

Optical and Tectonic Corneal Transplant Outcomes in a Tertiary Hospital in Singapore within the Singapore Corneal Transplant Registry

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Abstract

Introduction: This study aimed to describe and compare corneal graft survival and optical outcomes following deep anterior lamellar keratoplasty (DALK) and Descemet's stripping automated endothelial keratoplasty (DSAEK) with penetrating keratoplasty (PK), and to document tectonic success of patch grafts. **Materials and Methods:** This was a retrospective, non-randomised, comparative and descriptive cohort study. A total of 139 eyes that underwent primary keratoplasty between 2000 and 2016 were included, and the following data was extracted: demographics, clinical diagnosis and primary indication, pre- and intraoperative risk factors, postkeratoplasty outcomes, and complications. Optical success was defined as good graft clarity and best corrected visual acuity (BCVA) of 6/12 or better. Graft failure was defined as irreversible corneal oedema and loss of clarity. Tectonic success in patch grafts was defined as tectonic integrity with no repeat tectonic surgical procedure required in the postoperative period. **Results:** The mean follow-up duration was 3.24 ± 3.47 years in the PK group ($n = 16$), 1.89 ± 0.86 years in the DALK group ($n = 37$), 2.36 ± 1.24 years in the DSAEK group ($n = 53$), and 2.17 ± 1.09 years in the patch graft group ($n = 33$). The 3-year probabilities of survival for PK, DALK, DSAEK and patch graft were 60.9%, 94.1%, 89.9%, and 67.1%, respectively. The overall percentage of complications was significantly higher for PK (81.3%), compared to DALK (48.6%), DSAEK (49.1%), and patch graft (21.2%). In the PK and DALK groups, 100% achieved BCVA of 6/12 or better, while in the DSAEK group, 96.43% achieved BCVA of 6/12 or better. **Conclusion:** From a similar study cohort of Asian eyes, graft survival was superior and complications were reduced for DALK and DSAEK compared to PK, but optical outcomes were comparable. Graft survival for patch graft was expectedly lower, but the incidence of complications was low.

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Introduction

Penetrating keratoplasty (PK), which involves full-thickness replacement of a diseased cornea with an allograft donor cornea, has long been a well accepted and highly successful procedure, with numerous reports of short-term graft success of 90% or higher.¹ However, allograft endothelial rejection rates are as high as 18% based on a Cochrane review,² with rejection rates of primary grafts ranging from 9% to 42% in randomised controlled trials (RCT).³ Graft rejection usually leads to loss of graft

clarity and optical graft failure.⁴ In recent years, new data on long-term graft survival has emerged,¹ suggesting more disappointing survival rates. This is largely due to an exponential loss in endothelial cell density over time, resulting in graft failure and ongoing irreversible allograft rejection.⁵

There has been an increasing trend in recent years towards partial-thickness replacement of the diseased cornea, namely deep anterior lamellar keratoplasty (DALK) and

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Descemet's stripping automated endothelial keratoplasty (DSAEK), for various corneal pathologies.

DALK involves replacement of diseased anterior corneal stroma, while preserving unaffected Descemet's membrane and endothelium, most commonly for keratoconus, anterior stromal dystrophies or for other forms of anterior stromal scarring.⁶ Compared to PK, it allows the conservation of the host endothelium, thus removing the risk of endothelial rejection and reducing risks of intraocular complications, which translates to better long-term outcomes. Stromal or epithelial rejection is much less common and less severe than endothelial rejection, and can usually be successfully reversed by topical steroids, with preservation of graft optical quality. In addition, unlike PK, DALK surgery avoids an open-sky surgical procedure, hence avoiding intraocular complications and the major risk of intraoperative expulsive haemorrhage, which is usually blinding. However, it is technically more demanding and if imperfectly performed, may result in suboptimal visual outcomes because of interface and refractive irregularities.

Corneal endothelial disorders such as Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy (PBK) or aphakic bullous keratopathy (ABK) are among the commonest indications for corneal transplantation, with PBK accounting for the majority of corneal transplants in Singapore. PK has long been the traditional transplant procedure of choice for endothelial dysfunction, but has recently been supplanted by endothelial keratoplasty (EK) procedures, which offer better graft survival, fewer complications, and better visual outcomes compared to PK.⁷ DSAEK is the commonest form of EK surgery, and has now become the "gold standard" for endothelial dysfunction, comprising a closed eye, small incision procedure where only the posterior lamella of a diseased cornea is replaced, while retaining the host cornea stromal tissue.⁸ DSAEK has several advantages over PK. For example, it avoids an open-sky procedure, requires minimal sutures, thus minimising induced astigmatism with a smoother anterior corneal surface, and prevents suture-related graft complications. DSAEK also provides enhanced tectonic integrity with only a 5 mm or less beveled incision—this results in fewer complications with regard to ocular surface conditions and a neurotrophic state in PK surgery, where severed corneal nerves take many months to regenerate in the donor cornea. Finally, early visual recovery and quality are greatly enhanced, with minimal refractive shifts or astigmatism, unlike what occurs in PK surgery which usually requires sequential corneal suture removal over many months.⁸

It is recognised that although PK offers patients similar visual improvement in the long-term,⁸ DALK and DSAEK are superior to PK in terms of visual rehabilitation, refractive stability (surgically-induced

astigmatism), graft rejection, wound dehiscence, suture-related problems, and intraocular complications.^{8,9}

Corneal patch grafting, which includes PK, lamellar, or peripheral grafts of various shapes and sizes, is a useful tectonic and/or therapeutic option in selected cases of corneal thinning and perforations because it effectively restores the integrity of the globe.¹⁰ In the Singapore Corneal Transplant Study (SCTS), graft survival rates following tectonic keratoplasty by PK were lower than optical graft survival rates, at 68.3% and 41.7% at 1 and 3 years, respectively. DALK has shown to offer a significant advantage over PK in terms of graft rejection and endothelial cell loss,¹¹ but for the purpose of this paper, we will only document the long-term tectonic success of patch grafts in general.

Many studies have looked at baseline risk factors for graft failure, including patient demographics and clinical diagnosis, preoperative recipient corneal tissue status, and donor corneal tissue status, as well as short-term outcomes. Most studies have demonstrated favourable short-term outcomes of DALK and DSAEK over PK, but with comparable visual acuity outcomes to PK.^{4,8} A Cochrane review also concluded that there was no strong evidence in terms of visual outcome and graft survival, to suggest that EK is superior to PK. However, various techniques of EK such as deep lamellar EK, Descemet's stripping EK, DSAEK and femtosecond laser-assisted EK were employed in this review, which may have a bearing on the findings.⁹ Still, relatively few studies have studied long-term outcomes such as graft survival and visual acuity. Apart from the SCTS,¹ there is no other local corneal transplant data available.

The SCTS is an ongoing prospective cohort study designed to prospectively track corneal transplant outcomes in Singapore.^{12,13} Initiated in Singapore, SCTS has tracked over 5000 transplants mainly performed at the Singapore National Eye Centre (SNEC) since its inception in 1991. SCTS prospectively captures preoperative clinical data, donor tissue data, operative data, and yearly postoperative updates for all corneal transplant patients at SNEC and its related subsidiary units from Changi General Hospital (CGH), Kandang Kerbau Hospital (KKH) (paediatric patients), and at SNEC faculty practice (SNEC Eye Associates) and Gleneagles Hospital. At the National University Hospital (NUH) Department of Ophthalmology, the Corneal Service developed its corneal transplantation in tandem with the SNEC Corneal Service since 2000, and both institutions perform all forms of corneal transplantation procedures including PK, DALK, DSEK and corneal patch grafts, utilising jointly developed surgical protocols. In coordination with the Singapore Eye Bank (SEB), which tracks SCTS, and the Singapore Eye Research Institute, NUH has adopted the SCTS database and is currently its second major clinical institution for corneal transplants.

The current SCTS database has now been expanded into a formal registry, and renamed the Singapore Corneal Transplant Registry (SCTR). SCTR currently tracks corneal transplants performed at SNEC, CGH, KKH, NUH and also involves the majority of corneal transplants performed at Gleneagles Hospital by corneal surgeons within the SNEC faculty practice (SNEC Eye Associates) and Eye & Cornea Surgeons (a division of the Eye & Retina Surgeons private group practice). Collectively, SCTR currently tracks approximately 85% of all corneal transplants performed in Singapore—in 2016, SCTR tracked 420 out of a total of 490 transplants performed.

This study analyses primary graft outcomes, complications and survival rates between the 3 main forms of optical transplants performed at the NUH Corneal Service, with direct comparison of conventional PK surgery to DALK and DSAEK, in terms of graft survival, optical outcomes and complication rates, as well as analysis of tectonic success in corneal patch grafts over a 15-year period. All surgeries were performed by 3 NUH corneal surgeons (DT, AT, MR) utilising similar surgical transplant protocols.

Materials and Methods

Corneal Donor Tissue Acquisition

The acquisition of corneal donor tissue in Singapore and within this study is from the SEB. The SEB is the sole provider for corneal tissue in Singapore since 1991. With the exception of grafts performed for emergency therapeutic or tectonic reasons, internal guidelines within the SEB releases grade A corneal tissue with endothelial cell counts exceeding 2200 cells/mm² and a death-to-surgery time generally not exceeding 7 days for elective keratoplasty for optical indications.¹

Methodology

A total of 218 eyes that underwent keratoplasty at a single tertiary institution, NUH, between 2000 and 2016 were identified from Computerised Patient Support System (CPSS) or Medical Records Office (MRO). Consecutive patients who underwent either a primary PK, DALK, DSAEK, or patch graft for optical (surgery performed primarily for visual recovery), tectonic (surgery performed to restore globe integrity of eyes with abnormally thin or perforated corneas), or therapeutic (surgery performed to eradicate corneal infection or neoplasia) reasons were included. This left a total of 139 primary grafts, including 9 bilateral cases, after excluding 66 grafts with follow-up of less than 1 year and 13 repeat grafts.

Case records were retrospectively reviewed and the following data extracted: demographics (age at time of keratoplasty, sex, and race); type of keratoplasty (PK,

DALK, DSAEK, or patch graft); clinical diagnosis and primary indication; duration of follow-up; preoperative risk factors (pre-existing glaucoma, cataract or uveitis, active inflammation or infection, ocular surface disease, lid disease, and globe perforation at time of surgery); additional intraoperative procedures at the time of keratoplasty; and postkeratoplasty best-corrected visual acuity (BCVA), immunosuppression regime, complications, subsequent surgeries or procedures, and graft failures.

Outcomes were measured at 1 month, 3 months, 6 months, and yearly thereafter. The main outcome measures were graft failure, defined as irreversible oedema and loss of clarity, and optical outcomes, determined by graft clarity and BCVA.

All grafts were performed by 1 of our 3 corneal surgeons (DT, AT, MR) from NUH over the same period (2000-2016) utilising unified surgical protocols.

The study adhered to the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board.

Long-Term Outcomes and Graft Failure

Long-term outcomes included glaucoma or raised intraocular pressure (IOP), allograft rejection, postoperative anterior synechiae at graft, late graft failure, epithelial problems, microbial keratitis, activation of herpes simplex virus (HSV) keratitis, suture-related infection, endophthalmitis, recurrence of primary disease, and other complications.

Graft failure was defined as irreversible oedema and loss of clarity in a graft that was previously documented to be thin and clear, with the date of onset of corneal clouding selected as the time-point of graft failure, with the precise clinical cause of graft failure as recorded by the surgeon in the case notes.

Clinical Diagnosis and Primary Indications for Keratoplasty

Cases were classified based on the International Classification of Disease (ICD-10) into 9 major clinical diagnoses: infectious keratitis, postinfectious scars, pseudophakic bullous keratopathy or aphakic bullous keratopathy (PBK/ABK), Fuchs' endothelial dystrophy (FED), keratoconus, corneal trauma, postglaucoma corneal endothelial decompensation, regrafts, and other diagnoses. In addition to clinical diagnosis, cases were classified into 3 primary indications: optical, therapeutic, and tectonic.

Statistical Analysis

Statistical analysis was performed by a statistician using the Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS, Inc, Chicago, Illinois, USA).

Kaplan-Meier survival analysis was used to estimate the cumulative probability of survival of PK, DALK, DSAEK, and patch graft groups. Other statistical analysis included descriptive statistics, where the mean values and standard deviations were calculated for continuous variables, and frequency distribution and percentages were calculated for categorical variables. Comparisons between categorical variables were conducted by Fisher's Exact tests, whereas 1-way analysis of variance was used for continuous variables. Statistical significance was defined as a <0.05 .

Results

Patient Data

A total of 218 corneal grafts, comprising PK ($n = 29$), DALK ($n = 62$), DSAEK ($n = 73$), and patch graft ($n = 54$), were initially identified. The eyes underwent keratoplasty between 2000 and 2016.

Overall mean age at the time of operation was 52.33 ± 23.24 (0.22-89.24) (mean $\pm$ standard deviation [SD] range) years. Mean age of PK, DALK, DSAEK, and patch graft groups were 47.16 ± 24.50 (0.56-88.10) years, 33.75 ± 18.39 (0.22-81.28) years, 61.79 ± 20.63 (0.69-89.24) years, and 63.65 ± 15.93 (5.80-82.66) years respectively. There were 15 paediatric recipients (recipients ≤ 16 years).

63.8% of patients were males. There were more males across PK, DALK, DSAEK, and patch graft groups. The difference in gender was not significant ($P = 0.285$).

The ethnic ratio of our Asian cohort approximated the ethnic ratio in Singapore, with Chinese being the predominant race (61.9%), and Malays (11.9%), Indians (16.1%), and other races (10.1%) making up the remaining cohort. Chinese was the predominant race across PK, DSAEK, and patch graft groups, except in DALK group, where Indians were the predominant race due to the predominance of keratoconus in this ethnic group.

Of the 218 corneal grafts, the majority was for optical indications ($n = 149$), followed by tectonic indications ($n = 61$), and therapeutic indications ($n = 8$). The common clinical diagnoses were PBK/ABK ($n = 6$, 20.7%), traumatic scarring ($n = 6$, 20.7%), and bacterial keratitis ($n = 4$, 13.8%) for PK, keratoconus ($n = 34$, 54.8%) and traumatic scarring ($n = 8$, 12.9%) for DALK, PBK/ABK ($n = 33$, 45.2%) and FED ($n = 15$, 20.5%) for DSAEK, and prior glaucoma surgery with glaucoma drainage implant (GDI) tube, plate exposure or scleral melting ($n = 41$, 75.9%) for patch graft.

A total of 139 out of 218 consecutive primary corneal grafts, comprising PK ($n = 16$), DALK ($n = 37$), DSAEK ($n = 53$), and patch graft ($n = 33$), were included for analysis of long-term outcomes. Of the 139 corneal grafts, 99 were for optical indications, 36 for tectonic indications, and 4 for

therapeutic indications. The eyes underwent keratoplasty between 2000 and 2016 and were followed up for 2.29 ± 1.59 (mean $\pm$ SD) years (range 0.00-15.19 years). Mean follow-up period was 3.24 ± 3.47 years in the PK group ($n = 16$), 1.89 ± 0.86 years in the DALK group ($n = 37$), 2.36 ± 1.24 years in the DSAEK group ($n = 53$), and 2.17 ± 1.09 years in the patch graft group ($n = 33$).

Graft Survival

Overall graft survival time for tectonic and therapeutic grafts compared to optical grafts were expectedly lower (2.99, 2.26, and 4.52 years, respectively) (Fig. 1), attributed to higher severity of disease, infection, inflammation, glaucoma, corneal vascularisation, ocular surface instability or limbal stem cell deficiency compared to optical cases, and this difference was significant (log rank $P = 0.02$).

Comparing PK, DALK, DSAEK, and patch graft groups, overall graft survival time for PK, DALK, DSAEK, and patch graft were 3.97 ± 0.50 mean [$\pm$ standard error], 3.67 ± 0.12 , 4.36 ± 0.23 , and 2.91 ± 0.28 years, respectively. A subgroup analysis revealed significant differences for DALK versus patch graft ($P = 0.009$) and DSAEK versus patch graft ($P = 0.007$). However, PK versus DALK, DSAEK, and patch graft, and DALK versus DSAEK were insignificant ($P = 0.105$, 0.221 , 0.498 , and 0.687 , respectively).

The Kaplan-Meier (KM) probabilities of survival for PK were 93.8%, 85.2%, and 60.9% at 1, 2, and 3 years respectively, compared to 94.1%, 94.1%, and 94.1% for DALK, 94.2%, 94.2%, and 89.9% for DSAEK, and 78.8%, 71.6%, and 67.1% for patch graft (Table 1). Lower probabilities of survival for patch graft were expected due to its tectonic indications. There were no differences in probabilities of survival comparing PK, DALK, and DSAEK

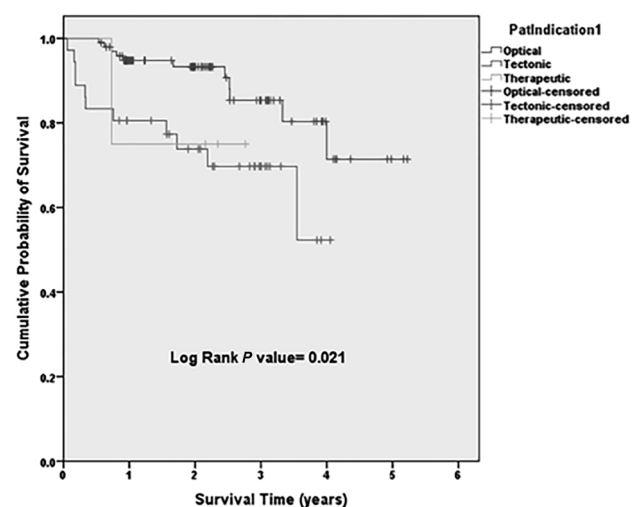


Fig. 1. Graft survival curves by optical, tectonic and therapeutic outcomes.

Table 1. Cumulative Kaplan-Meier Graft Survival Probabilities Comparing PK, DALK, and DSAEK

Year	PK		DALK		DSAEK	
	n	Survival Rate	n	Survival Rate	n	Survival Rate
1	15	93.8%	31	94.1%	48	94.2%
2	10	85.2%	31	94.1%	48	94.2%
3	5	60.9%	31	94.1%	21	89.9%
4	5	60.9%			5	68.7%
5	5	60.9%				

DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; PK: Penetrating keratoplasty

at 1 year (93.8% vs 94.1% vs 94.2%). However, we note a drop in probability of survival for PK at 2 years (93.8% vs 85.2%), while probabilities of survival for DALK and DSAEK did not change at 2 years. There was a significant drop in probability of survival for PK at 3 years, while that for DALK remained unchanged and DSAEK dropped more modestly.

The KM probabilities of survival (Fig. 2) demonstrate that the best long-term survival was seen in the DALK group (Fig. 3), followed by the DSAEK group (Fig. 4), and lastly by the PK group. Statistical significance compared to PK was not achieved due to the small sample size.

Complications

Overall percentage of complications was significantly higher for the PK group (81.3%) compared to the DALK group (48.6%) and the DSAEK group (49.1%). Of note, the patch graft had a significantly lower percentage of complications (21.2%), which could be attributed to smaller grafts and no need for long-term immunosuppression.

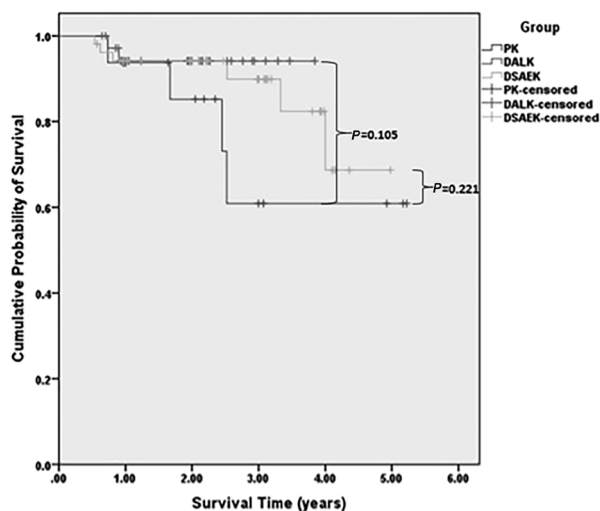


Fig. 2. Graft survival curves comparing PK, DALK and DSAEK. PK: Penetrating keratoplasty; DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty.

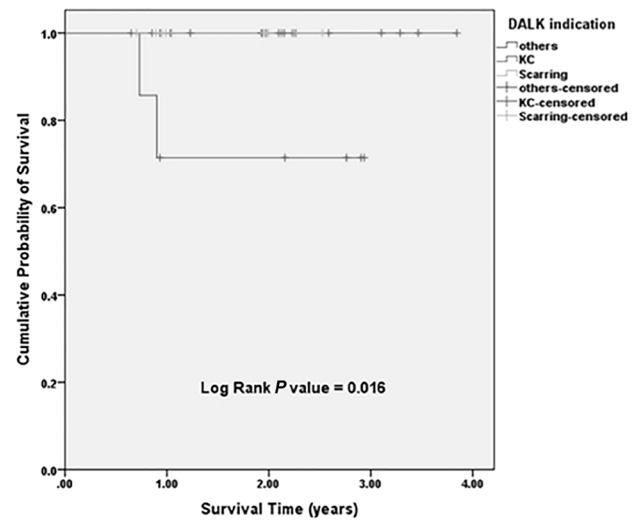


Fig. 3. Graft survival curves of DALK by primary clinical diagnoses. DALK: Deep anterior lamellar keratoplasty; KC: Keratoconus.

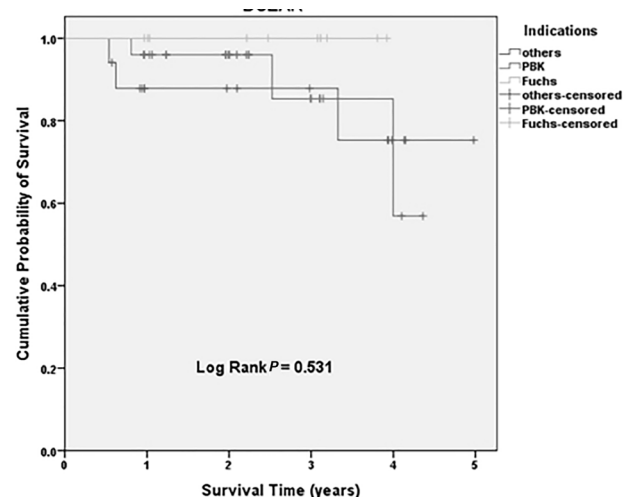


Fig. 4. Graft survival curves of DSAEK by primary clinical diagnoses. DSAEK: Descemet's stripping automated endothelial keratoplasty; PBK: Pseudophakic bullous keratopathy.

Raised IOP ($n = 28$), epithelial problems ($n = 14$) and allograft rejection ($n = 11$) were the most common complications (Table 2). In our study, 29 eyes had pre-existing glaucoma, comprising 5 eyes from the DSAEK group and 24 eyes from the patch graft group. The most frequent complications were glaucoma or raised IOP (31.3%), allograft rejection (18.8%) and epithelial problems (18.8%) for the PK group, glaucoma or raised IOP (29.7%) and epithelial problems (10.8%) for the DALK group, glaucoma or raised IOP (20.8%), allograft rejection (9.4%) and epithelial problems (9.4%) for the DSAEK group, and epithelial problems (6.1%) and microbial keratitis (6.1%) for the patch graft group.

Table 2. Complications Comparing PK, DALK, DSAEK, and Patch Graft Groups over the Follow-up Period

Complication	PK (n = 16)	DALK (n = 37)	DSAEK (n = 53)	Patch Graft (n = 33)
Glaucoma or raised IOP	5	11	11	1
Allograft rejection	3	2	5	1
Late graft failure	0	0	2	0
Epithelial problems	3	4	5	2
Microbial keratitis	1	1	0	2
Activation of HSV keratitis	1	0	3	1
Suture-related infection	1	2	0	0
Endophthalmitis	0	0	0	1
Recurrence of primary disease	0	1	0	3
Other complications	1	3	1	10

DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; HSV: Herpes simplex virus; IOP: Intraocular pressure; PK: Penetrating keratoplasty

Late graft failure occurred in only 2 cases of DSAEK (3.8%). Of note, there was a higher incidence of allograft rejection in the PK group (18.8%) compared to the DALK group (5.4%), DSAEK group (9.4%) and patch graft group (3.0%).

Optical Outcomes

BCVA was measured using a Snellen chart. For the purpose of this outcome measure, only cases with optical indications were included. Of these optical cases, failed grafts and eyes with pre-existing comorbidities (cloudy graft, amblyopia, glaucoma, cataract, retinal or macular disease) were excluded, leaving a total of 48 preoperative eyes and 52 postoperative eyes at 1 year for comparison, based on the available data at the time-point (Table 3, Fig. 5).

There was an overall significant improvement in visual acuity after keratoplasty. All eyes had better BCVA postoperatively compared to preoperatively. By 1 year

Table 3. Best Corrected Visual Acuity of Optical Cases Preoperatively and 1 Year Postoperatively

Visual Acuity	Preoperative		Postoperative	
	n	%	n	%
6/12 or better	9	18.75	51	98.08
6/15 – 6/48	25	52.08	1	1.92
6/60 – 6/120	3	6.25	0	0
CF or worse	11	22.92	0	0
Total	48	100	52	100

CF: Counting fingers

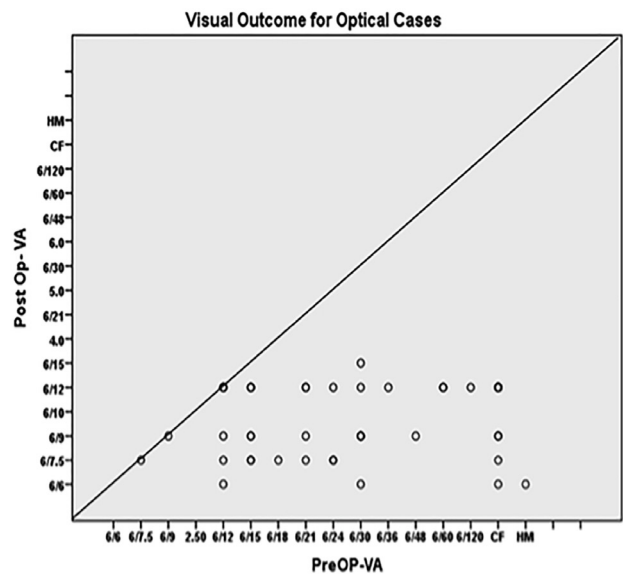


Fig. 5. Comparison of best-corrected visual acuity of optical cases preoperatively and 1 year postoperatively. VA: Visual acuity

postoperatively, all but 1 eye (98.08%) achieved BCVA of 6/12 or better.

Preoperative and postoperative BCVA in the PK, DALK, and DSAEK groups were individually analysed and compared (Table 4). In the PK and DALK groups, 100% achieved BCVA of 6/12 or better, while in the DSAEK group, 98.08% achieved BCVA of 6/12 or better. However, the difference in the percentage of patients achieving BCVA of 6/12 or better at postoperative year 1 between the PK, DALK, and DSAEK groups was not significant.

Of note, 100% of the patients in the PK group had preoperative BCVA of counting fingers (CF) or worse, compared with 23.81% in the DALK group and 16.00% in the DSAEK group. This generally reflects the higher visual compromise in eyes requiring total corneal replacement with disease involvement of both corneal stroma and corneal endothelium, in the PK group, as opposed to the DALK group with only stromal disease, or DSAEK group with primarily only endothelial dysfunction.

Discussion

PK has been the gold standard graft for corneal transplantation for over a century. However, in the last decade, the evolution of corneal transplant surgery has seen the emergence of modern techniques in selective lamellar replacement of corneal tissue, in the form of anterior lamellar (DALK) or posterior lamellar (DSAEK) transplantation, as important watersheds to the field.¹² Still, the major goals of keratoplasty, which are visual improvement and prolonged

Table 4. Best Corrected Visual Acuity of PK, DALK, and DSAEK Groups Preoperatively and 1 Year Postoperatively

Visual Acuity	PK		DALK		DSAEK	
	Preoperative n (%)	Postoperative n (%)	Preoperative n (%)	Postoperative n (%)	Preoperative n (%)	Postoperative n (%)
6/12 or better	0 (0)	3 (100)	4 (19)	21 (100)	5 (20)	27 (96.4)
6/15 – 6/48	0 (0)	0 (0)	11 (52.4)	0 (0)	14 (56)	1 (3.6)
6/60 – 6/120	0 (0)	0 (0)	1 (4.8)	0 (0)	2 (8)	0 (0)
CF1 or worse	2 (100)	0 (0)	5 (23.8)	0 (0)	4 (16)	0 (0)
Total	2 (100)	3 (100)	21 (100)	21 (100)	25 (100)	28 (100)

CF: Counting fingers; DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; PK: Penetrating keratoplasty

graft survival, remain unchanged, and in this study, we evaluated graft survival, postoperative complications, and optical outcomes of the various techniques of keratoplasty, and compared the outcomes of PK with DALK and DSAEK.

A review of literature reveals heterogeneous conclusions of graft success.^{8,11,14,15,16} While numerous clinical studies specifically evaluating success rates in DALK and DSAEK compared with PK have shown the superiority of these lamellar procedures in terms of visual outcomes, graft survival, and complication rates, most of these studies were efficacy studies involving limited numbers of surgeons and specific or controlled indications, often with exclusion of high-risk comorbidities. The Australian Corneal Graft Registry (ACGR) has recently suggested that the survival of DALK and DSAEK may in fact be worse than the survival of PK performed over the same time frame, when analysed in a “real world” clinical situation, involving major cohort registry with many surgeons at different stages of the learning curve and varied indications.¹⁷ In the ACGR, most of the DSAEKs that failed were the results of primary graft failure, and the majority of DSAEKs failed within the first 12 months after surgery, suggesting that the surgical technique rather than the PK, DALK, or DSAEK procedure itself may be an important factor for graft survival.

At NUH, graft survival for PK, DALK, and DSAEK was comparable at 1 year, but subsequently, the graft survival of PK was poorer than that of DALK and DSAEK. The poor graft survival of PK may be attributed to the fact that the majority of patients who underwent PK had endothelial disease (ABK/PBK), and the SCTS had previously demonstrated that corneal endothelial health was an important overall predictor of graft survival. In DALK surgery, however, host endothelial function was generally normal, and was not replaced. In the study, endothelial indications (PBK/ABK, FED, and regraft) represented the 3 disease groups with the lowest graft survival, where the most common cause of graft failure was immunologic rejection (29.15%) (with endothelial rejection as the dominant form), followed by late endothelial failure (21.36%).¹ Similar

findings have been reported in other studies.⁷ Our findings mirror the results seen in other SCTS publications, where DALK and DSAEK were seen to have longer graft survival compared with PK.^{6,7,11,15}

Our study also supports the advantage of DALK and DSAEK over PK in terms of a lower incidence of complications, although the PK group had a smaller sample size compared to the DALK and DSAEK groups and hence may not be a fair comparison. This is a conceivable finding, because PK is an intraocular procedure, in contrast to DALK, which is essentially extraocular and non-penetrating.⁴ While DSAEK—as an essentially small incision procedure—results in less suture-related and wound-related complications as compared to PK. Of significance, the incidence of allograft rejection was significantly higher with PK (18.8% vs 9.4% and 5.4% in DSAEK and DALK, respectively). In DSAEK, less donor corneal tissue is transplanted, which results in less antigenicity challenge, while in DALK, the obviation of the possibility of endothelial rejection with DALK is a major advantage over PK,⁴ and we have demonstrated that the incidence of allograft rejection is indeed significantly reduced with DALK. As anterior lamellar and endothelial keratoplasty techniques improve, we expect further improvements in clinical outcomes tacking on to its recognised advantages, but more definitive studies are needed.

Of note, we notice that glaucoma or raised IOP was the overall most common complication, and recognise that it would be important to ascertain if these patients have an underlying history of glaucoma, which will have a bearing on the findings. Many of our patients experienced only a transient rise in IOP that was largely steroid-induced. Few patients progressed to chronic glaucoma. However, the incidence of transient elevated IOP or glaucoma after DALK or DSAEK compared with PK seems to be comparable, or even reduced. One study comparing PK and DSAEK found no significant difference in the 5-year incidence of postoperative glaucoma.⁷ In our study, the 5-year cumulative incidence of transient elevated IOP was 22.4 +/- 4.1

(cumulative incidence $\pm$ 95% confidence interval) for the PK group and 23.6 $\pm$ 4.1 for the DSAEK group ($P = 0.689$). All PK and DSAEK patients in this study received a standard postoperative relatively high-dose steroid regimen. Another study comparing PK and DALK found a higher incidence of postoperative glaucoma in the PK group.⁴ As a result of the lower risk of allograft rejection, DALK patients in this study required a shorter postoperative steroid regimen than PK patients, which may contribute to the lower rate of glaucoma. This is further suggestive that postoperative steroid is an important cause of glaucoma after keratoplasty. A targeted study evaluating steroid-induced glaucoma after PK reported a significant overall frequency of 73% and 60.3% in eyes with keratoconus and Fuchs dystrophy, respectively.¹⁸ Yet another study found steroid-induced IOP elevation as the most frequent cause of the incidence of IOP elevation, compared with other risk factors such as pre-existing glaucoma, preoperative lens status, preoperative diagnosis, age, preoperative IOP, preoperative synechiae, and combined surgery.¹⁹ In conclusion, IOP may be elevated after keratoplasty. However, the elevated IOP is commonly steroid-induced, often benign and transiently elevated, and do not all progress to chronic glaucoma. Moreover, steroid-induced transient elevated IOP can normally be treated effectively by antiglaucoma medications, tapering steroids, or changing steroids. Of note, postoperative administration of steroids is effective in reducing postoperative inflammation and preventing the development of peripheral anterior synechiae,¹⁹ which has shown to be one of the main complications of elevated IOP after keratoplasty.²⁰ Further studies are needed to investigate the optimal medication schedule after keratoplasty.

PK currently remains the most common form of corneal transplantation in the world at present, although it is increasingly being replaced by lamellar keratoplasty in various conditions, especially in more developed countries with well established corneal transplant programmes.²¹ It also appears that the rate of adoption of lamellar keratoplasty is highly variable between geographic regions, and between developed and less developed countries. This dichotomy is attributed to many factors, such as the availability of surgical training in the newer procedures, access to appropriately dissected donor tissue including appropriate instrumentation, relative cost issues for performing the procedures, and the inherent variability in the types and severity of corneal diseases pertinent to specific populations.⁶

Conclusion

Our study shows that corneal transplantation remains a highly successful vision-restoring procedure. All the patients achieved good postoperative BCVA at the level of 6/12 or better. It should be noted that the baseline BCVA of patients

who subsequently underwent PK was generally worse than those who underwent DALK and DSAEK, and this may be attributed to PK being selected as the procedure of choice for later stage disease involving multiple corneal layers, but nonetheless the optical success of PK in our series remains comparable to DALK and DSAEK.

The main drawback of this study is its retrospective nature, resulting in limited long-term follow-up data due to patients who were lost to follow-up. However, the KM analysis generally takes into account the length of follow-up of approximately 3 years.

We also recognise the smaller sample size of our PK group as our centre shifted mainly to lamellar surgery in the later years. Previous randomised controlled trials (RCTs) comparing DALK with PK have had small sample sizes and short follow-up periods. One RCT comparing EK with PK encountered incomplete enrolment as EK techniques changed rapidly.²² Still, we are aware that interpreting outcomes between different studies can be difficult when outcome definitions vary, preoperative characteristics are not well defined, and outcome assessments are not standardised.²² Hence we believe that evaluating a relatively newer surgical technique should be performed under standardised conditions to identify specific differences in outcomes of interest. This is what we aimed to achieve in our corneal transplant study.

Future long-term, large-cohort studies are definitely needed to assess and compare the advantages of the various techniques of keratoplasty. Baseline risk factors and clinical indications must also be analysed to understand the interplay between preoperative factors and choice of keratoplasty technique. However, we acknowledge that this corneal transplant study at NUH is at a relative early stage, and as the database continues to mature, we anticipate additional data relevant to prospective, nested studies in a larger cohort. We propose further prospective cohort studies or retrospective nested cohort studies based on the database as the next best alternatives. We believe that such a registry that is under annual audit at NUH provides the advantages of a large prospective cohort to minimise selection bias in a controlled setting of multiple surgeons with varying degrees of surgical experience, and at the same time utilising standardised surgical techniques and postoperative management. This will hence continue to provide valuable insights into the long-term outcomes of the various techniques of keratoplasty in the same study population.⁷ Finally, this study validates the development of a national corneal transplant programme across Singapore with similar surgical protocols and training standards within the SCTR. It also confirms the feasibility of adopting national surgical transplant protocols and standards across clinical institutions, and with many surgeons at different stages of training. More

importantly, SCTR data analysis enables us to evaluate the ongoing development of newer surgical techniques and transplant procedures in selective lamellar keratoplasty as they are being adopted and also as younger generations of corneal surgeons are trained and accredited. Our study confirms that with unified and updated surgical protocols and techniques, excellent visual outcomes and graft survival rates are achievable in selective lamellar keratoplasty that continues to largely replace conventional PK.

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