• Investigation •

Indications for penetrating keratoplasty and anterior lamellar keratoplasty during 2010-2017

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Abstract

• AIM: To review the indications of penetrating keratoplasty (PK) and anterior lamellar keratoplasty (ALK) at Qingdao Eye Hospital, Shandong Eye Institute, Qingdao, China, from 2010 to 2017.

• METHODS: The data of all patients undergoing PK or ALK from January 2010 to December 2017 was retrospectively reviewed, with the indications during 2010-2013 and 2014-2017 compared.

• RESULTS: A total of 1869 eyes were included, among which 1405 eyes (75.2%) had PK and 464 eyes (24.8%) had ALK. The leading indications were suppurative keratitis (36.8%), keratoconus (15.5%), herpes keratitis (13.1%), and regraft (10.5%). In eyes undergoing PK, the top four indications were suppurative keratitis (38.7%), herpes keratitis (15.3%), keratoconus (12.6%), and regraft (12.5%) during 2014-2017, with the proportion of suppurative keratitis and herpes keratitis decreased while regraft and keratoconus increased compared with 2010-2013. In eyes with ALK, suppurative keratitis (30.8%), keratoconus (24.1%), corneal dystrophies and degenerations (10.6%), and corneal dermoid tumor (9.7%) were the top four indications, and there was no significant difference for the proportion of each indication between 2010-2013 and 2014-2017.

• CONCLUSION: Suppurative keratitis is the most common indication for PK and ALK at Qingdao Eye Hospital during 2010-2017, followed by keratoconus, herpes keratitis, and regraft. In eyes treated with PK, the proportion of suppurative keratitis and herpes keratitis decrease while regraft and keratoconus increase during 2014-2017 compared with 2010-2013.

• KEYWORDS: penetrating keratoplasty; anterior lamellar keratoplasty; indications

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INTRODUCTION

Corneal transplantation, also called keratoplasty, has become the most frequently performed type of transplantation since the first successful keratoplasty in human being was reported by Zirm in 1905[1]. Penetrating keratoplasty (PK), a procedure with full-thickness replacement of the cornea, predominated for more than half a century[2-4]. However, some studies demonstrated that the long-term corneal graft survival rates following PK were unsatisfactory, which was attributed mainly to the endothelial immunological allograft rejection and the continual loss of endothelial cells of the donor corneas[2-3]. This explains why anterior lamellar keratoplasty (ALK), especially deep anterior lamellar keratoplasty (DALK), has increasingly been valued in recent years[5]. ALK can preserve the healthy corneal endothelium in cases of keratopathy with the endothelium uninvolved and thus eliminate the risk of endothelial rejection[6].

The indications for PK and ALK vary by geographic regions along with economic development and social conditions. In USA and Europe, keratoconus and corneal edema after cataract surgery were reported as the leading indications for PK, and ulcerative keratitis was the major indication for ALK[7-11]. However, suppurative keratitis and corneal scarring were the leading indications for PK[12-15], and corneal burns and suppurative keratitis were the dominant indications for ALK[14,16] in some developing countries.

In this study, we reviewed the data of patients who underwent PK or ALK at Qingdao Eye Hospital, Shandong Eye Institute, China from 2010 to 2017, with the indications compared between 2010-2013 and 2014-2017.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board of Shandong Eye Institute and conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. The medical charts of all patients undergoing PK or ALK at

Table 1 Indications for keratoplasty during 2010-2013 and 2014-2017 *n* (%)

Indication	Time period		χ^2	*P*
	2010-2013	2014-2017		
Suppurative keratitis	379 (42.7)	308 (31.4)	25.889	0.000[a]
Keratoconus	113 (12.7)	176 (17.9)	9.578	0.002[a]
Herpes keratitis	131 (14.8)	113 (11.5)	11.018	0.001[a]
Regraft	65 (7.3)	132 (13.4)	18.475	0.000[a]
Bullous keratopathy	69 (7.8)	50 (5.1)	5.646	0.017[a]
Corneal dystrophies and degenerations	51 (5.7)	66 (6.7)	0.749	0.387
Corneal scar	27 (3.0)	32 (3.3)	0.070	0.791
Immunologic disorders of the cornea	20 (2.3)	31 (3.2)	1.429	0.232
Corneal dermoid tumor	14 (1.6)	31 (3.2)	4.942	0.026[a]
Corneal burn	6 (0.7)	33 (3.4)	16.433	0.000[a]
Others	12 (1.4)	10 (1.0)	0.448	0.503
Total	887 (100)	982 (100)		

[a]*P*<0.05.

Qingdao Eye Hospital, Shandong Eye Institute from January 2010 to December 2017 were retrospectively analyzed. Data of patients, including age, sex, surgical techniques, and preoperative primary diagnosis, were reviewed.

Diagnostic Categories of Primary Diseases The diagnoses of diseases for keratoplasty were divided into 11 categories[14]: suppurative keratitis, keratoconus, regraft, herpes keratitis, corneal dystrophy and degeneration, bullous keratopathy, corneal dermoid tumor, corneal scar, corneal burn, immunologic disorders of the cornea, and others. According to the different pathogens, suppurative keratitis was further classified into fungal keratitis, bacterial keratitis, acanthamoeba keratitis, and keratitis with unclear pathogens. Herpes keratitis included herpes simplex keratitis and herpes zoster keratitis. Corneal scars included the legacy after a variety of keratitis (except herpes keratitis), adhesive corneal leucoma, stable corneal scars after trauma, congenital corneal leucoma, and unexplained corneal opacity. Corneal burns included chemical burns and thermal burns.

Indication Selection for Penetrating Keratoplasty or Lamellar Keratoplasty The surgical selection for PK or ALK was made as follows. PKs were chosen for patients with corneal full-thickness perforation[17] or lesions involving Descemet's membrane (DM) and corneal endothelial layers. As for the lesions with DM and endothelial layers uninvolved, ALKs were first chosen, and PK would also be performed when the posterior stroma in proximity to DM was involved in inflammatory infiltration, especially for some patients with suppurative keratitis to reduce the risk of recurrence. For keratoconus, PKs were chosen if there were deep posterior corneal scarring, prior hydrops with discontinuity in DM, post-PK regrafting, and for the cases with high-steep average corneal curvature >65 diopter, and ALKs were considered for the other eyes. ALKs were chosen for patients with corneal dermoid tumor, and ALK would be transferred to PK only in the cases with the occurrence of corneal perforation during surgery.

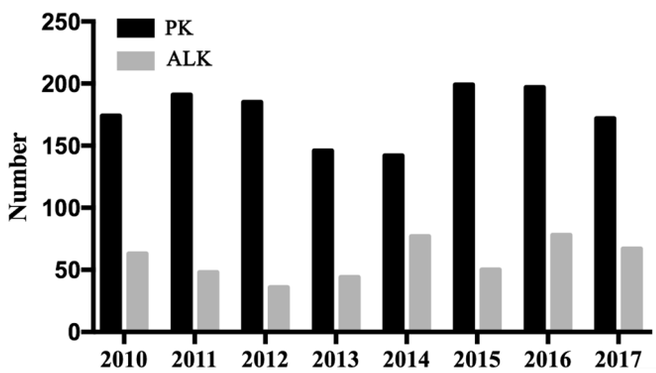

Figure 1 The annual number of PK and ALK from 2010 to 2017.

Statistical Analysis SPSS software version 25.0 was used for statistical analysis. The proportion of indications in keratoplasties, including PK and ALK, during 2010-2013 and 2014-2017 were analyzed using the Chi-square test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 1869 patients, including 1273 males (68.1%) and 596 females (31.9%) were involved, with a ratio of 2.14:1. The age of patients was from 4mo to 84 years old. PK was performed in 1405 cases (75.2%) and ALK in 464 cases (24.8%; Figure 1). Over the 8y from 2010 through 2017, the leading indications for keratoplasties were suppurative keratitis (687 cases, 36.8%), keratoconus (289 cases, 15.5%), herpes keratitis (244 cases, 13.1%), and regraft (197 cases, 10.5%; Table 1).

Indications for Keratoplasties The proportion of suppurative keratitis in the indication for keratoplasties declined from 42.7% during 2010-2013 to 31.4% during 2014-2017 (χ^2=25.889, *P*=0.000; Table 1). Among the suppurative

keratitis, fungal infection (499 cases, 72.6%) was much more than bacterial (72 cases, 10.5%) and amoebic infections (28 cases, 4.1%; Table 2). There was no statistical difference in the proportion of fungal keratitis, bacterial keratitis and amoebic keratitis between 2010-2013 and 2014-2017. The proportion of unclear pathogens declined significantly from 15.6% during 2010-2013 to 9.4% during 2014-2017 (χ^2=5.757, P=0.016; Table 2).

PK or ALK was performed in 289 patients (15.5%) with keratoconus from 2010 through 2017, which was the third indication of keratoplasties during 2010-2013 and increased to the second place during 2014-2017 (χ^2=9.578, P=0.002; Table 1). There were 244 patients (13.1%) with herpes keratitis undergoing PK or ALK, which was the second indication during 2010-2013 and decreased to the fourth place during 2014-2017 (χ^2=11.018, P=0.001; Table 1).

As the fifth indication during 2010-2013 and increased to the third indication during 2014-2017 (χ^2=18.475, P<0.001; Table 1), regrafts were performed for 197 patients (10.5%). The indications for regrafts were graft endothelial dysfunction (61 cases, 31.0%), graft ulceration (54 cases, 27.4%), graft opacities (33 cases, 16.8 %), recurrence of the primary diseases (31 cases, 15.7%), and others (18 cases, 9.1%).

Moreover, there were 119 patients (6.4%) with bullous keratopathy treated by PK, which was the fourth indication during 2010-2013 and decreased to the sixth place during 2014-2017 (χ^2=5.646, P=0.017; Table 1). The proportions of corneal dermoid tumor (χ^2=4.942, P=0.026; Table 1) and corneal burns (χ^2=16.433, P<0.001; Table 1) increased during 2014-2017 compared with 2010-2013. There was no statistical difference for the proportion of the other indications during the two time periods (Table 1).

The proportions of PK and ALK in the top four indications during 2010-2013 and 2014-2017 are shown in Figure 2. The proportion of PK in suppurative keratitis (Figure 2A; 82.1% during 2010-2013 and 75.6% during 2014-2017, P<0.05) and herpes keratitis (Figure 2C; 92.4% during 2010-2013 and 83.2% during 2014-2017, P<0.05) decreased. The proportion of PK in keratoconus (Figure 2B; 54.0% during 2010-2013 and 65.9% during 2014-2017, P<0.05) increased. However, there was no statistical difference in the proportion of PK or ALK in regraft (Figure 2D; 89.2% during 2010-2013 and 88.6% during 2014-2017, P>0.05) between the two periods of time.

Indications for Penetrating Keratoplasty Suppurative keratitis (544 cases, 38.7%) was the leading indication for PK, followed by herpes keratitis (215 cases, 15.3%), keratoconus (177 cases, 12.6%), regraft (175 cases, 12.5%), bullous keratopathy (119 cases, 8.5%), corneal dystrophies and degenerations (68 cases, 4.8%), corneal scar (47 cases, 3.3%), corneal burn (25 cases, 1.8%), immunologic disorders of the cornea (18 cases, 1.3%), and others (17 cases, 1.2%). Among the top four indications of PK, the proportions of suppurative keratitis (χ^2=20.683, P<0.001) and herpes keratitis (χ^2=4.615, P=0.032) decreased during 2014-2017 compared with 2010-2013 (Table 3). Conversely, the percentages of regraft (χ^2=21.493, P=0.000) and keratoconus (χ^2=18.408, P=0.000) increased during 2014-2017 compared with 2010-2013 (Table 3).

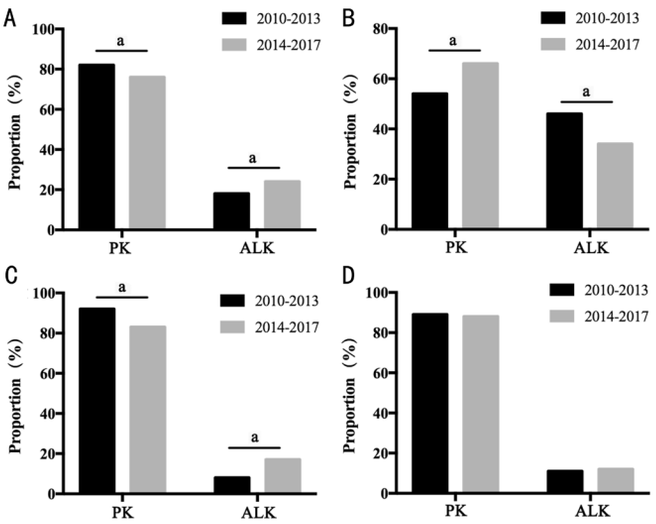

Figure 2 Proportion of PK and ALK in the top four indications for keratoplasty during 2010-2013 and 2014-2017 A: Suppurative keratitis; B: Keratoconus; C: Herpes keratitis; D: Regraft. [a]P<0.05.

Table 2 Suppurative keratitis as indication for keratoplasty during 2010-2013 and 2014-2017 *n* (%)

Indications	Time period		χ^2	P
	2010-2013	2014-2017		
Fungal keratitis	273 (72.0)	226 (73.4)	0.155	0.694
Bacterial keratitis	32 (8.4)	40 (13.0)	3.739	0.053
Amoebic keratitis	15 (4.0)	13 (4.2)	0.030	0.862
Unclear pathogen	59 (15.6)	29 (9.4)	5.757	0.016[a]
Total	379 (100)	308 (100)		

[a]P<0.05.

Indications for Anterior Lamellar Keratoplasty The top four indications for ALK was suppurative keratitis (143 cases, 30.8%), keratoconus (112 cases, 24.1%), corneal dystrophies and degenerations (49 cases, 10.6%), and corneal dermoid tumor (45 cases, 9.7%). Due to the small numbers of corneal scarring and corneal burns, they were categorized into the others when performing statistical analyses. There was no statistical difference for the proportion of each indication between 2010-2013 and 2014-2017 (Table 4).

DISCUSSTION

Keratoplasty, including PK, ALK, and endothelial keratoplasty (EK), was the main method for visual rehabilitation once disease has affected corneal clarity. PK was the most popular keratoplasty for the treatment of corneal diseases with stroma or endothelial cells involved[4]. The reasons lie in there was no

Table 3 Indications for PK during 2010-2013 and 2014-2017 *n* (%)

Indications	Time period		χ^2	*P*
	2010-2013	2014-2017		
Suppurative keratitis	311 (44.7)	233 (32.9)	20.683	0.000[a]
Herpes keratitis	121 (17.4)	94 (13.3)	4.615	0.032[a]
Keratoconus	61 (8.8)	116 (16.4)	18.408	0.000[a]
Regraft	58 (7.3)	117 (16.5)	21.493	0.000[a]
Bullous keratopathy	69 (7.8)	50 (7.1)	3.710	0.054
Corneal dystrophies and degenerations	33 (5.7)	35 (4.9)	0.029	0.865
Corneal scar	21 (3.0)	26 (3.7)	0.459	0.498
Corneal burn	6 (0.7)	19 (2.7)	6.640	0.010[a]
Immunologic disorders of the cornea	6 (2.3)	12 (1.7)	1.915	0.166
Others	10 (1.4)	7 (1.0)	0.594	0.441
Total	696 (100)	709 (100)		

[a]*P*<0.05.

Table 4 Indications for ALK during 2010-2013 and 2014-2017 *n* (%)

Indications	Time period		χ^2	*P*
	2010-2013	2014-2017		
Suppurative keratitis	68 (35.6)	75 (27.5)	3.483	0.062
Keratoconus	52 (27.2)	60 (22.0)	1.690	0.194
Corneal dystrophies and degenerations	18 (9.4)	31 (11.3)	0.444	0.505
Corneal dermoid tumor	14 (7.3)	31 (11.3)	2.079	0.149
Immunologic disorders of the cornea	14 (7.3)	19 (7.0)	0.023	0.879
Herpes keratitis	10 (5.2)	19 (7.0)	0.570	0.450
Regraft	7 (3.7)	15 (5.5)	0.833	0.361
Others	8 (4.2)	23 (8.4)	3.235	0.072
Total	191 (100)	273 (100)		

corneal lamellar interface problems, the surgical technique of PK was relatively undemanding, and the corneal lesions could be cleared more easily than ALK, especially in some cases with corneal infections such as fungal or bacterial keratitis, and thus PK could greatly decrease the risk of infection recurrence[4]. Compared with PK, ALK leaves the healthy endothelium of the recipient cornea intact, which decreases the rate of postoperative endothelial rejection, endothelial loss and subsequent regraft[18]. EK preserves the corneal epithelia, most or all stroma and corneal nerves, so postoperative immune rejection and ocular surface complications are rare[19]. In addition, EK provides faster and more predictable visual rehabilitation and allows patients to resume daily activities sooner[19]. EK has now been a popular surgery for the treatment of Fuchs dystrophy[8] and endothelial decompensation[10]. Therefore, there are advantages and disadvantages for different form of keratoplasties, and to choose PK, ALK, or EK according to the characteristics of keratopathies can minimize the complications of corneal transplantation.

Only PKs and ALKs are included in this study, while EK is not included, and the reason mainly lies in that EK is only used to treat endothelial keratopathies, whose indication was quite different from that for PK and ALK. The indications for PK and ALK are keratopathies with corneal stroma involved. In addition, the number of EK performed at our hospital is still quite limited, with the dominating reason being the shortage of enough high-quality donor grafts. There are no pre-cut donor grafts for EKs offered by eye banks, and the donor grafts have to be prepared during the surgery of EKs. Unavoidably, there will be additional loss in the number of corneal donors during the procedure of preparing for the donor grafts. Therefore, EKs was only performed when there are enough high-quality corneal donors at our hospital, and some patients with endothelial dysfunction and obvious stromal edema were performed PK but not EK.

There are some discrepancies in the indications for PK and ALK between the developed and developing countries. In this study, the data of indications for PK and ALK from 2010 to 2017 were reviewed, with the indications compared between time periods of 2010-2013 and 2014-2017. Suppurative keratitis was shown to be the leading indication for keratoplasties during 2014-2017, followed by keratoconus, herpes keratitis, and regraft, and they accounted for 75.9% in the preoperative indications. In patients undergoing PK, the

top four indications were suppurative keratitis, herpes keratitis, keratoconus, and regraft, while in patients receiving ALK, the leading indications were suppurative keratitis, keratoconus, corneal dystrophies and degenerations, and corneal dermoid tumor.

The proportion of suppurative keratitis in keratoplasties decreased during 2014-2017 compared with that during 2010-2013. Suppurative keratitis was the top indication for both PK and ALK, with the main surgical purpose of eliminating pathogens and controlling infection. The results are consistent with the report from India[12] and the previous data from our hospital[13-14]. As the biggest developing country, there are a large number of farmers and workers in China, and ocular injuries in labor lead to the high incidence of corneal infection[13-14]. In addition, when some patients with suppurative keratitis were referred to our hospital, severe corneal infection and even corneal perforation had occurred due to the previous delayed diagnosis and improper treatments, which can explain why suppurative keratitis was the top indication for keratoplasties in this study.

During 2014-2017, there was an increase for ALK but a decline for PK in the treatment of suppurative keratitis compared with 2010-2013 (Figure 2A). Fungi were the dominating pathogens in suppurative keratitis in China[13-14]. Different hyphal growth patterns, horizontal or vertical, were reported in various fungal species, and hyphae grew horizontally in most cases, which is an important theoretical basis for ALK in the treatment of fungal keratitis[20]. Based on the results, more ALKs, instead of PKs, were performed for fungal keratitis at our hospital because of the obviously lower risks of intraoperative complications and postoperative immune graft rejection[14].

The proportion of keratitis with unclear pathogens declined from 15.6% during 2010-2013 to 9.4% during 2014-2017, and the difference was statistically significant. The result was related to the improvement of laboratory diagnostic techniques and application of confocal microscopy in recent years, which have greatly increased the accuracy in the diagnosis of suppurative keratitis with definite pathogens at our hospital. However, there was no significant difference in the proportion of fungal keratitis, bacterial keratitis, and amoebic keratitis between the periods of 2014-2017 and 2010-2013.

Keratoconus was shown as the second indication for keratoplasties in our series, with a proportion increasing from 12.7% during 2010-2013 to 17.9% during 2014-2017, and the difference was statistically significant. Keratoconus was reported as the dominating indication for PK and ALK in some developed countries, such as New Zealand (41.7%)[8], Italy (45.1%)[10], and Arabia (53.1%)[21]. The difference can be attributed to the discrepancies in agricultural and economic status between the developing and developed countries.

Keratoconus increased from the third indication for keratoplasties during 2010-2013 to the second place during 2014-2017. The difference in the proportion of keratoconus in PK was statistically significant but insignificant in ALK. PK had been considered as the gold standard for the treatment of advanced keratoconus for decades owing to its safety and good visual acuity outcomes[6]. In our hospital, PKs were usually preferred for eyes with the mean corneal curvature more than 65 diopters. However, ALK, especially DALK, has become increasingly popular since it keeps the healthy endothelium of the recipient cornea intact so as to eliminate endothelial rejection after surgery and prevent postoperative endothelial loss and subsequent graft failure[22-24]. Several studies have documented that the surgical effect of DALK is inferior to that of PK[25-26]. Visual outcomes after DALK were comparable with those after PK[6,18,27]. In a Meta-analysis[22], PK was found to achieve better visual acuity by calculating best corrected visual acuity. In this study, an increase in the number of PK and a decline of LK in the treatment of keratoconus were shown during 2014-2017 compared with 2010-2013. This may be related to the high proportion of advanced keratoconus patients with high-steep corneal curvature.

Herpes keratitis was reported as a major cause of keratoplasty in the previous reports from our hospital[13-14]. In the current study, the proportion of herpes keratitis in indications for keratoplasties declined from 14.8% during 2010-2013 to 11.5% during 2014-2017, and the difference was statistically significant. This may be due to the increased number of effective antiviral agents available for herpes keratitis, so keratoplasties were eventually avoided for many patients. The proportion of herpes keratitis in PK procedures decreased during 2014-2017 (13.3%) compared with 2010-2013 (17.4%). Besides PK, ALK is an alternative and safe procedure for the treatment of herpes keratitis in patients with the healthy endothelium[28-29], which contributed to the increase of ALK and decrease of PK in the treatment of herpes keratitis in this study.

There were 196 patients (10.5%) who underwent regraft, with a similar proportion in keratoplasties from USA (11.3%-18.0%)[7], Canada (17.1%)[30], Italy (11.8%)[10] and France (13.6%)[11]. In this study, regraft was the fifth indication during 2010-2013 and increased to the third place in 2014-2017, which is related with the large number of patients with keratoplasties in the previous years. The difference in the proportion of regraft was statistically significant in PK between the two time periods but not significant in ALK.

Endothelial dysfunction (31.0%) was the dominating reason for regraft, which was similar to the reports from other countries[31-33]. Graft ulcer (27.4%) was another important cause of regraft. The ability of corneal grafts to resist infection

is lower than that of a native cornea, which leads to the occurrence of corneal ulcer after keratoplasty, and some patients failing in medical treatment had to be regrafted. Moreover, graft opacities (16.8 %) and recurrence of the primary diseases (15.7%) were also important reasons for regraft.

In summary, suppurative keratitis was the leading indication for keratoplasties at Qingdao Eye Hospital from 2010 through 2017, followed by keratoconus, herpes keratitis, and regraft. In patients treated by PK, there was a decline in the proportion of suppurative keratitis and herpes keratitis but an increase in keratoconus and regraft during 2014-2017 compared with 2010-2013. However, there is no statistically significant difference in the proportion of indications for LK between the two time periods.

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