The Incidence of Glaucoma Following Deep Anterior Lamellar Keratoplasty and Penetrating Keratoplasty

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INTRODUCTION

Keratoplasty is a surgical intervention for ophthalmic rehabilitation, preservation of ocular anatomical integrity, and cosmetic purposes. All layer corneal tissue replacement is performed in penetrating keratoplasty (PK), while DALK procedures, which is a newer technique than PK, are generally performed in eyes with anterior corneal pathology. ^[1-4] All keratoplasty procedures have some undesirable complications, including glaucoma, graft rejection and refractive irregularities.^[5]

Glaucoma after keratoplasty is one of the most challenging complications due to the risk of endothelial cell loss, graft failure, irreversible optic nerve damage, and visual loss. ^[5-7] Several factors are contributed to the development of glaucoma after keratoplasty including, anatomic distortion of the iridocorneal angle, postoperative inflammation, vitreous prolapse into the angle, iatrogenic injury of the

ABSTRACT

Objective: To evaluate the incidence of glaucoma and the response rates to anti-glaucoma treatment after deep anterior lamellar keratoplasty (DALK) in comparison with penetrating keratoplasty (PK).

Methods: In this retrospective study, 146 patients with DALK and 156 patients with PK were evaluated. All patients were followed up on the 1st, 3rd, 6th, 12th and 24th days after the keratoplasty procedure. The risk factors and incidence of glaucoma and glaucoma treatments were assessed in both the DALK and the PK groups.

Results: A total of 156 eyes with DALK procedure and 163 eyes with PK procedure were included. Eleven eyes in the DALK group (7.05%) and 16 eyes in the PK group (9.81%) were diagnosed with glaucoma (p=0. 42). The median number of anti-glaucoma drugs was 1.0 in DALK groups and 1.5 in PK groups (p=0.01). Trabeculectomy with mitomycin C was performed in 4 of the 16 eyes (25%) with glaucoma after the PK (p=0.01). In the DALK group, patients were followed up with mono anti-glaucoma treatment therapy without surgical intervention.

Conclusion: In our study group, the incidence of glaucoma was 7% in eyes with DALK and 9.8% in eyes with PK. However, the number of glaucoma drugs was significantly higher in eyes with PK procedure than eyes with DALK procedure (p=0.01). Moreover, eyes with DALK have needed less trabeculectomy with mitomycin C compared to eyes with PK. Therefore; our results suggested that the DALK procedure might be more appropriate and safer than PK concerning glaucoma development.

angle, using topical steroid, graft rejection, and presence of preoperative glaucoma. $^{[2\mathchar`]}$

The incidence of glaucoma and elevated intraocular pressure (IOP) after PK has been reported in a range from 5.3% to 47.9%.^[7-9] The incidence of glaucoma and increased IOP after the DALK was evaluated in a few studies and determined in a range of 0-17%.^[10-13]

The aim of this study was to compare the incidence of glaucoma and the response rates to anti-glaucoma treatment after DALK and PK.

MATERIALS AND METHODS

The institution's ethics committee approved the study protocol, and the study was conducted in accordance with the Declaration of Helsinki. This retrospective, comparative, single-center study was performed at the Kartal Dr. Lutfi Kırdar City Hospital, Department of Ophthalmology. The eyes underwent corneal transplantation between 2013 and 2015 were enrolled in the study. One hundred fifty-six eyes of 146 patients who underwent the DALK procedure and 163 eyes of 153 patients who underwent the PK procedure were included. All indications for keratoplasty were recorded. The exclusion criteria for the study were patients with previous corneal surgery, trauma, hydrops, atopic keratoconjunctivitis, or vernal conjunctivitis, and a history of pre-existing glaucoma, complications during surgery, or those with postoperative complications, such as endophthalmitis, microbial keratitis, herpes simplex infection, or recurrence of graft herpetic keratitis, suture abscess, poor epithelial healing, primary graft failure, or peripheral anterior synechiae.

For all patients, medical and surgical history, an indication of keratoplasty, evaluation of preoperative and postoperative best-corrected visual acuity, IOP measurement with Tonopen (Tono-Pen AVIA, Reichert, USA), surgical techniques, postoperative treatment and complications were recorded. Patients were examined at 1, 3, 6, 12, and 24 months after the keratoplasty.

The diagnosis of glaucoma after keratoplasty has some challenges including pre-operative and post-operative assessment of the optic nerve and visual field, and sometimes IOP measurements due to high and irregular astigmatism, insufficient corneal transparency. Post-keratoplasty glaucoma is defined as elevated in intraocular pressure above 21 mm-Hg at different time points, which requires the introduction of anti-glaucoma medication or surgical intervention, independent of the optic nerve or visual field changes.^[6,8] All anti-glaucoma treatments (medications and surgical procedures) to reduce the IOP were recorded. Timolol maleate 0.5% twice daily was used as a first-line topical treatment. If IOP levels could not be managed within the normal range, additional medication, such as topical carbonic anhydrase inhibitors, alpha-2 selective adrenergic agonists, and prostaglandin analogues, were administered. If IOP reduction was not satisfactory, oral acetazolamide was added. Trabeculectomy with mitomycin C was performed in cases resistant to medical treatment. Patients who underwent trabeculectomy with mitomycin C displayed normal IOP levels postoperatively without requiring additional medical treatment.

Surgical technique

Anwar and Teichmann described Anwar technique, which a big-bubble technique for the dissection of the Descement membrane (DM) from the corneal stroma for deep lamellar keratoplasty. The anterior stromal layer was trephined to a depth of approximately 50%–70% using a Hessburg–Barron suction trephine (7.00 or 7.5 mm) (JedMed Instrument Co, St. Louis, MO., USA). A 27-gauge needle attached to an air-filled 5-ml plastic syringe was introduced into the cornea in the bevel-down position at the base of the trephine incision and parallel to the corneal surface 2–4 mm to the mid-periphery. Air was injected to create a big bubble between the DM and the corneal stroma, allowing the trephination margins to be reached. After bubble formation, the anterior corneal stromal tissue was manually dissected. The stromal tissue remaining in the central portion of the cornea was perforated using a slit knife with the help of the secure space provided by the previously locked-in air anterior to the DM, and the remnant deep stromal tissue was dissected. The donor cornea, 0.25 mm larger than the host cornea, was trephined on a donor punch and stripped of the DM and endothelium as well as the surface epithelium. The donor cornea was sutured using interrupted 10–0 nylon sutures and 16 single running sutures.

Penetrating keratoplasty

PK surgeries were performed with a standard technique using a suction trephine (7.00 or 7.50 mm). The trephine was elevated after the vacuum was evacuated, following the anterior chamber fluid was removed. The incision was completed with keratoplasty scissors, and the recipient bed was prepared. A 0.25-mm larger donor cornea was punched on a donor punch. The donor cornea was fixed with 8 interrupted 10–0 nylon sutures, and 16 single running sutures were added.

For both techniques, subconjunctival 2 mg dexamethasone and 20 mg gentamycin was injected at the end of each procedure. Dexamethasone 0.1% and moxifloxacin hydrochloride 0.5% were administered topically five times a day during the postoperative period. All patients received topical moxifloxacin hydrochloride 0.5% for 1 to 2 weeks. Dexamethasone 0.1% administration was discontinued after 4–6 months in the DALK group, while it was tapered after 6 months and continued up to 12 months in the PK group.

Statistical analysis

Outcome measures of the DALK and PK patients were analyzed using the SPSS program version 17 (SPSS Inc, Chicago, Illinois, USA). Data distrubition was analysed with the Kolmogorov Smirnov or Shapiro Wilk test. Fisher's exact tests and chi-square tests were used to compare categorical data. Independent Student t-tests and one-way analyses of variance were used to compare quantitative data. P values <0.05 were considered significant.

RESULTS

There were 156 eyes of 146 patients (70 male and 76 female) who had undergone DALK procedure. The mean age of the patients with DALK was 26.6 ± 8.4 years. The most common indications for DALK were listed as; keratoconus in 138 (88.4%) eyes, corneal granular dystrophy in 9 (5.7%) eyes, corneal macular dystrophy in 7 (4.4%) eyes, and post LASIK corneal ectasia in 2 (1.2%) eyes.

In the PK group, there were 163 eyes of 153 patients (74 male and 79 female) with a mean age of 25.0 ± 13.7 years. The most common indications for PK were listed as; kera-

toconus in 148 (94.8%) eyes, corneal granular dystrophy in 8 (4.9%) eyes, and corneal macular dystrophy in 7 (4.2%) eyes. There were no statistically significant differences between the two groups in terms of age, gender distribution, duration of follow-up, and distribution of indication (p>0.05). The demographics and clinical features in patients with DALK and PK are summarized in Table 1.

The mean pre-operative IOP in patients with DALK was 14.06 ± 4.27 mm Hg and in patients with PK was 15.21 ± 5.73 mm Hg (p=0.62). The mean glaucoma diagnosis time after the keratoplasty procedure was 5.06 ± 20 months and 5.04 ± 20 months in the DALK and PK groups, respectively (p=0.49). Comparing IOP at the the glaucoma visit diagnosis between the two groups, the mean IOP was 26.34 ± 8.70 mm Hg in DALK group and 32.25 ± 6.20 mm Hg in the PK group. The patients with PK group had statistically significantly higher IOP compared to patients with DALK (p=0.02). Eleven eyes (7%) with DALK were diagnosed with glaucoma while 16 eyes (%9.8) with PK were diagnosed with glaucoma. There were no statistically significant differences in glaucoma development between the groups (p=0.42).

Anti-glaucoma treatment was initiated, while corticosteroid ophthalmic drop treatment was continued in patients with IOP levels above 21 mmHg. Timolol maleate 0.5% was used as a first-line topical treatment twice daily. This treatment adequately controlled the IOP in the DALK group, but six eyes (54%) in the PK group required a second anti-glaucoma ophthalmic drop, and for one patient (9%) in the PK group, IOP levels were successfully decreased with the administration of oral acetazolamide 250 mg four times a day. The median number of anti-glaucoma drugs used was 1.0 and 1.5 in the DALK and PK groups, respectively (p=0.01). When the IOP could not be decreased with the maximal medical therapy, which occurred in 4 out of 16 eyes (25%) with glaucoma in the PK group (p=0.01), trabeculectomy with mitomycin C was performed,

In the cases with trabeculectomy with mitomycin C, the IOP remained within the normal range without pharmacotherapeutic intervention, postoperatively. Anti-glaucoma treatments were discontinued in all patients whose IOP decreased sufficiently after corticosteroid ophthalmic drops treatment was discontinued in the PK and DALK groups. In the DALK group, none of the patients required glaucoma surgery. At the last visit (24^{th} month), the mean IOP was 17.26±6.80 mm Hg and 19.15±8.22 mm Hg in patients with DALK and PK groups, respectively. There were no statistically significant differences in IOP at the last visit between the two groups (p=0.42). The mean IOP was 18±3.26 mm Hg at the last visit in patients with PK who underwent trabeculectomy with mitomycin C procedure.

Immunogenic graft rejection was detected in 8 eyes in the DALK group (5.1%) and 12 eyes in the PK group (7.3%), all of which improved with topical corticosteroid ophthalmic drops. Graft failure occurred in two eyes (1.2%) in the PK group during follow-up, and was attributed to low endothelial cell counts. Cases with spontaneous suture loosening in the early postoperative period after DALK and PK were successfully managed.

DISCUSSION

Glaucoma after keratoplasty is a serious problem due to its high incidence and difficulties in diagnosis, treatment, and management.^[6,7] Therefore, we aimed to compare the incidence of glaucoma and response rates to anti-glaucoma treatments after DALK and PK procedures.

In the current study, we found that the glaucoma incidence after the PK procedure was 9.8% (16 eyes), and after the DALK procedure was 7.05% (11 eyes). The difference in glaucoma incidences between the two groups was not statistically significant (p=0.42). The IOP was maintained below 20 mmHg in glaucoma eyes with a single drug, but the median number of drugs needed in the PK group was 1.5 (p=0.01). Moreover, trabeculectomy with mitomycin C was required in 4 of the 16 eyes (25%) that developed glaucoma in the PK group. Our result suggested that patients with glaucoma after keratoplasty were significantly decreased with the DALK procedure. Also, we managed glaucoma treatment with less medication in the DALK group than the PK group.

There are many studies focusing on the frequency and risk factors of glaucoma development after PK. The frequency of glaucoma ranges from 5.3% to 47.9%.^[8,14,15] The varying

Parameters	Deep anterior lamellar keratoplasty	Penetrating keratoplasty	р
Number of cases (eye)	156	163	
Age (mean±SD, year)	26.67±8.42	25.07±13.72	.289
Sex (male/female)	(70/76)	(74/79)	.517
Mean follow-up (mean±SD, month)	25.69±8.06	25.30±11.73	.422
Indications for surgery, n (%)			
Keratoconus	I 38 (88.4%)	148 (90.80%)	.582
Corneal stromal dystrophy	16 (10.25%)	15 (9.20%)	.851
Post LASIK ectasia	2 (1.28%)	_	

Data are presented as mean±standard deviation. DALK: Deep anterior lamellar keratoplasty; PK: Penetrating keratoplasty; SD: Standard deviation.

rates of glaucoma in these studies might be related to different inclusion criteria; diagnosis, varying follow-up times, and the degree of post-operative deterioration of the ophthalmic anatomy and lack of study standardization. However, there are only a few studies evaluating the frequency and risk factors of glaucoma development after the DALK procedure.^[13] Borderie et al.^[10] followed 142 patients with DALK procedure for an average of 42 months, and 142 patients with PK procedure for an average of 80 months. Despite the 6% ocular hypertension after DALK, similar to our current findings, the rate after PK (26%) was significantly higher, which might be related to their different approach to the glaucoma definition. They thought that the differences in the rates of ocular hypertension were associated with the different surgical techniques in groups with a similar preoperative diagnosis. Although we did not encounter any graft failure cases associated with ocular hypertension, they reported three graft failure cases related to ocular hypertension in the PK group and none in the DALK group.^[10] Han et al.^[11] evaluated the glaucoma incidence in 100 patients undergone PK procedure and 25 patients with the DALK procedure due to keratoconus. They found that 14 patients in the PK group had glaucoma and none of the patients in the DALK group had glaucoma. In addition, Tan et al.^[16] compared the DALK and PK procedures with the same number of patients (103 eyes) and found the incidence of glaucoma was 15% and 9% in the PK and DALK groups, respectively. Glaucoma surgery was required in 10 of 15 eyes (67%) in the PK group, while surgical treatment was not required in the DALK group. These results were similar to ours. Although, the number of patients with glaucoma was higher in the PK group, the difference between the groups was not statistically significant. Also, glaucoma had a more aggressive clinical process in cases with the PK group. Furthermore, Kim et al.^[17] applied DALK procedure in one eye and PK procedure in the contralateral eye in 8 patients with keratoconus, and reported only one case with glaucoma in their 32 months follow-up and this case was effectively treated by antiglaucoma treatment. The development of glaucoma after PK procedure and not after DALK procedure emphasizes the importance of different surgical techniques when all other parameters are similar. Interestingly, Shmizaki et al.^[18] found a significantly higher IOP at 12 months in the PK group (13 eyes) among preoperative and postoperative IOP levels (p=0.04); however, we did not observe significant differences in pre- and post-operative IOP levels. The difference among the studies might be related to the small size of their study group and the corneal diseases included in the study, such as corneal scars and post-herpetic keratitis, having a high risk of glaucoma. The risk of postoperative glaucoma is associated with the systemic and ocular conditions of the patients including diabetes mellitus, preoperative diagnosis of corneal disease, and previous history of keratoplasty. A recent study evaluated the incidence, risk factors, and treatment outcomes of post-PK intraocular hypertension and/or glaucoma and revealed that diabetes mellitus, bullous keratopathy, infectious keratitis, and recurrent PK were highly associated with post-PK glaucoma, whereas high IOP was less likely to develop in cases with keratoconus. But in this study, the authors included only the patients with PK and not patients with DALK.^[19] When all the diagnostic groups were compared to analyze the risk of developing postoperative PK glaucoma, the lowest risk values were found in keratoconus and corneal stromal dystrophy.^[8,14,15] The current study group was composed of keratoconus, corneal dystrophy, and corneal ectasia. The incidence of glaucoma was not statistically significant between the DALK and PK groups. This is explained by the fact that the PK patient group had fewer risk factors for the glaucoma development. Therefore, the glaucoma incidence in the PK and the DALK groups was thought to be close to each other. In all highlighted studies, the duration of postoperative corticosteroid use among the PK and DALK groups was reported as a major reason for the difference in the incidence of IOP elevation, consistent with our results. The exact mechanism of steroid-induced glaucoma is not fully understood, but decreased trabecular meshwork outflow is regarded as the main cause of IOP elevation.^[20,21] We used 0.1% topical dexamethasone five times a day in the DALK group for 4-6 months postoperatively, and five times a day in the PK group for the first 6 months postoperatively, and then tapered off monthly for 12 months. The longer use of corticosteroids in the PK group prevented the development of immune rejection, but produced many adverse effects, especially increased rates of glaucoma and cataracts, decreased wound strength, and deterioration of local ocular surface immunity.^[1] In our study, 8 eyes (5.1%) in the DALK group and 12 (7.3%) eyes in the PK group had an immune rejection, which was treated with topical corticosteroid drop. Another reason for the difference in increased IOP can be attributed to the different surgical techniques between the PK and DALK procedures. The DALK procedure has provided some advantages over PK, such as the absence of immune rejection of the corneal endothelium, earlier suture removal, shorter use of corticosteroids, less corneal endothelium loss, and increased resistance of the eye to blunt globe trauma.[1] These advantages could account for the lower glaucoma rate obtained following the DALK procedure than the PK procedure.

Preoperative glaucoma has been identified by previous studies as a major risk factor for postoperative glaucoma. ^[8,14,15] Karadag et al.^[8] examined 32 patients with preoperative glaucoma who received medical or surgical treatment prior to the PK procedure. In this study, the incidence of postoperative glaucoma was 59.4% in eyes with pre-existing glaucoma in contrast to 14.6% without pre-existing glaucoma (p=0001). Similarly, Huang et al.^[13] assessed four eyes with pre-existing glaucoma. Also, they observed that IOP control was difficult in eyes with preoperative glaucoma. We did not include eyes with preoperative glaucoma in the PK and DALK groups; therefore it was possible to evaluate the IOP elevations together with other factors during the postoperative period without any confusion. The current study has some limitations. First of all, this study design was performed in only one tertiary clinic with a retrospective design. Second, the diagnosis of glaucoma after keratoplasty is a challenging issue due to difficulties in the measurement of IOP. We used the Tonopen for IOP measurement, which is the most recommended method for irregular corneas. Third, the study group was composed of keratoconus, corneal dystrophy, and corneal ectasia, which had a lower risk for glaucoma compared to other diseases.

In conclusion, the DALK procedure presents great promise for its lower rate of complications compared to the PK procedure. In this study, we compared the glaucoma incidence and management outcomes following the PK and DALK procedures and reported a lower glaucoma incidence and a better recovery after the anti-glaucoma treatment in the DALK group as the most fundamental advantages of this surgical technique. We believe that the current study is of significant value because it has one of the longest follow-up times with the largest sample. In the light of these findings, the DALK procedure should be considered preferably in cases with healthy corneal endothelium requiring keratoplasty due to the lower risk of postoperative glaucoma.

Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kirdar Training and Research Hospital Clinical Research Ethics Committee (Date: 27.12.2016, Decision No: 2016/514/98/6).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: U.K., S.K., B.K.; Design: U.K., S.K., B.T.; Supervision: U.K., S.K., B.K.; Fundings: S.K., B.K.; Materials: S.K., B.K.; Data: U.K., S.K., B.K.; Analysis: U.K., B.T., H.S.K.; Literature search: U.K., B.T., H.S.K.; Writing: U.K., B.T., H.S.K.; Critical revision: S.K., B.K., H.S.K.

Conflict of Interest

None declared.

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Derin Anterior Lameller Keratoplasti ve Penetran Keratoplasti Sonrası Glokom İnsidansı

Amaç: Derin anterior lameller keratoplasti (DALK) ve penetran keratoplasti (PK) sonrası gelişen glokom insidansını ve anti-glokomatöz tedavisiye yanıtı karşılaştırmalı olarak değerlendirmek.

Gereç ve Yöntem: Bu geriye dönük çalışmada 146 DALK'li ve 156 PK'li hasta değerlendirildi. Tüm hastalar keratoplasti işleminden sonra 1., 3., 6., 12. ve 24. aylardada takip edildi. Glokom ve glokom tedavilerinin risk faktörleri ve insidansı hem DALK hem de PK gruplarında değerlendirildi.

Bulgular: Çalışmaya DALK prosedürü olan 156 göz ve PK prosedürü olan 163 göz dahil edildi. DALK grubundaki 11 göze (%7.05) ve PK grubundaki 16 göze (%9.81) glokom tanısı kondu (p=0.42). Ortanca anti-glokom ilacı sayısı DALK gruplarında 1.0 ve PK gruplarında 1.5 idi (p=0.01). PK sonrası glokomlu 16 gözün 4'üne (%25) mitomisin C ile trabekülektomi yapıldı (p=0.01). DALK grubunda hastalar cerrahi müdahale olmaksızın tek anti-glokomatöz tedavi ile takip edildi.

Sonuç: Çalışma grubumuzda glokom insidansı DALK'li gözlerde %7, PK'li gözlerde %9.8 idi. Ancak, glokom ilacı sayısı PK işlemi olan gözlerde DALK işlemi olan gözlere göre anlamlı olarak daha yüksekti (p=0.01). Dahası, DALK'li gözlerde, PK'li gözlere kıyasla mitomisin C ile trabekülektomi cerrahisine daha az gereksinim duyulmuştur. Bu nedenle; sonuçlarımız, DALK prosedürünün glokom gelişimi açısından PK'den daha uygun ve daha güvenli olabileceğini düşündürdü.

Anahtar Sözcükler: Derin anterior lameller keratoplasti; glokom; penetran keratoplasti; trabekülektomi.