

## Treatment of Keratoconus in Egypt with Deep Anterior Lamellar Keratoplasty vs Penetrating Keratoplasty - Long-term Follow Up

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### Abstract

**Purpose:** To compare postoperative outcomes of full-bed deep anterior lamellarkeratoplasty (DALK) with penetrating keratoplasty (PK) in keratoconus.

**Methods:** This retrospective study included 52 eyes of 50 patients who underwent full-bed DALK and 52 eyes of 49 patients who underwent PK between June 2008 and August 2011. Full-bed DALK was performed using Yao's hooking-detaching technique. PK was performed using a standard technique. Intra operative and postoperative complications, visual acuity, rejection, graft survival, endothelial cell density, corneal sensation recovery, and re-innervation were compared between the 2 groups.

**Results:** The duration of postoperative follow-up was  $46.9 \pm 28.0$  months in the full-bed DALK group and  $60.2 \pm 34.6$  months in the PK group. A best-corrected visual acuity of 0.5 (20/40) or better was achieved in 90.7% and 92.3% of the eyes after full-bed DALK and PK, respectively. By the third postoperative year, graft endothelial cell loss reached 34.6% in the PK group vs. 13.9% in the full-bed DALK group. Intra operative complications included micro perforation in 5 (9.6%) of 52 eyes in the DALK group, with two eyes developing a temporally double anterior chamber postoperatively. Post operative complications in the PK versus the full-bed DALK groups, respectively, were rejection (7.7% vs. 0%,  $P=0.015$ ), high intraocular pressure (46.2% vs. 1.3%), secondary glaucoma (9.6% vs. 0%), complicated cataract (19.2% vs. 0%), and wound dehiscence (9.6% vs. 0%).

**Conclusions:** Both full-bed DALK and PK can offer long-term satisfactory visual outcomes for keratoconus. Graft rejection, secondary glaucoma, complicated cataracts, and constant endothelial cell loss were observed only after PK.

**Keywords:** Keratoconus; DALK; Graft; Ectasia

### Introduction

Keratoconus was first discriminated from other corneal ectatic diseases in 1854. Since that time the morphological characteristics of keratoconic progression have been invaluable in the diagnosis of the condition. Keratoconus is a non-inflammatory, progressive thinning, and ectatic disorder of the cornea [1-3]. Based on the natural course and severity of corneal thinning and ectasia, keratoconus may be divided into four stages: the preclinical stage, the early clinical stage, the advanced stage, and the complication stage. In the advanced stage, keratoconus is characterized by a significantly localized steep conical protrusion associated with prominent stromal thinning in the cone and the adjacent area of the cornea [2]. Highly irregular astigmatism and high myopia in the advanced stage make spectacle correction unsatisfactory or impossible. They also make contact lens correction intolerable, because of the poor fit between the lens and the cornea [2-4]. Following the advanced stage, keratoconus may further progress to the complication stage, with spontaneous Descemet's membrane tears causing highly acute stromal edema [5], and even the occasional occurrence of perforation [6]. Although keratoconus with acute hydrops can often resolve spontaneously, a residual scar will persist [2,7]. Therefore, corneal transplantation becomes the only

feasible therapeutic approach for keratoconus in the advanced and complication stages. Through transplantation, the corneal stroma can recover its normal thickness, the protruded cone of the cornea returns to its normal curvature, and irregular astigmatism and high myopia will be markedly reduced, even to normal refraction, which significantly improves vision. We conducted a retrospective study of patients with keratoconus who underwent full-bed deep anterior lamellar keratoplasty (DALK) or penetrating keratoplasty (PK) to compare the outcomes with these two procedures.

### Methods

All data for the study were collected and analyzed in accordance with the policies and procedures of the Institutional Review Board at Farwaniya Hospital, Kuwait City, Kuwait, in accordance with the Declaration of Helsinki.

### Study Design

In this retrospective study, the records were reviewed of consecutive patients with keratoconus who underwent full-bed deep anterior lamellar DALK grafts, using Yao's hooking-detaching technique [8-10], or PK grafts from June 2008 through August 2011. Keratoconus was diagnosed on the basis of clinical slit-lamp findings (stromal thinning, conical protrusion, a Fleisher ring, Vogt striae, and subepithelial scarring) and characteristic topographic patterns. The development of these features made spectacle correction unsatisfactory and the use of contact lenses intolerable. Inclusion criteria included a minimum follow-up of 12 months after surgery. Exclusion criteria included patients who had not undergone grafting by a primary transplant or had a history of previous intraocular surgery, had coexistent other ocular disease (such as retinal disorders or glaucoma) and ocular conditions in addition to keratoconus, or had postoperative follow-up of less than 12 months.

The choice of surgical approach was based on the patient's personal preference after both surgical options were thoroughly discussed with the patient. The potential risks, advantages, and disadvantages of full-bed DALK and PK for keratoconus were explained to the patients. Patients who had a history of acute hydrops were encouraged to receive PK rather than full-bed DALK.

### Surgical Procedures

All surgery was performed by the same surgeon (Ahmed Hathout). Full-bed DALK was performed as described in previous publications [8-10]. In brief, a small area of Descemet's membrane was exposed using the stromal hooking technique, to create a pocket in the recipient bed at 12 o'clock after a trephination of 7.25 mm to 8.00 mm diameter. The full stroma was detached by viscoelastic material injection through the pocket and then removed in a single layer to completely expose Descemet's membrane in its entirety. In cases where the primary exposure did not exactly reach the layer of the Descemet's membrane, a secondary hooking-detaching procedure was performed. A cryopreserved donor corneal button was grafted using a continuous 10-0 nylon suture or 16 bites of interrupted 10-0 nylon sutures. The size of the donor graft chosen to match the bed depended on the axial length of the recipient eye. If the axial length was equal to or shorter than 23.75 mm, the graft was 0.5 mm oversized; if it was longer than 23.75 mm but shorter than 25.00 mm, the graft was 0.25 mm oversized; and if it was longer than 25.00 mm, the graft was equal to the recipient bed.

In PK, a standard surgical procedure was carried out in all cases. The recipient bed was created by trephination using a 7.25-mm to 8.00-mm diameter trephine. A fresh donor button, preserved in a moist chamber, was secured by a continuous 10-0 nylon suture or by 16 bites of interrupted 10-0 nylon sutures. The process for selecting a graft size to match the bed was the same as that for full-bed DALK grafting. If a planned full-bed DALK for one eye was switched to PK due to a large tear of Descemet's membrane, the eye was included in the PK group for analysis.

### Postoperative Medication and Follow-up

In the full-bed DALK group, 0.5% (5 g/L) levofloxacin or 0.3% (3 g/L) ofloxacin and 0.1% (1 g/L) fluorometholone eye drops were administered 4 times daily. The PK group received 0.1% (1 g/L) dexamethasone sodium phosphate combined with 0.3% (3 g/L) tobramycin eye drops (Tobradex, Alcon, Fort Worth, TX, USA), 4 times daily. Steroid eye drops were administered for 6 months after full-bed DALK

and for at least 12 months after PK, and then gradually reduced according to the clinical outcome. The application of steroid eye drops was reduced when the intraocular pressure (IOP) increased during follow-up. If dosage reduction did not lower IOP sufficiently, topical anti-glaucoma medication was administered.

Rejection episodes were treated with Tobradex eye drops every 1 to 2 hours initially and then reduced over several weeks, depending on the clinical response. With both full-bed DALK and PK follow-up, patients were scheduled to be seen for their first postoperative visit at 2 weeks, followed by visits at 1, 3, 6, 12, 18, and 24 months, and then every year thereafter. A detailed clinical examination was performed at each visit, including assessments of IOP, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), refraction, graft clarity, rejection episodes, corneal endothelial cell density and the density of the sub-basal nerve fibers, and assessment for the development of cataracts and secondary glaucoma. Patients were evaluated at shorter intervals or on an emergency basis as needed.

The occurrence of interrupted sutures during follow-up in both groups was managed by selective removal of the suture on the basis of refractive astigmatism and was guided by topography. Suture removal was completed in most cases by the end of the follow-up period.

### Major Measurements

Corneal endothelial cell density was determined by counting and averaging the number of cells in an area of 0.05 mm<sup>2</sup> from 3 confocal microscopic images of the central cornea. The corneal endothelial cell loss was calculated as the decrease in cell density from 1 month postoperatively (baseline) to 1, 2, 3, 4, and 5 years postoperatively, expressed as a percentage of the cell density observed at 1 month after surgery.

Visual acuity was recorded using decimal charts and was converted to the logarithm of the minimum angle of resolution (logMAR). Vision levels of counting fingers and hand movements were substituted by logMAR values of 1.7 and 2.0, respectively.

All intra operative and postoperative complications were reviewed, including micro-perforation of Descemet's membrane, large tears of the Descemet's membrane, double anterior chambers, graft rejection, graft failure, high IOP, and secondary glaucoma. The diagnosis of graft rejection, graft failure, high IOP, secondary glaucoma, and complicated cataract was based on the clinical manifestation.

## Results

### General Characteristics

Of the 104 eyes (99 patients) that met the criteria for inclusion in this study, 52 eyes (50 patients) underwent full-bed DALK grafts and 52 eyes (49 patients) underwent PK grafts. There were no significant differences between the 2 groups regarding age, gender, graft size, and host-graft size discrepancy. The postoperative follow-up period was  $46.9 \pm 28.0$  months for the full-bed DALK group, which was shorter follow-up than the  $60.2 \pm 34.6$  months for the PK group. Complete suture removal was carried out earlier in the full-bed DALK group than in the PK group ( $16.9 \pm 6.0$  months vs.  $22.8 \pm 9.3$  months) and the full-bed DALK group needed less frequent visits than the PK group ( $0.29 \pm 0.16$  times/month vs.  $0.35 \pm 0.20$  times/month).

### Intraoperative and Postoperative Complications

During full-bed DALK surgery, micro perforation of Descemet's membrane occurred in 5 (9.6%) of the 52 eyes. Double chambers appeared temporarily after surgery in 2 of these eyes, but they resolved spontaneously without any specific intervention. A large Descemet's membrane tear occurred in 1 eye during insertion of the scissor tips between the detached stroma and Descemet's membrane to cut the stromal layer around the trephined margin. In the PK group, there were no intraoperative complications.

Postoperative and late complications in the PK group included endothelial graft rejection in 4 (7.7%) of the 52 eyes. The rejection-free survival rate in the PK group was 98.0% at 1 year, 95.9% at 2 years, and 90.5% from 3 to 10 years. The median duration of a rejection episode in the PK group was  $24.7 \pm 7.5$  months (range, 17-33 months). All rejection episodes in the PK grafts were reversible by hourly topical steroid medication. In contrast, the complete absence of any such postoperative rejection episode in the 52 eyes with full-bed DALK grafts was a marked difference between the two procedures.

Only one (2%) of the 52 eyes in the DALK group developed temporary elevated IOP on the first postoperative day, possibly caused by air injection in the anterior chamber for tamponade of a micro perforation of Descemet's membrane during surgery. The IOP returned to normal on the second postoperative day by administration of a dehydrolyzing agent and did not need anti-glaucoma medication thereafter, but the elevated IOP and air injection in the anterior chamber caused irreversible mydriasis and a tonic pupil. None of the eyes in the full-bed DALK group developed steroid-induced IOP elevation or glaucoma. In the PK group, however, 24 (46.2%) of the 52 eyes developed high IOP. Of these, 4 eyes returned to normal IOP following the switching of Tobradex to 0.1% (1 g/L) fluorometholone eye drops, and 15 returned to normal IOP following a reduction of the topical steroid dose together with administration of topical anti-glaucoma medication. The remaining 5 eyes developed secondary glaucoma despite switching topical steroid eye drops and adding anti-glaucoma medications, and needed a trabeculectomy to control the IOP. Ten (19.2%) of the 52 eyes in the PK group developed complicated cataracts, and 8 required cataract surgery during the follow-up period. No complicated cataracts were observed in the full-bed DALK group.

Graft-host junction dehiscence occurred in 5 (9.6%) of the 52 eyes in the PK group. Three were the result of trauma and 2 were due to spontaneous wound dehiscence after suture removal at 15 and 23 months after surgery, respectively. No wound dehiscence occurred in the full-bed DALK group.

### **Graft Survival and Endothelial Cell Changes After Surgery**

By the last visit, all 52 grafts (100%) were clear in the full-bed DALK group, whereas in the PK group, 51 grafts (98.1%) were clear and one (1.9%) failed due to recurrence of keratoconus with acute hydrops at 30 months after surgery. Overall, probabilities of graft survival were 100% 1 to 5 years after full-bed DALK and 97.4% 3 to 5 years after PK. There was no significant difference in graft survival between the two groups.

In the full-bed DALK group, the mean preoperative corneal endothelial cell density was  $2634 \pm 319$  cells/mm<sup>2</sup>, significantly higher than the 1-month postoperative endothelial cell density of  $2230 \pm 404$  cells/mm<sup>2</sup> (n= 52), with a mean 1-month endothelial cell loss translating to a  $14.2\% \pm 11.7\%$  reduction in cell density. The mean 1-month endothelial cell loss was significantly higher in the 6 eyes with perforation of Descemet's membrane than in the 46 eyes without perforation. Among the 6 eyes with perforation of Descemet's membrane, the 4 in which air was injected into the anterior chamber suffered more endothelial cell loss than the 2 not managed with air injection during surgery.

Compared with the endothelial cell density at 1-month postoperatively, cell loss of graft corneal endothelium in the full-bed DALK grafts was slight: a mean of 8.6%, 14.0% and 13.9% at 1, 2 and 3 years, respectively. By contrast, in PK grafts, a continuous relative decline in corneal endothelial cell density was observed from the baseline 1-month postoperative value, as reflected in a 14.3% reduction at year 1, a 19.9% at year 2, and a 25.4% at year 3, making the loss in cell density significantly higher in PK grafts than in full-bed DALK grafts.

### **Visual and Refractive Outcomes**

Preoperative BCVA appeared to be worse in the PK group than in the full-bed DALK group, possibly because more eyes in the PK group had incurred acute hydrops and more significant stromal scarring.

During the final visit, a BCVA equal to or better than 0.5 was achieved in 90.7% of the eyes in the full-bed DALK group and in 92.3% of the eyes in the PK group. In only 1 eye (1.9%) in the PK group was the BCVA lower than 0.1 (20/200), and it was due to a recurrence of acute hydrops. Postoperative myopia in both immediate and long-term follow-up was significantly less in the full-bed DALK group than in the PK group. More eyes in the full-bed DALK group had the absolute spherical equivalent within 1 diopter of Plano, whereas the distribution of astigmatism was similar in the two groups. No statistically significant differences in BCVA were found between the 2 groups at any postoperative follow-up visits.

Recovery of central corneal sensation along with restoration of the sub-basal nerve layer occurred sooner in the PK group than in the full-bed DALK group, but the difference between the two groups was not statistically significant throughout the entire follow-up period. The earliest appearance of the sub-basal nerve layer was found at about 6 months after surgery in both groups.

### Discussion

The purpose of corneal transplantation for advanced keratoconus includes reconstruction of normal corneal thickness of the thinning cornea, restoration of the normal curvature of the protruded cornea, and improvement of the refractive state of the eye to achieve significantly better vision. Consistent with many previous studies [11-14], our data show that full-bed DALK can achieve at least the same effect as PK in long-term clinical observation. However, our results and those of many others [11-14] contradict, to some extent, the findings of a multiple center study [15] that suggested the improvement in vision achieved by DALK may not be as favorable as that created by PK. However, an important caveat to the interpretation of the data is that DALK surgery is very dependent on the technique and skill of the individual surgeon. Only when surgical techniques among groups of surgeons are matched consistently can meaningful multicenter comparisons be made. Therefore, further studies are needed to compare conclusively the improvement in vision achievable with DALK and PK. Our current study also indicates that refraction and astigmatism created by full-bed DALK and by PK are not significantly different, with a mean astigmatism of 3 to 4 diopters found in both groups, consistent with the results of other studies [11,14,15].

Regardless of the need for further multicenter studies, the current study suggests that full-bed DALK has many advantages over PK. The most important advantage of full-bed DALK is the absence of allograft rejection, attributable to the retention in situ of the recipient's Descemet's membrane together with endothelium for grafting. Moreover, the use of cryopreserved donor tissue for grafting in full-bed DALK clearly contributes to the absence of postoperative rejection, since no live cells are retained in the cryopreserved donor tissue [8,9,16]. Epithelial and stromal types of rejection may occur when fresh donor tissue is used in DALK for grafting [15,17,18]. The absence of allograft rejection in the full-bed DALK group is consistent with previous studies in which other corneal diseases were treated using the same technique of full-bed DALK grafting [8-10]. Another advantage of the use of cryopreserved donor tissue in DALK grafting is that the potential cornea donor pool would expand because there is no need to consider the health of the endothelium for long-term cryopreservation of donor tissue. Thus, corneal tissue from an elderly donor or a donor with unhealthy endothelium but healthy stroma can still be used effectively in full-bed DALK grafting. Widening the pool of potential donors of corneal tissue is particularly important in countries with an extreme shortage of cornea donors for transplantation.

A second and also very important advantage of full-bed DALK is that it requires only very mild anti-inflammatory medications, such as 0.1% fluorometholone eye drops for short-term use postoperatively, which certainly helps reduce the incidence of steroid-related postoperative complications.

Moreover, simple, short-term, and very mild anti-inflammatory medications for full-bed DALK grafts are very safe and convenient for patients who live in remote areas or for patients who comply poorly with regular follow-up visits and medication instructions. In such situations the patient's lack of diligent follow-up and compliance will not affect the quality of graft survival. In the PK group, not only was there a 7.7% incidence of allograft rejection but also there was an increase in complications, presumably induced by topical steroids. These results are strikingly different from those in the full-bed DALK group. To prevent postoperative allograft rejection of PK grafts, we routinely prescribe Tobradex eye drops (0.1% dexamethasone sodium phosphate with 0.3% tobramycin), 4 times daily for at least 12 months. The difference between the DALK and PK groups in the use postoperative medications is clearly associated with the different incidences of elevated IOP (46.2% in PK grafts vs. 1.3% in full-bed DALK grafts), secondary glaucoma (9.6% in PK grafts vs. 0% in full-bed DALK grafts), and complicated cataracts (19.2% in PK grafts vs. 0% in full-bed DALK grafts).

Potential graft failure and postoperative endothelial cell loss are other concerns in cornea transplantation. Our current study shows that, in the PK group, the overall probability of graft survival was 97.3% after 3 to 5 years. Although there was 7.7% allograft rejection rate, it did not cause graft failure by endothelial de compensation. Our results regarding PK for keratoconus are very consistent with many previous reports [11-13,19,20]. Only 1 graft failure in the PK group was observed, which was due to recurrence of keratoconus in the graft with acute hydrops. Our findings suggest that long-term graft survival, even in the PK group, is quite satisfactory. However, when endothelial cell loss is considered, the difference between PK and full-bed DALK groups is remarkable. Our data show a mean decline in corneal endothelial cell density in PK grafts of 14.3%, 19.9%, and 25.4% at 1, 2, and 3 years, respectively, a significantly higher loss than

8.6%, 14.0%, and 13.9% loss at 1-, 2-, and 3-year follow-up in the full-bed DALK group. In the PK group, a steady and continuous decline in endothelial cell density was observed, even in the absence of allograft rejection. This suggests that chronic cell loss in the graft endothelium induced by non-immunologic factors may lead to eventual graft failure in extended long-term observation [21,22].

Although the degree of endothelial cell loss was significantly lower in the DALK grafts than the PK grafts, full-bed DALK grafts were not exempt from cell loss. The most critical period for cell loss was within 1 month after full-bed DALK, when cell loss reached 14.2% compared with the preoperative endothelial cell density. This result suggests that thorough removal of the recipient stroma and complete exposure of Descemet's membrane, even using our viscoelastic detaching technique, may lead to a certain degree of endothelial cell loss due to the indirect impact of surgical manipulation of the endothelium. Endothelial cell loss within 1 month after DALK was also observed in other studies of different DALK techniques [23-27]. We observed a slight decline in endothelial cell density in the full-bed DALK grafts 1 year after surgery, although the decline was significantly less than that in the PK grafts. The occurrence of endothelial cell loss 1 year after full-bed DALK surgery was in contrast to the results of other studies [24,28], and also contradicted our own previous study using full-bed DALK to treat herpetic corneal scars [10]. Further study is needed to explain why a slight endothelial cell loss occurred following full-bed DALK over the 3-year period after surgery.

### Conclusion

The treatment of keratoconus in Egypt with DALK and PKP both showed excellent results, with DALK having the advantage of less astigmatism, fewer rejection episodes, better endothelial cell counts and greater patient satisfaction overall. It is our opinion that DALK should be considered a first line treatment for keratoconus with PKP reserved for keratoconus patients that have complications including Desmetocoele, infection, failed DALK procedures or low preoperative endothelial cell counts.

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