were followed for 2–3 years and compared to a historical control group who received Molteno implants without mitomycin. Failure was defined as IOP less than 6 mm Hg or greater than 21 mm Hg, addition of glaucoma medications, reoperation for glaucoma, or tube removal. Success in the mitomycin-C group was 68% at 1 year and 35% at 2–3 years, compared to 17% in the control group. In another study, Susanna et al. reported 76% of the 21 patients had IOP less than 21 mm Hg at a mean follow-up of 9.4 months without additional glaucoma medications. On the other hand, Cantor et al. concluded that adjunct mitomycin-C did not demonstrate a significant difference compared with placebo in pressure-ridge Molteno implant surgery. Lee et al. came to similar conclusions after studying 49 patients with single-plate Molteno implants and adjunct mitomycin-C. All the studies have shown the incidence of hypotony (10–63%), flat anterior chambers (18–43%), and choroidal effusions (up to 71%) to be higher in the mitomycin-C group. In all the studies, the operation was performed using some form of ligature or the rip-cord technique to control the rate of flow of the glaucoma drainage device. Ayyala et al. reported using mitomycin-C in 6 out of 85 eyes that underwent the Ahmed glaucoma valve insertion. Four of the six eyes exhibited a hypertensive phase that was controlled with either medications alone (two patients) or needling of the bleb with 5-FU injections and medications (two patients). Two patients developed conjunctival necrosis with end-plate exposure within the first postoperative month. In both patients, conjunctival grafts were tried without success and the implant had to be removed.

### 4. Cyclodestructive Procedures

Cyclodestructive procedures attempt to control the IOP by decreasing aqueous humor production by destroying part of the ciliary body. Cyclocryotherapy has been commonly used since it was first described in 1950. Newer procedures, including transscleral cyclophotocoagulation with Nd:YAG, semiconductor diode, Krypton laser energy, are being evaluated as alternative cyclodestructive procedures for patients with intractable glaucoma after penetrating keratoplasty.

Cyclocryotherapy has been a principal mode of treatment of post-keratoplasty glaucoma. West et al. found that IOP was controlled in 15 of 23 eyes. They claim the one-time freeze technique is the safest and most-effective method. They felt that the freeze-thaw-refreeze technique represented too vigorous a therapy and resulted in significantly more complications. Binder et al. reported a 100% success rate in the control of glaucoma after penetrating keratoplasty using cyclocryotherapy. Of the 36 patients analyzed in the study, IOP was controlled in 30 with one procedure (23 patients with additional glaucoma medications), whereas the rest required multiple applications of cryotherapy. The corneal graft remained clear in 82% of the patients during the study period (2–50 months; average of 19.4 months).
months). These authors placed the glaucoma probe for 1 minute, 3 mm behind the limbus, three spots per quadrant, at a temperature of \(-50^\circ\) C. One patient each developed phthisis bulbi, vitreous hemorrhage, and macular edema. Based on their experience, Binder et al suggest that cryotherapy done early in the course of the post-keratoplasty glaucoma may prevent graft damage and salvage useful visual acuity. This is based on the fact that all eight transplants that failed had the cryotherapy 38 weeks after penetrating keratoplasty (average time) while most of the successes were treated 1 to 4 weeks after penetrating keratoplasty.

Kirkness,\(^{50}\) on the other hand, demonstrated poor success with cycloductive procedures after penetrating keratoplasty. In his study, 0/13 eyes maintained both a clear graft and normal IOP. In addition to loss of vision, graft failure, and considerable discomfort, cyclocryotherapy may result in phthisis bulbi, persistent inflammation, corneal decompensation, macular edema, and vitreous hemorrhage.\(^{24,27,31,37,59,69,87,102,110}\)

The parameters recommended by Bellows and Grant\(^{11}\) appear to be the most appropriate. The glaucoma cryoprobe is placed for 1 minute, 3 mm behind the corneoscleral limbus. Six burns are made with equidistant spots involving the inferior 180 degrees of the globe at a temperature of \(-60^\circ\) to \(-80^\circ\) C. The superior half of the globe is almost never treated. The treatment is repeated in exactly the same fashion when indicated.

Beckman and Sugar\(^{9}\) initiated Nd:YAG transscleral cyclophotocoagulation in glaucomatous human eyes in 1973. Recently, encouraging results have been reported\(^{24,37,50,102,110}\) in the treatment of post-keratoplasty glaucoma with use of noncontact Nd:YAG transscleral cyclophotocoagulation. Adequate control of IOP was obtained, on average, in 78% of the patients (64–85%). Twenty-two to fifty-six percent (average of 43.5%) of the patients, however, had significant decrease in the Snellen visual acuity, with 32.8% (range, 11–65%) developing graft failure. Persistent hypotony occurred in 8.6% of the patients. This complication occurred mostly in eyes with previous cyclocryotherapy or filtering procedure. Other complications associated with this procedure include anterior uveitis, epithelial defects, loss of vision, severe pain, phthisis bulbi, hyphema, hypopyon, intractable pain, sympathetic ophthalmia, scleral thinning and vitreous hemorrhage.\(^{24,27,31,37,50,69,87,102,110}\)

It is recommended that Nd:YAG (Microruptor 11, LASAG, Thun, Switzerland) be used in a maximally defocused position. Approximately 15 evenly spaced burns are placed 1–1.5 mm from the limbus for 180 degrees. The mean energy level recommended is 4.1–9.3 joules. Postoperative pain medication and topical steroids are indicated. Low energy settings are preferred in patients previously treated with cyclocryotherapy or filtering procedure to avoid hypotony. Repeated applications may be necessary before adequate control is achieved.

The advantages of this procedure are its simplicity, its noninvasive nature, and cost effectiveness, as compared to glaucoma drainage implant surgery. The recent reports of sympathetic ophthalmia after this procedure caution us to be extremely careful before using this technique routinely. Future studies will help to define the role of this procedure in the treatment of intractable glaucoma.

The semiconductor diode laser, with a wavelength of 810 nm, has lower scleral transmission than the Nd:YAG laser (1,064 nm) but greater absorption by melanin.\(^{94}\) Also, because semiconductor diode lasers have solid-state construction, they have the advantages of portability, durability, and smaller size, as compared with the Nd:YAG lasers. The recommended power setting with the diode laser is between 1,750 and 3,000 mW, with a 2-second exposure time. An initial power setting of 1,750 mW is increased or decreased by 250-mW increments until it is 250 mW below that producing an audible popping sound. In a recent prospective study, Yoon et al\(^{115}\) compared the surgical outcomes of Nd:YAG cyclophotocoagulation versus the semiconductor diode laser in the treatment of refractory glaucoma, with a mean follow-up of 10.4 months. While acknowledging the technological advantages of diode laser, such as portability, durability, smaller size, and less energy, they did not find significant differences in either IOP control or visual acuity change. Seventeen percent of patients in the YAG group versus 26% in the diode laser group had decreased vision. Four patients in the diode laser group lost light perception, and none in the YAG group did. Three patients in the diode laser group and one in the YAG group developed hyphema. Two other studies have documented 28–30% visual loss in the short term (10 months mean follow-up).\(^{18,112}\)

Bloom et al\(^{18}\) followed 210 eyes following cyclodiode treatment. Corneal decompensation was seen in two of the 21 eyes that had previously undergone penetrating keratoplasty. Overall success rate (IOP < 22 mm Hg) was 66% at a mean follow-up of 10 months. Spencer et al\(^{96}\) reported reduction of visual acuity by more than one Snellen line in 32% of the patients with preoperative vision better than 20/200 and in 24% of the patients with preoperative vision worse than 20/200. The mean follow-up in this study was 19 months, and a total of 58 eyes were included.

It would appear from the studies published that the incidence of graft failure and successful IOP control are similar in patients treated with glaucoma drainage implant surgery or cyclophotocoagulation.
There are no randomized studies to date comparing the two procedures in patients with post-keratoplasty glaucoma.

V. Summary

Uncontrolled IOP after penetrating keratoplasty is one of the leading causes of graft failure and visual loss in this patient population. It is mandatory that the IOP be monitored on a regular basis after corneal transplantation. Uncontrolled IOPs should be aggressively treated. Any patient with pre-existing glaucoma must be carefully evaluated prior to the corneal transplant.

Patients with uncontrolled IOPs or patients with borderline IOP control on two or more medications may be treated with either mitomycin-C trabeculectomy or glaucoma drainage implant surgery prior to or combined with the planned corneal transplant. This is suggested because multiple studies have documented preoperative glaucoma to be a high risk factor for the development of post-keratoplasty glaucoma96 and higher incidence of graft failure after glaucoma operations in eyes that have undergone penetrating keratoplasty.78

Post-keratoplasty glaucoma that does not respond to medications should be treated surgically. Mitomycin-C trabeculectomy appears to be the safest operation both in terms of IOP control and graft survival. Published results support a combined mitomycin-C trabeculectomy with corneal graft operation in patients with pre-existing glaucoma who are to receive a corneal transplant.5,10,22,24,30,63,78,102,103,110,113,116 Additional surgical procedures should be avoided, if possible, at the time of the trabeculectomy, as this is associated with higher incidence of trabeculectomy failure.113,116

Implantation of a glaucoma drainage device appears to be preferred over other surgical options for patients with post-keratoplasty glaucoma and extensive limbal conjunctival scarring, shallow anterior chamber, extensive peripheral anterior synchiae, and failed trabeculectomy. It appears to be superior to cyclodestructive procedures in cases that have failed mitomycin-C trabeculectomy or in those in which mitomycin-C trabeculectomy is contraindicated (i.e., contact lens-wearing patients). The graft failure rate following glaucoma drainage implant surgery and cyclodestructive procedures may be the same, but there appears to be a higher incidence of permanent visual loss and hypotony following cyclodestructive procedures (Table 3).

Cyclodestructive measures should be reserved for patients who have failed all other interventions. Apart from the higher incidence of permanent visual loss and hypotony, the reported incidence of sympathetic ophthalmia following cyclophotocoagulation is worrisome. In a retrospective study that compared the surgical outcomes of mitomycin-C trabeculectomy, glaucoma drainage implant surgery, and Nd:YAG cyclophotocoagulation in the management of intractable glaucoma after penetrating keratoplasty, Ayyala et al6 found no differences among the three procedures with respect to controlling IOP and graft failure. However, patients treated with Nd:YAG cyclophotocoagulation tended to have a higher incidence of graft failure, glaucoma failure, hypotony, and visual loss by more than one line, although this was not statistically significant. The study was limited by the small number of patients in each group. Randomized, prospective studies are needed to determine which of the currently available treatment options should be the treatment of choice in the post-keratoplasty glaucoma population. Research should be directed toward finding glaucoma drugs that are not toxic to the corneal epithelium. Corneal surgeons should be aware of glaucoma and treat it aggressively where indicated. With the development of safer glaucoma procedures and glaucoma drainage implants, early surgery may become the mainstay of treatment in this patient population.

VI. Method of Literature Search

The MEDLINE database was searched for the years 1966–2000, using the key words glaucoma, penetrating keratoplasty, trabeculectomy, glaucoma drainage devices, cyclocryotherapy, Nd:YAG cyclophotocoagulation, and diode laser cyclophotocoagulation. Several articles that were not found by our MEDLINE search were taken from the references from other articles. Inclusion or exclusion of articles was based on the relevance to the subject and the need to avoid redundancy. English abstracts of non-English articles were reviewed.

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Outline

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V. Summary

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