Glaucoma Associated with Penetrating Keratoplasty

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ABSTRACT **Objective :** To study the incidence and risk factors associated with the development of glaucoma after penetrating keratoplasty.

Materials and Methods : A retrospective study of 190 patients who underwent penetrating keratoplasty from July 1997 to June 2002 at the Department of Ophthalmology, Ramathibodi Hospital, Bangkok, Thailand.

Results : One hundred ninety patients who underwent 231 penetrating keratoplasties were enrolled. The follow-up period ranged from 12 to 60 months (27.5 ± 17.9 months). The patients' age ranged from 9 months to 92 years (51.7 ± 21.2 years). The mean intraocular pressure in patients who developed glaucoma after penetrating keratoplasty increased from 15.43 ± 10.56 mmHg to 28.52 ± 7.13 mmHg (45.9%). In the group which did not develop glaucoma, IOP increased from 13.69 ± 6.85 mmHg to 20.50 ± 10.3 mmHg (33.2%). Of 231 keratoplasties performed, 63 eyes had preexisting glaucoma with well-controlled intraocular pressures while 97 eyes (57.7%) developed glaucoma afterwards. The development of glaucoma following penetrating keratoplasty was significantly related to graft failure (P = 0.017). On the contrary, the graft failure was not related to the glaucoma treatment (P = 0.374). Glaucoma surgery was required in 23 eyes. The incidence of graft failure was higher in patients who developed glaucoma.

Conclusion : The incidence of glaucoma after penetrating keratoplasty was high. The risk factors for developing glaucoma were preexisting glaucoma, combined procedures, aphakia and pseudophakia. **Thai J Ophthalmol 2005 ; July-December : 19(2) : 185-193.**

Keywords : *Glaucoma, Penetrating Keratoplasty*

Introduction

One of the most serious complications following penetrating keratoplasty (PKP) is glaucoma. The incidence varies from 9% to 31% in the early postoperative period and 18%-35% in the late postoperative period.[1] It can lead to permanent blindness from the direct optic nerve damage or graft failure.

The causes of glaucoma following PKP are trauma, inflammation, advanced age, aphakic bullous keratopathy, combined PKP and intracapsular cataract extraction (ICCE), preexisting glaucoma, corneal perforation, and previous PKP. In 1969, Irvin and Kaufman reported increased intraocular pressure (IOP) after PKPin different lens status ; IOP elevations of 24 mmHg in phakic eyes, 40 mmHg in aphakic eyes, and 50 mmHg in combined cataract and PKP.[2]

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Reinheart et al. reported that postoperative rising of IOP may cause endothelial cell loss in glaucoma eyes.[3] This will lead to graft failure and permanent visual loss.

Materials and Methods

The medical records of 190 patients with 231 PKPs performed from July 1997 to June 2002 at the Department of Ophthalmology Ramathibodi Hospital, Bangkok, Thailand were reviewed.

Baseline demographic and clinical information was collected. The baseline clinical examination included age, gender, intraocular pressure (pre and post penetrating keratoplasty), laterality, indication for surgery, lens status, history of intraocular surgery.

In this study, the definition of glaucoma was based on IOP exceeding 21 mmHg because the evaluation of optic nerve, nerve fiber layer defect, and visual field tests may be inaccurate or unable to perform in this group of patients. In addition, most of the glaucomas associated with penetrating keratoplasty were secondary to angle closure mechanism, except for patients with preexisting glaucoma which may have glaucoma from other mechanisms. Secondary glaucoma in postkeratoplasty is mostly pressure dependent. Complete ocular examination was performed at initial visit and IOP was measured with Goldmann applanation tonometry during the follow up period. In cases with astigmatism the applanation prism was rotated 180^0 apart and the average was taken into account.

The definition of postkeratoplasty-glaucoma in this study were grouped as follows.

1. With no preexisting glaucoma
   a. Glaucoma : IOP exceeding 21 mmHg
   b. No glaucoma : IOP below 21 mmHg
2. With preexisting glaucoma
   a. Uncontrolled glaucoma : IOP exceeding 21 mmHg with previous or additional medication(s)
   b. Controlled glaucoma : IOP controlled below 21 mmHg postkeratoplasty from previous glaucoma surgery (trabeculectomy or glaucoma drainage implant)

In developing glaucoma cases, the IOP was followed for 1 month after the patient's last change in glaucoma treatment regimen.

Inclusion criteria were as follows :

1. PKP performed in the study period.
2. Intraocular pressure prior to the study did not exceed 21 mmHg.
3. In preexisting glaucoma patients the IOP was well controlled (below 21 mmHg) either with medication or surgery.
4. Patients were able to be followed for at least 1 year after PKP performed.

Patients with corneal pathologies that interfere with the measurement of intraocular pressure using Goldmann applanation tonometry was excluded i.e. corneal ulcer, descematocele, and corneal perforation.

Penetrating keratoplasty was performed under local anesthesia in most cases. Flieringa ring was used for the support of the globe and the corneal buttons were performed with Hessburg-Baron trephination. The donor graft was 0.5 mm larger than the recipient site. Corneal wound was sutured with 10-0 nylon using simple interrupted stitches.

Data Analysis

The number of pentetrating keratoplasties was analyzed. One patient may have multiple surgeries either in one or both eyes. In patients with re-grafting, we chose the last procedure performed as the included eye. Survival analysis was used for baseline demographic and clinical data. Univariate and multivariate Cox proportional hazard ratios were used for estimating the development of postkeratoplasty-glaucoma in the surgical eye and their 95% confidence intervals (CI) was reported for each predictive factor. Statistical significant was defined as $p < 0.05$.

Results

Baseline demographic and clinical information of patients who developed postkeratoplasty-glaucoma were reported in Table 1. Of 190 patients with 231 kerato plasties performed, the follow up period was from 12 to 60 months. Ages ranged from 9 months old to 92 years (51.7 ± 21.2 years) with predominance of male 59.47% (113/190 patients). Preexisting glaucoma was found in 27.3% (63/231 PKPs) mostly with phakic eyes (53.2%). Patients developed glaucoma in 97 of 168 (231-63) PKPs (57.7%).

Univariate and multivariate hazard ratios with 95% CI were reported for each predictive factor for the development of postkeratoplasty-glaucoma. (Table 2, Table 3). In univariate and multivariate analyses, factors significantly predictive for the development of postkeratoplasty-glaucoma were lens status (aphakia or pseudophakia), previous surgery, preexisting glaucoma, and combined procedures. Aphakia tendd to be the most predictive cause of postkeratoplasty-glaucoma with hazard ratio of 2.5 (95% CI, 1.44-4.35, $p < .001$). Other factors for developing postkeratoplasty-glaucoma were pseudophakic eyes with hazard ratio of 1.98 (95% CI, 1.25-3.15), combined procedures 1.93 (95% CI, 1.28-2.90), and preexisting glaucoma 1.71 (95% CI, 1.11-2.63) respectively.

The mean preoperative IOP in patients who did not develop glaucoma was 13.69 ± 6.85 mmHg and the mean postoperative IOP was 20.50 ± 10.39 mmHg. In the group of the patients with developing glaucoma, the mean preoperative IOP was 15.43 ± 10.56 mmHg and the mean postoperative IOP was 28.52 ± 7.13 mmHg.

Table 1 Patients' demographic data (231 keratoplasties)

Number of patients	190
Age range	9 months - 92 years
Gender	
Male	113
Side	
Right	77
Ocular status	
Previous ocular surgery	141
Preexisting glaucoma	63
Lens status (231 Keratoplasties)	
Phakic	123
Aphakic	74
Pseudophakic	34
HSV infection	13

Note : HSV = Herpes Simplex Virus

Table 2 Univariate analyses of predictive risk factors for the development of glaucoma after penetrating keratoplasty (231 Keratoplasties)

Factors	No. of PKPs	No. of glaucoma	Incidence at risk
Lens status (p = .0001)			
Phakia	123	37	.000525
Pseudophakia	74	40	.0014864
Aphakia	34	20	.0018255
Previous ocular surgery (p = .0004)			
Yes	141	72	.0013388
No	90	25	.0004582
HSV infection (p = .1467)			
Yes	13	3	.0002524
No	218	94	.0009746
Preexisting Glaucoma (p = .001)			
Yes	63	36	.0015654
No	168	61	.0007148
Bullous keratopathy (p = .1094)			
Yes	60	31	.0011566
No	171	66	.0008095
Graft failure (p = .0020)			
Yes	58	33	.0022091
No	172	64	.0006852
Corneal dystrophy (p = .6748)			
Yes	21	8	.0006538
No	210	89	.0009261
Corneal ulcer (p = .4339)			
Yes	23	11	.0010322
No	208	86	.0008804
Trauma (p = .1803)			
Yes	14	9	.0012193
No	217	88	.0008716
Corneal perforation (p = .2305)			
Yes	10	2	.0002602
No	217	95	.0009438
Operation (p = .0054)			
PKP alone	120	40	.0006673
Combined	111	5	.0011779
Surgeon (p = .1272)			
Resident	7	2	.0003358
Fellow	129	61	.0012084
Staff	95	34	.0006551

Note : HSV = Herpes simplex virus, PKP = penetrating keratoplasty, PKPs = penetrating keratoplasties, combined = combined procedures

Table 3 Multivariate Hazard Ratio and 95% Confidence Intervals for the development of glaucoma after PKP (231 PKPs)

Factors	Coefficient (Std.Err)	P value	Hazard ratio (95% CI)
Operation			
PKP alone	-	-	1
Combine procedures	.66 (.21)	.002	1.93 (1.28-2.90)
Preexisting glaucoma			
Yes	.54 (.22)	.015	1.71 (1.11-2.63)
No	-	-	-
Lens status			
Phakia	-	-	1
Pseudophakia	.68 (.24)	.004	1.98 (1.25-3.15)
Aphakia	.92 (.28)	.001	2.50 (1.44-4.35)

Note : CI = confident interval, PKP = penetrating keratoplasty

Both groups show increased IOP 33.2% and 45.9% respectively. The mean IOP after receiving glaucoma treatment was 16.61 ± 4.64 mmHg.

Glaucoma was controlled with medications in 74 cases, with surgery in 5 cases and required both medication and surgery in 18 cases. From 23 surgical cases, trabeculectomy with mitomycin-C was performed in 20 cases ; glaucoma drainage device was implanted in 4 cases and cyclocryotherapy in 1 case (some cases had multiple surgeries performed). Of 97 eyes, the number of postkeratoplasty-glaucoma with medications was few due to the favorable surgical outcome.

Comparing the development of glaucoma and graft outcome, our study showed that glaucoma was related to graft failure (Table 4, p = .0107). Although with adequate IOP lowering treatment, the graft failure was not related to the glaucoma treatment mentioned (Table 5).

Discussion

In our study, the incidence of postkeratoplasty-glaucoma was higher than the previous studies (57.7%, 18-35% respectively). This was probably due to the different demographic information such as race, age, gender, indication for PKP, and preoperative status.

From the previous studies, bullous keratopathy was the most important risk factor for developing glaucoma.[6] But in our study, bullous keratopathy was statistically insignificant. Graft failure was strongly related

Table 4 Incidence of glaucoma VS Graft outcome (231 penetrating keratoplasties)

Glaucoma/Graft outcome	Survive	Fail	Total
Yes	41	56	97
	(34.45%)	(50.00%)	(41.99%)
No	78	56	134
	(65.55%)	(50.00%)	(58.01%)
Total	**119**	**112**	**231**

Pearson chi2 = 5.7247 Pr = 0.0107

Table 5 Glaucoma management VS Graft outcome

Glaucoma management	Graft outcome		Total
	Survive	Fail	
Medication	34	40	74
	(82.93%)	(71.43%)	(76.29%)
Surgery	7	16	23
	(17.08%)	(28.57%)	(23.71%)
Total	**41**	**56**	**97**

Pearson chi2 = 1.7300 P r = 0.188

to postkeratoplasty-glaucoma. Table 6 shows the indications for penetrating keratoplasty such as corneal edema, previous graft failure, corneal scar, corneal dystrophy, and corneal perforation.

In the aspect of preoperative status, preexisting glaucoma was a significant risk factor in several other studies,[1,5-7,14] the incidence for developing glaucoma ranged from 12.2%-21.25%.[4-6] The difference in our study

Table 6 Indications for Penetrating keratoplasty

Indications	No. of patients	No. of patients with preexisting glaucoma
Corneal edema	60	22
Graft failure	58	28
Corneal scar (from ulcer)	39	4
Corneal dystrophy	21	4
Active corneal ulcer	23	6
Corneal scar (from trauma)	14	2
Corneal perforation	10	1
Others	13	0

was that preexisting glaucoma was found to be higher (27.3%).

The multivariate hazard ratio showed that the significant risk factors were combined procedures, preexisting glaucoma and lens status (both aphakia and pseudophakia), which were similar to the other studies.[1,5-7] The other suspected risk factors were analyzed, Herpes Simplex Virus infection and trauma, but there was no statistical significance.

Previous surgery and graft failure were highly related to the development of glaucoma, but there was no statistical significance in our study.

The onset of developing glaucoma ranged from 1 to 463 days (68.8 ± 85.1 days). Interestingly, the range of time-onset varies widely, so close follow-up for glaucoma is necessary since the first postoperative day and all follow-up visits.

In treating postkeratoplasty-glaucoma, most cases were successful with glaucoma medication alone (74.23%). Of the 97 keratoplasties who developed glaucoma, 25 (25.8%) needed glaucoma surgery.

Our study pointed out that graft failure was not related to glaucoma surgery whereas other studies revealed that the most important complication after all types of glaucoma surgery (trabeculectomy with mitomycin C, glaucoma drainage device and cyclodestructive procedures) in postkeratoplasty-glaucoma was graft failure.[1,12-14] In addition, achievement in IOP control should be considered.[10,11] Although in our study, glaucoma surgery was not significantly related to graft failure, probably due to the small numbers of patients who underwent glaucoma surgery and there were many other factors which affected the graft outcome other than glaucoma surgery.

There were many studies evaluated on combined operation between trabeculectomy with mitomycin-C or

glaucoma-drainage device implantation and penetrating keratoplasty in the patients with coexisting corneal disease and glaucoma, the outcome of such approach was found that the outcome was not better than glaucoma surgery after penetrating keratoplasty.[8,10,11,14]

Conclusions

The incidence of developing glaucoma was high in patients performing penetrating keratoplasty. Risk factors in the development of glaucoma following penetrating keratoplasty were preexisting glaucoma, combined procedures, aphakia and pseudophakia. The incidence of graft failure was higher in patients who developed glaucoma. Glaucoma assessment was required in patients whom undergone keratoplasty in order to maintain long-term graft survival.

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บทคัดย่อ **วัตถุประสงค์** : เพื่อทำการศึกษาอุบัติการณ์การเกิดต้อหินและปัจจัยที่เกี่ยวข้องหลังการผ่าตัดเปลี่ยนกระจกตา

วิธีการ : เก็บรวบรวมข้อมูลของผู้ป่วยที่ทำการผ่าตัดเปลี่ยนกระจกตา ย้อนหลังจากเวชระเบียนในโรงพยาบาลรามาธิบดีตั้งแต่ กรกฎาคม 2540 ถึง มิถุนายน 2545

ผลการศึกษา : ผู้ป่วยที่เปลี่ยนกระจกตา 190 คนได้ทำการผ่าตัดทั้งหมด 231 ครั้ง มีอายุตั้งแต่ 9 เดือนถึง 92 ปี (51.5 ± 21.22 ปี) ทำการติดตามผู้ป่วยเป็นเวลาตั้งแต่ 12 ถึง 60 เดือน (27.5 ± 17.89 เดือน) พบว่าความดันลูกตาหลังการผ่าตัดเปลี่ยนกระจกตามีค่าที่สูงขึ้น ในการผ่าตัด 231 ครั้งพบว่ามี 63 ตาที่มีต้อหินก่อนการผ่าตัดและสามารถควบคุมความดันตาได้หลังเปลี่ยนกระจกตา ในขณะที่มี 97 (57.7%) ตาเกิดต้อหินขึ้นตามหลังการผ่าตัดเปลี่ยนกระจกตา การเกิดต้อหินสัมพันธ์กับการเสื่อมของกระจกตาที่เปลี่ยนไป ($p = .017$) ในทางตรงข้ามการเสื่อมของกระจกตาไม่ได้สัมพันธ์กับการเกิดต้อหิน ผู้ป่วย 23 คนที่เกิดต้อหินจำเป็นต้องได้รับการผ่าตัดรักษา และอุบัติการณ์เกิดกระจกตาเสื่อมพบได้มากขึ้นในผู้ป่วยที่เกิดต้อหิน

สรุป : พบอุบัติการณ์ของต้อหินสูงหลังการผ่าตัดเปลี่ยนกระจกตา โดยปัจจัยเสี่ยงประกอบด้วย การเป็นต้อหินอยู่เดิม การผ่าตัดหลายชนิดในครั้งเดียวกัน ภาวะที่ไม่มีเลนส์แก้วตาหรือมีเลนส์แก้วตาเทียมอยู่ในดวงตา **จักษุเวชสาร 2548 ; กรกฎาคม-ธันวาคม 19(2) : 185-193.**

***ภาควิชาจักษุวิทยา คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล**