Glaucoma Escalation after Penetrating Keratoplasty

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Abstract

Purpose: Glaucoma following penetrating keratoplasty (PK) continues to be a serious problem that may ultimately become sight threatening. Knowledge of the risk factors for development of glaucoma following PK, such as preexisting glaucoma, pseudophakia, aphakia, and previous PK, can limit the occurrence and improve the outcome of the keratoplasty. The management of postkeratoplasty (Post-PK) glaucoma remains controversial with a wide range of treatment modalities available, including newer classes of drugs, laser therapy, filtering surgery with mitomycin C, and implantation of glaucoma drainage devices (GDDs), as well as various cycloablative treatment modalities, including cyclocryotherapy and cyclophotocoagulation (CPC) with noncontact and contact neodymium: yttrium-aluminum-garnet (Nd:YAG) laser, a semiconductor diode, and endoscopic cyclophotocoagulation (ECP).

Methods: A literature search was conducted on the Medline database using the search terms glaucoma, PK, trabeculectomy, GDDs, cyclocryotherapy, Nd:YAG CPC, diode laser CPC, and ECP for the 35-year period between 1975 and 2010. Several articles that were not found by Medline search were cited in the references of other articles. Articles were included because of their subject relevance or were excluded so as to avoid redundancy. Abstracts written in English of non-English-language articles were also reviewed.

Keywords: Glaucoma, Penetrating Keratoplasty, Postkeratoplasty Glaucoma, Trabeculectomy, Glaucoma Drainage Devices, Cyclophotocoagulation

Introduction

Glaucoma is the leading cause of irreversible blindness after penetrating keratoplasty (PK).\(^1\) In addition to inducing damage to the optic nerve, increased intraocular pressure (IOP) can compromise graft endothelium and lead to graft failure.\(^2\)

Prevalence

The recorded prevalence of postkeratoplasty (Post-PK) glaucoma varies greatly in the literature,\(^1-12\) with estimates from as low as 10\(^\%\)\(^7\) to as high as 34\(^\%\)\(^5\) (Table 1).

Table 1. Prevalence of post-penetrating keratoplasty glaucoma

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of eyes</th>
<th>Mean follow-up (Months)</th>
<th>Incidence of glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karesh et al(^9) (1983)</td>
<td>80</td>
<td>22</td>
<td>20</td>
</tr>
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<td>Foulks et al(^7) (1987)</td>
<td>502</td>
<td>36</td>
<td>18</td>
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<tr>
<td>Kirkness et al(^11) (1988)</td>
<td>305</td>
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<td>30</td>
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<tr>
<td>Simmons et al(^8) (1989)</td>
<td>229</td>
<td>21</td>
<td>34</td>
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<td>Kirkness et al(^37) (1992)</td>
<td>1122</td>
<td>NA</td>
<td>14</td>
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<td>Sekhar et al(^3) (1993)</td>
<td>190</td>
<td>14.5</td>
<td>27.4</td>
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<tr>
<td>Franca et al(^8) (2002)</td>
<td>228</td>
<td>17.14</td>
<td>21.5</td>
</tr>
<tr>
<td>Al-Mohaimeed et al(^40) (2007)</td>
<td>715</td>
<td>32.2</td>
<td>42.4</td>
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<tr>
<td>Karadag et al(^3) (2010)</td>
<td>749</td>
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<td>16.6</td>
</tr>
</tbody>
</table>

The presence or absence of preoperative glaucoma may significantly influence postoperative prevalence. Simmons and colleagues\(^5\) documented a 34\(^\%\) incidence of post-PK glaucoma in a series of 229 patients, 27\(^\%\) of whom had controlled preoperative glaucoma. Goldberg and associates\(^6\) noted that among 137 patients, 28\(^\%\) had preoperative glaucoma and 27\(^\%\) developed chronic pressure elevation. In comparison, Thoft et al\(^7\) reported post-PK glaucoma in only 10\(^\%\) of eyes without preoperative glaucoma. Polack\(^10\) noted that the prevalence of post-PK glaucoma varied according to the surgical indication for keratoplasty, with a 2\(^\%\) prevalence in eyes with Fuchs’ dystrophy, 20\(^\%\) in eyes with aphakia, and 25\(^\%\) in eyes with pseudophakia.

The wide variation in the reported prevalence of post-PK is related not only to different patient populations undergoing keratoplasty but also to the absence of a strict standardized definition for the term glaucoma escalation. For example, some studies include any eye in which topical antiglaucoma medications are required after PK to maintain a “safe” level of IOP, irrespective of whether or not there was preexisting glaucoma. Other studies include any documented IOP over 22 mmHg at any time during the postoperative period in the criteria for the diagnosis, including transient elevation of IOP that is caused by viscoelastics in the postoperative period or by a reversible corticosteroid-induced effect in the late postoperative period.

To encourage standardized reporting of this complication of post-PK, we prefer to define glaucoma escalation as either (1) new onset glaucoma in an eye in which it was not present preoperatively or (2) increased medication requirement or surgical intervention in eyes with a diagnosis of preoperative glaucoma. “Surgical” escalation refers to eyes in which surgical intervention is required, irrespective of the presence or absence of preexisting glaucoma, whereas “medical” escalation refers to eyes with increased medication requirements for IOP control.

Standardizing the criteria for establishing a diagnosis of surgical escalation can be carried out by simply including all eyes requiring surgical intervention after PK. However, standardizing the criteria for establishing a diagnosis of medical escalation is more difficult because the issue of sustainability of increased medication requirements and the target IOP for adequate control need to be addressed. In fact, a diagnosis of medical escalation requires that the eye be on an increased postoperative number of antiglaucoma medications either (1) on a sustained basis (≥3 consecutive postoperative clinic visits) or (2) at the time of the most recent postoperative visit. Most, but not all, cases of transient viscoelastic-induced elevation of IOP in the early postoperative period and reversible steroid-induced glaucoma in the late postoperative period would not be included under the present definition. Finally, in recognition that the treating surgeon always establishes the target IOP for adequate control based on individual circumstances (i.e., optic disc status and visual field changes), we prefer to use the therapeutic actions of the treating physician,
rather than arbitrarily defining a specific level of IOP (e.g., 22 mmHg), as criteria for adequate management.

For example, ophthalmologist A may determine that an eye with PK for keratoconus (KC) with an IOP of 27 mmHg in the early postoperative period, no previous history of glaucoma, and a healthy disc does not need treatment. In comparison, ophthalmologist B may determine that the same patient needs a topical glaucoma medication until the first postoperative visit, after which the glaucoma medication is discontinued. According to the older definitions, both patients would fit the diagnostic criteria for glaucoma (IOP>22 mmHg) or escalation (Requirement of 1 topical medication), whereas neither patient would be included under the current definition.

Later in the postoperative course, each of these patients once again develops increased IOP into the upper 20s while on topical corticosteroids. Ophthalmologist A may simply switch the patient to a glaucoma-sparing topical steroid and recheck the pressure in a week, whereas ophthalmologist B may switch topical steroid coverage but decide to “cover” the patient with a topical antiglaucoma medication on a short-term basis. Once again, both patients would meet previously published criteria for post-PK glaucoma, but neither would meet the current criteria.

As a final example, consider a case treated by ophthalmologist C in which a patient with prior glaucoma, visual field loss, and an average IOP of 13 mmHg on 1 topical medication before surgery has an average IOP of 19 mmHg on 1 topical medication after surgery. Because of visual field loss progression, an additional topical medication is administered, reducing the average IOP to 14 mmHg. Even though the recorded IOP values do not exceed 20 mmHg, this case meets the criteria of medical escalation based on the treating physician’s action to increase the number of topical medications administered so as to obtain a “safe” level of IOP, which has been defined by the action of adding a second medication to the treatment regimen. Conversely, ophthalmologist D chooses to treat a patient with prior glaucoma without visual field loss and an average IOP of 21 mmHg on 1 topical medication before surgery, with the same regimen after surgery, despite an average IOP of 23 mmHg. In many studies, this patient would be classified as having glaucoma escalation because of a sustained IOP of >22 mmHg, despite the use of glaucoma medications. However, this case does not fit the present definition based on the treating physician’s action. By not administering a second glaucoma medication, the treating physician indicated that adequate IOP control was being achieved with a single medication.

**Diagnosis**

In addition to issues associated with establishing a precise diagnosis of glaucoma escalation, practical problems arise in obtaining accurate IOP measurements after PK. Goldmann applanation tonometry is sometimes difficult to perform and is unreliable, specially if the graft is edematous and has high astigmatism. In the early postoperative period, IOP can be measured with the pneumatic applanation tonometer, Tono-Pen, or Mackay-Marg electronic applanation tonometer, and in the late postoperative period with the Goldmann applanation tonometer. To obtain an accurate reading with the Goldmann applanation tonometer, the prism should be rotated so that the red mark on the prism holder is set at the least curved meridian of the cornea (Along the negative axis). If high astigmatic error is present, the average of two applanation tonometry readings taken 90° apart should be used. The IOP measurement will be inaccurately low if corneal epithelial edema or stromal edema exists, or if a soft contact lens is present. It will be inaccurately high if corneal scarring is present. Digital palpation can be used to measure the IOP in cases with complete tarsorrhaphy.

Ultrasound biomicroscopy (UBM) can be used to assess the angle, specially in eyes with a failed graft where anterior segment details are not clearly visible. Dada et al conducted UBM research and concluded that secondary angle closure caused by anterior synechiae formation is one of the important causes of glaucoma after PK in eyes with opaque grafts. Optical coherence tomography (OCT) is similar to ultrasound in that it allows visualisation through opaque corneas. However, OCT has an advantage in that it
requires neither contact nor immersion for evaluating the depth of the anterior chamber angle and the causes of secondary angle closure.²³

**Risk factors and pathogenesis**

Risk factors contributing to glaucoma escalation can be classified as preoperative, intraoperative, or postoperative risk factors.²⁴⁻⁴⁶ Glaucoma escalation can occur at any time in the postoperative course after PK. Between 9% and 31% of cases have been reported as having an elevated IOP (Usually defined as IOP of >22 mmHg) in the early postoperative period,¹,⁹,¹⁰ whereas between 18% and 35% of cases have been reported in the late postoperative period.¹⁴,⁶,¹¹⁻¹⁵

The major preoperative risk factors are the surgical diagnosis for which the procedure is performed,²,⁵,⁶,¹⁰,³⁶⁻⁴⁰ and the presence of aphakia/pseudophakia²,³⁶,³⁷ or preexisting glaucoma.³⁸⁻⁴⁴ Eyes with aphakic or pseudophakic bullous keratopathy have a significantly increased risk of glaucoma escalation²,³⁶,³⁷ whereas those with KC, stromal dystrophies, or endothelial dystrophies are less likely to develop this complication.⁵,⁶,¹⁰,³⁹ Al-Mohaimeed and associates⁴⁰ found that the highest prevalence of post-PKP glaucoma was in eyes with tectonic PKP (Performed for ulceration and/or perforation [31.7%]), followed by failed previous graft (26.9%) and pseudophakic/aphakic bullous keratopathy (20.3%); eyes with stromal dystrophy (2.2%) and KC (2.6%) had the lowest prevalence. They also determined the prevalence of glaucoma escalation to be 34.9% in eyes with preexisting glaucoma compared with 11% of eyes without glaucoma.

Operative factors contributing to glaucoma escalation are usually related to factors that result in distortion of the anterior chamber angle and trabecular meshwork.²⁶⁻²⁸ Zimmerman et al²⁶ postulated that the trabecular meshwork needs both posterior support and anterior support, which are provided by the ciliary body-lens support system and Descemet’s membrane, respectively. The anterior support of the trabecular meshwork may be compromised after PKP if Descemet’s membrane is stretched.²⁶⁻²⁸ This is more likely to happen when tissue compression occurs secondary to the use of long suture bites, tight sutures, very large (≥9.0 mm) or small (<7.0 mm) trephination sizes, and same donor and recipient trephination sizes.²⁸,³³⁻³⁵ A prospective, randomized study comparing 13 eyes that underwent deep lamellar keratoplasty (DLKP), in which Descemet’s membrane was intact and not stretched, and an equal number of eyes that underwent PKP revealed that the IOP was higher in eyes that had undergone PKP (Mean IOP, 18.4 mmHg) than in those that had undergone DLKP (Mean IOP, 13.3 mmHg) at 12 months.⁴⁵ Posterior support of the trabecular meshwork can be compromised in aphakic or pseudophakic eyes.²⁶

The most common cause of an immediate postoperative IOP elevation is retained viscoelastics in the anterior chamber. Burke and colleagues³⁰ reported that when 62 keratoplasty patients were randomly assigned to receive either sodium hyaluronate (Healon) or chondroitin sulfate (VisCoat), pressures greater than 30 mmHg were measured in 42% to 55% of patients within the first 24 hours after surgery. No significant difference in pressure-raising potential was detected between the two viscoelastic agents. The most common causes of late postoperative IOP elevation are the development of anterior segment synchiae (With progressive angle closure) and prolonged use of topical corticosteroids in steroid-sensitive eyes.⁴⁻⁴⁹ Foule⁴ reported that 14% of cases of post-PKP glaucoma were because of progressive angle closure. Lass and Pavan-Langston,⁴⁶ proposed that
post-PKP glaucoma could be caused by the development of fine peripheral anterior synechiae, which may occur because of chronic and uncontrolled inflammation.

Moderate IOP elevation in response to topical corticosteroid use occurs in 20% to 30% of the general population, and significant elevation occurs in approximately 5% of patients. Some topical steroids, such as fluorometholone or rimexolone, are much less likely to cause IOP elevation but are less effective in controlling inflammation. Cyclosporine A may be used as a steroid-sparing agent; however, its efficacy as a single agent in controlling inflammation and suppressing rejection remains to be determined.

**Management**

Managing post-PKP glaucoma is imperative in preventing graft failure caused by endothelial damage and irreversible loss of vision caused by optic nerve damage. Glaucoma escalation is significantly associated with decreased graft survival, presumably because of increased endothelial attrition. Just as the prevalence of glaucoma escalation has been shown to vary significantly with the surgical indication for PKP, the likelihood of graft failure after the development of glaucoma escalation has been shown to vary significantly with the surgical indication for PKP. A wide variety of treatment options are available, including medications, laser therapy, filtering procedures, tube surgeries, and cyclodestructive procedures.

Preoperatively, a decision must be made about the need for a concomitant glaucoma surgical procedure, such as trabeculectomy with mitomycin C or implantation of a glaucoma drainage device (GDD). In cases of poorly controlled glaucoma, it is imperative to perform one of these procedures at the time of PKP. In well-controlled glaucoma, consideration should be given to performing one of these procedures if more than 2 topical medications are required for adequate IOP control, especially in older patients with coexisting ocular surface disease.

Intraoperatively, proper graft and donor size selection may reduce the risk of subsequent glaucoma escalation. If possible, the recipient trephination should be at least 7.0 mm and smaller than 9.0 mm in size, and the donor cornea should be at least 0.25 mm larger than the recipient trephination. If possible, peripheral anterior synechiae should be lysed. Long, excessively tight, superficial sutures should be avoided in favor of short, appropriately tight, deep sutures, which should provide edge-to-edge approximation of Descemet’s membrane. Most or all viscoelastic material should be removed from the anterior chamber at the conclusion of the procedure.

The initial treatment of elevated IOP in both the early and late postoperative periods is medical therapy. Currently available medications include beta-adrenergic blocking agents (e.g., timolol), adrenergic agents (e.g., dipivefrin), alpha-2-adrenergic agonists (e.g., brimonidine), miotics (e.g., pilocarpine), prostaglandin analogs (e.g., latanoprost), and topical (e.g., dorzolamide) and systemic carbonic anhydrase inhibitors (e.g., acetazolamide). Beta-blockers can cause impairment of quality and quantity of the mucous layer of the tear film, leading to dry eyes. Adrenergic agents should be used with caution in aphakic or pseudophakic patients because they can cause or aggravate cystoid macular edema. Carbonic anhydrase inhibitors adversely affect corneal endothelium pump function and should be used with caution in a graft with compromised endothelium. Prostaglandin analogs cause disruption of the blood-aqueous barrier and should be used with caution in eyes with chronic inflammation. Some studies have suggested that they may reactivate herpes simplex virus keratitis and that they should be avoided in these eyes. Miotic agents increase the risk of retinal detachment in aphakic patients and increase inflammation and risk of graft rejection by disrupting the blood-aqueous barrier. The chronic use of epinephrine can lead to a significant reduction in the endothelial cell count.

Adequate IOP control after PKP is often difficult to achieve with medical therapy alone. Argon laser trabeculoplasty (ALT) is recommended in eyes with a clear graft, open angles, and moderate elevation of IOP (25–30 mmHg) on glaucoma medications. IOP lowering can be achieved in approximately 80% of these types of cases, with an average IOP reduction of 9 mmHg. The effect tends...
to diminish with time, with only about a 50% success rate after 5 years. Research suggests that trabeculectomy is associated with fewer complications, especially graft failure, than other surgical options in the management of post-PKP glaucoma that has not adequately responded to medical therapy or ALT. Before the introduction of antifibrotic agents, the success rate of trabeculectomy after PKP was poor. Gilvarry and coworkers reported that a continuation of glaucoma medications was required in 91% of eyes that underwent trabeculectomy after PKP and that additional surgery was required in 48.6% of cases. The success rate of post-PKP trabeculectomy has improved since the introduction of antimetabolites, such as 5-fluorouracil (5-FU) and mitomycin C, which inhibit fibroblast proliferation and reduce the risk of graft failure. Heuer et al reported the prevalence of corneal epithelial toxicity to be as high as 50% with the use of 5-FU. Because mitomycin C is associated with lower corneal epithelial toxicity, most investigators prefer its use. Ishioka et al demonstrated that performing trabeculectomy after PKP achieved satisfactory IOP control in 73% of eyes when mitomycin C was used compared with only 25% when it was not used. Kirkness et al demonstrated that combined drainage surgery and keratoplasty offers a better management option for patients with coexisting glaucoma and corneal disease. The IOP dropped from a mean of 28.9 mm Hg preoperatively to 14 mm Hg at 12 months. There was a 5-year probability of 70% of maintaining a clear graft.

When filtration surgery is unlikely to succeed because of extensive conjunctival scarring, GDDs offer an effective means of controlling post-PKP glaucoma. Successful IOP control has been achieved in a high percentage of cases in all published series (mean, 84.8%; range, 71–96%). Unfortunately, a relatively high rate of graft failure is associated with the use of GDDs in comparison to trabeculectomy. Al-Torbak demonstrated that the cumulative probabilities of successful IOP control were 92% and 86% at 1 and 3 years, respectively, after combined PKP and Ahmed implantation but that graft survival rates at the same time intervals were 92% and 50%, respectively. Coleman et al reported a graft success rate of 62% at 20 months with simultaneous PKP and Ahmed implantation.

### Table 2. Graft failure rate with glaucoma drainage devices for post-penetrating keratoplasty glaucoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean follow-up (Months)</th>
<th>Graft failure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonnell</td>
<td>13</td>
<td>41</td>
</tr>
<tr>
<td>Coleman</td>
<td>20</td>
<td>38</td>
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<tr>
<td>Sherwood</td>
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<td>42</td>
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<td>Ayyala</td>
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<td>0</td>
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<tr>
<td>Alvarenga</td>
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<td>Beebe</td>
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<td>Kirkness</td>
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<td>Kwon</td>
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<td>45</td>
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<tr>
<td>Al-Torbak</td>
<td>36</td>
<td>50</td>
</tr>
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</table>

The implantation of a GDD after PKP is associated with a much higher risk of graft failure than when it is carried out before PKP or at the same time as PKP to achieve satisfactory IOP control. Rapuano et al reported a graft survival rate of 56% when a GDD was implanted after PKP, compared with 71% and 69% when implanted at the same time or before PKP, respectively. The most likely mechanism of graft failure in these cases is mechanical damage to the contact of the tube with the endothelium. Bates et al found that most corneal transplants undergo a 60% reduction in the central endothelial cell count during the first 2 years after implant surgery. McDonnell et al reported graft rejection in 5 of 17 patients undergoing double-plate Molteno implantation. Of these 5 patients, 4 had a GDD within the anterior chamber and 1 in the vitreous cavity. In one study, GDD implantation within the vitreous cavity showed a higher graft survival (83%) compared with the anterior chamber (48%) after 1 year.

When medical or surgical interventions fail to control post-PKP glaucoma, cyclodestructive procedures can be performed. Cycloablative procedures, which are very successful in treating refractory post-PKP glaucoma (With success rates as high as 80%), decrease aqueous humor
production by destroying part of the ciliary body. However, these procedures are associated with many complications, including hypotony, macular edema, corneal decompensation, persistent inflammation, and phthisis bulbi. Ayyala et al. reported success rates of 76.5% after trabeculectomy with mitomycin C, 80% after GDD implantation, and 63.6% after CPC. West et al. found that IOP was controlled in 15 of 23 eyes with post-keratoplasty glaucoma that had undergone cyclocryotherapy. Various cycloablative treatment modalities are available, including cyclocryotherapy and cyclophotocoagulation (CPC) with noncontact and contact neodymium: yttrium-aluminum-garnet (Nd:YAG) laser or a semiconductor diode. Compared with cyclocryotherapy, CPC is a more easily tolerated procedure and is associated with less discomfort and fewer complications.

Endoscopic cyclophotocoagulation (ECP) was introduced as an alternative to transscleral CPC for treating refractory glaucomas so as to minimise complications such as phthisis bulbi and hypotony by providing direct visualisation of the ciliary processes. If possible, cyclodestructive procedures should be performed only as a last resort after medical therapy, conventional filtration surgery, and GDD implantation have failed to achieve adequate IOP control.

**Conclusion**

Uncontrolled IOP after PKP may result in endothelial cell loss and graft failure or progressive optic nerve cupping with irreversible visual loss. It is important to utilize preventive measures such as proper surgical timing, meticulous attention to surgical maneuvers that minimize the risks of disturbing the anterior chamber angle and of causing pupillary block, and careful monitoring of the postoperative IOP, specially in response to topical corticosteroids. Any patient with preexisting glaucoma must be carefully evaluated before corneal transplantation. The management of glaucoma in PKP patients remains a clinical challenge. The initial treatment of elevated IOP in both the early and late postoperative periods is medical therapy. Surgical intervention is necessary for poorly controlled IOP after PKP when medical therapy has failed (i.e., inadequate control of IOP or development of unacceptable side effects). For eyes with clear grafts, open angles, and moderate elevation of IOP (25-30 mmHg), ALT is recommended before progressing to filtration surgery. Trabeculectomy (With antimetabolites) and procedures that utilize GDDs are both effective in controlling elevated IOP; however, a relatively high rate of graft failure is associated with GDD implantation in comparison to trabeculectomy. Cyclodestructive procedures may also be used, but they are associated with a high incidence of complications, including hypotony, chronic inflammation, choroidal and retinal detachment, maculopathy, sympathetic ophthalmia, and phthisis bulbi.

**References**