Original Article

Changing Indications and Surgical Techniques for Corneal Transplantation Between 2004 and 2009 at a Tertiary Referral Center

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ABSTRACT

Purpose: The aim of this study is to report the indications, techniques, and clinical outcomes of corneal transplantation and investigate any changing trends in surgical techniques over a 6 year period.

Materials and Methods: Records of patients who had undergone any kind of corneal transplantation at Labbafinejad Medical Center, Tehran, Iran, from January 2004 to December 2009 were reviewed to determine the indications and types of corneal transplantation. Postoperative best-corrected visual acuity, refractive error, graft clarity, and complications were reported.

Results: During this period, 1859 eyes of 1624 patients with a mean age of 41.3 ± 21.3 years underwent corneal transplantation. The most common indication was keratoconus (38.4%) followed by aphakic/pseudophakic bullous keratopathy (11.7%), previous failed grafts (10.6%), infectious corneal ulcers (10.1%), non-herpetic corneal scars (7.6%), trachoma keratopathy (4.7%), stromal corneal dystrophies (4.6%), post-herpetic corneal scar (3.7%), Fuchs' endothelial dystrophy (0.8%), and congenital hereditary endothelial dystrophy (0.4%). Techniques of corneal transplantation included penetrating keratoplasty (PKP; 70.9%), deep anterior lamellar keratoplasty (DALK; 20.1%), conventional lamellar keratoplasty (LKP; 4.4%), and Descemet's stripping automated endothelial keratoplasty (DSAEK; 2.3%). Over the study period, there was a significant increase in the relative frequency of infectious corneal ulcers, failed grafts, and trachoma keratopathy. Additionally, a significant reduction was observed in PKP and LKP procedures, and volume of DALK and DSAEK increased significantly. At final follow-up, 69.0% of grafts were clear in the PKP group. This figure was 82.6%, 82.7%, and 97.6% in the DALK, LKP, and DSAEK groups, respectively.

Conclusion: Keratoconus was the most common indication and PKP was the most prevalent technique used for corneal transplantation. However, significant changes in the indications and surgical techniques were observed from 2004 to 2009.

Key words: Corneal Transplantation, Deep Anterior Lamellar Keratoplasty, Descemet Stripping Automated Endothelial Keratoplasty, Indication, Lamellar Keratoplasty, Penetrating Keratoplasty, Surgical Technique

Access this article online

Website: www.meajo.org

DOI: 10.4103/0974-9233.97941

Quick Response Code:

INTRODUCTION

Corneal blindness due to infection, corneal dystrophy or other pathology is a major health problem worldwide.[1] Indications for corneal transplantation have changed over time and differ based on the country. For example, bullous keratopathy seems to be the most common indication for corneal transplantation in developed countries,[2-7] infectious corneal diseases and corneal scars are more prevalent in developing countries.[8-10] Familiarity with the epidemiology of corneal pathologies in each region facilitates the appropriate allocation of resources. Furthermore, other alternatives have

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been introduced, and full thickness corneal transplantation is no longer a procedure of choice for many corneal pathologies involving one layer of the cornea. Therefore, it is important for centers, where corneal transplantation is performed, to remain current regarding indications and techniques of corneal transplantation as the epidemiology of certain corneal pathologies has changed over time and new procedures including deep anterior lamellar keratoplasty (DALK) and Descemet's stripping automated endothelial keratoplasty (DSAEK) have been introduced. Herein, we report the indications and techniques of corneal transplantation performed at the Labbafinejad Medical Center, a tertiary training and referral center in Tehran, Iran, over a 6 year period to determine any changes in the frequency of indications for corneal transplantation and trends in surgical techniques during this period. Additionally, overall outcomes and complications encountered during this period are presented.

MATERIALS AND METHODS

In this retrospective study, hospital records of patients who had undergone corneal transplantation at the Labbafinejad Medical Center from January 2004 to December 2009 were reviewed for demographic data, indications for keratoplasty, surgical techniques, postoperative best-corrected visual acuity (BCVA), postoperative refraction, graft clarity, and complications. Indications for keratoplasty consisted of the clinical diagnosis made by the surgeon at the time of surgery. In this study, non-herpetic corneal scar refers to corneal opacification in the absence of any active bacterial or viral infection. Mechanical and chemical trauma as well as previous bacterial, fungal, or viral (except for herpes simplex virus) keratitis were the speculative underlying causes for non-herpetic corneal scars. However, causative agents were apparent in a small proportion of patients. Old corneal scars caused by herpes simplex virus and trachoma species were separately reported, because the history and distinctive clinical features make it possible to diagnose herpetic and trachoma keratopathy with certainty. The causes of active infectious corneal ulcers were determined by clinical findings (especially for active herpes simplex keratitis), confocal biomicroscopy (Confoscan 3.4; Nidek Co. Ltd, Gamagori, Japan), smears, cultures, and/or histopathologic examinations performed on the removed corneal buttons.

When multiple transplantations were performed, the diagnosis was considered to be regraft regardless of the initial indication for transplantation and the type of previous keratoplasties. Aphakic or pseudophakic patients who underwent keratoplasty for corneal decompensation were considered to have aphakic bullous keratopathy (ABK) or pseudophakic bullous keratopathy (PBK), regardless of the underlying mechanism of corneal decompensation (e.g. Fuchs' endothelial dystrophy, toxic anterior segment syndrome, and complicated surgery). If tectonic or therapeutic corneal transplantation was performed for ulcer or perforation, respectively, the primary pathologies leading to an urgent keratoplasty were considered.

General data including age, postoperative BCVA, and refraction were expressed as mean ± standard deviation using SPSS software version 15 (SPSS Inc., Chicago, IL, USA). The absolute number and relative frequency of each indication and surgical technique are provided, as well. To investigate any shift in the indications and surgical techniques over time, the data corresponding to two follow-up periods (between 2004 and 2006 and between 2007 and 2009) were compared using Fisher's exact test. One-way analysis of variance (ANOVA) was used to determine the significance of risk factors for endothelial graft rejection in the PKP group. A P value < 0.05 was considered statistically significant.

RESULTS

Overall, 1859 eyes of 1624 patients including 1036 (63.8%) male and 588 (36.2%) female subjects underwent corneal transplantation during the period of the study. Of these, 36 (1.9%) eyes belonged to 28 children (<16 years). The mean age was 41.3 ± 21.3 years (range, 10 days to 89 years) with a median of 39 years. Patients with congenital hereditary endothelial dystrophy (CHED) were the youngest (mean age, 19.7 years) and subjects with Fuchs' endothelial dystrophy (FED) were the oldest (mean age, 68.4 years). The most common indication for keratoplasty was keratoconus (n = 714, 38.4%) followed by ABK or PBK (n = 218, 11.7%) with pseudophakos constituting the majority of cases (86.8%), previous failed grafts (n = 197, 10.6%), infectious (bacterial, fungal, herpetic, or acanthamoebic) corneal ulcers (n = 188, 10.1%), non-herpetic corneal scars (n = 142, 7.6%), trachoma keratopathy (n = 87, 4.7%), corneal stromal dystrophies (n = 86, 4.6%), post-herpetic corneal scar (n = 69, 3.7%), FED (n = 15, 0.8%), and CHED (n = 8, 0.4%). The remaining indications (n = 135, 7.3%) included Terrien's marginal degeneration, post-LASIK keratectasia, peripheral ulcerative keratitis, calcific band-shape keratopathy, and corneal opacity due to trauma or inborn errors of metabolism such as mucopolysaccharidosis. Conditions which led to corneal transplantation in children were CHED (n = 3), anterior segment dysgenesis (n = 13), corneal opacity due to inborn error of metabolism (n = 11), trauma (n = 5), or corneal ulcer (n = 4).

Of 188 eyes undergoing corneal transplantation for the management of infectious corneal ulcers, 70 (37.2%) had bacterial keratitis and 65 (34.6%) had fungal keratitis. Active herpes simplex keratitis was diagnosed in 18 (9.6%) eyes and 4 (2.1%) eyes had *Acanthamoeba* keratitis, while the rest remained undiagnosed. Bacterial keratitis was diagnosed preoperatively

in 49 eyes using smear and culture from ulcers and/or contact lens cases. However, in 21 eyes, the causative bacterial agents were determined postoperatively by the microbiologic and/or histopathologic examinations of the removed tissues. Fungal keratitis was chiefly diagnosed by confocal biomicroscopy (52 eyes) preoperatively, while 13 eyes were diagnosed using microbiologic and/or histopathologic examinations. History and clinical picture were used for diagnosing all cases with active herpetic keratitis and *Acanthamoeba* keratitis was confirmed in all patients using confocal biomicroscopy.

Macular corneal dystrophy was the most common corneal dystrophy necessitating corneal transplantation in this series (56 out of 86 eyes, 65.1%), followed by granular ($n = 19$, 22.1%) and lattice ($n = 11$, 12.8%) corneal dystrophies.

Techniques of corneal transplantation included penetrating keratoplasty (PKP; $n = 1318$, 70.9%), DALK ($n = 373$, 20.1%), conventional lamellar keratoplasty (LKP; $n = 81$, 4.4%), and DSAEK ($n = 42$, 2.3%) in descending order. The remaining methods included automated lamellar therapeutic keratoplasty (ALTK), endothelial keratoplasty, and sclerokeratoplasty. Figure 1 demonstrates alterations in the frequency of each technique over the study period. To determine any change in the indications and techniques over time, two study periods (from 2004 to 2006 and from 2007 to 2009) were considered. As Table 1 demonstrates, keratoconus was at the top of the list in both periods. However, there was a significant increase in the relative frequency of infectious corneal ulcers, failed grafts, and trachoma keratopathy.

Comparing the surgical techniques between these two periods, there was a significant decrease in the relative frequency of patients who underwent PKP (711, 91.6% versus 607, 56.0%, $P < 0.001$) and LKP (44, 5.7% versus 37, 3.4%, $P = 0.02$), while those receiving DALK and DSAEK significantly increased from 108 (13.9%) to 265 (24.5%, $P < 0.001$) and from 6 (0.8%) to 36 (3.3%, $P < 0.001$), respectively. Figures 2-7 demonstrate and compare the technique of corneal transplantation performed for each major indication during the study period. As indicated, DALK has become the dominant technique for keratoconus since 2006 and PKP and DSAEK were nearly equally used for bullous keratopathy in 2009. PKP was the dominant technique for infectious corneal ulcers during the study period, while DALK has recently been attempted in few cases when deep stroma and endothelium remain spared. In patients with trachoma keratopathy, PKP was first used. Due to ocular surface abnormalities and relatively spared posterior stromal layers in this condition, however, LKP has chiefly been used since 2006. PKP remains the main surgical approach for failed grafts and corneal scars.

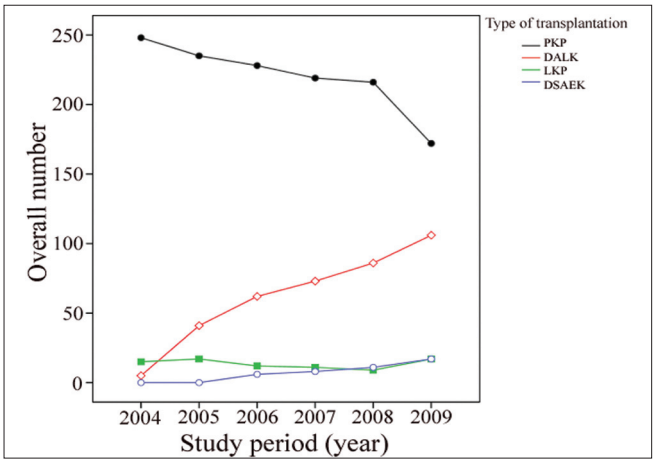

Figure 1: Change in the frequency of different corneal transplantation techniques over the study period

OUTCOMES AND COMPLICATIONS

In the PKP group, final BCVA (after eliminating failed grafts) of 20/40 or better was achieved in 33.3% patients, 20/50 to 20/150 in 41.7% of patients and 20/200 or worse in 25% of patients. The mean postoperative spherical equivalent refractive error and keratometric astigmatism were −3.73 ± 1.32 D (range, −10.5 to +7.25 D) and 4.82 ± 3.26 D (range, 0.75−8.5 D), respectively. For keratoconus, 55.6% of patients achieved final BCVA of 20/40 or better, followed by patients with corneal scar (14.3%), patients with ABK/PBK (13.6%), and patients with corneal ulcer (8.2%).

Overall, 909 (69.0%) of the grafts were clear at final follow-up (median, 58 months) in this group. Eyes with keratoconus had highest graft survival (88.9%) followed by ABK/PBK (75.0%), non-herpetic corneal scar (68.6%), failed graft (46.7%), trachoma keratopathy (41.3%), and active infectious ulcer (32.6%). The main reason of graft failure was endothelial graft rejection which occurred in 31.9% of eyes and led to graft failure in 11.4%. The risk factors for this type of graft rejection in the

Table 1: Comparison of the frequency of indications for corneal transplantations between two study intervals

Indication	2004–2006 *n* (%)	2007–2009 *n* (%)	*P* value
Keratoconus	317 (40.8)	397 (36.7)	0.27
ABK/PBK	90 (11.6)	128 (11.8)	0.80
Non-herpetic corneal scars	62 (8.0)	80 (7.4)	0.61
Failed graft	61 (7.9)	136 (12.6)	0.001
Infectious corneal ulcers	61 (7.9)	127 (11.7)	0.006
Trachoma keratopathy	26 (3.3)	61 (5.6)	0.02
Others	159 (20.5)	154 (14.2)	0.76
Total	776	1083	–

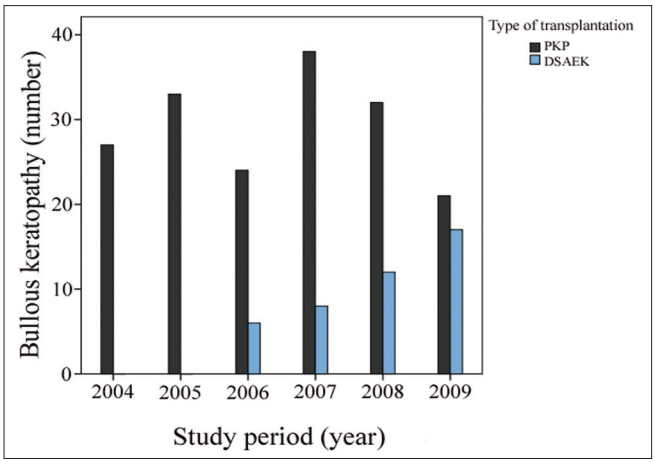

Figure 2: The frequency of PKP and DSAEK performed each year for ABK/PBK

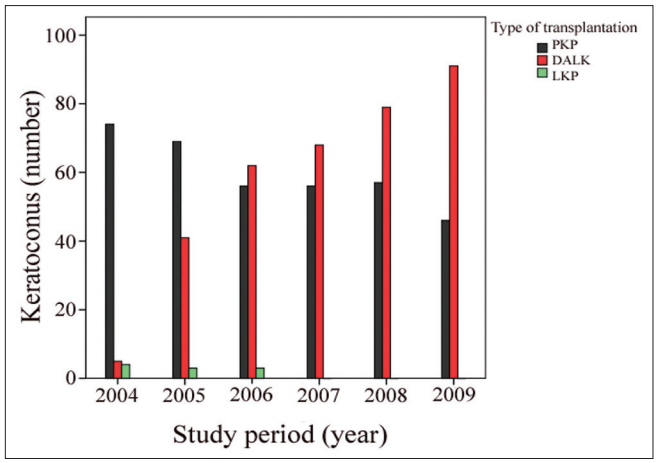

Figure 3: The frequency of PKP, DALK, and LKP performed each year for keratoconus

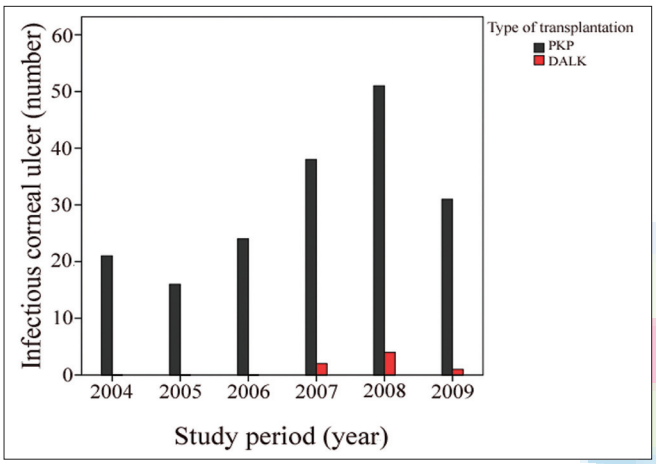

Figure 4: The frequency of PKP and DALK performed each year for infectious corneal ulcers

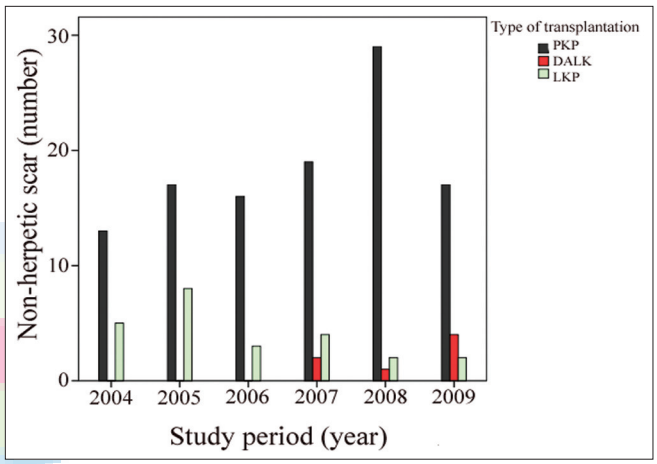

Figure 5: The frequency of PKP, DALK, and LKP performed each year for non-herpetic corneal scars

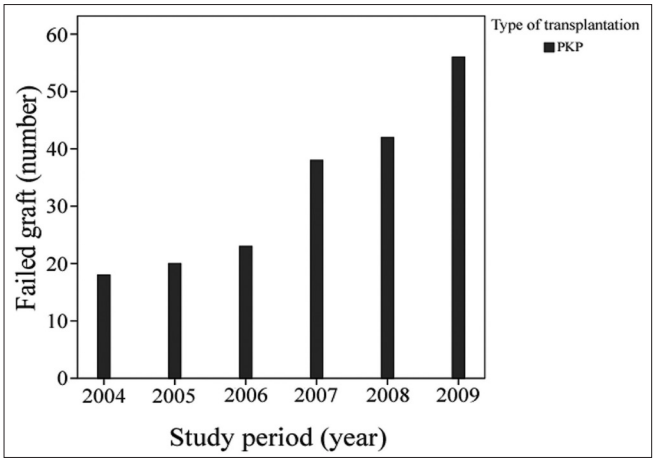

Figure 6: The frequency of PKP performed each year for failed grafts

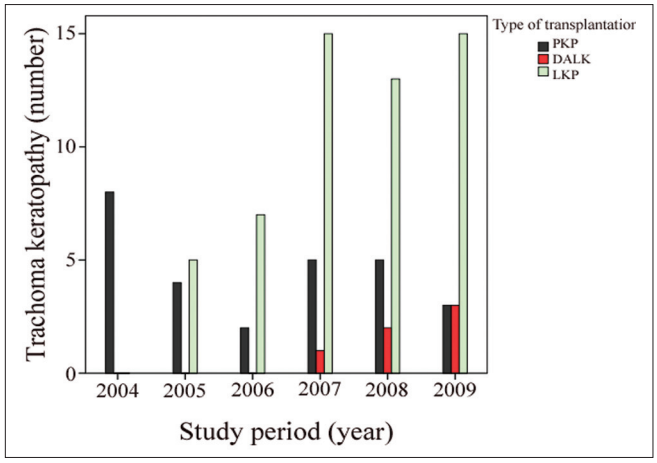

Figure 7: The frequency of PKP, DALK, and LKP performed each year for trachoma keratopathy

PKP group are presented in Table 2. As demonstrated, significant contributing factors were recipient corneal vascularization, regrafting, anterior synechiae, history of prior graft rejection, and eccentric graft ($P < 0.05$). However, patients' age, size of donor cornea, and bilateral transplantation were not significant risk factors ($P > 0.05$).

Table 2: Risk factors for endothelial graft rejection in PKP patients

Risk factor	Relative frequency (%)	Graft rejection (%)	*P* value
Age			
<40 yrs	62	28.4	0.1
≥40 yrs	38	37.8	
Corneal vascularization			
No	70.9	27.8	0.015
One or more quadrant	29.1	48.3	
Number of grafts			
Primary graft	87.5	29.5	0.025
Regraft	12.5	48.6	
Laterality of graft			
Unilateral	82.5	28.1	0.07
Bilateral	17.5	30.8	
Size of donor			
<8 mm	29.8	30.5	0.3
≥8 mm	67.9	29.8	
Iridocorneal adhesion			
No	93.5	21.6	<0.001
Yes	6.5	64.7	
Eccentric graft			
No	96.9	31.9	0.038
Yes	3.1	66.7	
History of previous rejection reactions			
No	95.6	28.1	0.002
Yes	4.4	69.2	

Other reasons of graft failure in this group were recurrence of primary conditions (9.8%), graft ulcer (7.1%), and traumatic wound dehiscence (2.7%). Other complications encountered in PKP patients were persistent epithelial defect (13.3%), suture vascularization or abscess (11.6%), glaucoma (8.2%), and endophthalmitis (1.7%).

In the DALK group which mainly consisted of keratoconic patients, BCVA of 20/40 or better was observed in 77.8% of patients, 20/50 to 20/150 in 16.7% of patients and 20/200 or worse in 5.5%. The postoperative mean spherical equivalent refractive error was −2.75 ± 1.68 D (range, −2.25 to +11.75 D) and keratometric astigmatism was 3.57 ± 1.3 D (range, 0 to 5.0 D).

At the final follow-up (median, 29 months), 308 (82.6%) of DALK grafts remained clear. The rest developed graft opacity due to persistent epithelial defect (8.4%), interface vascularization (6.1%), and graft ulcer (2.9%). Other complications included subepithelial or stromal graft rejection (14.3%), suture abscess or vascularization (13.5%), glaucoma (4.1%), and atonic pupil (1.6%).

BCVA of 20/40 or better was observed in 56.1% of LKP patients, 20/50 to 20/150 in 20.7% and 20/200 or worse in 23.2%. The postoperative mean spherical equivalent refractive error was −4.12 ± 2.31 D (range, −6.25 to +5.50 D) and keratometric astigmatism was 2.57 ± 1.3 D (range, 0.5 to 4.5 D).

At the final follow-up (median, 61 months), 67 (82.7%) of LKP grafts remained clear. The main cause of graft failure was significant interface opacity with vascularization which developed in 9 (11.1%) eyes. Other causes were retained opacities in stromal bed (3.7%), persistent epithelial defect (2.1%), and graft ulcer (0.4%).

DSAEK which was only performed in patients with ABK/PBK resulted in postoperative BCVA ≥ 20/40 in 41.6% of cases, 20/50 to 20/150 in 48.7% of patients and 20/200 or worse in 9.7%. Postoperatively, the mean spherical equivalent refractive error was 0.85 ± 0.95 D and the mean keratometric astigmatism was 1.15 ± 1.0 D. There was no graft rejection or infection within the follow-up period (median, 21 months). However, one patient developed graft failure after 3 months due to intractable secondary glaucoma. There was no primary graft failure during the first 3 months. Pupillary block occurred in three cases on the first postoperative day and improved by full dilation of the pupil and head positioning. Partial non-attachment of graft occurred in seven cases which was resolved after 3 weeks. Donor tissue dislocation occurred in six (8%) cases within 72 h of surgery and all were reattached after rebubbling, which was done on the same day on emergency basis.

DISCUSSION

A nationwide report by Kanavi *et al*.[11] on the indications for PKP in Iran between 1997 and 2003 showed that the most common indication was keratoconus followed by corneal opacities and scars, PBK, corneal dystrophies, ABK, and regrafts in descending order. The current study was performed in a University Hospital which deals with patients referred from around the country. Therefore, it can reflect a recent change in indications for corneal transplantation and surgical techniques in Iran. However, it is possible that this report consists of more challenging and complicated patients that are not usually managed in private and less-qualified centers. For example, in the nationwide report by Kanavi *et al*.,[11] bullous keratopathy and regrafts were the least common indications, while these indications rank second and third in the present report, respectively.

Keratoconus was the most common indication in our report and remained at the top of the list over the 6 year period. Similarly, it constitutes the most common indication in other countries.[2,3,8,12,13] There is no report on the prevalence of keratoconus in Iran, but it appears to be relatively high. One explanation may be the association between keratoconus and vernal keratoconjunctivitis which is very common in Iran.[11] On the other hand, it can be the result of genetic and/or climatic factors that may contribute to a higher prevalence of keratoconus.[9,10] The fact that the leading indication for corneal transplantation is keratoconus can be explained not only by its

high prevalence but also by a tendency for early operation due to favorable outcomes, especially with the recent resurgence of interest in DALK and easy access to donor corneas procured from the Eye Bank of the Islamic Republic of Iran.

ABK/PBK was the second most common indication. This is the leading indication for corneal transplantation in many countries.[2-7] The majority of cases of bullous keratopathy included pseudophakic patients (86.8%). Such an increase can be attributed to the shift in the technique of cataract surgery from extracapsular extraction to phacoemulsification with more damage to endothelial cells.[14,15]

A striking finding was the low incidence of regrafts (10.6%) in our study which concurs with the nationwide report,[11] while in contrast with reports from the USA,[6] Britain,[16] and Canada.[17] The lower incidence of regrafts in our study can be explained by good-quality grafts harvested from young donors. However, there was a significant increase in the incidence of regrafts from the fourth place in the first 3 year period to the second in the following period. This trend was similarly observed in many studies,[6,9,18,19] indicating that the longevity of a PKP graft is a function of time. On the other hand, it can reflect the increasing number of PKP recipients in the population.

Active infectious keratitis which ranked fourth was an uncommon condition in this report, leading to corneal transplantation in 10.1%. The most common causative agents were bacteria followed by fungi, herpes simplex virus, and *Acanthamoeba* species. However, the relative frequency of this indication doubled in the second half of the study period which could result from the expansion of the indications for keratoplasty to other pathologies or increasing prevalence of risk factors such as contact lens wear, keratorefractive surgery, and use of topical steroids. Simply, it can be attributed to the fact that our center is a referral tertiary care center. In countries with large rural populations such as Taiwan,[9] India,[8,10] and China,[14] active infectious keratitis caused by fungal agents is the leading indication for corneal transplantation.

Non-herpetic corneal scars was the fifth most common indication in our study, while in some developing countries it is the leading indication for corneal transplantation (ranging from 27.9% to 38.0%).[4,17,20-22] Despite the fact that the prevalence of this indication remained stable over the follow-up period, the frequency of corneal opacities caused by trachoma demonstrated a threefold increase which was statistically significant. It can hint that in some endemic areas such as the southern and southwestern regions of the country, trachoma is still a common infection necessitating better sanitation to control this potentially preventable disease. On the other hand, because of acceptable results of LKP for trachoma keratopathy as compared to PKP, there is now a tendency to perform corneal transplantation more frequently in this condition than before which can explain the significant increase observed in the second half of the study period.

Many studies conducted in western countries reported FED as an important indication with a rate of 9.3% to 23.2%.[6,13] However, it was a rare condition in the present study (0.8%) as well as in the Middle East and Mediterranean basin. Macular corneal dystrophy was the most common dystrophy requiring corneal transplantation in the current study, accounting for 65.1% of all patients with corneal stromal dystrophies. This finding supports the report by Kanavi *et al*.[11]

In the current series, PKP was the most common technique of corneal transplantation (70.9%) followed by DALK (20.1%), conventional LKP (4.4%), and DSAEK (2.3%). However, there was a significant alteration in the relative frequency of each surgical technique over the 6 year period, reflecting the introduction of new techniques of corneal transplantation which selectively address the underlying pathologies. DALK using either the Anwar big-bubble or Melles technique was exclusively used for keratoconus in our center and its relative frequency was doubled in the second 3 year follow-up period as compared to the first one. The significant decrease in the frequency of PKP paralleled the more frequent application of DALK for keratoconic patients which was the leading indication in the current study. Similarly, a sixfold increase was observed in the prevalence of DSAEK. This significant increase in the frequency of recently introduced techniques indicates improvements in the ability of surgeons who have already passed the learning curve and emerging of acceptable clinical outcomes, and advantages of these techniques over PKP. For example, DALK eliminates the complications encountered during open-sky surgery (PKP) and endothelial graft rejection reactions, and DSEK is associated with fast visual rehabilitation and lower postoperative morbidity such as suture-related complications.

Regarding the clinical outcomes, our study is similar to other corneal transplant registry reports.[23,24] For example, the incidence of endothelial rejection was 31.9% in PKP eyes in the present study which lies within the range (12% to 44%) reported by other studies.[23-26] Various risk factors for graft rejection have been reported including loose sutures, early suture removal, extent and severity of recipient cornea vascularization, increasing number of regrafts, bilateral graft, anterior synechia, ocular inflammation at the time of transplantation, young age of recipient, size of donor cornea, graft eccentricity, uncontrolled glaucoma, atopic dermatitis, and dry eye states.[23-28] In the current study, significant contributing factors were recipient corneal vascularization, regrafting, anterior synechiae, history of prior graft rejection, and eccentric graft. However, patients' age, size of donor cornea, and bilateral transplantation were not significant risk factors. Differences in reported risk factors can

be attributed to differences in study population, indications for corneal transplantation, criteria for the definition of rejection episodes, and steroid and immunosuppressive usage.

In conclusion, keratoconus remained the leading indication for keratoplasty, concurring with previous reports from Iran. However, there was a significant change in the prevalence of other indications such as regrafts, infectious corneal ulcers, and trachoma keratopathy. Similarly, a significant shift was observed in the techniques of corneal transplantation from more to less invasive surgeries such as DALK and DSAEK as their advantages have emerged and corneal surgeons have been mastering the technique of surgery.

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Cite this article as: Zare M, Javadi MA, Einollahi B, Karimian F, Rafie AR, Feizi S, *et al*. Changing indications and surgical techniques for corneal transplantation between 2004 and 2009 at a tertiary referral center. Middle East Afr J Ophthalmol 2012;19:323-9.

Source of Support: Nil, **Conflict of Interest:** None declared.