The Incidence and Risk Factors of Post-penetrating Keratoplasty Glaucoma

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Abstract

Purpose: To evaluate the incidence and significant risk factors of glaucoma after penetrating keratoplasty (PK) operation.

Methods: A retrospective cohort study was carried out on 62 eyes of 61 patients who underwent penetrating keratoplasty from January 2020 to December 2022 in Thammasat University Hospital, Thailand. Age, sex, preoperative diagnosis, presence of preoperative glaucoma, presence of peripheral anterior synechiae, recipient graft size, lens status, and additional surgery performed during keratoplasty, which may affect the postoperative intraocular pressure, were evaluated for risk factors of glaucoma after penetrating keratoplasty.

Results: The overall incidence of post-penetrating keratoplasty glaucoma (PPKG) was 37.1%. The patients' ages ranged from 20 to 95 years (with a mean of 63.53 ± 15.58 years). Twenty-nine patients (47.54%) were male. Preoperative diagnosis of inflammatory diseases such as corneal perforation (relative risk [RR] = 2.95), keratitis on graft (RR = 2.18), trauma (RR = 1.38), and infectious keratitis (RR = 1.24) were found to be risk factors for the development of glaucoma. Other significant risk factors included recipient size ε 8 mm, peripheral anterior synechiae (PAS) or shallow anterior chamber (AC), and pre-existing glaucoma (p = 0.03, 0.001, and 0.002 respectively). The average period to develop glaucoma after PK was 3.77 ± 4.81 months.

Conclusion: IOP monitoring should be started in the early postoperative period and as a routine in the follow-up period especially in patients presenting significant risk factors such as large recipient graft, pre-operative peripheral anterior synechia formation, and pre-existing glaucoma. Patients with glaucoma history should be carefully evaluated both pre- and post-operatively in PK operation.

Keywords: Peripheral anterior synechiae, Penetrating keratoplasty, Post-penetrating keratoplasty glaucoma

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Introduction

Despite technological advances in corneal preservation, surgical techniques, and post-operative care, many compli-cations may occur after penetrating keratoplasty (PK). Allograft rejection, ocular surface disease, recurrent herpes simplex keratitis and infective keratitis are complications which compromise visual outcomes following penetrating keratoplasty. Moreover, post-penetrating keratoplasty glaucoma (PPKG) is one of the most serious complications for its high incidence, severity and difficulty in diagnosis and treatment.[1] Beside the irreversible damage to the optic nerve, an increase in intraocular pressure (IOP) after PK causes a significant endothelial cell loss. Additionally, the risk for immune graft reactions increases in eyes with glaucoma and PK.[2,3] Thereafter, early diagnosis of glaucoma following penetrating keratoplasty is crucial to preserve optimal graft clarity and optic nerve function.[4]

Irvine and Kaufman were the first to describe the association of glaucoma after PK.[5]

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They demonstrated the rise of IOP as a biphasic phenomenon. The first was in the immediate post-operative periods with IOP returning to normal levels within one to two weeks after glaucoma treatment. The incidence has been reported from 9 to 31%.[6-9] The second phase was in late postoperative periods ranging from weeks to months with the report of 18 to 42% incidence.[6,7,10-13]

In most studies, important risk factors developing post-penetrating keratoplasty glaucoma include aphakic and pseudophakic bullous keratopathy, anterior mesenchymal dysgenesis, irido-corneal-endothelial syndrome, pre-existing glaucoma, previous PK, combined PK with cataract extraction, and concomitant anterior vitrectomy.[6-9,12-14] Certain factors are modifiable; hence, identification of these factors with their timeline can help in prompt diagnosis with appropriate mana-gement. The purpose of the present study was to determine the incidence as well as the risk factors for developing glaucoma after penetrating kerato-plasty operations in Thammasat University Hospital from January 2020 to December 2022.

Methods

This retrospective cohort study was approved by the Research Ethic Committee of Thammasat University Hospital, Thammasat University, with adherence to the Declaration of Helsinki, project number MTU-EC-OP-0-025/66. Data were reviewed retrospectively for patients who had undergone penetrating keratoplasty from January 2020 to December 2022 from the Epis database of Thammasat University Hospital. Patients undergoing the operation within the study period with follow-up of at least six months were included in the study. The exclusion criteria included patients with age less than 10 years old and those of steroid responder which is defined as intraocular pressure (IOP) returning to normal after stopping or switching steroids to lower potencies without anti-glaucoma medication or surgery.

The baseline data included gender, age, history of glaucoma or other ocular pathology with treatment, pre- and post-operative visual acuity, pre- and post-operative IOP, lens status, presence of posterior anterior synechiae (PAS) or shallow anterior chamber (AC), indication of surgery, surgery technique with additional procedure combined with PK, recipient's graft size and treatment applied for glaucoma control. For this study, post-penetrating keratoplasty glaucoma (PPKG) is defined as the presence of persistent elevated intraocular pressure above 21 mmHg, with or without abnormalities in optic disc and visual field, that required the introduction of anti-glaucoma drops or surgical intervention at any time. In cases of pre-existing glaucoma, PPKG developed in worsening of the condition which additional medication or surgery is required.[15]

Surgical procedure

All procedures were done under general anesthesia. During the operation, corneal center was identified and Flieringa ring was sutured. The donor graft 0.5 mm larger than recipient's size was punched by a disposable trephine from the endothelial surface. The host corneal bed was prepared using a vacuum trephine. Additional surgical procedures were performed where necessary. The donor cornea was placed and sutured with recipient cornea with interrupted 10-0 nylon sutures. Anterior chamber was formed by balanced salt solution and wound leakage was checked.

The post-operative medi-cation included topical antibiotic four times per day for 1 month and preservative-free methylprednisolone hourly, which was tapered slowly during the follow-up. Routine follow-up schedule was every week for the first month, every two weeks for the second and third months, every month until sixth month, and then every three months. In high intraocular pressure cases, topical prostaglandin analog, alpha-2 agonists, beta-blockers, and/or carbonic anhydrase inhibitors were prescribed. However, if IOP remained high in spite of maximum anti-glaucoma eye drops, surgical management was initiated.

Statistical analysis

Data were initially entered into a Microsoft Excel spreadsheet and then transferred to SPSS software (Statistical Package for the Social Sciences, version 23, SPSS Inc., Chicago, IL, USA). Visual acuity was converted from Snellen chart to logarithm of the minimum angle of resolution (LogMAR)[16] and the equivalent

logMAR of count fingers (CF) (CF at 1, 2 and 3 feet are equivalent to 2, 1.6 and 1.8 LogMAR, respectively), hand motion (HM = 3 LogMAR), and perception of light (PL = 3.3 LogMAR) were used. The quantitative factors such as age, recipient graft size, additional procedures, and mean time to develop PPKG and qualitative factors such as gender, laterality, indications of PK, lens status, pre-existing glaucoma and presence of PAS were included in the data. Data of continuous measurements were expressed in terms of means ± standard deviations and results on categorical measurements were presented in number or percentage. Continuous variables were analyzed using independent *t*-tests and categorical data were assessed using Chi-square analyses. A comparison was termed statistically significant if the *p*-value was < 0.05.

Results

Among 71 eyes of 66 patients that underwent penetrating keratoplasty, 62 eyes of 61 patients were included in the study because 5 eyes developed uncontrolled corneal ulcer associated with endophthalmitis and had evisceration whereas 4 other eyes lost follow-up. The mean age of patients was 63.53 ± 15.58 years ranging from 20 to 95 years with 29 (47.54%) male and 32 (52.46%) female. Before surgery, patients had visual acuity of 2.24 ± 0.84 logMAR (range, 0.54 to 3.3 logMAR) with the mean IOP of 12.05 ± 4.89 mmHg (range, 6 to 21 mmHg). 12 out of 62 eyes (19.35%) had a history of glaucoma treated with surgery in 5 eyes and 7 eyes under anti-glaucomatous medi-cations: 1 eye on 1 medication, 3 eyes on 2 medications, and 3 other eyes on 4 medications (Table 1).

Table 1: Patient's demographic features

Patient characteristics		**No. of Patients N = 61 (62 eyes)**	**Percentage (%)**
Age (year-old)		63.53 ± 15.58 (20 – 95)	
Sex	Male	29	47.54
	Female	32	52.46
Laterality	Right	29	46.8
	Left	33	53.2
Pre-operative VA (logMAR)		2.24 ± 0.84 (0.54 – 3.3)	
Pre-operative IOP (mmHg)		12.05 ± 4.89 (6 – 21)	
Pre-existing glaucoma		12	19.35
No. anti-glaucoma medications	1 medication	1	1.61
	2 medications	3	4.84
	4 medications	3	4.84
Surgical history		5	8.06

Table 2: Indications for Penetrating Keratoplasty

Indications	Number of Patients	Percentage
PBK	17	27.4%
Corneal scar	10	16.1%
Infectious keratitis	9	14.5%
Graft failure	5	8.1%
Corneal dystrophy	5	8.1%
Trauma	4	6.5%
Keratitis on graft	4	6.5%
Corneal perforation	3	4.8%
Corneal thinning	3	4.8%
Keratoconus	2	3.2%
Total	62	100%

The indications for PK are listed in Table 2 including 17 eyes or 27.4% of pseudophakic bullous keratopathy (PBK) followed by 10 eyes (16.1%) of corneal scar, 9 eyes (14.5%) of infectious keratitis, 5 eyes (8.1%) of graft failure, 5 eyes (8.1%) of corneal dystrophy, 4 eyes (6.5%) of trauma, 4 eyes (6.5%) of keratitis on graft, 3 eyes (4.8%) of corneal perforation, 3 eyes (4.8%) of corneal thinning, and 2 eyes (3.2%) of keratoconus.

In the present study, 23 out of 62 eyes developed glaucoma after penetrating keratoplasty giving an overall incidence of 37.10%. The mean IOP of post-PK glaucoma cases was 32.02 ± 7.77 mmHg. The pre-operative diagnoses of patients developing glaucoma after PK was pseudophakic bullous keratoplasty in 5 (21.7%) eyes, infectious keratitis in 4 (17.4%) eyes, keratitis on graft in 3 (13%) eyes, corneal perforation in 3 (13%) eyes, graft failure in 2 (8.7%) eyes, corneal dystrophy in 2 (8.7%) eyes, trauma in 2 (8.7%) eyes, corneal scar in 1 (4.3%) eye, and corneal thinning in 1 (4.3%) eye. The risk factors for developing glaucoma were corneal perforation (relative risk [RR] = 2.95), keratitis on graft (RR = 2.18), trauma (RR = 1.38), and infectious keratitis (RR = 1.24) (Table 3). Among them, corneal perforation and keratitis on graft present the two most important risk factors.

Table 3: Number of Eyes Developing Glaucoma after Penetrating Keratoplasty

Diagnosis	Overall No.	No. PPKG	Relative Risk	95% Confidence Interval
PBK	17	5 (21.7%)	0.735	0.32-1.67
Infectious keratitis	9	4 (17.4%)	1.24	0.55-2.80
Keratitis on graft	4	3 (13.0%)	2.18	1.12-4.24
Corneal perforation	3	3 (13.0%)	2.95	2.07-4.21
Graft failure	5	2 (8.7%)	1.09	0.35-3.35
Corneal dystrophy	5	2 (8.7%)	1.09	0.35-3.35
Trauma	4	2 (8.7%)	1.38	0.49-3.90
Corneal scar	10	1 (4.3%)	0.24	0.04-1.56
Corneal thinning	3	1 (4.3%)	0.89	0.17-4.59
Keratoconus	2	0	-	-
Total	62	23	-	-

In the present study, the age and sex of patients were not significant risk factors for post-PK glaucoma (p = 0.35 and 0.09 respectively). Moreover, the lens status of patients including 28 (45.2%) phakic eyes and 34 (54.8%) pseudophakic eyes was not associated with glaucoma after PK (p = 0.84). For the surgical procedures, 15 out of 47 eyes (31.91%) who underwent PK alone developed glaucoma while 8 out of 15 (53.33%) eyes who had combined procedures had IOP increase after surgery. In the combined procedures, there were 5 patients undergoing triple operations, 2 triple operations with anterior vitrectomy, 1 PK with anterior vitrectomy, and 6 IOL manipulations with anterior vitrectomy. Surgical procedure, in addition, was not found to be a significant risk factor for glaucoma after PK (p = 0.14) (Table 4).

Table 4: Association between development of PPKG and its various risk factors

Variables	Without glaucoma, *n* (%)	With glaucoma, *n* (%)	Total	*p* value
Age (years)				
δ 40	2 (40%)	3 (60%)	5	I^2: 1.22
> 40	37 (64.91%)	20 (35.09%)	57	p = 0.35
Sex				
Male	15 (51.72%)	14 (48.28%)	29	I^2: 2.92
Female	23 (71.87%)	9 (28.13%)	32	p = 0.09
Lens status				
Phakic	18 (64.29%)	10 (35.71%)	28	I^2: 0.04
Pseudophakic	21 (61.76%)	13 (38.24%)	34	p = 0.84
Surgical procedure				
PK alone	32 (68.09%)	15 (31.91%)	47	I^2: 2.24
Combined procedure	7 (46.67%)	8 (53.33%)	15	p = 0.14
Recipient size				
< 8 mm	36 (69.23%)	16 (30.77%)	52	I^2: 5.53
ε 8 mm	3 (30%)	7 (70%)	10	p = 0.03
PAS/ shallow AC				
Absent	32 (78.05%)	9 (21.95%)	41	I^2: 11.90
Present	7 (33.33%)	14 (66.67%)	21	p = 0.001
Pre-existing glaucoma				
Absent	36 (72%)	14 (28%)	50	I^2: 9.16
Present	3 (25%)	9 (75%)	12	p = 0.002

During PK operation, 16 of 52 (30.77%) recipient eyes which had a trephination size of < 8 mm developed high IOP whereas 7 of 10 (70%) eyes whose recipient graft size ε 8 mm developed glaucoma after surgery. The different size of recipient graft was found to be a significant risk factor of PPKG (p = 0.03). In addition, the presence of pre-operative peripheral anterior synechiae or shallow anterior chamber was observed to be significantly associated with glaucoma post-PK (p = 0.001). The incidence of PPKG was 66.67% in eyes with PAS or AC shallow and 21.95% in eyes without PAS. 12 eyes (19.35%) had a pre-operative diagnosis of glaucoma. After PK operation, glaucoma developed in 75% of eyes with pre-existing glaucoma and 28% of eyes without a history of glaucoma. Pre-existing glaucoma was, therefore, a significant risk factor for post-PK glaucoma (p = 0.002) (Table 4).

Table 5: The Mean Time to Develop PPKG in its various risk factors

Risk factors	Mean time to develop PPKG (Months)	No. PPKG
Indication		
Corneal perforation	3.90 ± 5.72	3 (13.0%)
Keratitis on Graft	4.75 ± 5.58	3 (13.0%)
Trauma	3.5 ± 0.71	2 (8.7%)
Infectious Keratitis	8.06 ± 8.98	4 (17.4%)
Recipient graft size		
< 8 mm	3.17 ± 2.62	16 (69.6%)
ε 8 mm	4.54 ± 4.92	7 (30.4%)
PAS/AC shallow		
Absent	5.06 ± 2.07	9 (39.1%)
Present	3.26 ± 0.95	14 (60.9%)
Pre-existing glaucoma		
Absent	4.34 ± 1.46	14 (60.9%)
Present	3.39 ± 1.16	9 (39.1%)

The average period to develop glaucoma after PK was 3.77 ± 4.81 months. The mean time to develop PPKG varied in different indications of PK with 3.5 ± 0.71 months in trauma, 3.90 ± 5.72 months in corneal perforation, 4.75 ± 5.58 months in keratitis on graft, and 8.06 ± 8.98 months in infectious keratitis. In patients with recipient graft size of < 8 mm, glaucoma developed in the meantime of 3.17 ± 2.62 months and 4.54 ± 4.92 months if recipient graft size ε 8 mm. In addition, patients presented with pre-operative PAS or shallow AC, IOP increased earlier in 3.26 ± 0.95 months and 5.06 ± 2.07 months comparing to those without PAS. Moreover, post-PK glaucoma developed early in patients with history of glaucoma in 3.39 ± 1.16 months and 4.34 ± 1.46 months in those without pre-existing glaucoma (Table 5).

Discussion

Glaucoma is a serious complication after PK because of its high incidence and difficulty associated with diagnosis and treatment.[1-5] The incidence of glaucoma after PK, reported by Karesh and Nirankanri, ranged from 9% to 31% in the early postoperative period and from 18% to 35% in the late postoperative period.[7] In the present study, the incidence of post-PK glaucoma was 37.10%. The higher incidence of this study is probably associated with higher incidence of preoperative glaucoma (19.35%) and the high ratio of preoperative inflammatory indications compared to non-inflammatory diseases like corneal dystrophy and keratoconus. Similarly, Oruçoglu et al. reported a high incidence of glaucoma after PK as 47.7% due to the higher incidence of pre-existing glaucoma in their patients (22.6%).[17] In addition, Simmons et al. mentioned the incidence of 34% of PPKG with 27.5% of pre-existing glaucoma in their patients.[18] On the other hand, Karadag et al. found out the incidence of glaucoma in later postoperative period of PK was on 16.6%.[19] They also mentioned the reason of their relative low incidence related to higher numbers of non-inflammatory indications. Chanbour et al., excluding history of glaucoma in their study population, demonstrated only 28.5% of incidence of glaucoma after PK.[20]

The incidence of increased IOP after PK is associated with pre-operative indications. In the present study, corneal perforations, keratitis on graft, trauma, and infectious keratitis were reported to be high risk factors. Sharma et al. elaborated in their study that secondary glaucoma developed in 29.3% of perforated ulcers and 15% of non-perforated ulcers ($p < 0.001$).[21] It is consistent to this study that corneal perforations from ulcers have a relative risk of 2.95 in developing glaucoma after PK compared to

infectious keratitis of 1.24 relative risk. In addition, Karadag et al. demonstrated the risk factors for developing glaucoma after PK were traumatic scar formation with relative risk (RR) of 2.66, graft abscess of 2.62, and corneal abscess of 1.52.[19] Chanbour et al. also mentioned in their study that pre operative indication is a significant risk factor for PPKG with corneal ectasia being the lowest risk.[20]

Age, sex, lens status, and combined surgery, in the current study, were found to be not significantly associated with glaucoma after PK. Some previous studies indicated that PK combined with any surgical procedure increased the risk of developing glaucoma after PK.[8,18] Although this study showed the incidence of 53.33% of glaucoma in combined surgery was higher than 31.91% in PK alone, they were not significant correlated ($p > 0.05$). Consistently, more studies reported non statistically significant differences in IOP after PK between different procedures.[6,10,19,20]

Recipient graft, in this study, was found to be a significant risk factor of post-PK glaucoma ($p = 0.03$). The finding was consistent with previous several studies. Raj et al., using both univariate and multivariate regression analysis, determined that recipient size of ε 8 mm was at higher risk 82% with odd ratio 6.66 (2.45-18.04) for increasing IOP after PK.[22] Another study by Pandal et al. reported an incidence of post operative glaucoma of 37% in eyes with 10 mm grafts compared to 14% in eyes with 6 to 7.5 mm grafts.[23] In addition, Sharma et al. found higher incidence of secondary glaucoma when using larger graft size. 8.9% developed glaucoma in graft < 9 mm, 33.33% in graft 9-11 mm and 47.61% in graft > 11 mm ($p < 0.01$).[21]

Peripheral anterior synechia formation preoperatively or after intraocular operation was found to be significantly associated with postoperative glaucoma development.[8,18,24] In the present study, post-PK glaucoma was observed in 66.67% of eyes with PAS or shallow AC and 21.95% in eyes without PAS ($p = 0.001$). Karadag et al. also found that pre-operative PAS formation was a significant risk factor developing glaucoma after PK ($p = 0.019$).[19]

The present study identified pre-operative glaucoma as a significant risk factor inducing glaucoma after PK with incidence of 75% in patients with history of glaucoma compared to 28% in patients without ($p = 0.02$). In many studies, pre-existing glaucoma was reported as a major risk factor for post-PK glaucoma. Karadag et al. recorded incidence of glaucoma in patient with pre-operative glaucoma history as 59.4% and 14.6% in cases without such history ($p = 0.0001$). Another study by Jonas et al. reported that on the first post operative day the IOP was significantly higher than before keratoplasty with the main predisposing factor being pre-existing high IOP.[25] Two major studies by Chien et al. and Oruçoglu et al. had analyzed risk factors using multivariate logistic regression and identified pre-existing glaucoma as leading risk factors for ocular hypertension after PK.[9,17]

The current study has several limitations. One major limitation is its small-scale study with few participants in each parameter, which might affect the analysis result. Another limitation is its retrospective method carried out in a single study center. The study population cannot represent a good sample size with limited information provided so the result cannot represent the population of Thailand. Moreover, the study included all surgeons during the study periods. It might lead to bias in the findings.

Conclusion

The incidence of post-PK glaucoma was 37.1% in the main age group of more than 40 years old. Significant risk factors associated with PPKG were size of recipient graft, pre-operative peripheral anterior synechia formation, and pre-existing glaucoma. IOP monitoring should be started in the early postoperative period and as a routine in follow-up period especially in patients presenting significant risk factors to avoid its deleterious effect on the health of graft. Patients with glaucoma history should be carefully evaluated both pre- and post-operatively in PK operation.

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