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Comparison of penetrating keratoplasty and deep anterior lamellar keratoplasty in keratoconus eyes with vernal keratoconjunctivitis

Sepehr Feizi, Mohammad Ali Javadi, Seyed-Mohamadmehdi Moshtaghion and Mohammad Abolhosseini

Abstract

Purpose: The purpose of the study is to compare outcomes after penetrating keratoplasty (PK) against deep anterior lamellar keratoplasty (DALK) for keratoconus in patients with vernal keratoconjunctivitis (VKC).

Methods: Keratoconic patients with VKC who received PK ($n = 55$, group 1) or DALK ($n = 62$, group 2) were retrospectively enrolled. The Student's t test, Mann–Whitney test, Fisher's exact test, chi-square test, and Kaplan–Meier survival curve were used to compare outcomes between the groups.

Results: The follow-up period was 59.4 ± 44.1 and 62.4 ± 38.9 months in groups 1 and 2, respectively ($p = 0.70$). Postoperative best spectacle-corrected visual acuity was 0.24 ± 0.18 and 0.29 ± 0.19 logMAR, respectively ($p = 0.13$). Graft rejection occurred in 34.6% and 25.8% of eyes in groups 1 and 2, respectively ($p = 0.30$). Groups 1 and 2 were comparable in the rates of cataract (3.6% and 12.9%, respectively, $p = 0.07$) and high intraocular pressure (3.6% and 8.1%, respectively, $p = 0.31$). Compared with the eyes with inactive VKC, PK eyes that experienced postoperative disease reactivation had a higher rate of suture abscesses (10.9% *versus* 50.0%, respectively, $p = 0.01$) and suture-tract vascularization (6.5% *versus* 33.3%, respectively, $p = 0.03$). Similarly, disease reactivation significantly increased suture abscesses from 27.3% to 51.7% ($p = 0.03$) and suture-tract vascularization from 18.2% to 49.6% ($p = 0.005$) in the DALK group. The graft survival rates were 95.3% in group 1 and 87.9% in group 2 at the 4-year follow-up, with mean durations of 14.4 and 11.1 months, respectively ($p = 0.20$).

Conclusion: The results indicate no difference in outcomes between PK and DALK for keratoconus in patients with VKC. Postoperative VKC reactivation increased the rate of suture-related problems after both techniques of keratoplasty.

Keywords: deep anterior lamellar keratoplasty, keratoconus, penetrating keratoplasty, vernal keratoconjunctivitis

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Correspondence to:
Sepehr Feizi
Ophthalmic Research Center and Department of Ophthalmology, Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Boostan 9 Street, Pasdaran Avenue, Tehran 16666, Iran.
sepehrfeizi@yahoo.com

Mohammad Ali Javadi
Seyed-Mohamadmehdi Moshtaghion
Mohammad Abolhosseini
Ophthalmic Research Center and Department of Ophthalmology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Introduction

Penetrating keratoplasty (PK) is an established technique of corneal transplantation for patients with keratoconus with acceptable clinical outcomes.[1–3] However, replacing the corneal endothelial layer in PK increases the risk of graft rejection and, hence, graft failure.[4] Deep anterior lamellar keratoplasty (DALK) is now considered to be the technique of choice for corneal transplantation in keratoconus when other less invasive options such as rigid-gas permeable contact lens fitting and intrastromal corneal ring

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implantations are not appropriate.[5] This therapy aims to selectively replace the abnormal corneal stroma while preserving the recipient's normal endothelium, thereby preventing endothelial graft rejection. Furthermore, DALK is an extraocular surgery and has minimal detrimental effects on corneal endothelial cell density.[6]

It is recognized that excellent visual outcomes and graft survivals can be obtained after the performance of both techniques, PK and DALK, for corneal transplantation in eyes with keratoconus and no ocular comorbidity.[1–5,7–11] The presence of co-existing ocular surface diseases, however, can negatively influence the success rate of keratoplasty for this indication. Vernal keratoconjunctivitis (VKC) is a chronic allergic conjunctivitis that can be associated with keratoconus in 26.8% of cases.[12] Theoretically, the prognosis following corneal transplantation might be less favorable in patients with keratoconus and concomitant VKC because of several confounding factors, including chronic inflammation, ocular surface abnormalities, and peripheral corneal neovascularization. Previously, no statistically significant differences were found in the visual outcomes or graft survivals following PK for keratoconus in eyes with or without a history of VKC.[13,14] Other authors, however, have reported a lower graft survival after PK for keratoconus with concomitant VKC compared with keratoconus alone.[15] Although acceptable visual outcomes and complication profiles were reported after DALK for keratoconus,[5–11] the majority of these reports did not specify whether keratoconus was associated with VKC. Only one study reported clinical outcomes following DALK in eyes with keratoconus and concomitant VKC and compared the results with those after DALK in eyes with only keratoconus.[16] To the best of our knowledge, no reports have compared the outcomes following PK against DALK for keratoconus and VKC to determine which technique is the better approach when corneal transplantation is indicated. In this study, a series of keratoconic patients with concomitant VKC who underwent PK or DALK were compared to identify differences, if any, in their clinical outcomes, complications, and graft survivals.

Methods

In this retrospective comparative interventional case series, we reviewed the records of all keratoconic patients with concomitant VKC who received a first corneal transplant in the 20-year interval from June 1998 to January 2017. All participants had a minimum follow-up time of 12 months. If both eyes of a patient received corneal transplantation and were eligible to be included in the study, the eye with longer follow-up was enrolled. Patients received two types of corneal transplantation during the study period. Before November 2006, all patients with VKC received a PK, but between November 2006 and January 2017, a DALK was the most common procedure. During the second period, PK was performed in advanced cases (seven eyes) when the corneal stroma was very thin or there were deep stromal scars, which was suggestive of previous hydrops. Moreover, DALK was converted into PK intraoperatively in five eyes with VKC due to a large tear in Descemet's membrane (DM). These 12 eyes that received a PK graft during the second period of the study were excluded. Other exclusion criteria included the co-existence of ocular pathologies apart from VKC in the preoperative period, such as cataract, retinal disorders, and glaucoma. This research adhered to the tenets of the Declaration of Helsinki. The Shahid Beheshti University Institutional Review Board approved the study protocol (IR.SBMU.ORCREC.1396.001), and all patients provided written informed consent to participate.

Preoperative findings included a complete ophthalmologic examination encompassing the measurement of uncorrected visual acuity (UCVA), manifest refraction (if possible), best spectacle-corrected visual acuity (BSCVA) using the Snellen acuity chart, slit lamp biomicroscopy, tonometry, and dilated fundoscopy. Keratoconus was diagnosed based on clinical findings (Fleischer's ring, corneal ectasia, stromal thinning, and Vogt's striae) and was confirmed by conventional corneal topography (TMS-1 Topographic Modeling System, version 1.61, Computed Anatomy Inc., New York, NY, USA). A diagnosis of VKC was accepted if the patients presented during the active phase of the disease (severe itching with characteristic signs, including giant papillae on the upper tarsal conjunctiva, limbal gelatinous infiltrates, and Horner-Trantas dots) or had a history of treatment for VKC with suggestive residual findings, such as pseudogerontoxon.

Indications for corneal transplantation included low visual acuity with rigid gas-permeable (RGP) contact lens due to corneal scar, inappropriate contact lens fit, or RGP contact lens intolerance.

All surgeries were performed under general anesthesia by a single experienced corneal transplant surgeon (MAJ). PK was done using the standard technique. DALK was performed using the big-bubble technique, as previously described.[5] In cases where a bared DM could not be achieved after several air injections, layer-by-layer stromal dissection down to DM was performed using a crescent knife. It was attempted to remove as much of the corneal stroma as possible in these eyes. In both study groups, donor corneas were sutured to the recipient bed using interrupted or combined suturing technique which was chosen at the discretion of the surgeon.

Fresh donor corneas were procured from the central eye bank of Iran. Our eye bank performed an overall quality assessment of the donor tissues based on endothelial cell density and qualitative features such as the extent of folds in DM and stromal edema. These features were used to rate the donor tissue quality as excellent, very good, good, and fair categories as previously described.[17] Donor epithelial status was not considered for the purpose of quality assessment.

Postoperative outcomes included UCVA, BSCVA, refraction, and keratometry readings. Additional outcomes measured included length of postoperative follow-up, duration of steroid therapy, time interval from surgery to initial and complete suture removal, postoperative complications [suture-related problems, intraocular pressure (IOP) >21 mmHg, and cataract formation], time and number of graft rejection episodes, reactivation of VKC, further surgical interventions (if needed), and graft transparency. Acute graft rejection was defined as the presence of subepithelial infiltration (subepithelial graft rejection) or stromal edema and infiltration with or without graft vascularization (stromal graft rejection) in both the PK and DALK groups. Endothelial graft rejection was characterized by the presence of keratic precipitates with or without graft edema in the PK group. Graft failure was defined as irreversible loss of graft clarity.

Perioperative management

Active VKC was controlled preoperatively using a topical short-term pulse steroid, mast cell stabilizers four times a day, and systemic antihistamines twice a day. After the cessation of topical steroids, all of the subjects were chronically maintained on the topical mast cell stabilizer and antihistamine throughout the hot season. Surgery was deferred until the cold season in cases with active VKC, and the disease was medically controlled or inactive in all participants at least 6 months before keratoplasty.

Postoperatively, daily evaluations were performed until complete graft reepithelialization. Thereafter, follow-up examinations were performed at 7 and 30 days; at 3, 6, 12, and 18 months, and at every 6 months thereafter. Follow-up examinations were scheduled more frequently if indicated, and patients had access to the surgeon if needed. Postoperatively, all cases received topical chloramphenicol 0.5% every 6 hours for 15 days and topical betamethasone 0.1% every 4–6 hours, tapered off at the discretion of the surgeon; topical steroid treatment was discontinued in all patients by postoperative month 12. This corticosteroid regimen was similar between the PK and DALK groups. Topical lubricants were added and a bandage contact lens (OmniFlex, Hydron, UK) was applied when graft epithelium was instable during the immediate postoperative period. In the event of VKC reactivation, the same preoperative topical regimen was resumed. No cases received topical or systemic immunomodulators (i.e. cyclosporine and tacrolimus) for the management of VKC reactivation before or after keratoplasty. Acute rejection reactions to the corneal transplants were treated by frequent topical betamethasone 0.1%. High IOP (>21 mm Hg) was treated by reducing the dose of topical steroids and initiating topical antiglaucoma medications.

In all cases, postoperative suture management included selective interrupted suture removal starting at month 3 to reduce keratometric astigmatism. Adjustment of running suture tension was not performed in any eyes. Suture abscesses were treated by increasing the frequency of topical betamethasone 0.1%, and other suture-related complications, including premature loosening or suture-tract vascularization, were managed by suture removal.

Statistical analysis

Data were analyzed using the SPSS statistical software version 25 (SPSS Inc., Chicago, IL, USA). Based on the results of a Kolmogorov–Smirnov normality test and the Q–Q plotting, Student's *t* test and the Mann–Whitney test were used to compare normally and non-normally

Table 1. Comparison of demographic and preoperative details between eyes with keratoconus and vernal keratoconjunctivitis that underwent penetrating keratoplasty (group 1) and those that underwent deep anterior lamellar keratoplasty (group 2).

Parameters	Group 1	Group 2	*p* value
Age (years)	26.2 ± 7.5 (12–47)	24.8 ± 6.2 (14–41)	0.30
Male/female	38/17	39/23	0.48
Right/left eye	26/29	35/27	0.32
BSCVA (logMAR)	1.50 ± 0.59 (0.70–2.60)	1.30 ± 0.51 (0.50–2.30)	0.07
Mean keratometry (D)	57.40 ± 6.50 (50.50–78.0)	55.95 ± 4.96 (49.50–62.60)	0.15
Keratometric astigmatism (D)	5.64 ± 3.51 (1.50–10.0)	6.09 ± 2.95 (2.0–12.0)	0.68

BSCVA, best spectacle-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution.

distributed continuous data, respectively, between the study groups. The Fisher's exact test and chi-square test were used for the comparison of the qualitative parameters. A logistic regression analysis of covariance and a Cox regression in survival analysis were used to adjust the study groups for the effects of confounding factors on postoperative complications. Binary logistic regression models were used to evaluate the correlation of preoperative use of antihistamines/mast cell stabilizers and suturing technique with postoperative complications in each group. The Kaplan–Meier survival curve and log-rank test were used to evaluate and compare the cumulative rate of graft survival between the study groups. A p value < 0.05 was considered statistically significant.

Results

A total of 117 eyes (61 right eyes) of 117 patients (77 men) with keratoconus and concomitant VKC who received a first corneal transplant during the 20-year interval met the inclusion criteria. Of these, 55 eyes (47.0%) received PK before November 2006 (group 1) and 62 eyes (53.0%) received DALK after November 2006 (group 2). In group 2, a bared DM was successfully achieved in 44 eyes, whereas predescemetic DALK was performed in 18 eyes. The duration of follow-up was 59.4 ± 44.1 (range = 13–188) months in group 1 and 62.4 ± 38.9 (range = 12–157) months in group 2 ($p = 0.70$). The number of PK patients who were lost to follow-up was 10, 16, 26, 33, 35, and 37 at postoperative 1.5, 2, 3, 4, 5, and 10 years, respectively. The corresponding figures were 6, 11, 18, 26, 34, and 41 in the DALK group.

Table 1 presents the demographic and preoperative data of two groups. As demonstrated, the two study groups were balanced for patient sex, patient age at the time of keratoplasty, preoperative BSCVA, mean keratometry, and keratometric astigmatism. Preoperatively, there was peripheral corneal vascularization in three eyes (5.5%) in group 1 and one eye (1.6%) in group 2 ($p = 0.25$). Sixteen eyes (29.1%) in group 1 and 21 eyes (33.9%) in group 2 were treated with antihistamines or mast cell stabilizers or both at the time of keratoplasty ($p = 0.59$). No cases received corticosteroids preoperatively. There was no significant difference between the two groups in donor and recipient trephination size, suturing technique, duration of steroid therapy, and time interval from surgery to initial and complete suture removal (Table 2). Corticosteroid was discontinued by postoperative month 6 in 92.7% and 85.5% of eyes in groups 1 and 2, respectively ($p = 0.21$). Table 3 compares the data relevant to the donor tissues between the two study groups. The two groups were comparable for donor age, donor sex, and storage time. The quality of the donor tissue transplanted in the PK group, however, was significantly better than that transplanted in the DALK group (Table 3).

Postoperative visual and refractive outcomes

The mean postoperative UCVA was 0.53 ± 0.40 (range = 0.10–1.70) logMAR (logarithm of the minimum angle of resolution) in group 1 and 0.67 ± 0.48 (range = 0.10–1.70) logMAR in group 2 ($p = 0.29$). The mean postoperative BSCVA was 0.24 ± 0.18 (range = 0.0–0.70) logMAR and 0.29 ± 0.19 (range = 0.0–1.30) logMAR in groups 1 and 2,

Table 2. Comparison of operative and postoperative details between eyes with keratoconus and vernal keratoconjunctivitis that underwent penetrating keratoplasty (group 1) and those that underwent deep anterior lamellar keratoplasty (group 2).

Parameters	Group 1	Group 2	*p* value
Recipient size (mm)	8.0 ± 0.22 (7.50–8.50)	7.98 ± 0.24 (7.50–8.50)	0.50
Donor size (mm)	8.27 ± 0.23 (7.75–8.75)	8.23 ± 0.23 (7.75–8.75)	0.47
Suturing technique, *n* (%)			0.38
Separate	23 (41.8)	21 (33.9)	
Combined	32 (58.2)	41 (66.1)	
Duration of steroid therapy (months)	3.9 ± 2.2 (2–12)	4.8 ± 2.2 (2–12)	0.14
Interval from surgery to initiation of suture removal (months)	9.4 ± 8.3 (1–31)	7.8 ± 7.0 (1–33)	0.36
Interval from surgery to suture removal completion (months)	16.3 ± 8.5 (10–28)	15.0 ± 8.1 (9–38)	0.52

Table 3. Comparison of data corresponding to donor corneas transplanted in eyes with keratoconus and vernal keratoconjunctivitis that underwent penetrating keratoplasty (group 1) and those that underwent deep anterior lamellar keratoplasty (group 2).

Parameters	Group 1	Group 2	*p* value
Age (years)	31.2 ± 11.4 (10–60)	34.6 ± 14.2 (14–70)	0.17
Male/female	35/20	36/26	0.54
Preservation-to-transplantation time (days)	1.3 ± 1.2 (0–5)	1.7 ± 1.5 (0–6)	0.20
Donor graft rating, *n* (%)			0.004
Excellent	11 (20.0)	11 (17.7)	
Very good	39 (70.9)	24 (38.7)	
Good	5 (9.1)	12 (19.4)	
Fair	0	15 (24.2)	

respectively ($p = 0.13$). Postoperative BSCVA of ⩾20/40 was achieved in 80.8% and 78.7% of eyes in groups 1 and 2, respectively ($p = 0.90$).

The mean postoperative spherical equivalent refractive error was significantly lower in group 1 (–3.45 ± 2.90 D; range = –10.5 to +1.75 D) than that in group 2 (–4.99 ± 3.30 D; range = –14.0 to +0.15 D, $p = 0.03$). The mean keratometry was 45.09 ± 2.33 D (range = 39.5–50.25 D) in group 1 and 47.31 ± 2.24 D (range = 43.0–52.0 D) in group 2 postoperatively ($p < 0.001$). No significant difference was observed between the study groups in the final keratometric astigmatism (4.16 ± 2.77 D; range = 0.50–12.0 D in group 1 *versus* 4.30 ± 2.36 D; range = 1.0–12.25 D in group 2, $p = 0.83$).

Complications

Graft epithelial problems were more frequently encountered after DALK; complete epithelial

healing was enhanced by bandage contact lenses in 5 eyes (9.1%) in group 1 and 16 eyes (25.8%) in group 2 ($p = 0.02$). The difference in graft epithelial problems was not significant after adjusting the results for the donor quality ($p = 0.38$). Postoperative reactivation of VKC was diagnosed in 6 eyes (10.9%) of group 1 and 30 eyes of group 2 (48.4%, $p < 0.001$). All episodes of the disease reactivation were treated successfully.

Suture complications were observed in 24 eyes (43.6%) in group 1 and 42 eyes (67.7%) in group 2 ($p = 0.01$). These complications included premature loosening (32.7% *versus* 50% in groups 1 and 2, respectively; $p = 0.06$), broken sutures (5.5% *versus* 9.7% in groups 1 and 2, respectively; $p = 0.39$), suture abscesses (14.6% *versus* 38.7% in groups 1 and 2, respectively; $p = 0.003$), and suture-tract vascularization (9.1% and 33.9% in groups 1 and 2, respectively; $p = 0.001$). The significant difference in suture-related complications between the study groups was observed even after controlling the confounding effect of different graft qualities. When the results were adjusted for the different rate of VKC reactivation, however, the study groups became comparable in terms of suture-associated problems.

IOP > 21 mmHg was observed in two eyes (3.6%) in group 1 and five eyes (8.1%) in group 2 during the follow-up period ($p = 0.31$). IOP was controlled medically in all of these eyes. Some degrees of steroid-induced cataracts developed in two eyes (3.6%) in group 1 and eight eyes (12.9%) in group 2 ($p = 0.07$). Cataract surgery was not indicated as BSCVA was ⩾20/40 in these eyes.

In all, 19 eyes (34.6%) in group 1 and 16 eyes (25.8%) in group 2 experienced at least 1 episode of graft rejection ($p = 0.30$). The time interval between surgery and the first episode of graft rejection was 7.8 ± 5.1 (range = 2–24) months in group 1 and 12.4 ± 7.5 (range = 5–31) months in group 2 ($p = 0.05$). Eight eyes (14.6%) of group 1 and seven eyes (11.3%) of group 2 experienced two or more episodes of graft rejection ($p = 0.60$). During the study period, the total number of graft rejection reactions was 41 (21 subepithelial, 1 stromal, and 19 endothelial) in group 1 and 27 (18 subepithelial and 9 stromal) in group 2. Timely diagnosis and frequent topical steroid treatment led to a reversal of rejection in 16 eyes of group 1 and 14 eyes of group 2.

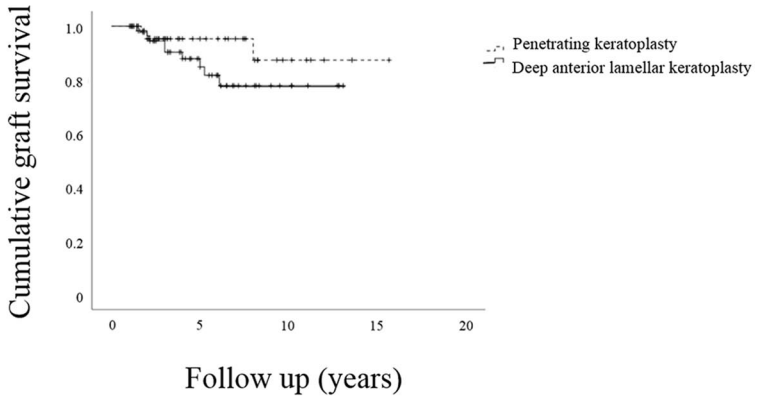
Graft survival

At the final follow-up examination, corneal graft remained clear in 52 eyes (94.6%) of group 1 and 53 eyes (85.5%) of group 2 ($p = 0.11$). Three eyes of group 1 lost a clear graft following irreversible endothelial graft rejection. Epithelium-related complications resulted in superficial graft opacity in two eyes of group 2. Other causes of graft failure in this group included graft vascularization after stromal rejection (two eyes) and interface haziness (five eyes). The reason for interface haziness was vascular proliferation in the interface caused by suture-tract vascularization (three eyes) and stromal graft rejection (two eyes). The vessels regressed upon appropriate managements in these eyes; however, extravasation of proteinaceous materials resulted in permanent interface haziness. At the 4-year follow-up examination (median of follow-up), the graft survival rates were 95.3% in group 1 and 87.9% in group 2, with mean durations of 14.4 [95% confidence interval (CI) = 13.0–15.8] months and 11.1 (95% CI = 9.9–12.3) months in groups 1 and 2, respectively ($p = 0.20$; Figure 1).

Post hoc power analysis was used to determine the study power. This analysis revealed that our study had a power of 64%, 58%, and 41% to detect the observed difference in the rates of suture-related problems, graft rejection, and graft failure between the study groups, respectively.

Risk factor analysis

Regression analysis revealed that suturing technique and preoperative use of medications had no significant association with postoperative complications, including suture-related problems, graft rejection, or graft failure (Table 4). The severity of VKC at the time of surgery was not included in this analysis as the disease was inactive in all patients at least 6 months preoperatively. Based on the postoperative reactivation of VKC, two subgroups were formed in each study group: one subgroup with medically controlled VKC at the time of surgery which experienced recurrence of the disease postoperatively and the other subgroup with an inactive form of the disease which only had a history of treatment for VKC. The mean patient age at the time of keratoplasty was not significantly different between subjects with medically controlled VKC and those with inactive disease in the PK group (26.0 ± 4.4 *versus* 26.2 ± 7.9 years, respectively,



Time to event (years)		1	1.5	2	3	4	5	10
PK	Number at risk	55	45	39	29	22	20	18
	Cumulative graft survival (%)	100	100	95.3	95.3	95.3	95.3	87.3
DALK	Number at risk	62	56	51	44	36	28	21
	Cumulative graft survival (%)	100	98.3	96.4	90.3	87.9	84.8	77.8

Figure 1. Kaplan–Meier survival curve. Four years (median follow-up) after corneal transplantation for keratoconus and concomitant vernal keratoconjunctivitis, the graft survival rate was 95.3% in the PK group *versus* 87.9% in the DALK group, with mean durations of 14.4 and 11.1 months, respectively ($p = 0.20$). The number of eyes and graft survival rate at each follow-up visit are provided.
DALK, deep anterior lamellar keratoplasty; PK, penetrating keratoplasty.

Table 4. Correlation coefficients and their statistical significance from binary logistic regression models that evaluate association of preoperative use of medications and suturing technique with complications after penetrating keratoplasty (group 1) and deep anterior lamellar keratoplasty (group 2).

Risk factors	Study group	Suture-related complications	Graft rejection	Graft failure
Preoperative use of medications	Group 1	$\beta = 0.91$, $p = 0.75$	$\beta = 1.40$, $p = 0.43$	$\beta = 4.16$, $p = 0.26$
	Group 2	$\beta = 2.08$, $p = 0.43$	$\beta = 5.01$, $p = 0.33$	$\beta = 0.54$, $p = 0.69$
Suturing technique	Group 1	$\beta = 0.02$, $p = 0.82$	$\beta = 0.03$, $p = 0.98$	$\beta = 0.11$, $p = 0.97$
	Group 2	$\beta = 2.98$, $p = 0.74$	$\beta = 8.11$, $p = 0.20$	$\beta = 0.44$, $p = 0.89$

$p = 0.95$) or in the DALK group (24.4 ± 5.6 *versus* 25.3 ± 6.8 years, respectively, $p = 0.56$). Similarly, comparison between the subgroups did not yield any significant difference in terms of visual and refractive outcomes, the rate of graft rejection, high IOP, steroid-induced lens opacity, or graft failure in each study group ($p > 0.20$ for all comparisons). Compared with the eyes with inactive VKC, PK eyes that experienced postoperative disease reactivation had a higher rate of suture abscesses (10.9% *versus* 50.0%, respectively, $p = 0.01$) and suture-tract vascularization (6.5% *versus* 33.3%, respectively, $p = 0.03$). Similarly, VKC reactivation significantly increased the odds of suture abscesses from 27.3% to 51.7% ($p = 0.03$) and suture-tract vascularization from 18.2% to 49.6% ($p = 0.005$) in the DALK group. To evaluate the effect of surgeon experience on the DALK outcomes, we divided the DALK eyes into two subgroups according to the surgery sequence number (cases 1–31 *versus* cases 32–62). Comparisons between these two subgroups revealed no significant differences in the rate of successful big-bubble formation (75% *versus* 64.7%, respectively, $p = 0.41$), interface haziness (9.7% *versus* 6.5%,

Table 5. Summary of studies evaluating clinical results and complications after corneal transplantation performed in eyes with keratoconus and vernal keratoconjunctivitis.

Authors	Type of keratoplasty	Eyes (*n*)	Patient age (years)	Follow-up (months)	BCVA ⩾ 20/40	Graft rejection	Clear graft	Complications
Cameron and colleagues[15]	PK	14	17 (11–28)	19.6 (4–60)	57.1%	NA	80%	Graft ulcer (20%)
Egrilmez and colleagues[14]	PK	23	16.6 ± 4.8 (10–27)	34 ± 16.3 (18–67)	91.3%	4.3%	100%	Glaucoma (8.7%), cataract (17.4%)
Mahmood and Wagoner[18]	PK	90	18.7	44.7 (24–144)	61.1%	13.3%	92.2%	Culture-positive bacterial keratitis (6.6%), recurrent herpes simplex virus keratitis (1.1%)
Wagoner and colleagues[13]	PK	80	20	58.6 (6.8–117.2)	76.2%	12.5%	97.5%	Early-onset PED (2.5%), late-onset PED (6.3%), bacterial keratitis (5%), glaucoma (3.8%), cataract (1.2%)
Feizi and colleagues[16]	DALK	28	27.2 ± 6.8 (15–41)	34.4 ± 20.9	88.5%	35.7%	96.4%	Epithelium-related problems (42.9%), suture-related complications (78.6%), high IOP (10.3%), cataract (25%)

BCVA, best-corrected visual acuity; DALK, deep anterior lamellar keratoplasty; IOP, intraocular pressure; NA, not accessible; PED, persistent epithelial defects; PK, penetrating keratoplasty.

respectively, $p = 0.64$), or graft failure (12.9% *versus* 16.1%, respectively, $p = 0.72$).

Discussion

A limited number of studies evaluated the effect of VKC on the outcomes of corneal transplantation in keratoconus (Table 5). Cameron and colleagues[15] reported that the addition of VKC was a significant risk factor for graft failure after PK. Mahmood and Wagoner[18] found that PK in eyes with keratoconus and VKC led to an excellent visual result and a low complication rate. Wagoner and colleagues[13] found that the visual outcomes, postoperative complications, and graft survival were comparable after PK for keratoconus in eyes with or without VKC. However, eyes with VKC were more likely to develop late-onset persistent epithelial defects.[13] Egrilmez and colleagues[14] found that the clinical outcomes after PK in eyes with keratoconus and VKC were comparable with those in eyes with keratoconus alone. However, loose sutures and steroid-induced cataracts were more frequently observed in cases with VKC.[14] Feizi and colleagues[16] reported comparable visual outcomes and graft clarity after DALK in keratoconic patients with and without VKC. Suture-related complications, however, were more common in the VKC group, leading to a significantly larger amount of graft astigmatism.[16] In this study, we retrospectively reviewed the postoperative outcomes in a consecutive series of keratoconic patients with VKC who underwent PK or DALK performed in the same setting by a single experienced surgeon. Our results indicate that comparably excellent visual outcomes and graft survival can be expected following both PK and DALK in eyes with VKC. The percentage of eyes achieving a final BSCVA of ⩾20/40 after either PK or DALK in this study was comparable or better than the results previously reported by similar studies (Table 5). With respect to refractive outcomes, DALK yielded a significantly higher spherical equivalent refraction and mean keratometry than did PK. Similarly, other investigators reported that patients with DALK have

significantly steeper grafts than those with PK; this difference is attributable to the surgical features of DALK, which is performed as a closed-system procedure.[19,20]

Our results showed that suture-related problems, including abscess formation and suture-tract vascularization, were more frequently observed in the DALK group than in the PK group. Using grafts with a lower quality cannot be the explanation for an increase in the prevalence of suture-related problems following DALK in the current series because the observed difference was still significant after the study groups were adjusted for the donor quality. Alternatively, our results suggest that difference between the two groups in suture complications is attributable to the postoperative reactivation of VKC, which was more frequently encountered in the DALK group than the PK group. In addition, the results of subgroup analysis revealed that postoperative reactivation of VKC could increase the odds of suture abscesses and suture-tract vascularization after both PK and DALK. Cameron and colleagues[15] reported that reactivation of VKC after keratoplasty can cause serious complications, which lead to graft failure, and recommended deferring corneal transplantation until VKC becomes inactive, rather than just medically controlled. Based on our experience, VKC reactivation had no detrimental effects on final visual and refractive outcomes, graft rejection, or graft survival. We believe that the control of ocular inflammation through the use of topical mast cell stabilizers and antihistamine agents in addition to a close follow-up regimen to detect and control postoperative complications could contribute to the favorable outcomes in the eyes that experienced VKC reactivation after keratoplasty.

The rate of steroid-induced high IOP and cataract in the groups of the current series compares favorably with other previous series reporting outcomes of corneal transplantation in VKC (Table 5). The prevalence of one or more episodes of graft rejection did not differ between the study groups. However, the first episode of graft rejection occurred earlier in the PK group than the DALK group. In addition, stromal graft rejection was more frequently encountered after DALK; this finding can be explained by the higher rate of suture-tract vascularization in the DALK group compared with the PK group. The incidence of graft rejection episodes was higher among our PK patients than had been previously reported by other authors following PK for keratoconus with concomitant VKC (Table 5). The rate of graft rejection in DALK cases of this series is comparable with that previously reported after DALK in eyes with keratoconus and VKC (Table 5), but is higher than the rate of immunologic rejection reported after DALK for keratoconus alone (3%–14.3%).[5,10,21,22] Theoretically, the rate of graft rejection might be higher in eyes with VKC due to chronic inflammation and peripheral corneal vascularization. In contrast, Wagoner and colleagues[13] suggested that the prevalence of graft rejection episodes may be less in eyes with VKC compared with those without VKC due to shift in the local immune response from the T-helper 1 phenotype to the T-helper 2 phenotype.

In this study, the rate of clear grafts, measured at the 4-year follow-up, was comparable between the PK (95.3%) and DALK (87.9%) groups. The underlying reasons for graft failure, however, were different between the two groups which is attributable to the replacement of the recipient's endothelium in the PK group and the presence of surgical interface in the DALK group. Interface haziness is a unique complication after lamellar keratoplasty that can develop because of postoperative vascular invasion into the potential space between the donor graft and recipient bed. Although these vessels regress after appropriate intervention, extravasation of proteinaceous materials from these abnormal vessels may lead to significant interface haziness as observed in five eyes in our series.

Our results should be interpreted in the context of the study limitations. PK and DALK were performed at different time points because there has been a major shift from full-thickness keratoplasty toward anterior lamellar keratoplasty for keratoconus in our center since 2006. Therefore, it was not possible to compare the clinical outcomes in patients with VKC who underwent PK or DALK contemporaneously. Our study is also limited by the fact that we did not use topical or systemic cyclosporine and tacrolimus in any cases during the study period. Postoperative use of these agents could have influenced VKC reactivation and surgical results. Another limitation is the retrospective design of the study that caused the two study groups were not balanced in the quality of donors used and the rate of postoperative VKC reactivation; the PK group chiefly contained patients with inactive disease at the time of corneal transplantation, whereas half of the eyes in the DALK group experienced disease reactivation postoperatively. This observation can be a reflection of the

surgeon's tendency to delay PK until VKC became inactive due to concerns regarding the association between active inflammation and endothelial rejection. We tried to control the confounding effects of these variables and adjust the results using a logistic regression analysis of covariance and a Cox regression in a survival analysis. Finally, the results of post hoc power analysis demonstrate that the current study is not strong enough to detect differences between two groups in postoperative complications due to small sample size.

Conclusion

In conclusion, excellent visual results were obtained after both PK and DALK for keratoconus in eyes with VKC, with no significant differences observed between the two study groups with respect to BSCVA, the percentage of eyes with a final BSCVA of ⩾20/40, graft rejection, and graft survival rate. Based on our results, both techniques of corneal transplantation can be considered in keratoconic eyes with medically controlled or inactive VKC. Reactivation of VKC could increase the rate of suture-related problems after corneal transplantation; therefore, counseling patients to be vigilant of VKC symptoms and seek early treatment is crucial for a successful outcome.

Author contributions

SF carried out the literature review. S-MM and MA participated in drafting the manuscript. SF and MAJ read and approved the final manuscript.

Conflict of interest statement

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ORCID iD

Sepehr Feizi https://orcid.org/0000-0003-4457-8077

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