Eye (2009) 23, 1288–1294

www.nature.com/eye

CLINICAL STUDY

Penetrating keratoplasty: indications, outcomes, and complications

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Abstract

Purpose **Corneal transplantation is the most common form of transplantation with approximately 2500 grafts undertaken annually in the United Kingdom. The modern day success of transplantation is attributed to eye bank storage techniques, ocular pharmacology, and improved surgical techniques.**
Methods **This retrospective case note review identified 203 penetrating keratoplasties (PKs) performed during a period from 1 January 2000 to 31 December 2003 at Manchester Royal Eye Hospital. Preoperative risk factors, surgical technique, postoperative complications, and Snellen acuity were analysed.**
Results **The mean age of the recipient group was 56.7 years, with 107 right eyes and 96 left eyes. The mean follow-up was 61 months. The overall 5-year survival was 82%, with keratoconus and corneal dystrophies at 93 and 89%, respectively. Visual acuity had improved to 6/12 or better in 48% of patients postoperatively, compared with 8% preoperatively. Forty-three donor grafts (21%) underwent at least a single episode of endothelial rejection. Glaucoma was a finding in 37 (18%) of patients following PK. In all, 16 grafts of 15 patients were noted to have suffered microbial keratitis (MK), an incidence of 8%.**
Conclusions **PK is currently an effective long-term treatment option for improving visual function. An overall survival rate of 82% over 5 years is comparable with other published studies and is largely dependent on recipient factors. This report emphasises the significant complications of immunological rejection, glaucoma, and microbial keratitis, which continue to limit success.**
Eye (2009) **23,** 1288–1294; doi:10.1038/eye.2008.305; published online 24 October 2008

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Received: 6 February 2008
Accepted in revised form: 28 August 2008
Published online: 24 October 2008

Financial/conflict of interest: None

Keywords: corneal transplantation; survival; complications; long-term follow-up; risk factors

Introduction

Corneal transplantation is the most common form of transplantation with over 2500 grafts in the United Kingdom[1] and 32 000 grafts undertaken in the United States[2] annually. Outcomes, including failure and complications of the procedure, are well known and appear dependent on several factors—recipient aetiology, preoperative comorbidity, and the health of the donor tissue. Modern-day success in transplantation is attributed to eye banking, storage techniques, ocular pharmacology, equipment, and modern surgical techniques.[3]

In this retrospective study, we reviewed our series of patients undergoing penetrating keratoplasty (PK) identifying complications, failure rates, and visual outcomes.

Materials and methods

This retrospective case note review identified 263 penetrating corneal transplants during the period from 1 January 2000 to 31 December 2003 at Manchester Royal Eye Hospital, through the UK Transplant database and operating department records. A total of 203 case notes were available for review with appropriate follow-up data.

Evaluation of preoperative risk factors

All donor material was stored in the UK Transplant organ culture storage system. Donor factors studied included age, time from death to enucleation, preservation time, and endothelial cell count. Recipient factors included age, indication for transplantation, prior grafts, and

preoperative ocular conditions (glaucoma, uveitis, infection, ocular surface disease, and corneal vascularisation (number of quadrants of superficial and deep vascularisation)).

Associated surgical procedures at the time of surgery, such as intraocular lens (IOL) exchange or removal, vitrectomy, or combined procedures were also documented.

Surgical technique

Corneal transplantation was performed in all cases by either a consultant or corneal fellow. Donor corneas were inspected and then trephined using vacuum trephination (Barron Hessberg®, Barron Precision Instruments, MI, USA) or non-vacuum trephine (Coronet®, Network Medical, Ripon, North Yorkshire, UK). Trephination of recipient corneas was undertaken where possible using the vacuum trephine. The donor cornea was sutured to the recipient using 16 10/0 nylon interrupted sutures as a routine, and subconjunctival antibiotic and steroid were given. If required, vitrectomy was performed using an automated motorised vitrector. Cataract extraction, if required, was performed using an extracapsular technique following a can opener or continuous curvilinear capsulorhexis. Soft lens matter (SLM) was aspirated using manual Simco aspiration. Insertion of an IOL was decided on a case-by-case basis.

Routine postoperative medication consisted of topical prednisolone 1% combined with topical antibiotic four times daily. Following discharge, the patient was seen on weeks 1, 3, and 7 followed by 3 months. Typically, antibiotic was reduced over the subsequent postoperative month and 1% prednisolone tapered down over 3 months with a change to 0.5% prednisolone once daily life long. All sutures were generally removed between 12 and 24 months. Following removal, steroids were increased to four times daily and reduced to once daily over 1 week with covering antibiotics. In general, episodes of immunological endothelial transplant rejection were treated with hourly prednisolone 1% for 1 week and reduced dependent on response. In severe cases, a single pulsed dose of i.v. methylprednisolone 500 mg may have been used. The definition used for severe rejection was the presence of acute diffuse corneal oedema affecting graft function (eg, thickening, oedema, and reduced vision) of donor tissue, extensive keratic precipitates, and anterior chamber activity with or without a hypopyon.

Transplant failure was defined as described by Price *et al*.[4] Refractive graft failures were not included in analysis of reasons for graft failure. The timing of transplant failure was defined as the time of the first postoperative examination when the corneal graft was described as failed. Graft failure because of endothelial decompensation was considered secondary to rejection if evidence of keratic precipitates and endothelial rejection lines or definite episodes of rejection had been documented.

Table 1 Indications for penetrating keratoplasty

	Total number of patients in cohort N = *number of patients (%)*	*Indications for penetrating keratoplasty in the United Kingdom from April2007 to March2008*[a] N = *number of patients (%)*
Regrafts	*41 (20)*	*329 (22.3)*
Rejection	16 (8)	74 (5)
Endothelial failure	8 (4)	122 (8.3)
Primary failure	1 (1)	48 (3.3)
High astigmatism	6 (3)	12 (0.8)
Other	10 (5)	73 (4.9)
Ulcerative keratitis	*11 (5)*	*122 (8.3)*
Rheumatoid	3 (1)	15 (1)
Other	8 (4)	28 (1.9)
Infective keratitis	*18 (9)*	*135 (9.1)*
Viral	8 (4)	61 (4.1)
Fungal	3 (1)	12 (0.8)
Bacterial	4 (2)	50 (3.4)
Protozoa	1 (1)	7 (0.5)
Other	2 (1)	5 (0.3)
Previous ocular surgery	*44 (22)*	*217 (14.7)*
Pseudophakic bullous keratopathy	37 (18)	175 (11.8)
Aphakic bullous keratopathy	6 (3)	34 (2.3)
Other	1 (1)	8 (0.5)
Dystrophies	*28 (14)*	*265 (18)*
Fuch's endothelial dystrophy	21 (10)	227 (15.4)
Other	7 (3)	38 (2.6)
Ectasia	*48 (24)*	*329 (22)*
Keratoconus	48 (24)	321 (21.7)
Other ectasia	0	8 (0.5)
Other	*13 (6)*	*160 (11)*
	203	1478

[a]Data obtained from the department of Statistics at the UK Transplant.[1]

Statistical analysis

Statistical analysis was performed using either χ^2- (2×2 contingency tables) or Fisher's exact tests for categorical data and unpaired *t*-tests for continuous data. Survival curves were created using the Kaplan–Meier method. Statistical comparisons were made by calculation of

relative risk (RR) or odds ratio (OR). Further analysis relating to risk factors for rejection and failure was undertaken using multivariate analysis. All tests were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Of the 203 transplants reviewed, 71 were undertaken on women and 115 men. Transplantation was performed on 107 right and 96 left eyes. The mean age of the recipient group was 56.7 years (SD +/−22.2; range: 8–93 years). The mean overall follow-up was 61 months. Table 1 outlines the indications for PK. Figure 1 shows the distribution of preoperative and postoperative visual acuity. In total, six patients proceeded to NPL post-PK. Of these, five suffered preoperative glaucoma, which worsened post-PK. Two of these patients underwent retinal detachment surgery through a keratoprosthesis before PK. The sixth patient underwent a third PK and suffered pthisis, requiring enucleation for a painful, blind eye.

The retrospective nature of this study made documentation of epithelial and stromal rejection difficult to ascertain from the notes. Therefore, rejection was confined to confirmed episodes of endothelial rejection using the classification of Maumenee.[5] Altogether, 43 grafts underwent a single episode of endothelial rejection. The mean age of this patient group was 48 years (SD +/−22; range: 18–91 years). The preoperative diagnosis showed regrafts accounted for nine cases (21%). Six of these regrafts were following prior rejection resulting in eventual corneal graft failure. In all, 13 (30%) of the 43 grafts were for keratoconus (KC), four (9%) for Fuchs' endothelial dystrophy (FED), and five (12%) pseudophakic bullous keratopathy (PBK). Eventually, 15 (35%) of these individuals underwent eventual graft failure following rejection. The average time for failure following rejection was 8.5 months, averaging 28 months from surgery to eventual failure.

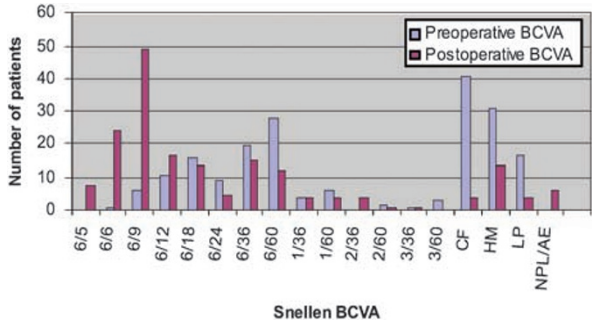

Figure 1 Distribution of BCVA (Snellen) comparing preoperative and postoperative vision.

Additional surgical intervention at the time of surgery failed to add to the risk of rejection. Cataract extraction, IOL removal or insertion in the anterior chamber or posterior chamber did not increase the risk of rejection (OR: 1 (CI:0.4–2.2), 0.76 (CI:0.1–3.0), 0.33 (CI:0.03–2.35), and 0.96 (CI:0.4–2.6), respectively).

Table 2 outlines the postoperative complications. Thirty-six (18%) grafts were documented as failed grafts in 33 patients. The failure group was made of 14 men and 19 women, with a mean age of 56.3 years. The mean overall 5-year survival, therefore, was 82%. The rate of graft failure from any cause was highest in the first 3 years of follow-up (Figure 2). However, the survival rates over 5 years for KC and corneal dystrophies were 93 and 89%, respectively. Survival rates for herpetic keratitis, regrafts, and PBK were 75, 76, and 77%, respectively.

Table 3 details the main causes of failure. Allograft rejection accounted for 16 (44%) cases, endothelial failure in nine cases (25%), six (17%) were secondary to MK, and glaucoma was the cause in four (11%) grafts. One patient underwent failure because of unknown aetiology. Endothelial rejection was the leading cause of failure in cases of regrafts. Of the 40 regrafts, 10 failed of which 8 were because of endothelial rejection, followed by endothelial failure in one case and glaucoma in the other. Preoperative variables of recipient vascularisation ($P = 0.0005$), inflammation ($P = 0.004$), infection (0.04),

Table 2 Complications postoperatively in all penetrating keratoplasty patients

Complication	*Number of patients (%)*
First rejection episode	43 (21)
Graft failure	36 (18)
Postkeratoplasty glaucoma	37 (18)
Microbial keratitis	16 (8)

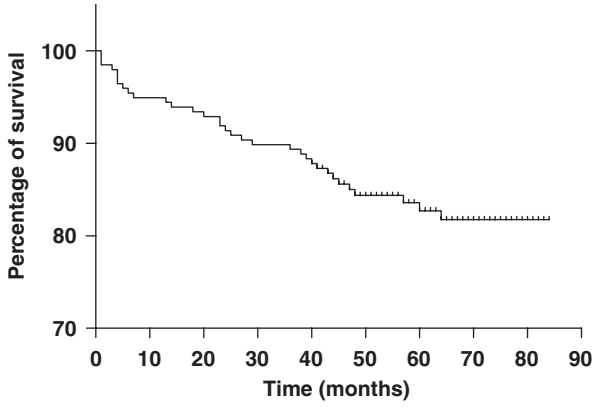

Figure 2 Kaplan–Meier survival curve showing graft survival.

and glaucoma ($P = 0.03$) were strongly associated with graft failure. Only vitrectomy as an adjunctive procedure at the time of PK had a significant effect on eventual graft failure ($P = 0.0003$).

Table 4 summarises donor and recipients factors associated with graft failure. Donor factors including donor age, death to enucleation time, endothelial cell count, and storage time, were not associated with an increased risk of eventual failure when the group of 167 non-failed patients is compared to the 36 transplants who failed. Donor size had no bearing on failure in this study ($P = 0.08$).

Table 3 Causes of corneal graft failure

Cause	*Number of cases*
Rejection	16 (44%)
Glaucoma	4 (11%)
Infection	6 (17%)
Endothelial failure	9 (25%)
Unknown	1 (3%)
Total	36

Glaucoma

Postkeratoplasty glaucoma (PKG) describes either the postoperative development of raised IOP (>21 mmHg) requiring long-term treatment, or the requirement for increased treatment in patients with previously controlled glaucoma. Glaucoma was a finding in 37 (18%) patients following PK. Table 5 shows RR of developing PKG. In this group, 30 (81%) had preoperative visual acuity of 3/60 or worse. In the non-PKG group, 74 (47%) had preoperative acuity of 3/60 or worse. Postoperatively, 16 (47%) of those that developed PKG obtained visual acuity of 6/36 or better, compared with 115 (76%) in the non-PKG group. The RR for graft failure in this group was 2.5 when compared with those without glaucoma ($P = 0.005$). Of the four patients with glaucoma-related failure, two required surgical lowering of intraocular pressure and two required laser cyclodiode. Patients with PKG had a significantly higher rate of graft failure ($P = 0.005$, RR: 2.5). Preexisting glaucoma was present in 31(16%) of the total sample. Patients with preexisting glaucoma had a higher rate of developing PKG ($P = 0.02$, RR: 2.44). All

Table 4 Analysis of factors associated with graft failure

	Cohort	*Graft failure*	P-*value*
Donor patients	$N = 167$	$N = 36$	
Average age (years)	58.1	56.3	0.58
Average death enucleation (h)	15.4	15.2	0.9
Average endothelial cell density (cells/mm^2)	2626	2668	0.36
Average storage time (days)	19	19.3	0.76
Recipient factors			
Average recipient age (years)	56.9	52.2	0.68
Inflammation	32 (20%)	15 (42%)	0.004
Infection	16 (9%)	8 (22%)	0.04
Glaucoma	19 (12%)	9 (25%)	0.03
Ocular surface disease	23 (14%)	9 (25%)	0.12
Vascularisation	65 (39%)	26 (72%)	0.0005
Additional procedures			
Cataract extraction	28 (17%)	5 (14%)	1
Intraocular lens removal	10 (6%)	3 (8%)	0.7
Anterior chamber Intraocular lens	10 (6%)	2 (6%)	1
Posterior chamber Intraocular lens	25 (15%)	4 (11%)	0.79
Vitrectomy	7 (4%)	9 (25%)	0.0003
Glaucoma	2 (1%)	0 (0%)	1
Graft size			
>8 mm	122 (74%)	20 (56%)	0.082
<8 mm	38 (23%)	13 (36%)	
Unknown	7 (4%)	3 (8%)	
Postoperative complications			
Microbial keratitis	13 (8%)	3 (8%)	0.44
Glaucoma	25 (15%)	11 (31%)	0.03
One rejection episode	29 (16%)	14 (31%)	0.05

Table 5 Relative risk of developing postkeratoplasty glaucoma

	No PKG (N = *167*)	*PKG* (N = *36*)	*Relative risk*	*95% CI*	P-*value*
Pseudophakic bullous keratopathy	20	11	2.21	1.20–4.11	0.03
Ulcerative keratitis	4	2	1.93	0.60–6.23	0.28
Fungal infection	2	1	1.90	0.37–9.71	0.45
Regrafts	35	11	1.50	0.80–2.81	0.27
Aphakic bullous keratopathy	3	1	1.42	0.25–7.97	0.54
Viral	7	2	1.27	0.36–4.47	0.66
Bacterial	4	1	1.13	0.19–6.70	1
Keratoconus	43	5	0.52	0.21–1.26	0.19
Corneal dystrophy	26	2	0.37	0.09–1.45	0.18
Others	23	1	0.34	0.07–1.23	0.15

cases of PKG developed within 6 months of surgery. Surgery performed for PBK had the highest RR for PKG (RR: 2.32, $P = 0.02$) of any group of aetiologies. The combined surgery did not have a significant risk (RR: 1.47, $P = 0.29$) compared with PK only surgery. No difference in PKG development was found between those given oversized and same-sized grafts.

Microbial keratitis

In all, 16 grafts of 15 patients were noted to have suffered postoperative MK, an incidence of 7.9%, with the majority 12 (75%) developing within the first 6 months (range:1–48 months). Corneal scrapes were carried out in all 16 cases and had a sensitivity of 94%, and 15 cases were culture positive. Corneal vascularisation was the most important host factor and suture-related problems were the most important graft factor implicated in MK following PK. The most common offending pathogens were; Gram-positive cocci with *Streptococcus pneumoniae* in four (25%) cases, *Staphylococcus epidermidis* in three (19%), and *Staphylococcus aureus* in one case (6%). *Pseudomonas* and *Candida* were implicated in two (13%) cases each. *Mycobacterium fortuitum* was isolated in one case because of recurrence of the primary infection in the graft. The eventual outcome was variable. In seven (44%) grafts, the infection settled with intensive topical antibiotic therapy and the graft maintained its clarity. One of these cases included a suture abscess where there was a wound gape following suture removal requiring resuturing. Three (19%) of these cases occurred in failing grafts and accelerated graft decompensation. In six (38%) cases, MK was commonly associated with graft failure, with the one patient with mycobacterium requiring evisceration of intraocular contents.

Discussion

Survival and complication rates of PK have been regularly reported in the developed, and indeed, the developing world. However, the treatment of complications is less frequently analysed, and the effectivity of the procedure has proved more difficult to evaluate.

The assessment of improved functional vision following transplantation, particularly for unilateral pathology, is complex. Relatively few analyses of corneal graft outcomes include final visual acuity, considering that the majority of PKs are performed for visual rehabilitation. Brahma *et al*[6] reported a prospective study evaluating visual function in a series of 18 KC patients. They found continued improvement in LogMar visual acuity, contrast sensitivity, and decreased glare following successful postoperative PK. These were positively correlated with an improved VF-14 score, confirming the efficacy of PK in KCs. In our study, 48% of patients achieved best-corrected Snellen acuity (BCVA) of 6/12 or better 5 years postoperatively, compared with 9% achieving the same visual acuity preoperatively. Similarly, the proportion of individuals obtaining counting fingers, hand movement, light perception, or worse reduced from 44% preoperatively to 14% postoperatively. This is encouraging, especially as 35% of grafted patients could be considered high risk, as defined by Vail *et al*,[7] in this review. In a similar cohort, Beckingsale *et al*[8] described a BCVA of 6/18 or better in over 50% of high risk patients over 5 years. Although, the goal of corneal grafting is to maximise visual potential of the eye, other than glaucoma, we did not evaluate associated ocular comorbidity that may have limited visual potential in the remaining 52% of patients at 5 years because of the retrospective nature of this review.

Our overall 5-year survival rate was 82%. Other studies have documented varying rates of survival 36–93%.[4,9–18] Specific indications for corneal transplantation, in particular KC and corneal dystrophies have comparatively high survival rates.[17,19] Studies with a selection bias towards low-risk grafting may result in more favourable survival rates. However, our case mix

encompasses a wide range of indications for grafting, ranging from KC (48 cases) to regrafts (40 cases), and therefore, represents a varied group of patients within a cohort of a tertiary referral centre. The 5-year survival of 82% is favourable and may reflect the 'centre effect' described by Thompson *et al*[20] and Vail *et al*,[7] whereby specialist centres performing regular corneal grafting achieve more favourable results.

It is difficult to isolate each factor as an individual risk for failure, as multiple pathologies may be involved. The risk factors identified in this study have been well documented in previous studies and confirm the significance of corneal vascularisation, additional surgical procedures, glaucoma, and rejection as significant risk factors in eventual failure.[4,9,10]

In our study, 21% of recipients experienced at least one episode of endothelial rejection over a mean follow-up of over 5 years. Of all PKs in this study, 7.4% suffered eventual graft failure following an episode of rejection emphasising the importance of vigilance and prompt treatment to maintain graft clarity in this setting. Most rejection episodes occur in the first 3 years following keratoplasty.[21] However, our mean time of rejection was 15.9 months, similar to the results of Alldredge *et al*[22] and Peleyer *et al*[21] who noted that the rejection appeared most frequently over the first 12 months, 29 and 43%, respectively. Their rates of rejection, on the other hand, were higher than our findings which were closer to that of Ing *et al*,[9] who over a 10-year period documented a cumulative probability of 21 and 23% over 15 years.[8] This may represent the difference in case mix, relatively lower levels of high-risk grafts, our practice of long-term use of topical corticosteroids, and the inclusion of only confirmed endothelial rejection.

The incidence of rejection in KC is somewhat surprising. Rejection episodes appear to be common and accounted for 30% of all cases of rejection. However, only 23% of KC rejection episodes led to graft failure. Reports on the incidence of allograft rejection following PK in KC have been variable. In 1974, Chandler and Kaufman[23] reported a high incidence of 35%. Sharif and Casey[24] documented a rate of 21%. Others, however, have stated far lower rates varying between 6 and 7.8%.[25,26] This observation in our study is the subject of further analysis.

We found the incidence of glaucoma after PK to be 18%, comparable with other studies.[27–29] Reported risk factors for developing glaucoma after PK include simultaneous cataract extraction, trauma, previous PK, aphakic BK, and preexisting glaucoma.[30–34] Graft failure was 2.5 times greater in the PKG group, confirming the importance of detection and management of PKG.

Patients with a preoperative history of glaucoma showed more than double the risk of developing postoperative intraocular pressure problems compared with those without a preoperative history of glaucoma. In our study, combined procedures did not increase the risk of developing PKG. However, we found a statistically significant increase in risk of PKG in the cases that underwent PK for PBK. This was a 2.32 times greater risk compared with other indications.

MK following corneal transplantation is a major complication with profound effects on overall success of the graft. An important host risk factor for MK in our cohort appears to be corneal vascularisation of host tissue, although the reason remains unclear. Persistent corneal epithelial defects and failed grafts are other important graft factors associated with increased incidence of MK in our cohort. Further, the presence of ocular surface disorder was an important aetiological factor predisposing to infective keratitis. Ocular surface disease, with associated dry eyes, was linked to almost 50% of all MK cases.

The main donor graft-related factor predisposing to the development of MK in our study was suture-related problems, that is, loose, broken sutures, or suture removal. Siganos *et al*[35] showed that bacteria are encountered at the site of suture erosion, and if sutures have been eroded for more than 24 h, the risk of bacterial invasion increases. Similarly, manipulation of corneal graft sutures potentially has the risk of infection.[36]

If previously failed grafts were excluded, MK was associated with graft failure in 46% of affected grafts in our study comparable to the findings of Tavakkoli and Sugar.[37] Despite aggressive treatment, the prognosis of patients with MK after PK is poor.

Conclusion

PK is overall an effective long-term treatment for improving visual function in selected patients. Our overall survival rate of 82% over 5 years is comparable with other published studies. However, postoperative complications limit graft clarity and surgical success. We found an unexpectedly high rate of rejection episodes in KC individuals, and of postoperative MK. Retrospective reviews of corneal transplantation continue to offer important insight into the complications and outcome of PK.

Acknowledgements

We thank Biostatistics Department at the UK Transplant, in particular Mark Jones, for their advice. We also thank the Eye Bank team at the Manchester Royal Eye Hospital for information and comments and Dr David Haider for assistance in data collection.

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