

An 11-Year Review of Keratoplasty in a Tertiary Referral Center in Turkey: Changing Surgical Techniques for Similar Indications

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Objectives: Study aims to evaluate the indications and surgical techniques for corneal transplantation and to report changes in trends for preferred keratoplasty surgical techniques.

Methods: Clinical records of 815 consecutive corneal transplantations between January 1, 2004 and December 31, 2014 in Haydarpaşa Numune Training and Research Hospital Eye Clinic were analyzed and classified into seven broad groups according to indications. Main outcome measures were change of leading indications and trends for surgical techniques.

Results: Leading indications for keratoplasty were keratoconus (KCN) (27.7%), bullous keratopathy (BK) (23%), postinfectious corneal scars (13.5%), regrafts (13.1%), corneal dystrophies (12.1%), and noninfectious corneal scars (5.4%). Regrafts were the only indication with a significantly increasing trend ($P < 0.01$). Since the introduction of lamellar keratoplasty (LK) techniques including deep anterior lamellar keratoplasty (DALK) and Descemet stripping automated endothelial keratoplasty (DSAEK), there was a significant increasing trend in number and percentage of both LK techniques (DALK; $P = 0.001$ and $P = 0.007$, and DSAEK; $P < 0.001$ and $P < 0.001$, respectively) and a significant corresponding decline in the percentage of penetrating keratoplasty (PK) ($P < 0.01$). Similarly, DALK and DSAEK replaced PK as the preferred surgical technique for KCN and BK indications, ($P = 0.007$ and $P = 0.01$, respectively). Although PK was the most common surgical technique over the 11-year period (54.7%), both anterior and posterior LK techniques showed an emerging trend as the procedures of choice when indicated.

Conclusions: No major shift was observed in the clinical indications for corneal transplantation over the previous 11 years, except for regrafts. Lamellar keratoplasty techniques largely overtook the PK technique, but PK was still the overall preferred technique in the era when both LK techniques were used.

Key Words: Deep anterior lamellar keratoplasty—Descemet stripping automated endothelial keratoplasty—Keratoplasty indications—Keratoplasty techniques—Penetrating keratoplasty—Trends.

(*Eye & Contact Lens* 2017;43: 364–370)

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The authors have no funding or conflicts of interest to disclose.

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Accepted March 28, 2016.

DOI: 10.1097/ICL.0000000000000274

Corneal transplantation is one of the most successful and most commonly performed transplantations worldwide.^{1–3} Over the last century, indications for corneal transplantation were shaped with respect to geographical location, developmental state of the country, changing demographics and socioeconomic profile of populations, technological advances in ocular surgeries, and patient expectations for a higher quality of life.^{1,3–7}

Despite its several drawbacks such as recurrent allograft rejection, postkeratoplasty astigmatism, and endothelial failure, (full thickness) penetrating keratoplasty (PK) has been the method of choice for all keratoplasty indications.^{8–10} In the last decade, improved (partial thickness) lamellar keratoplasty (LK) techniques that focused on replacing the diseased layers of the cornea were introduced and implemented widely in developed countries.^{1,11} Major advantages of anterior LK over PK are elimination of endothelial allograft rejection with a concomitant reduction in overall graft rejection rates and lower long-term endothelial cell loss of host endothelium. Posterior LK techniques afford much faster visual rehabilitation with less postoperative astigmatism and better anatomical results when compared with PK. As a result of these significant clinical advantages, full-thickness corneal transplantation is no longer reported as the standard surgical technique for most indications in the developed world. Accordingly, a major shift has begun away from PK and toward LK in developing countries as well.^{1,7,11,12}

With these improved outcomes associated with LK techniques, we believe it is necessary for tertiary referral centers in the developing world to stay up to date and use increase utilization of these state-of-the art treatment modalities. Therefore, we initiated this study to determine the trends of clinical indications and corneal transplantation techniques in “2004 to 2014” period, which includes implementation of anterior and posterior LK techniques to our clinics.

MATERIALS AND METHODS

A retrospective chart review of 815 eyes, which underwent corneal transplantation in Haydarpaşa Numune Training and Research Hospital Eye Clinic between January 1, 2004 and December 31, 2014 was conducted. Ethics approval was obtained from Haydarpaşa Numune Training and Research Hospital Ethics Board. Informed consent was obtained from all patients before surgeries and all protocols of this study adhered to the tenets of the Declaration of Helsinki.

Data obtained from the medical records included indication for keratoplasty, preferred surgical technique, and the year of

the surgical procedure. Clinical indications were categorized into seven major groups: keratoconus (KCN), bullous keratopathy (BK) infectious corneal scars, noninfectious corneal scars, corneal dystrophies, regrafts, and other causes. Detailed analyses of these major groups (and subgroups) are shown in Table 1.

Annual numbers and percentage of each group (and subgroup) of clinical indications for each surgical technique were calculated. To evaluate trends for clinical indications, each group of indication was analyzed separately with respect to year of the surgery and preferred surgical technique. Surgical techniques were categorized as follows: PK, deep anterior lamellar keratoplasty (DALK), and Descemet stripping automated endothelial keratoplasty (DSAEK). In addition, to evaluate major shifts in changing indications and surgical techniques, the study period was divided into two parts (2004–2009 and 2010–2014). The rationale for the selected time intervals was that both partial thickness LK techniques (both anterior and posterior LK together) have been used from 2010 on.

In this study, data were analyzed per surgery (used donor cornea). Thus, each repeat corneal transplantation was considered as a new surgery with “regrafts” indication, but indications for primary corneal transplantation are also presented in Table 1. Indications for corneal transplantation were classified according to the primary diagnosis, for example, if an eye with Fuchs Endothelial Dystrophy (FED) showed BK after cataract surgery; it was grouped under corneal dystrophies indication.

To assess the time trend for changes in clinical indication and type of surgery over the study period, linear regression analysis was used. Chi-square analysis was used to determine the statistical significance of changes in the preferred surgical technique between the two study periods. NCSS (Number Cruncher Statistical

System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software programs were used for statistical analysis. A *P* value of ≤ 0.05 was considered significant and all *P* values were 2-tailed.

RESULTS

The study included 815 consecutive keratoplasty procedures which were performed in 735 eyes of 612 patients. Mean age was 45.57 ± 22.39 (2–93) and mean donor age was 50.47 ± 15.8 (4–75) years. Sex ratio (female: male) was 285/327 (46, 6%/53, 4%).

Over the 11-year period, annual number of corneal transplantations demonstrated a statistically significant increasing trend with time ($P < 0.001$). Number and percentage of surgical techniques with respect to indication groups (and subgroups) are shown in Table 1. Figure 1 shows the number and percentage of each surgical technique performed each year.

There was a significant decrease in the percentage of PK after the introduction of LK techniques (DALK in 2008 and DSAEK in 2010) ($P < 0.01$). However, the number of PKs remained stable ($P = 0.17$) corresponding to the increasing number of overall corneal transplantations performed each subsequent year. Linear regression analysis showed a statistically significant increasing trend in the number and percentage of both lamellar techniques (For DALK; $P = 0.001$, $R^2 = 0.75$, and $P = 0.007$, $R^2 = 0.57$, for DSAEK; $P < 0.001$, $R^2 = 0.77$, and $P < 0.001$, $R^2 = 0.80$, respectively).

In Table 2, the number and percentage of indications for corneal transplantation are shown for 2004 to 2009 and 2010 to 2014 periods. There was a major shift in clinical indications for PK between these periods.

TABLE 1. Number and Proportion of Each Indication Group (and Subgroups) With Respect to Surgical Techniques

	PK, n (%)	DALK, n (%)	DSAEK, n (%)	Overall Proportion, n (%)
Keratoconus	51 (22.6)	175 (77.4) ^a	0	226 (27.7)
Bullous keratopathy	112 (59.6) ^a	0	76 (40.4) ^a	188 (23)
Aphakic	9 (69.2)	0	4 (30.8)	13 (1.5)
Pseudophakic	103 (58.9)	0	72 (41.1)	175 (21.4)
Postinfectious corneal scars	80 (72.7) ^a	30 (27.3) ^a	0	110 (13.5)
Nonviral keratitis	51 (76.1)	16 (23.9)	0	67 (8.2)
Viral keratitis	29 (67.4)	14 (32.6)	0	43 (5.2)
Regrafts	94 (87.9) ^a	8 (7.5)	5 (4.6) ^a	107 (13.1)
Indication of primary graft				
Bullous keratopathy	23 (88.5)	0	3 (11.5)	26 (3.1)
Postinfectious corneal scars	21 (100)	0	0	21 (2.5)
Noninfectious corneal scars	16 (100)	0	0	16 (1.9)
Other causes	34 (77.2)	8 (18.1)	2 (4.5)	44 (5.3)
Corneal dystrophies	38 (38.4)	56 (56.6) ^a	5 (5) ^a	99 (12.1)
Corneal stromal dystrophies	24 (30)	56 (70)	0	80 (9.8)
Lattice dystrophy	3 (37.5)	5 (62.5)	0	8 (0.9)
Granular dystrophy	8 (29.6)	19 (70.4)	0	27 (3.3)
Macular dystrophy	9 (25)	27 (75)	0	36 (4.4)
Other causes (Avellino and Reis-Bucklers dystrophy)	4 (44.4)	5 (55.5)	0	9 (1.1)
Corneal endothelial dystrophies	14 (73.7)	0	5 (26.3)	19 (2.3)
Fuchs endothelial dystrophy	7 (63.6)	0	4 (36.4)	11 (1.1)
Other causes (CHED and PPCD)	7 (87.5)	0	1 (12.5)	8 (0.9)
Noninfectious corneal scars	41 (93.2)	3 (6.8)	0	44 (5.4)
Posttraumatic mechanical injuries	39 (97.5)	1 (2.5)	0	40 (4.9)
Chemical injuries	2 (50)	2 (50)	0	4 (0.4)
Other causes	29 (69.0)	11 (26.2)	2 (4.8)	42 (5.1)

^aThe top three indications for each surgical technique.

PK, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; CHED, congenital hereditary endothelial dystrophy; PPCD, posterior polymorphous corneal dystrophy.

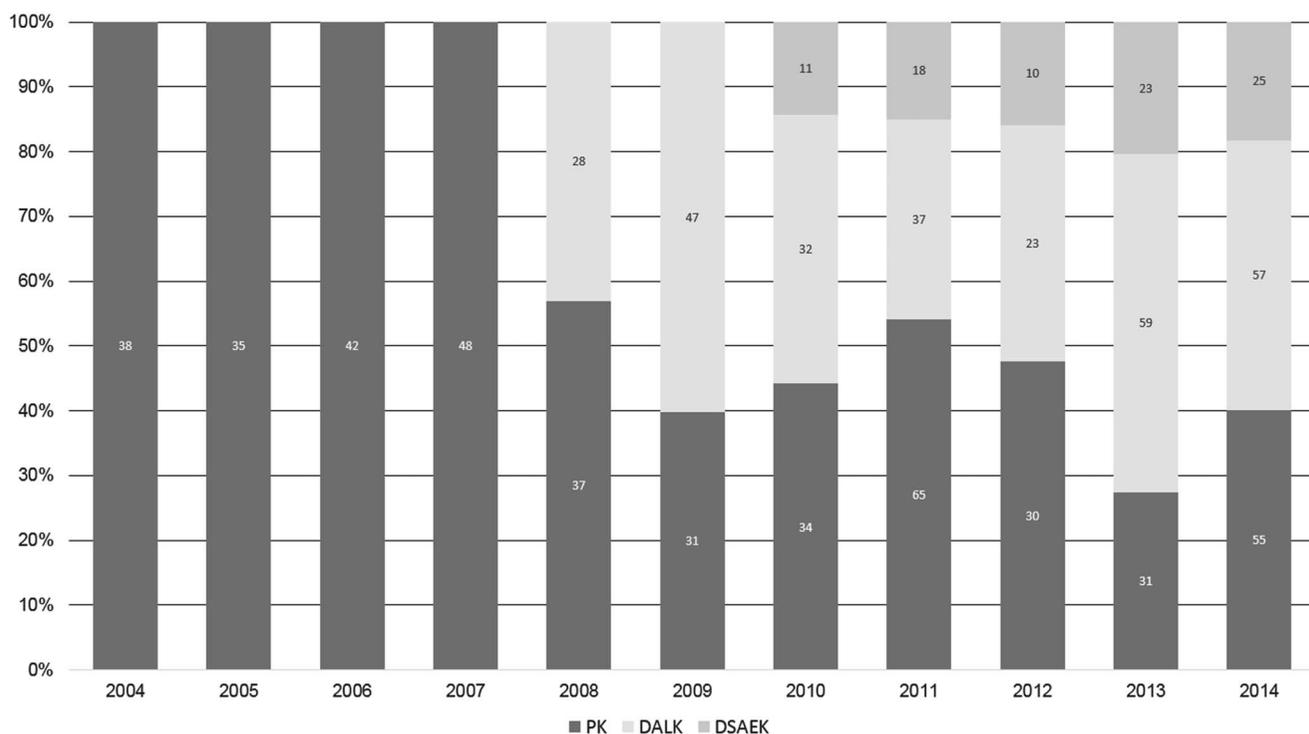


FIG. 1. Annual number and percentages of surgical techniques. PK, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty.

Trends in Indications With Respect to Surgical Techniques

Keratoconus

Keratoconus was the leading indication for corneal transplantation (27.7%) over the study period, and it was among the top three indications for corneal transplantation at each time point. There was a statistically significant increase in the number of corneal transplantations for KCN ($P=0.008$, $R^2=0.559$). However, the percentage of KCN as a keratoplasty indication did not demonstrate a significant increase ($P=0.29$) (Fig. 2, top left).

Figure 3 shows the number and percentage of PK and DALK for KCN through the study period. DALK was found to be significantly preferred over PK during 2010 to 2014 period (91%) versus 2004 to 2009 period (58%) for KCN indication ($P<0.01$).

Bullous Keratopathy

During the study period, 188 corneal transplantations were performed for BK. Overall percentage of BK did not change significantly and, in fact, there was a trend toward a decrease ($P=0.15$) (Fig. 2, top right). Figure 4 shows the number and percentage of PK and DSAEK for BK through the study period. Between 2004 to 2009 and 2010 to 2014 periods, number of DSAEK increased from 0 (0%) to 76 (67.9%) and DSAEK was preferred over PK for surgical treatment of BK between 2010 and 2014 (76 DSAEK vs. 36 PK).

Postinfectious Corneal Scars

In this series, postinfectious corneal scar was the third most common indication for corneal transplantation ($n=110$ [13.5%]). The number and percentage of keratoplasties for postinfectious corneal scars did not significantly change over the study period ($P=0.3$ and $P=0.07$, respectively) (Fig. 2, middle left).

Noninfectious Corneal Scars

Forty-four eyes (5.4%) underwent corneal transplantation for surgical treatment of noninfectious corneal scars (Table 1). The number of keratoplasties for noninfectious corneal scars did not change significantly over the study period ($P=0.9$), but the percentage of keratoplasties performed for noninfectious corneal scars showed a significant gradual decline ($P=0.03$, $R^2=0.63$) (Fig. 2, bottom right).

TABLE 2. Clinical Indications and Surgical Techniques for Corneal Transplantation Between 2004 to 2009 and 2010 to 2014 Periods

	2004–2009, N (%)	2010–2014, N (%)
Indications		
Keratoconus	93 (30.4)	133 (26.1)
Bullous keratopathy	76 (24.8)	112 (22.0)
Postinfectious corneal scars	47 (15.4)	63 (12.4)
Regrafts	23 (7.5)	84 (16.5)
Corneal dystrophies	27 (8.8)	72 (14.1)
Noninfectious corneal scars	21 (6.9)	23 (4.5)
Other causes	19 (6.2)	23 (4.5)
Surgical techniques		
PK	231 (75.5)	214 (41.9)
DALK	75 (24.5)	208 (40.8)
DSAEK	0 (0)	87 (17.1)
Total	306	509

PK, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty.

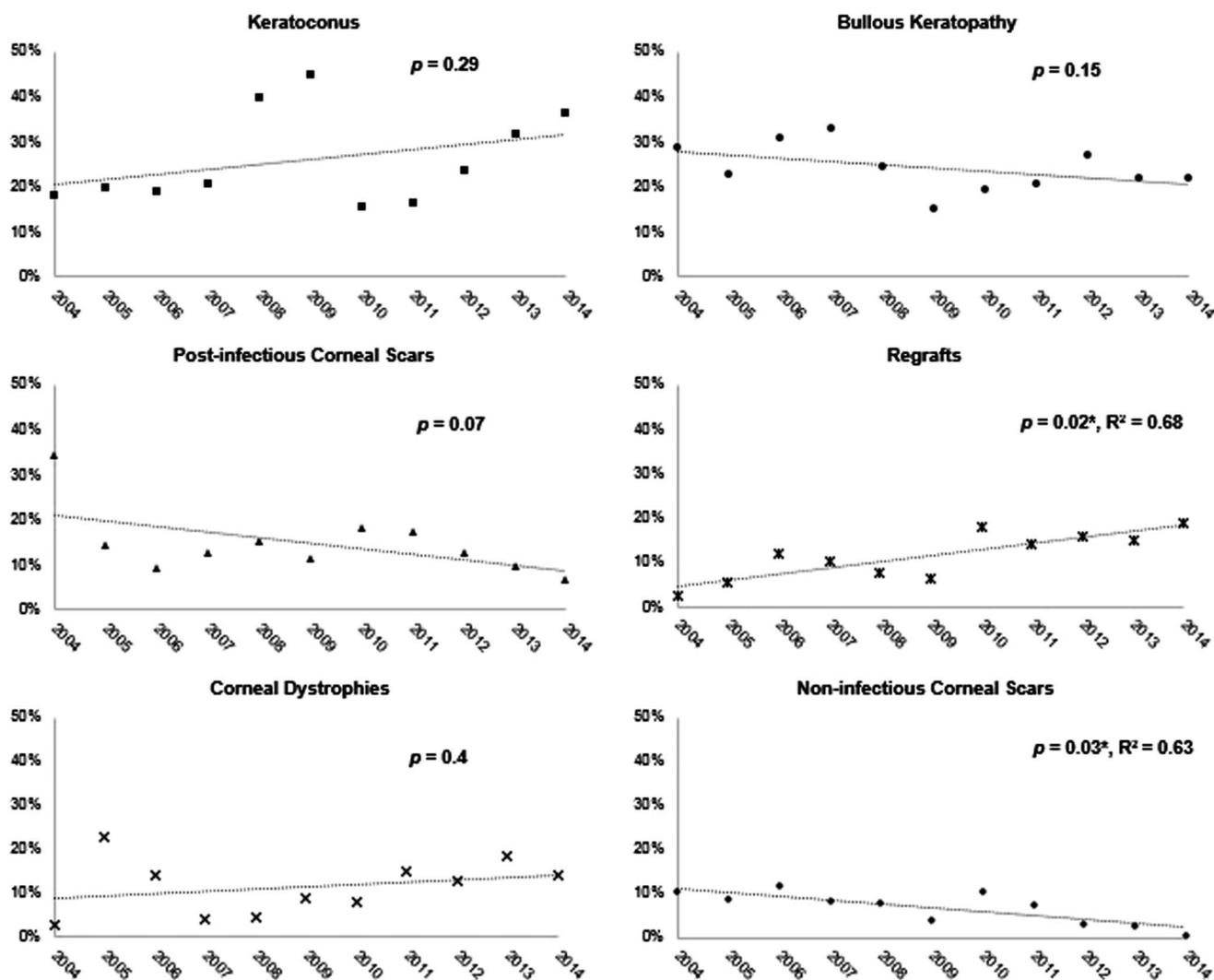


FIG. 2. Trends for percentages of 6 leading indications for corneal transplantation between 2004 and 2014. Regrafts (middle right) showed a statistically significant increasing trend ($P=0.02$) and non-infectious corneal scars (bottom right) decreased significantly ($P=0.03$). Keratoconus (top left) and corneal dystrophies (bottom left) showed a statistically nonsignificant increasing trend ($P=0.29$ and $P=0.4$, respectively), whereas bullous keratopathy (top right) and postinfectious corneal scars (middle left) declined nonsignificantly ($P=0.15$ and $P=0.07$, respectively).

Corneal Dystrophies

Over the years, the number of keratoplasties performed for a corneal dystrophy indication showed a significant increase ($P=0.004$, $R^2=0.61$) but the change in percentage of keratoplasties performed for corneal dystrophy indications was not significant ($P=0.4$) (Fig. 2, bottom left). For corneal stromal dystrophies, the number of PK performed did not differ significantly ($P=0.59$). However, the percentage of PK performed for corneal dystrophy indications dropped significantly ($P=0.006$, $R^2=0.57$). As expected, both the number and percentage of DALK performed as a surgical treatment for a stromal corneal dystrophy increased significantly ($P<0.01$, $R^2=0.77$ and $P=0.006$, $R^2=0.57$, respectively). DALK became the preferred surgical technique for corneal stromal dystrophies from 2004–2009 to 2010–2014 (increasing from 33.3% to 83.1%, respectively). The preferred surgical technique for corneal endothelial dystrophy indications was not analyzed because of small sample size.

Regrafts

Over the study period, both the number and percentage of regrafts increased significantly ($P<0.01$, $R^2=0.80$ and $P=0.02$, $R^2=0.68$, respectively) (Fig. 2, middle right). There was no change in the preferred surgical method for regrafts between 2004 to 2009 and 2010 to 2014 ($P=0.37$).

DISCUSSION

To the best of our knowledge, this study provides the first report evaluating the trends in the clinical indications and surgical techniques for corneal transplantation in Turkey. The setting of this study, a tertiary referral hospital based in Istanbul, the largest city in Turkey with an ever-growing population (currently over 15 million, representing 20% of Turkey’s population) offers a clinically useful opinion on the current nationwide trends of indications for corneal

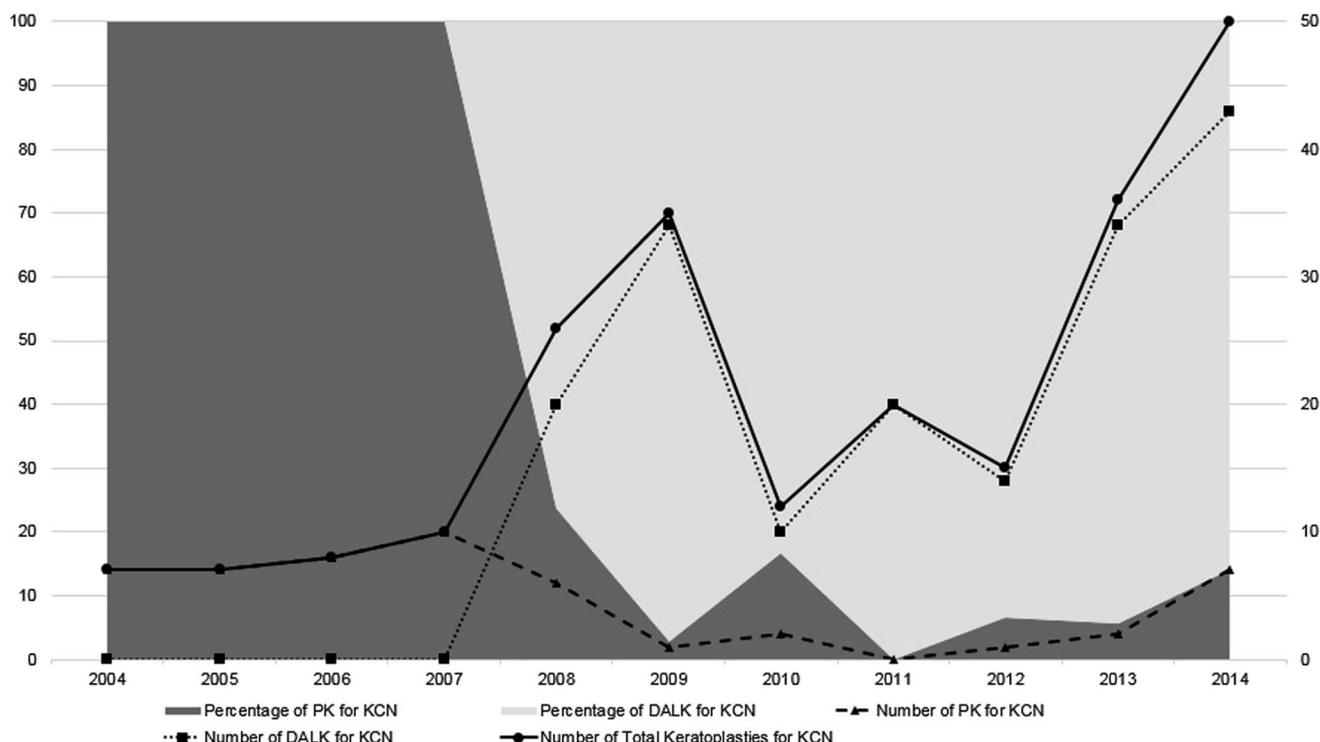


FIG. 3. Number and percentage of penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) for keratoconus (KCN) over the study period. Turning point for preferred surgical treatment of KCN was 2008 when 76.9% of keratoplasties for KCN was DALK. There was a significant increase in both the number and percentage of DALK for KCN ($P=0.007$, $R^2=0.575$ and $P<0.001$, $R^2=0.763$, respectively). The number of PK for KCN did not differ significantly ($P=0.27$), but percentage of PK decreased significantly with linear regression analysis ($P<0.01$, $R^2=0.75$).

transplantation in Turkey. However, this study may be biased toward increased numbers of clinical indications appropriate for LKs because many patients from all over Turkey were referred to our clinic to undergo DALK or DSAEK during 2010 to 2014 period.

Trends in Surgical Techniques

After the adoption of DALK at our institution in 2008, most of the eyes with anterior corneal disease underwent DALK. Accordingly, there was a significant increasing trend in both the percentage and number of DALK. In fact, last two years demonstrated a twofold increase as opposed to 2008. This finding of an increasing trend toward DALK was consistent with reports from western countries, albeit with a slight delay.^{1,6,7,12,13}

DALK was the most common surgical technique chosen for KCN and stromal corneal dystrophy indications in this series. Given comparable visual rehabilitation outcomes, DALK is an excellent alternative to PK and is the preferred surgical practice for anterior corneal diseases.^{1,14,15} We postulate that the value of DALK may have augmented the prevalence of KCN and stromal corneal dystrophies as a clinical indication for corneal transplantation in this series because many patients who were not eager to undergo full-thickness keratoplasty were specifically referred to our clinic for a second opinion and consideration for DALK.

In western countries over recent years, endothelial keratoplasty has been reported as having a significant increasing trend for major indications like FED and BK.^{1,2,6,12,13,16} An increasingly aging population of FED patients in these countries seems to be a major

contributing factor to this trend. A more rapid visual recovery with DSAEK compared with PK has allowed surgeons and patients to consider earlier interventions for FED and BK indications.^{2,6} In our clinic, the first DSAEK was performed in 2010. To date, Descemet membrane endothelial keratoplasty has not been performed, yet. The fact that DSAEK is highly technical with a steep surgical learning curve, requires dedicated surgical instruments, and presents unique challenges to the surgeon regarding donor preparation (Turkish eye banks did not prepare precut donor tissues until 2014), may explain the delayed adoption of DSAEK when compared with DALK, which can be performed largely without unique instrumentation or preparation. In addition, need for establishment of an anterior LK technique was more than an endothelial keratoplasty technique because KCN was the most common indication and only 1.1% of eyes underwent corneal transplantation for FED in this series. Nevertheless, after its introduction, number of DSAEKs has significantly increased with a doubling of the number of surgeries in last two years of the study compared to 2010. This study showed that DSAEK was preferred significantly over PK for the surgical treatment of BK, with 87.4% of corneal transplants performed as DSAEK for BK indications.

Our study observed that although the total number of corneal transplants increased significantly over the 11-year period, the number of PK remained stable. The reason for this overall increase in volume was mainly due to the introduction and adoption of LK techniques. Despite this significant trend, PK remained the most common surgical method in this series, even through the 2010 to 2014 period. This finding is consistent with many other studies

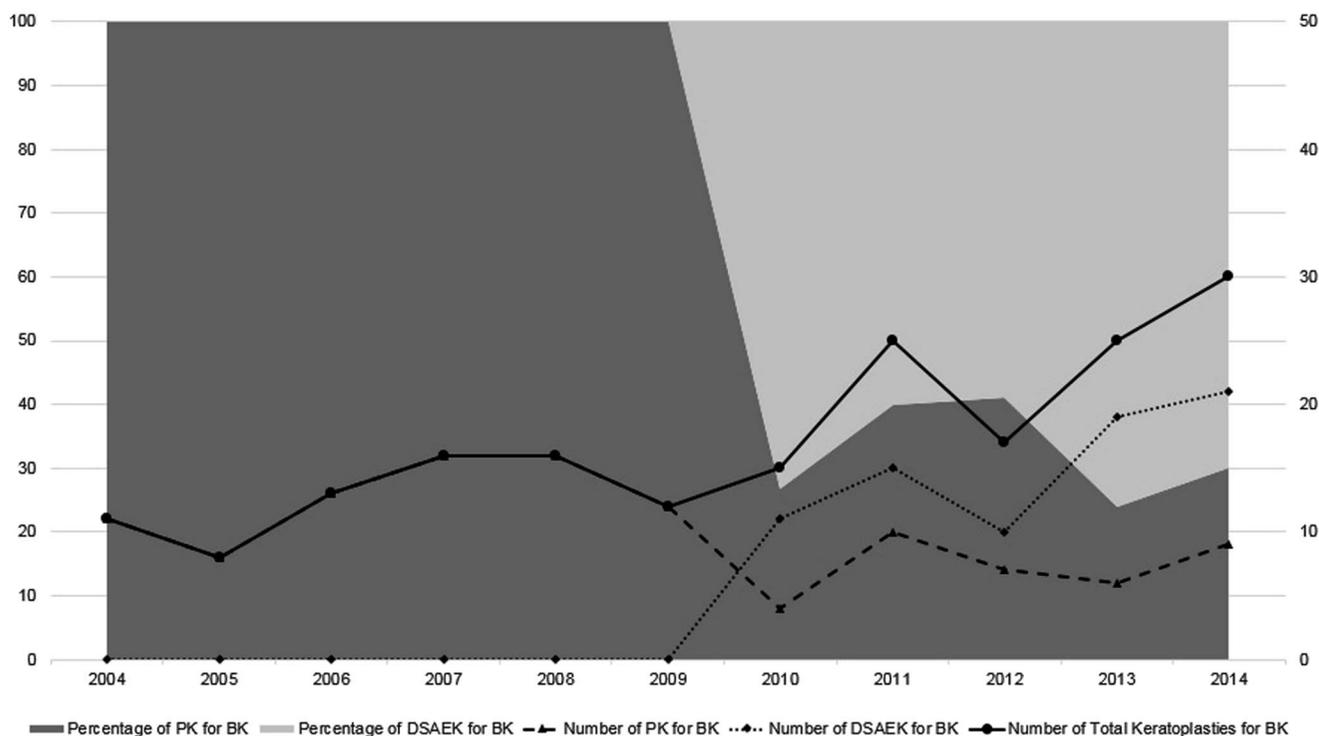


FIG. 4. Number and percentage of penetrating keratoplasty (PK) and Descemet stripping automated endothelial keratoplasty (DSAEK) for bullous keratopathy (BK) over the study period. All corneal transplantations for BK were in the form of PK before the introduction of DSAEK in 2010. After 2010, DSAEK was preferred over PK, and there was a significant decrease in the percentage of PK for surgical treatment of BK ($P=0.01$, $R^2=0.749$). Owing to the increase in the overall number of corneal transplantations, the number of PK for BK did not differ significantly ($P=0.15$). Both the number and percentage of DSAEK for BK showed a statistically significant increase ($P<0.01$, $R^2=0.799$ and $P=0.01$, $R^2=0.749$, respectively).

conducted after introduction of LK techniques.^{1,2,8,12,13,16} However, one recent study conducted in the US concluded that DSAEK is the most preferred technique and surpassed PK from 2011 on.¹¹ In fact, predominance of lamellar techniques in the last years of the study periods was reported in several studies including present one.^{1,2,7,10,12,16} Thus, current data indicate that PK will decrease in prevalence relative to lamellar techniques in the future.

Trends in Indications for Corneal Transplantation

In our study, KCN and BK were the leading indications for corneal transplantation, each representing about one quarter of overall volume (27.7% and 23%, respectively) with no significant changes in prevalence comparing 2004–2009 to 2010–2014.

Keratoconus was reported as the leading indication or one of the major indications in studies throughout the world.^{1,4,5,7–9,11,12,17–20} Distribution of KCN is affected from differences of genetic demographics and geography (climates)^{5,12} There tends to be a higher percentage of patients undergoing corneal transplantation for KCN in Turkey and its neighboring countries as compared with the rest of the world. We think that this may be attributed to its close relation with atopy, which is an important factor for contact lens intolerance.^{4,12,21} Appropriately, the findings in our study are consistent with similar studies originating from Iran, Greece, and Israel.^{4,5,19} We found similar results for the BK indication, which was found

to be another major indication in many studies.^{5–8,11,16,19,20} However, most studies concluded that there is a trend toward BK as a decreasing indication for corneal transplantation, despite higher number of aging patients undergoing cataract surgery, presumably due to ever-improving phacoemulsification techniques, intraocular lens designs, advances in microsurgery, and adequate endothelial protection with better viscoelastics.^{1,4,6,7,11,12,16,17,21} We think that functioning as a tertiary referral center capable of performing DSAEK might have caused a similar bias to DALK and KCN because patients with BK were specifically referred by cataract surgeons to our clinic for the management of this indication.

Evaluating eyes with corneal scars as an indication for corneal transplantation is challenging because there are many, varied pathophysiologic causes of corneal scars, and they are reported in different ways in several studies.^{3,4,10,17,22} In our series, we believe that classifying corneal scars according to etiologies as postinfectious or noninfectious corneal scars was most helpful for interpretation of the data and making comparisons with the peer-reviewed literature. Regardless of the method and the cause, corneal scars have been reported as a leading indication in up to 66% of cases in the developing world.^{3,9,22–24} In our series, corneal scars represent the third most common indication and are responsible for 18.9% of all eyes undergoing corneal transplantation, which is in accordance with reports from some developed countries.^{1,5,17,19} Considering the tertiary referral profile of our

institution, this may indicate inadequate preventive care and poor medical management for infectious keratitis in Turkey.^{9,22} Fortunately, it is a promising finding for future that the percentage post-infectious corneal scar indication showed a decreasing trend over the study period that was almost statistically significant ($P=0.07$).

In this study, regrafts (11.3%) were the only indication, which showed a significantly increasing trend (in both number and percentage). In fact, it is an anticipated finding because the prevalence of the regrafts indication is closely related to the increasing number of corneal transplantations over the study period. This phenomenon is well-recognized in studies originating from institutions reporting a high volume of corneal transplantations.^{1,2,8,11–13,16,20} As the number of eyes with corneal grafts (which may eventually fail in future) increases because of technological advances in surgical techniques, better patient care and improving eye bank capabilities, so does the number of regrant cases. It is not surprising that all of these reports were from developed countries that have better access to corneal tissue and whose patients are from higher socioeconomic strata, affording them easier access to these procedures. Accordingly, these findings do not indicate that developing countries have better results in graft survival but that developing countries have long waiting lists, donor shortages, and lower socioeconomic profiles, causing patients to give up a regrant procedure, removing them from the study pool, leading to a lower percentage of regrafts as an indication for corneal transplantation.^{3,4} Another aspect of our study worth noting is that the increasing prevalence of DALK might decrease the percentage of regrafts in future, given the lower incidence of graft rejection in the DALK population compared with the PK population.^{25,26}

Corneal dystrophies comprised 12.1% of the clinical indications for corneal transplantation in our series (Table 1). Macular Dystrophy was the most common stromal corneal dystrophy (36%) similar to studies from Iran.^{4,18} Only 19% (2.3% of the total series) of eyes transplanted in our series showed endothelial corneal dystrophies with only 11 eyes having FED. This is in great contrast to studies from USA and Canada where FED is reported to be one of the major indications for endothelial keratoplasty.^{2,6,11,13} Favorable outcomes of endothelial keratoplasty techniques represent the major reason for these increasing trends. For similar reasons in our study, the DALK has an increasing prevalence for stromal corneal dystrophy indications. Because patients with stromal corneal dystrophies often have relatives affected by the disease, word of mouth referrals from existing patients represent an important factor for increasing referrals for second opinion by our colleagues.

In conclusion, over the 11-year study period, there was an increasing trend in the number of corneal transplantations performed, and major shifts were observed in the trends for a preferred surgical technique based on the indication. Lamellar keratoplasty techniques have largely replaced PK when indicated, but PK remained the most common technique during the 2010 to 2014 period when both lamellar techniques were introduced. In terms of indications, “KCN and BK” remained stable as the top 2 most common indications over the entire 11-year study period. It should be highlighted that lamellar techniques became the method of choice for these leading indications (DALK for KCN and DSAEK for BK). Therefore, we think that evaluation of trends for corneal transplantation techniques might be helpful to predict future trends for clinical indications when tertiary referral centers are in question.

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