Post penetrating keratoplasty glaucoma: Cumulative effect of quantifiable risk factors

Ashok Sharma, Suresh Sharma, Surinder S Pandav, Kanwar Mohan

Purpose: To ascertain the incidence, identify risk factors and calculate cumulative effect of risk factors in patients developing glaucoma following optical penetrating keratoplasty. Materials and Methods: We carried out retrospective analysis of 445 patients, those underwent optical PK and had a minimum follow up of 6 m. Data on post-operative intra-ocular pressure (IOP) recorded at 3, 6, 9, 12 and 18 m or more was analyzed. Various risk factors including age, sex, indications for penetrating keratoplasty, pre-existing glaucoma and type of surgical procedures performed were analyzed by using univariate analysis and logistic regression technique. Results: Ninety (21%) of eyes developed post-PK glaucoma. On applying logistic regression, age, sex, indication of surgery, pre-existing glaucoma were found to be significant risk factors for the development of post-PK glaucoma (P < 0.05). Using logistic regression equation the cumulative risk of developing post-PK glaucoma in an individual patient can be calculated. Conclusions: Male patients, aged more than 40 years, having opaque grafts as an indication and with pre-existing glaucoma were found to be higher risk of developing post-PK glaucoma. Patients at higher cumulative risk for development of post-PK glaucoma may be closely monitored during follow-up.

Key words: Glaucoma, intraocular pressure, penetrating keratoplasty, post-PK glaucoma

The introduction of new microsurgical techniques, availability of good quality donor corneas and adequate management of post keratoplasty astigmatism has greatly enhanced the visual outcome of corneal transplant surgery. Allograft rejection, ocular surface disease, recurrent herpes simplex keratitis and infective keratitis may compromise visual results in high-risk patients. In addition, post penetrating keratoplasty (PK) glaucoma may cause an irreversible damage to the optic nerve. An accelerated chronic endothelial cell loss following PK in glaucoma eyes may result in graft failure. The complexity of post-PK glaucoma lies in the inherent difficulty in detecting, monitoring and treating this often-silent problem.

Post-PK glaucoma refers to an elevation of intraocular pressure (IOP) to greater than 21 mm of Hg with or without associated visual field loss or optic nerve changes. IOP rise following penetrating keratoplasty has been reported as a biphasic phenomenon. Following PK immediate rise within days to few weeks has been reported in 9 to 31% cases. In most cases, the acute elevation of IOP is transient and returns to normal levels within one to two weeks of the treatment. However, it is the persistent rise of IOP that causes a major concern. In the literature, 18 to 42% incidence of late onset post-PK glaucoma has been reported. In most studies aphakia, preoperative glaucoma, repeat grafts, combined cataract extraction with PK and concomitant anterior vitrectomy have been identified as the risk factors for development of glaucoma. It is not certain whether the recent introduction of improved microsurgical techniques, effective management of vitreous loss and control of pre-existing glaucoma have altered the prevalence of post-PK glaucoma. Medical therapy remains the key in the management of post-PK glaucoma. However, trabeculectomy with or without mitomycin C, glaucoma valve and cyclophotocoagulation procedures have been advocated for medically uncontrolled glaucoma.

Reports on epidemiological data on post-PK glaucoma from developing countries are limited. The cumulative effect of the various predisposing factors on development of post PK glaucoma in an individual patient has not been evaluated. The purpose of our study is to investigate the incidence, time of onset, identification of risk factors, evaluation their cumulative effect and report on treatment outcome of late onset post-PK glaucoma.

Materials and Methods

After obtaining approval from the Cornea Centre Institution Review Board, a retrospective, non comparative case series was conducted with adherence to the Declaration of Helsinki. Consecutive patients who underwent optical PK in the Cornea Centre from January 2002 to March 2011 were included in this retrospective study. Patients having IOP greater than 21 mmHg on two different visits after surgery, with or without associated disc and/or visual field changes, were diagnosed to have post-PK glaucoma in the study. Patients who had raised IOP in the immediate postoperative period were labeled as post-PK glaucoma only if the rise in IOP persisted beyond three weeks after the surgery. Patients with IOP controlled 21 mmHg or lower with topical medication before surgery (pre-existing glaucoma), but IOP was greater than 21 mmHg after PK and needed further intervention (oral acetazolamide or surgical procedure for glaucoma)
were also labeled as post PK glaucoma. A total 468 patients were identified. Fourteen patients with incomplete records or post-operative follow up of less than 6 m were excluded. Nine patients who had undergone trabeculectomy for glaucoma prior to optical PK were also excluded. Four hundred and forty five eyes (445 patients) were included in this retrospective study.

Data on demographic profiles of the patients, indications for surgery, type of surgical procedure and additional surgical procedures such as iridoplasty, goniosynechiolysis, concomitant cataract extraction, intraocular lens (IOL) implantation, IOL exchange and anterior vitrectomy was retrieved from the corneal transplant data bank. Information on age, sex, pre and post operative IOP and details of post operative management was also extracted. Patients in our Cornea Centre undergo a complete ophthalmic examination including slit lamp biomicroscopy, IOP recording, retinal evaluation and ultrasonography before considering PK.

We record the corneal lesions using standard color-coded documentation and slit lamp photographs before undertaking optical PK. Patients having concomitant corneal pathology and cataract were considered for a combined PK, extra capsular cataract extraction and PCIOL implantation (corneal triple procedure). Patients suffering from pseudophakic bullous keratopathy (PBK) underwent PK, goniosynechiolysis, iridoplasty, anterior vitrectomy, and IOL exchange. These patients were grouped into PK with concomitant anterior segment reconstruction. We implanted posterior chamber IOLs in eyes with adequate posterior capsular support and scleral fixed IOLs in eyes with absent posterior capsular support.

Patients having aphakic bullous keratopathy (ABK) underwent similar procedure with either secondary posterior chamber IOL or scleral fixed IOL implantation. Patients having pre-existing glaucoma were controlled (IOP < 21 mmHg) prior to PK. Those requiring 3 or more topical anti glaucoma drugs and/or tab. acetazolamide were subjected to glaucoma filtration surgery. On each follow up visit the best corrected visual acuity, IOP, keratometry, refraction, ocular surface problems and graft rejection were recorded in the cornea clinic database.

A single surgeon (AS) had performed all PK procedures. Donor corneas were preserved in MK medium and used within 72h of preservation time. We used disposable corneal trephines (7.5 mm) to trephine host cornea and endothelial punch (8.0 mm) to obtain donor button. Sodium Hyaluronate 0.1% (Healon, Pharmacia and Upjohn A, B, Uppasala, Sweden) was used to protect corneal endothelium. A combination of 8 interrupted sutures and a 16 bite continuous suture (10 '0' monofilament nylon, Alcon Surgical) was used for wound closure. Sixteen interrupted sutures were used to secure donor buttons in vascularised corneas. At the end of the surgery sodium hyaluronate was irrigated out of the anterior chamber. A subconjunctival injection containing gentamicin (20 mg) and dexamethasone (4 mg) was given at the completion of the surgery. A sterile pad and patch was applied.

All the patients were put on topical prednisolone acetate (0.1%) six times, gatifloxacin (0.3%) four times and cyclopentolate hydrochloride (1%) three times a day in the post operative periods. Tab. prednisolone (1 mg/kg body weight) was prescribed postoperatively in patients having a high risk of graft rejection due to deep vascularization and previous opaque grafts. Patients having severe post operative uveitis were also given oral prednisolone. Patients having IOP more than 21 mmHg within 3 weeks were given timolol maleate (0.5%) eye drops twice a day. We used timolol maleate (0.5%), as the first line drug; topical acetazolamide or topical brimonidine purite (0.15%) and latanoprost (0.005%) as second line of drugs. Patients in whom IOP could not be controlled with topical medication were given tab. acetazolamide 250 mg every 8 hours. We monitored patients corneal epithelial healing, post operative uveitis and IOP during the early post operative period. Later we monitored these patients for IOP rise, graft rejection, infective keratitis, post PK astigmatism and cystoid macular edema.

Post operative IOP was recorded using Goldman applanation tonometer once corneal epithelial defect has healed during first week, at weekly intervals for 3 weeks, every month for three month and every three months thereafter. Visual fields and gonioscopy were performed whenever needed or possible. Optic disc evaluation was done with the 90 D lens using slit lamp biomicroscopy. Details of IOP lowering drugs and surgical management when needed were also recorded.

Data analysis

Univariate and multivariate analyses were performed using the IBM SPSS package (Version 20.0) to identify potential risk factors and investigate their association with post-PK glaucoma. In order to quantify risk of various factors, the multiple logistic regression analysis was applied and a P value of 0.05 or less was considered significant. Using forward maximum likelihood method, we also derived an equation to predict the cumulative effect of risk factors on development of post PK glaucoma in an individual patient. The following multiple logistic regression model in its general form was applied to predict risk of post-PK glaucoma.

\[ z = \beta_0 + \beta_1 V_1 + \cdots + \beta_k V_k \]  

is an index representing combination of k risk factors in terms of V's.

All the five risk factors which were significant in univariate analysis [Table 1], viz. age (V1), Sex (V2), indications of surgery (V3), pre-existing glaucoma (V4) and type of surgery (V5) were included into the logistic model. We observed independent variable V1, V2, V3, V4, and V5 on a sample of 445 eyes, for which we also determined post PK glaucoma status, as either “1” if with post-PK glaucoma or “0” if without post PK glaucoma. In logistic regression model, we used this information to quantify the effect of various risk factors for development of post PK glaucoma in an individual. On applying the logistic model to our data, only four factors (excluding V5) were significant and the following equation was obtained:

\[ Z = -2.595 + 1.33*V_1 - 0.760*V_2 - 0.251*V_3 + 4.670*V_4 \]  

The value of Z can be computed after substituting the values of V1, V2, V3 and V4 in equation (2), and then the predicted risk can be obtained from equation (1).

Results

Four hundred and forty five eyes having undergone optical PK satisfied the inclusion criteria in this study. Three hundred and three (68.1%) were male and 142 (31.9%) were female. The mean age of the patients was 56.5 (range 14 to 84) years. The indications for PK included aphakic or pseudophakic bullous
keratopathy in 129 (29%) eyes, corneal opacity in 126 (28.3%) eyes, adherent leukoma in 72 (16.2%) eyes, previous opaque graft in 61 (13.7%) eyes and corneal dystrophy 57 (12.8%) eyes. Forty four (9.9%) eyes had pre-existing glaucoma and 401 (90.1%) eyes did not have pre-existing glaucoma.

Considering the type of surgery, of the 304 eyes those underwent PK alone 63 (20.72%), of the 92 eyes those underwent cornea triple 1 (11.96%) and of the 49 eyes those underwent concomitant anterior segment reconstruction 16 (32.65%) developed post PK glaucoma ($P = 0.013$) [Table 1].

The time interval between PK and detection of raised IOP for the first time is represented in the bar diagram [Fig. 2]. The mean time interval for the development post PK glaucoma was 5.7 (range 3 to 38) [Fig. 3]. Of the 90 eyes, 87 (97%) developed post PK glaucoma within 12m of optical PK.

### Table 1: Univariate analysis of risk factors and odds ratio for post penetrating glaucoma

| Risk factors and codes | Total | Controls (%) | Cases (%) | Chi-square ($P$ value) | Odds ratio $+$ (C.I) |
|------------------------|-------|--------------|-----------|------------------------|---------------------|
| Age ($V1 \leq 40$ ($V1=1$) | 132 | 114 (86.4) | 18 (13.6) | 5.049 (0.025) | 1.89 (1.08-3.32) |
| Age ($V1 >40$ ($V1=2$) | 313 | 241 (77.02) | 72 (23.01) | 4.873 (0.027) | 0.56 (0.32-0.94) |
| Sex ($V2$) Male ($V2=1$) | 303 | 233 (76.90) | 70 (23.10) | 0.17 (0.02-1.34) | Reference category |
| Sex ($V2$) Female ($V2=2$) | 142 | 122 (85.92) | 20 (14.08) | 3.54 (1.74-7.20) | Reference category |
| Indications for surgery ($V3$) | | | | | |
| Adherent leukoma ($V3=1$) | 72 | 53 (73.61) | 19 (26.39) | 38.057 (0.0001) | 3.41 (1.54-7.53) |
| Corneal destrophy ($V3=2$) | 57 | 56 (98.25) | 1 (1.75) | Reference category |
| ABK/PBK* ($V3=3$) | 129 | 94 (72.87) | 35 (27.13) | 3.45 (1.74-7.20) | Reference category |
| Opaque graft ($V3=4$) | 61 | 38 (60.53) | 23 (39.47) | 5.75 (2.61-12.65) | Reference category |
| Corneal opacity ($V3=5$) | 126 | 114 (90.48) | 12 (9.52) | Reference category |
| Pre-existing glaucoma ($V4$) | | | | | |
| Absent ($V4=1$) | 401 | 351 (87.53) | 50 (12.47) | 151.20 (0.0001) | 70.2 (24.09-204.59) |
| Present ($V4=2$) | 44 | 4 (9.09) | 40 (99.91) | Reference category |
| Type of surgery ($V5$) | | | | | |
| PK** alone ($V5=1$) | 304 | 241 (79.28) | 63 (20.72) | 8.636 (0.013) | Reference category |
| Corneal triple ($V5=2$) | 92 | 81 (88.04) | 11 (11.96) | 0.52 (0.26-1.03) | Reference category |
| PK+A S R*** ($V5=3$) | 49 | 33 (67.35) | 16 (32.65) | 1.86 (0.96-3.58) | Reference category |

$+:\text{Computed using multiple logistic regression,} ^*:\text{ABK/PBK: Aphakic bullous keratopathy/pseudophakic bullous keratopathy,} ^{**}\text{PK: Penetrating keratoplasty,} ^{***}\text{A S R: Anterior segment reconstruction}$

---

**Figure 1:** Survival curve showing percentage of eyes without post-PK glaucoma

**Figure 2:** Distribution of eyes with post-PK glaucoma in relation to time intervals between PK and onset of glaucoma
Univariate analysis revealed that all the five variables including age (V1), sex (V2), indications of surgery (V3), pre-existing glaucoma (V4) and type of surgery (V5) as significant risk factors for development of post-PK glaucoma [Table 1]. All these five significant risk factors were included into the logistic model. However, on applying the logistic model to our data (445 eyes), only four factors including age (V1), sex (V2), indications of surgery (V3) and pre-existing glaucoma (V4) were found to be significant. Of various indications, patients with opaque graft have nearly 6 times, ABK/PBK and adherent leukoma approximately three and half times more risk of developing post-PK glaucoma compared to those with corneal opacities (Odds ratio, Table 1). Patients with corneal dystrophy have approximately 6 times less risk of developing post-PK glaucoma compared to those with corneal opacities (Odds ratio, Table 1). Those patients who underwent PK with concomitant anterior segment reconstruction have almost twice risk compared to those who underwent PK alone developing post-PK glaucoma compared to those with corneal opacities (Odds ratio, Table 1). In addition one may obtain, the predicted cumulative risk of an individual from equation (1), after substituting the value of Z from equation (2). For example, a 48 years old (V1 = 2), female (V2 = 2), patient has an opaque graft (V3 = 3), without any history of pre-existing glaucoma (V4 = 1) and undergoes PK, has a predicted cumulative risk of 9% for the development of post-PK glaucoma. The same patient in presence of pre-existing glaucoma (V4 = 2) would have 92% predicted cumulative risk of developing post-PK glaucoma.

The classification table of multiple logistic regression shows that individual risk can be predicted with 88% accuracy using this model. We further plotted receiver operating characteristic (ROC) curve. ROC is based on the probabilities predicted by the model (1), as shown in Fig. 4. The sensitivity of this ROC is about 50% at 90% of specificity.

Post-PK glaucoma was managed medically in 57 (63.33%) eyes, with trabeculectomy in 21 (24.33%) eyes, glaucoma filtering surgery with Ahmed Glaucoma Valve in 8 (8.89%) and with cyclodestructive procedures in 4 (4.45%) eyes [Figs. 5 and 6].

**Discussion**

The prevalence of post-PK glaucoma in our study (21%) is comparable to that reported in the literature.[3,4,8-11] Using multiple logistic regression analysis, we derived an equation to obtain the predicted risk of developing post PK glaucoma in an individual patient. As mentioned in the example, a patient with some specified set of values of age, sex, opaque graft...
and without history of pre-existing glaucoma undergoes PK, has a predicted cumulative risk of 9% for the development of post-PK glaucoma. The same patient in presence of pre-existing glaucoma would have 92% predicted cumulative risk of developing post-PK glaucoma.

In most of the studies, univariate analysis has been used to elucidate various risk factors affecting development of post PK glaucoma. Simmons et al.,[12] have also reported a four-fold increase in the prevalence of post-PK glaucoma in patients with pre-existing glaucoma in comparison to those without pre-existing glaucoma. Several authors have reported aphakic/pseudophakic corneal edema,[3,5,12] corneal triple procedure,[1,2] and concomitant anterior vitrectomy[5,19] as risk factors for developing post PK glaucoma. We also found association of aphakic/pseudophakic corneal edema and pre-existing glaucoma with higher risk of post-PK glaucoma. We found that anterior segment reconstruction that encompasses penetrating keratoplasty, anterior vitrectomy, IOL exchange, iridoplasty and goniosynechiolysis had significant association with higher risk of post-PK glaucoma on univariate analysis. However type of surgery did not show any association with post-PK glaucoma on multiple logistic regression analysis. As reported by other authors,[8,20] patients with keratoconus and corneal dystrophies showed a significantly lower risk of post-PK glaucoma (1.75%).

Several authors have demonstrated biphasic rise of IOP following keratoplasty.[3-6] Rise in IOP immediately after PK has been reported in 9 to 31% of patients.[5,6,20] In this study only those patients who had persistent rise of IOP after three weeks of keratoplasty were included. In the recent reports term glaucoma has used more precisely to define secondary glaucomas. The presence of glaucomatous optic neuropathy or visual fields in addition to raised IOP have been considered as definition of post-PK glaucoma. However, in this study, patients having IOP greater than 21 mmHg on two different visits after surgery, with or without associated disc and/or visual field changes, were diagnosed to have post-PK glaucoma. The use of term post-PK IOP elevation has been suggested. The mean period of 5.7 m for the onset of glaucoma following keratoplasty is similar to six m reported in the literature.[12] Majority of the patients (97%) developed glaucoma within 12 m following PK. Two of our patients developed raised IOP at 30 and 38 m following PK. It is difficult to speculate on the exact cause of raised IOP in these cases. Both these patients had iris-supported ACIOLs which were removed and replaced by PCIOls. Low grade intraocular inflammation due to iris-supported ACIOLs may have compromised outflow facility leading to raised IOP. Since the other eye of these patients was normal, possibility of primary glaucoma is unlikely. These observations indicate the necessity of long term monitoring of IOP following PK.

Management of post-PK glaucoma is crucial as high IOP is detrimental to both optic nerve fibers and endothelial cells of the corneal graft. Medical therapy using topical timolol maleate (0.5%), brimonidine purite (0.15%), latanoprost (0.005%) and topical acetazolamide (2%) remains the first option. Oral carbonic anhydrase inhibitors may be subsequently added if needed. Shekhar et al.,[11] were able to control post-PK glaucoma with medical treatment in 74% patients, where as 26% required surgical intervention. In our study nearly two third of patients responded to medical treatment where as one third of patients required surgery. Twenty one (23.33%) eyes underwent trabeculectomy, 8 (8.89%) eyes filtering surgery with Ahmed Glaucoma Valve and four eyes (4.45%) eyes needed cyclophotocoagulation. Trabeculectomy with mitomycin has been reported to safe and effective in controlling post-PK glaucoma.[15,16] Trabeculectomy with mitomycin C, glaucoma drainage devices and Nd: YAG cyclophotocoagulation have been found equally effective in controlling IOP, although cyclophotocoagulation was associated with increased incidence of graft failure and hypotony. Recently, filtering surgery with Ahmed Glaucoma Valve has been reported safe and effective surgical treatment of post-PK glaucoma.[14]

To our knowledge there is no study in the literature quantifying the cumulative effect of various risk factors. We used an equation based on multiple logistic regression model to quantify the cumulative effect of various risk factors in an individual patient with 88% accuracy. The validity of the equation in predicting the development of post-PK glaucoma may be evaluated in a prospective study on patients undergoing optical PK.

Acknowledgment

The authors thank Dr Vandana Saroha, Consultant, Eye-q superspeciality hospital, Udaipur, Rajasthan and Dr Anand Vinekar, Consultant, Narayana Nethralaya, Bangalore, Karnataka for valuable contribution in preparation of the article.

References

1. Reinhard T, Bohringer D, Sundmacher R. Accelerated chronic endothelial cell loss after penetrating keratoplasty in glaucoma eyes. J Glaucoma 2001;10:46-51.
2. O’Day DG. Glaucoma after Penetrating keratoplasty. In: Krachmer J, Mannis M, Holland E, editors. Cornea. St. Louis: CV Mosby; 1997. p. 1719-30.
3. Foulks GN. Glaucoma associated with penetrating keratoplasty. Ophthalmology 1987;94:871-4.
4. Karesh JW, Nirankari VS. Factors associated with glaucoma after penetrating keratoplasty. Am J Ophthalmol 1983;96:160-4.
5. Kirkness CM, Ficker LA. Risk factors for the development of postkeratoplasty glaucoma. Cornea 1992;11:427-2.
6. Chien AM, Schimidt CM, Cohen EJ, Rajpal RK, Spener LT, Rapuano CJ, et al. Glaucoma in the immediate postoperative period following penetrating keratoplasty. Am J Ophthalmol 1993;115:711-4.
7. Wood TO, West C, Kaufman HE. Control of intraocular pressure in penetrating keratoplasty. Am J Ophthalmol 1972;74:724-8.
8. Franca ET, Arcieri ES, Arcieri RS, Rocha FJ. A study of glaucoma after penetrating keratoplasty. Cornea 2002;21:284-8.
9. Polack FM. Keratoplasty in aphakic eyes with corneal edema: results in 100 cases with 10 year follow up. Ophthalmic Surg 1988;11:701-7.
10. Goldberg DB, Schanzlin DJ, Brown SI. Incidence of increased intraocular pressure after keratoplasty. Am J Ophthalmol 1981;92:372-7.
11. Shekhar GC, Vyas P, Nagarajan R, Mandal AK, Gupta S. Post penetrating keratoplasty glaucoma Indian J Ophthalmol 1995;41:181-4.
12. Olson RJ, Kaufman HE. Prognostic factors of intraocular pressure after aphakic keratoplasty. Am J Ophthalmol 1978;86:510-5.
13. Simmons RB, Stern RA, Teekhasaenee C, Kenyon KR. Elevated intraocular pressure following penetrating keratoplasty. Trans Am Ophthalmol Soc 1989;87:79-1.
14. Panda A, Prakash VJ, Dada T, Gupta AK, Khokhar S, Vanathi M.
Ahmed glaucoma valve in post-penetrating-keratoplasty glaucoma: A critically evaluated prospective clinical study. Indian J Ophthalmol 2011;59:185-9.

15. Sharma A, Kumar S, Ram J, Gupta A. Trabeculectomy with mitomycin C for postkeratoplasty glaucoma: A preliminary study. Ophthalmic Surg Lasers 1997;28:891-5.

16. Ishioka M, Shimazaki J, Yamagami J, Fujushima H, Shimmura S, Tsubota K. Trabeculectomy with mitomycin C for post-keratoplasty glaucoma. Br J Ophthalmol 2000;84:714-7.

17. Hollander DA, Lin SC. Delayed therapeutic success with endoscopic cyclo-photocoagulation in treating refractory post-penetrating keratoplasty glaucoma. Br J Ophthalmol 2003;87:792-3.

18. Ayyala RS, Pieroth L, Vinals AF, Goldstein MH, Schuman JS, Netland PA, et al. Comparison of mitomycin C trabeculectomy, glaucoma drainage device implantation, and laser neodymium: YAG cyclophotocoagulation in the management of intractable glaucoma after penetrating keratoplasty. Ophthalmology 1998;105:1550-6.

19. Kleinbaum DG. Logistic Regression, Statistics in the Health Sciences. Springer-Verlag; 1994. p. 4-28.

20. Sihota R, Sharma N, Panda A, Aggarwal HC, Singh R. Post penetrating keratoplasty glaucoma: Risk factors, management and visual outcome. Aust NZ J Ophthalmol 1998;26:305-9.

21. Irvine RA, Kaufman HE. Intraocular pressure following penetrating keratoplasty. Am J Ophthalmol 1969;68:835-44.

Cite this article as: Sharma A, Sharma S, Pandav SS, Mohan K. Post penetrating keratoplasty glaucoma: Cumulative effect of quantifiable risk factors. Indian J Ophthalmol 2014;62:590-5.

Source of Support: Nil. Conflict of Interest: None declared.