Post penetrating keratoplasty glaucoma – A review

P Gupta, A Sharma, P Ichhpujani
Department of Ophthalmology, Government Medical College and Hospital, Sector – 32, Chandigarh, India

Abstract

Glaucoma following penetrating keratoplasty remains a challenge for the treating ophthalmologist. Its frequent occurrence, difficult diagnosis and recalcitrant nature coupled with the propensity to cause irreversible visual loss makes it essential to identify the problem early and manage it effectively.

A careful pre-operative assessment along with appropriate intra-operative measures can help to reduce the chances of developing glaucoma in the post-operative period. Wherever indicated, prompt therapy should be initiated to lower intraocular pressure and salvage vision. Effective management of post-operative keratoplasty glaucoma remains an enigma with no single therapy being suited for all cases. One has to weigh the risks and benefits of the anti-glaucoma drugs on the corneal graft. However, it should be kept in mind that although there is a potential option for a graft exchange, vision lost from glaucomatous optic nerve damage cannot be recovered.

This review aims at highlighting the magnitude of the problem, assessing the risk factors that predispose to post-penetrating keratoplasty glaucoma along with the methodology for its diagnosis and management.

Key words: Glaucoma, intraocular pressure, keratoplasty

Introduction

Irvine and Kaufman (1969) were the first to describe an association between penetrating keratoplasty (PK) and glaucoma. Post-penetrating keratoplasty glaucoma (PPKG) is one of the most challenging problems because of its frequent occurrence, difficult diagnosis, recalcitrant nature, irreversible visual loss due to damage to optic nerve as well as the donor endothelium and management difficulty (Foulks GN, 1987).

Magnitude of the problem

Glaucoma is the leading cause of irreversible blindness following PK and has an incidence of 10 - 53 % (Greenlee & Kwon, 2008). Also, graft rejection following glaucoma is the second leading cause of graft failure (Arroyave et al 2001). Recent evidence also suggests that intraocular pressure (IOP) rise and subsequent glaucoma may also occur following lamellar keratoplasty procedures like DSEK and DALK (Nieuwendaal et al 2013; George et al 2010).

Prevalence of PPKG varies significantly with the presence or absence of preoperative glaucoma. In a study by Simmons et al (1989), in a series of 229 patients, 34 % prevalence of PPKG was reported, 27 % of whom had pre-operative controlled glaucoma. In another study,
Thoft and associates (1974) noted glaucoma in only 10% of their patients without preoperative glaucoma.

The criteria for defining PPKG vary among different studies leading to differences in the prevalence rate. Cases in which topical medications and/or surgery is used to maintain adequate pressure control have been included in some studies, whereas cases in which there has been an “escalation of glaucoma therapy” with either a need for more topical medications and/or surgery to maintain appropriate postoperative IOP control on eyes with pre-existing glaucoma have been included in others. Any documented IOP above 22 mm Hg at any time during the postoperative period including a transient rise caused by viscoelastics in the postoperative period or by a reversible steroid-induced effect in the late postoperative period have been included in the criteria for diagnosis in some studies.

This brief review will throw light on the major mechanisms of PPKG and the available management options.

**Risk Factors & Mechanisms**

The major risk factors leading to PPKG can be grouped into preoperative, intra-operative and postoperative factors. After PK, the IOP rise can occur at any time, with the incidence in the early postoperative reported to be 9% to 31% (Ayyala 2000; Sekhar et al 1993; Polack FM 1988) and between 18% to 35% in the late postoperative period (Kirkness & Moshegov 1988; Foulks GN 1987; Thoft et al 1974; Irvine & Kauffman 1969).

**Preoperative risk factors:**

The most important preoperative risk factors are the presence of pre-existing glaucoma, indication for which keratoplasty is being performed, and the lens status (aphakic, pseudophakic or phakic). Keratoconus, corneal stromal and endothelial dystrophies are associated with a lower risk of PPKG (Kirkness & Ficker 1992; Simmons et al 1989), whereas aphakic and pseudophakic bullous keratopathy, graft rejection, previous history of trauma and glaucoma, mesodermal dysgenesis and herpes simplex keratitis are considered as high risk factors (Wagoner et al 2003; Kirkness & Ficker 1992; Wilson & Kauffman 1990; Kirkness and Moshegov 1988).

Sihota and associates (1998) have shown adherent leucoma (whether following trauma or following a healed perforated corneal ulcer) to be significantly associated with PPKG. Aphakia and a history of anterior segment reconstruction and anterior vitrectomy also carried high risk of glaucoma in their series.

Karadog et al (2010) reported that traumatic corneal scar, graft thinning, graft abscess, corneal abscess, bullous keratopathy and graft rejection were all high-risk factors. They also concluded that eyes that had undergone previous anterior segment surgery or had a pre-existing inflammatory condition had a higher chance of developing glaucoma post-operatively than eyes without any pre-existing inflammation.

A change in the geometry of the anterior chamber angle following PK in aphakic patients has been argued as the cause of PPKG in this most common cause of PPKG, and it has been suggested by Olson and Kaufmann (1975) that with appropriate manipulation of the host and donor button sizes, this complication can be avoided. Using a donor button which is trephined and 0.5 mm larger than that used for the host bed has been shown to decrease the incidence of PPKG, especially when a 7.5 mm trephine is used (Zimmerman et al 1978). No significant alteration in outflow facility occurred in a phakic eye following corneal grafting, but in aphakes the outflow facility was reduced by an average of 37% when midstromal suturing was employed, and not when through and through suturing was used, as demonstrated using perfusion studies on cadaver eyes (Zimmerman et al 1978).
Does size of the graft matter?
In a retrospective series, Bourne et al (1982) found that oversized graft buttons had better “control” than same size buttons in eyes with no pre-existing glaucoma. Giving emphasis on the fact that it is the “excised” graft size and not the trephine size which is important, Olson also pointed out the protective role of larger grafts in a similar study by Perl et al (1981).

Intraoperative risk factors:
Important intra-operative adverse factors which can decrease the outflow facility following keratoplasty, as suggested by Olson and Kaufmann (1977) using a mathematical model, include tight suturing, larger trephine sizes (> 8 mm), long bites of individual sutures, increased peripheral corneal thickness and graft-host disparity (donor smaller than host) (Olson RJ 1978). Zimmerman (1978) gave the concept of trabecular collapse in aphakic eyes which was later on invoked by Olson and Kaufmann to support the evidence of increased risk of PPKG in these patients. It was postulated that the trabecular system requires posterior fixation which is normally associated with an intact lens-ciliary body system.

In aphakes the trabeculum relaxes, but when the angle is compressed following transplantation, the outflow gets compromised.
Retained viscoelastic material in the anterior chamber is the most common cause of IOP rise in the immediate post-operative period (Burke et al 1990).

Postoperative risk factors
Development of fine or broad based peripheral anterior synechiae (Figure 1) could lead to PPKG in the extended post-operative period (Lass & Pavan-Langston 1979). In combination with the above described ideas of Olson and Zimmerman, synechial formation can explain the cause of PPKG in many situations including PK performed in perforated corneal ulcers. In suppurative keratitis and perforated ulcers, there is a greater likelihood of significant angle damage either from development of peripheral anterior synechiae or from the severe intraocular inflammation. In a recent study using Ultrasound Biomicroscopy (UBM), Dada et al (2008) concluded that in eyes with opaque grafts, secondary angle closure caused by anterior synechiae formation is one of the important causes of glaucoma after PK. Iris suturing during keratoplasty limits synechial formation (Cohen et al 1982).

An association between topical steroid use and IOP elevation following keratoplasty has been widely reported. Steroids are often started in the post-operative period as prophylaxis against graft rejection and also to reduce the inflammation. Reported rises in IOP vary widely from in 2 % (Kirkness & Ficker 1992) to up to in 73 % (Erdurmus et al 2009) of cases. Manipulation of steroid therapy has been suggested for controlling pressure spikes (Thoft et al 1974), but it is not feasible in the majority of the cases. Other steroids, such as fluorometholone or rimexolone, cause less IOP elevation but also have decreased anti-inflammatory effects (Stewart & Kimbrough 1979). Efficacy of Cyclosporine A as a single agent for controlling inflammation and suppressing rejection remains to be determined as yet (Perry et al 1997).

Full thickness keratoplasty vs. lamellar keratoplasty
Over the past decade, corneal grafting trends suggest that there has been an increase in the frequency of lamellar corneal grafting, especially where healthy host endothelium is present. Since there is no disruption of Descemet’s membrane in DALK, there should be no distortion of the anterior chamber angle, which is thought to be a major mechanism leading to PPKG. Also, the stromal bed left behind the Descemet’s
membrane should theoretically be protective against drainage angle distortion. In a recent study by Musa et al, it has been suggested that the slight rise in IOP after DALK may be explained to some degree by the limitations of applanation tonometry. Since keratoconus is the most important indication for DALK, IOP is likely to be underestimated pre-operatively due to the thinner corneas. After DALK, corneas are relatively thick because of the retained pre-descemetic host stroma in addition to the full donor corneal thickness resulting in the potential for overestimation of IOP. Also, corneal rigidity changes after surgery, which has a greater effect on the accuracy of IOP measurements (Musa et al 2012).

Wandling and colleagues (2010) have shown that elimination of the use of corneal sutures with DLEK is not associated with better results with respect to either the prevalence of escalated glaucoma therapy or its poor prognostic implications as compared with PKP. Pre-existing glaucoma was the most significant risk factor associated with IOP rise in their study.

Maier et al (2013) conducted a study to look for IOP elevation post DSEK and the incidence of post-DSEK glaucoma. They reviewed 59 eyes of patients who underwent DSEK and found a 28.8 % incidence of IOP elevation following the procedure while the incidence of glaucoma was 11.9 %. The major risk factor for development of glaucoma was the use of corticosteroids post-operatively. However, in 3 of the 11 patients of steroid-induced glaucoma, a rise in the IOP was noted even after tapering of steroids and normalizing of IOP. The authors concluded that some other factors such as angle closure due to crowding of the angle, peripheral anterior synechiae or progression of a pre-existing glaucoma could also lead to an increase in IOP.

**Diagnosis**

Irvine (1969) drew attention to the problems encountered in the assessment of raised IOP in patients undergoing keratoplasty procedures. Severe astigmatism in the post-operative period, graft edema and thick and inaccurate fluoroscein meniscus or tonometer mires (especially when graft size is 7-7.5mm) make applanation tonometry unreliable. Falsely low readings would be obtained in case of corneal epithelial or stromal edema or if a soft contact lens is present. Corneal scarring leads to inaccurately high IOP values. Pneumatic applanation tonometer (West et al, 1972), Tono-Pen (Rootman et al, 1988), or Mackay-Marg electronic applanation tonometer (McMillan & Forster, 1975) can be used in the early postoperative period. Though the Mackay-Marg tonometer was recommended, it did not acquire widespread use because of the difficulty in interpretation of the readings. In the late postoperative period, IOP can be measured with Goldmann applanation tonometer (Erdurmus et al, 2009; Wandling et al, 2010). For accurate readings using Goldmann tonometer, the prisms 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). The average of two readings taken 90° apart should be used if a high astigmatic error is present (Holladay et al, 1983). In cases with complete tarsorrphy or where none of the aforementioned methods is possible, digital palpation can be used for IOP assessment (Rubifeld et al, 1998).

Salvetat et al (2011) compared the IOP readings in patients following penetrating keratoplasty with iCare tonometer and Goldmann applanation tonometry. They found that the IOP recordings were reproducible in normal subjects and in patients who underwent anterior lamellar therapeutic keratoplasty or DSAEK. The agreement between the two tonometers was poor with respects to cases who had undergone penetrating keratoplasty. They found that the iCare tonometer underestimated IOP as compared to GAT in these patients. The iCare tonometer, however, was less affected by corneal
hydration as compared to the Goldmann applanation tonometer. They found no correlation between the IOP measurements by the tonometers and central corneal thickness and attributed this to a change in corneal biomechanics.

Visual field recording is even more cumbersome. Significant astigmatism which keeps changing along with the aphakic status of most susceptible patients leads to faulty field recordings and difficulty in comparing fields done on different dates.

Disc assessment is difficult in these patients because of compromised graft clarity; hence, only gross changes which are not accurate for regular monitoring can be appreciated.

In eyes with a failed graft where anterior segment details are not clearly visible, and, hence, gonioscopy is not possible, UBM can be used for angle assessment (Lass & Pavan-Langston, 1979). Visualisation through opaque corneas can also be done using anterior segment optical coherence tomography (AS-OCT). As compared to UBM, AS-OCT requires no contact or immersion for evaluation of the depth of the anterior chamber angle and the causes of secondary angle closure (Memarzadeh et al, 2007).

Careful observation of IOP is recommended for patients after penetrating keratoplasty, with prompt treatment of IOP elevation when indicated. Early filtering surgery should be preferred if medical treatment is not sufficient. Despite anti-glaucoma therapy, good visual outcome can remain a chimera in spite of a clear graft. While there is a potential option for graft exchange, damage to the optic nerve from end-stage glaucoma can lead to irreversible visual loss (Huber et al, 2013).

PPKG is therefore extremely difficult to monitor and manage.

**Management**

As PPKG can be sight threatening, managing it is extremely important. Increased endothelial cell loss associated with a rise of the IOP can lead to decreased graft survival chances and ultimately graft rejection. Moreover, progressive optic nerve damage can cause irreversible loss of vision. Multiple treatment options including medications, laser therapy, filtering surgeries, glaucoma drainage devices and cyclodestructive procedures are available (Memarzadeh et al, 2007; Rubinfeld et al 1998; Figueiredo et al, 1996; Holladay et al, 1983).

In cases of uncontrolled pre-existing glaucoma, a decision must be made preoperatively, about the need for a combined glaucoma surgery, such as trabeculectomy with an antimetabolite (such as mitomycin C) (Figueiredo et al, 1996) or implantation of a glaucoma drainage device (GDD) (Al-Torbak A, 2003) along with penetrating keratoplasty (Insler et al, 1985). In elderly patients with coexisting ocular surface disorders, either of the above mentioned procedures should be performed if the glaucoma is well controlled on more than two topical drugs.

Intra-operative considerations include selection of proper graft and donor size; wherever possible, trephining the recipient cornea at least 7 mm and smaller than 9 mm in size and donor cornea at least 0.25 mm larger than the recipient (Foulks et al, 1979; Olson RJ, 1978); lysis of
peripheral anterior synechiae if possible; using short, adequately tight, deep sutures to provide edge-to-edge approximation of Descemet’s membrane and avoiding long, superficial, tight sutures (Zimmerman et al, 1978). At the completion of the surgery, most of the viscoelastic should be removed from the anterior chamber.

Medical management
Most patients who develop PKPG in the early or late post-operative period show good response to medical treatment. The oral carbonic anhydrase inhibitor Acetazolamide has been the mainstay of medical management since it is taken systemically and thereby avoids the risk of toxicity to the graft epithelium. Topical carbonic anhydrase inhibitors (e.g. Dorzolamide) are usually avoided in eyes with compromised endothelium as they interfere with the function of the endothelial pump and lead to graft failure. Beta blockers such as timolol maleate have become more popular these days, but pustate epitheliopathy in the graft epithelium has been noted following their use (Wilson et al 1980). Miotics such as pilocarpine can be used with caution, though they are less likely to be effective in eyes with extensive secondary angle closure. They can also cause allograft rejection by promoting a mild grade anterior segment inflammation and also increase the risk of retinal detachment in aphakes. Adrenergic agents such as Dipivefrin can lead to and aggravate cystoid macular edema, and therefore should be used with caution in aphakic or pseudophakic patients. Chronic use of epinephrine has been associated with significant reduction in endothelial cell count. Prostaglandin analogs (e.g. travoprost, latanoprost) can be used but are usually avoided in eyes with chronic inflammation as they disrupt the blood-aqueous barrier and promote inflammation. They may also reactivate herpes simplex virus keratitis and hence should not be used in such eyes.

Surgical management
Van Meter et al (1988) for the first time, described the use of laser trabeculoplasty as a management option in PPKG. In eyes with a clear graft, open angles and a moderately high pressures (25 - 30 mm Hg) on medical treatment, argon laser trabeculoplasty (ALT) has been suggested (Shingleton et al 1987; Zimmerman et al, 1978). An average IOP reduction of 9 mm Hg can be achieved in approximately 80 % of cases, though the effect diminishes with time and the success rate is only 50 % after five years (Nakakura et al, 2009; Wilson et al, 1980). It is a safe procedure as far as the graft endothelium is concerned and is useful early in the management of PPKG.

In cases non-responsive to either medical therapy or ALT, trabeculectomy is advised. Standard filtering surgeries, such as trabeculectomy alone, are often difficult due to extensive conjunctival scarring subsequent to multiple surgical procedures in addition to keratoplasty (especially in aphakes and pseudophakes). The presence of peripheral anterior synechiae extending up to the graft-host junction blocks any attempt to make a fistula. The success rate of trabeculectomy in the pre-antifibrotic agents era was poor (Figueiredo et al, 1996) and it was seen that 91 % of the eyes required continuation of anti-glaucoma therapy with about 50 % patients needing an additional procedure (Gilvary et al, 1989). With the introduction of antimetabolitic agents, such as 5-Fluorouracil (5 - FU) and Mitomycin C, which inhibit fibroblast proliferation, there has been an improvement in the success rate of trabeculectomy following PPKG (Ishioka et al, 2000; Chowers and Ticho 1999; Mattox, 1995; Heuer et al, 1986). As compared to 5 - FU, mitomycin C is associated with reduced risk of corneal epithelial toxicity and hence is preferred by most surgeons. In a study by Ishioka et al (2000), it has been demonstrated that mitomycin C use has been
associated with satisfactory IOP control in 73% of eyes as compared to only in 25% when it wasn’t used. In situations where there is extensive anterior segment disorganization and where trabeculectomy has failed once, repeated trabeculectomy may be tried, but this has rapidly diminishing success prospects. Sihota et al (2010) performed ab-externo cyclodialysis enhanced trabeculectomy in 45 eyes of patients with refractory glaucoma after penetrating keratoplasty. They found in a two-year follow-up that the IOP was well controlled in all but two patients post-surgery. There were also no associated incidences of graft failure following the procedure.

Molteno (1969) was the first to describe the use of silicone drainage tubing in the management of advanced glaucoma after successful animal experiments (Molteno, 1969). Schocket et al (1982) modified this technique and replaced the acrylic plate which is placed in the orbit with an inverted silicone gutter encircling the eye. GDDs offer an effective means for IOP control when filtering surgeries are less likely to be successful. Although all published data report a good success rate of glaucoma control in high percentage of cases (mean 84.8%, range 71-96%) (Alvarenga et al, 2004; Sherwood et al, 1993; Kirkness et al, 1988), GDDs are also associated with a relatively high rate of graft failure as compared to filtering surgeries. Almousa et al (2013) retrospectively analysed IOP control and corneal graft survival in 59 eyes that had PK who underwent Ahmed Glaucoma Valve (AGV) insertion. They found that 96% of the eyes had good IOP control at one year following surgery which fell to 83% at five years. Furthermore, a subsequent surgery after AGV implantation doubles the risk of failure of IOP control. Clear corneal grafts were seen in 47% cases after five years of follow-up. They showed that avoiding antimetabolites and having no complications in relation to AGV insertion can have a favorable prognosis for corneal graft survival. Beebe at al (1990) demonstrated that the use of molteno implant for treatment of PPKG was associated with a 51% risk of graft failure at a mean follow up of 25 months. The risk of graft failure also depends upon the time the GDD is implanted (Memarzadeh et al, 2007), with a higher rate when it is implanted before (69%) or at the same time (71%) of keratoplasty as compared to implantation later on (56%) (Rapuano et al 1995). Most corneal transplants have a 60% reduction in the central corneal endothelial count during the first two years after surgery as reported by Bates et al (1992). The tube touching the endothelium causing mechanical damage to the cells is the most likely mechanism of graft failure (Lim KS, 2003; Beebe et al, 1990).

Cyclodestruction has been used as the surgical procedure of choice in difficult and advanced cases when medical or surgical interventions fail to control the IOP. Cycloablation decreases aqueous humour production by destruction of ciliary body and has a success rate of around 80% in treating refractory glaucoma (Shah et al, 2001; Wong et al, 1997; West et al, 1973). Cyclocryotherapy and cyclophotocoagulation (CPC) with non-contact and contact Neodymium: Yttrium-Aluminium-Garnet (Nd:YAG) laser or a semiconductor diode are the various options available. A success rate of 63.6% after CPC, 76.5% after trabeculectomy with mitomycin C and 80% after GDD implantation has been documented by Ayyala et al (1998). Cyclodestructive procedures are associated with complications, such as hypotony, persistent inflammation, macular edema, corneal decompensation, choroidal and retinal detachment, sympathetic ophthalmia and sometimes pthisis bulbi (Lim KS, 2003; Threlkeld & Shields, 1995; Assia et al, 1991). To minimise these complications, endoscopic cyclophotocoaguation (ECP) was introduced as an alternative to transscleral CPC. ECP provides direct visualisation of the ciliary processes and
hence reduces chances of complications (Hollander & Lin, 2003). Cyclodestructive procedures should be resorted to only as the last option when medical and surgical therapy have failed in controlling the IOP.

**Conclusion**

Post-penetrating keratoplasty glaucoma remains one of the leading causes of graft failure and visual loss. Knowledge of the risk factors such as pre-existing glaucoma, pseudophakia, aphakia and previous PK may help to limit the occurrence of glaucoma and to increase the chances of success of PK. Timely diagnosis of PPKG along with aggressive and timely management remains the cornerstone for preserving optimal graft clarity and visual function following keratoplasty procedures.

**References**


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