Deep Anterior Lamellar Keratoplasty as an Alternative to Penetrating Keratoplasty

A Report by the American Academy of Ophthalmology

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Objective: To review the published literature on deep anterior lamellar keratoplasty (DALK) to compare DALK with penetrating keratoplasty (PK) for the outcomes of best spectacle-corrected visual acuity (BSCVA), refractive error, immune graft rejection, and graft survival.

Methods: Searches of the peer-reviewed literature were conducted in the PubMed and the Cochrane Library databases. The searches were limited to citations starting in 1997, and the most recent search was in May 2009. The searches yielded 1024 citations in English-language journals. The abstracts of these articles were reviewed, and 162 articles were selected for possible clinical relevance, of which 55 were determined to be relevant to the assessment objective.

Results: Eleven DALK/PK comparative studies (level II and level III evidence) were identified that compared the results of DALK and PK procedures directly; they included 481 DALK eyes and 501 PK eyes. Of those studies reporting vision and refractive data, there was no significant difference in BSCVA between the 2 groups in 9 of the studies. There was no significant difference in spheroequivalent refraction in 6 of the studies, nor was there a significant difference in postoperative astigmatism in 9 of the studies, although the range of astigmatism was often large for both groups. Endothelial cell density (ECD) stabilized within 6 months after surgery in DALK eyes. Endothelial cell density values were higher in the DALK groups in all studies at study completion, and, in general, the ECD differences between DALK and PK groups were significant at all time points at 6 months or longer after surgery for all of the studies reporting data.

Conclusions: On the basis of level II evidence in 1 study and level III evidence in 10 studies, DALK is equivalent to PK for the outcome measure of BSCVA, particularly if the surgical technique yields minimal residual host stromal thickness. There is no advantage to DALK for refractive error outcomes. Although improved graft survival in DALK has yet to be demonstrated, postoperative data indicate that DALK is superior to PK for preservation of ECD. Endothelial immune graft rejection cannot occur after DALK, which may simplify long-term management of DALK eyes compared with PK eyes. As an extraocular procedure, DALK has important theoretic safety advantages, and it is a good option for visual rehabilitation of corneal disease in patients whose endothelium is not compromised.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to evaluate the peer-reviewed scientific literature, to distill what is well established about the technology, and to help refine the important questions to be answered by future investigations. After appropriate review by all contributors, including legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment is to review the published literature on deep anterior lamellar keratoplasty (DALK) to compare it with penetrating keratoplasty (PK) for the outcomes of best spectacle-corrected visual acuity (BSCVA), refractive error, rejection, and graft survival.

Background

Penetrating keratoplasty refers to a corneal transplant, or graft, in which the entire thickness of the cornea is replaced. In conventional posterior lamellar keratoplasty (LK) and the newer endothelial keratoplasty (EK) procedures, the inner layers of the cornea are transplanted. Variants of these

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procedures include deep lamellar EK, Descemet's stripping (automated) EK (DSEK or DSAEK), Descemet's membrane EK, and Descemet's membrane automated EK. The health of the corneal endothelium is the main criterion for deciding if an anterior or posterior LK procedure is indicated. Diseases involving the corneal endothelium can be managed with EK or PK, and those diseases involving both the corneal endothelium and the corneal stroma usually require PK. In conventional anterior LK, only a portion of the corneal thickness is replaced.

The first successful human partial penetrating corneal transplant was performed by Zirm[1] in 1905 using a spring-driven trephine originally designed by von Hippel[2] in 1888 for performing partial LK. Over the last half of the 20th century, PK became the standard of care for managing the surgical correction of most axial diseases of the cornea. Lamellar keratoplasty was usually reserved for the tectonic surgical correction of less common corneal conditions, such as peripheral ectasias, perforated ulcers, and traumatic loss of tissue. However, there has always been a cadre of ophthalmic surgeons, including Paufique,[3] Malbran,[4] Anwar,[5] and others, who have used lamellar corneal transplant surgery as an alternative to PK for the optical correction of axial corneal diseases with normal corneal endothelium, such as keratoconus, stromal corneal dystrophies, and corneal scars from traumatic injury or infection. In the 1970s, there was increased interest in lamellar corneal transplantation.[6] As a result of the technical difficulty of the procedure and the reduced postoperative acuity typically following LK, however, PK has remained the dominant corneal transplant procedure for the optical correction of corneal disease.

There has been increased interest in newer anterior lamellar corneal procedures for vision restoration, as noted by publications in peer-reviewed journals, articles in industry-supported publications, and instructional courses both in private venues and at educational meetings of ophthalmological organizations. One of the most publicized of the various anterior lamellar corneal procedures, DALK, involves the removal of central corneal stroma while leaving host corneal endothelium and Descemet's membrane (DM) intact. Descemet's membrane may or may not be exposed in DALK procedures. The major theoretic advantages of DALK over PK procedures are the absence of potential corneal endothelial cell immune rejection and the expected retention of most recipient corneal endothelial cells in DALK surgery compared with the rapid decrease in donor corneal endothelial cell density (ECD) after PK surgery.

Several surgical techniques have been developed to accomplish removal of all, or almost all, of the corneal stroma in a lamellar dissection bed, which is the most critical aspect of a successful DALK. A brief overview of DALK techniques will be summarized in this article.

When Sugita and Kondo[7] first presented their technique for baring DM, they called the technique "deep anterior lamellar keratoplasty," or DLK. Because that term later became widely used to refer to the diffuse lamellar keratitis associated with LASIK surgery, in this assessment the abbreviation DALK is used to refer to deep anterior LK procedures in general. Anwar and Teichmann[8] suggested that the term "maximum depth anterior lamellar keratoplasty" be used to refer to baring of DM. In this assessment, the terms "DALK" and "maximum depth DALK" (MD-DALK) are used. The literature does not always distinguish between cases in which DM baring was planned (i.e., MD-DALK) but not achieved because of perforation, surgeon caution, and so forth, and cases in which enough deep corneal stroma was left in the surgical bed to qualify as a DALK but not as an MD-DALK. In other techniques that are discussed, DM exposure is not the goal of the DALK, although DM exposure is occasionally achieved, and this distinction is not usually identified.

The perimeter of the DALK bed is usually defined using a trephine diameter of 7 to 8.5 mm to partially cut through the anterior stromal fibers, but not deep enough to enter the anterior chamber, depending on the host corneal diameter and the corneal disease being treated. This partial-thickness trephination may be performed initially, as in the hydrodelamination technique of Sugita and Kondo[7] or the big-bubble technique of Anwar and Teichmann;[9] after expansion of the corneal stroma with air, as in the air injection technique of Archila,[10] as modified by Morris et al[11] and Coombes et al;[12] or after the limbal dissection of a deep lamellar pocket that is then filled with an ophthalmic viscosurgical device (OVD) using the Melles technique.[13]

Sugita and Kondo's[7] method of direct dissection after partial trephination involves removal of the anterior two thirds of corneal stroma, followed by injection of fluid into the remaining stromal bed and spatula delamination for removal of the deeper stromal layers. This is followed by hydrodelamination and exposure of DM in the central 5 mm of the trephine bed. Rostron's direct dissection method involves expanding the corneal thickness with air injection before trephination and then removing the overlying stroma by direct dissection. If DM is detached during the air injection, all overlying stroma will be removed. As do Sugita and Kondo, Anwar first performs a partial-depth trephine cut but then forcibly injects air deep in the stromal bed to detach DM, producing a "big bubble" that greatly facilitates the removal of all stroma in the trephine bed. The direct dissection DALK techniques using air or fluid often result in baring of DM. Sugita and Kondo's technique requires peeling off the final thin layer of deep stroma, at least in the central 5 mm or so, whereas the big-bubble technique, when successful, results in separation of DM from the deep corneal stroma. Otherwise, layer-by-layer deep dissection with the aid of air, fluid, or an OVD may be required to attempt DM exposure.

The Melles technique requires a limbal approach and depends on the surgeon's visual determination of the depth of the lamellar dissection. A full-corneal diameter pre-DM pocket is created by lamellar dissection and filled with an OVD, and then trephination is performed to remove the anterior stromal button. The thickness of the residual stromal bed is dependent on the surgeon's ability to judge visually how close the lamellar dissection blade can come to DM without puncturing it.

Rostron's DALK procedures generally use full-thickness, lyophilized donor lenticules, whereas Sugita and Kondo's[7] earlier efforts used cryolathed lenticules. Glycerin-cryopreserved corneal tissue has also been acceptable.[14] One study specifically compared eyes that had received lyophilized donor corneas or donor corneas kept in Optisol GS (Bausch & Lomb, Inc., Rochester, NY) and found no statistical differences between the 2 methods of donor corneal preservation.[15] According to the recent literature, most surgeons use full-thickness donor lenticules obtained from corneal sclera rims preserved in intermediate storage media (e.g., Optisol GS) or organ culture media, as is common in Europe. The donor endothelium can be removed with a dry surgical sponge. However, many surgeons also remove DM. In either case, the posterior face of the donor graft will have a smooth interface apposed to the smooth bed of the exposed (bared) host DM. The antigenic load of the donor is also decreased by removing the endothelial cells. In DALK procedures where some residual stroma remains, the interface will not be as regular, and presumably even less regular if the donor lenticule has also been obtained through surgical dissection, such as described by Tsubota et al[16] and Panda et al.[17]

Question for Assessment

The objective of this assessment is to address the following question: How does DALK compare with PK for the outcomes of BSCVA, refractive error, rejection, and graft survival?

Description of Evidence

A search of the peer reviewed English-language literature was conducted in the PubMed database on December 14, 2006, and October 1, 2007, and a search of the Cochrane Library database was conducted on December 18, 2006, and October 1, 2007, limited to citations starting in 1997. Key words in the search were the MeSH heading *corneal transplantation* combined with text words *deep anterior lamellar keratoplasty* or *DALK* or *deep lamellar keratoplasty* or *Descemet's membrane baring* or *maximum depth anterior lamellar keratoplasty*. The authors assessed the 236 citations resulting from the electronic searches and selected 88 citations that definitely or potentially met the inclusion criteria.

The authors obtained the full copy of these 88 articles for further assessment. The reviewers were not masked to trial results or publication details. The authors reviewed the full text of these articles to assess their inclusion according to the selection criteria. One additional article was identified from review of an article reference list. The authors selected 42 articles for methodological review, and they chose an additional 19 articles to send to the first author for assistance in writing the first draft. These 19 articles were review articles, single-case reports of complications, or single-case reports of technique, and they did not receive methodological review.

The methodologist assigned ratings of level of evidence to each of the selected articles. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies or poor-quality randomized clinical trials; and a level III rating was assigned to case series, case reports, and poor-quality case-control or cohort studies. Two studies were randomized controlled trials that were rated as level II evidence because of insufficient power, lack of masking, and a less rigorous randomization method.[15,18] All other articles were comparative and noncomparative case series, prospective and retrospective, or case reports and were rated as level III evidence.

An updated search, conducted on May 28, 2009, included the additional search term *penetrating keratoplasty* (MeSH and text) and retrieved 788 citations, of which an additional 73 possibly relevant studies were identified and reviewed. Of these, 13 were judged relevant. In addition, surveillance of the literature identified more recent relevant publications. These additional studies were rated as level III evidence.

Published Results

Detailed descriptions and Tables (1–6) of the outcomes from the included studies are included in the Appendix (available at http://aaojournal.org).

Eleven published studies were identified in which the operative and postoperative results of DALK and PK procedures were compared directly. Only 1 study[18] was assigned a level II rating, and the other 10 studies were rated as level III. All were single-institution studies, often with one operative surgeon, and attempts were made to control for common factors such as diagnosis or age. These 11 studies are particularly useful for comparing the visual, refractive, early postoperative ECD results, and surgical complications of the 2 procedures. These data are presented in Table 1 (available at http://aaojournal.org). The DALK data from 10 of these 11 studies were then abstracted and compiled along with DALK data from 31 other clinical studies (1 study rated as level II and 30 rated as level III) to obtain a broader view of the operative complications of DALK, as well as postoperative visual, refractive, and ECD data. The results of those 41 studies are presented, in part, in Table 2 (available at http://aaojournal.org).

The 11 identified clinical comparative DALK/PK studies include data on a total of 481 eyes that had DALK and 501 eyes that had PK. Eight studies had ≤26 eyes in each group,[17–24] one study had 41 DALK and 43 PK eyes,[25] one study had 135 DALK and 76 PK eyes,[26] and one study had 150 in each group.[27] Seven of the studies[19–24,26] enrolled only patients with keratoconus, one study enrolled only patients with lattice or macular corneal dystrophy,[25] and the remaining 3 studies included various corneal stromal diseases.[17,18,27]

Table 3 (available at http://aaojournal.org) lists the reported complications for the 1843 eyes in the 41 studies for planned DALK procedures only. The most common operative complication was DM perforation(s), which occurred in 11.7% of cases. Air or gas injections into the anterior chamber at the time of surgery or in the postoperative period can result in loss of corneal endothelial cells, gas-induced pupillary block, or a failure of a DM detachment to resolve. Postoperative double anterior chamber, presumably also related to operative perforations of DM, required a subsequent operative intervention in 2.2% of cases and, when not successful, was the most common cause of delayed PK conversions in 0.4%. There were 5 (0.3%) repeat DALK procedures. Donor lamellar graft recipient-bed interface complications such as interface haze, DM wrinkling, and interface vascularization were uncommon at 0.7%, 0.5% and 0.5%, respectively. These complications are unique to DALK procedures, whereas the remaining complications noted in Table 3 (available at http://aaojournal.org) were individually less than 0.5% and could have occurred with PK or DALK.

Of the 11 comparative studies, there was no significant difference in the postoperative BSCVA between the DALK and PK groups in 6 studies,[17,18,22,23,25,26] and there was better BSCVA in the DALK group in one study[27] and better BSCVA in the PK group in 4 studies.[19–21,24] The one study[27] reporting better postoperative vision in the DALK group had the largest number of eyes in each group (150/150). Overall, there was no significant difference between spherical refractive error or astigmatism between the DALK and PK groups.

Twenty-seven of the additional 31 studies listed in Table 2 (available at http://aaojournal.org) presented data about postoperative visual acuity, refractive correction, and astigmatism of DALK eyes. There was no significant difference in postoperative visual acuity between DALK or PK eyes as a group, although there was a tendency for lower visual acuity in DALK eyes in which DM was not bared and residual stroma in the bed exceeded 10% of total stromal thickness.

Immune-mediated donor-graft rejection can be classified as epithelial, stromal, endothelial, or some combination of these. Because corneal endothelium is not replaced in DALK, donor endothelial immune-medicated rejection cannot occur as it can in PK. Stromal graft rejection can also occur during the postoperative period after DALK and PK. There were 18 immune rejections recorded (1.0%) for the 1843 DALK eyes reported in Table 2 (available at http://aaojournal.org). One study[28] reported 7 of 29 patients with DALK for keratoconus who had graft rejections, 2 of whom had progressive vascularization of the graft interface with opacification. One recent study,[29] not included in Table 2 (available at http://aaojournal.org), of 129 consecutive eyes of 121 patients with DALK for keratoconus recorded 14 of 129 episodes (10.9%) of subepithelial graft rejection and 4 of 129 episodes (3.1%) of stromal graft rejection, all successfully treated with a 3- to 6-week course of topical corticosteroids. The majority of graft rejection episodes (n=13) occurred in the first year after surgery and in patients with a history of vernal keratoconjunctivitis (66.3%). Eighteen of the 129 eyes had a history of vernal keratoconjunctivitis that was inactive at the time of surgery.

Six of the 11 studies in the DALK/PK comparison group (Table 1; available at http://aaojournal.org) evaluated postoperative ECD of the host corneal endothelium for the DALK groups and of the donor graft endothelium for the PK groups. All demonstrated significantly higher ECD in the DALK groups: at 12 months postoperatively in 2 studies,[17,20] at 24 months in one study,[18] at 3 years in one study,[25] and at all intervals up to 5 years in the one study.[26] The ECD data for the DALK/PK comparative studies highlight significant differences between these surgical techniques (Table 1; available at http://aaojournal.org), with consistently higher ECD in post-DALK eyes compared with post-PK eyes.

Discussion

The advantages of DALK over PK surgery are as follows:

- Immune rejection of the corneal endothelium cannot occur.
- The procedure is extraocular and not intraocular.
- Topical corticosteroids can usually be discontinued earlier with DALK.
- There is minor loss of ECD.
- Compared with PK, DALK may have superior resistance to rupture of the globe after blunt trauma.
- Sutures can be removed earlier with DALK.

The most obvious advantage of DALK is that the host corneal endothelium is not subject to immune rejection in DALK. Larger grafts approaching the limbus can be used with DALK if the goal is complete removal of ectatic tissue in keratoconus. Normal-risk patients undergoing PK who are phakic are generally tapered off of topical corticosteroids in 6 months, although continuing a daily topical corticosteroid drop for an additional 6 months provided additional protection against immunologic rejection in a large, prospective randomized interventional trial of 406 eyes.[30] However, this advantage of DALK over PK is not as great as one might expect, because immune rejection after PK for keratoconus is less likely and keratoconus is the most common indication for DALK. The major long-term advantage of DALK surgery over PK relates to long-term preservation of host corneal endothelial cells as measured by specular microscopy and reported as ECD.

Certain patients require PK, such as patients with keratoconus who also have coexisting Fuchs' endothelial dystrophy. Patients with corneal scarring from conditions such as herpes simplex virus, varicella zoster virus, microbial corneal ulcers, or macular corneal dystrophy who have a compromised corneal endothelium should have PK surgery. However, in the presence of a relatively normal host corneal endothelium, not having to use long-term topical, periocular, or systemic immunosuppressive agents to manage the graft is a definite advantage for DALK, especially if the patient is a corticosteroid responder or is phakic.

Deep anterior lamellar keratoplasty avoids the intraocular, open-sky segment of the PK procedure. Complications, including positive pressure, iris prolapse, and choroidal effusion/hemorrhage, are completely avoided with DALK. Transmission of bacterial infection from donor to recipient should theoretically remain limited to keratitis rather than endophthalmitis.

Deep anterior lamellar keratoplasty can reduce ECD, especially if microperforations occur, and even more so if anterior chamber injection of gas is required to manage DM detachments or double anterior chamber.[7,31–34] Corneal endothelium can be compromised by pupillary block angle closure after anterior chamber gas injection or by the air bubble itself. With recognition of these exceptions, continued or accelerated loss of ECD after DALK surgery does not seem to occur after 6 months as it does post-PK. Endothelial cell density loss after the immediate postoperative time period is likely to mimic the gradual ECD decrease of a normal cornea.

Because topical corticosteroids can usually be discontinued 3 to 4 months after DALK, there is a lower incidence of corticosteroid-associated intraocular pressure (IOP) elevation. With DALK, there is increased wound strength compared with the PK wound, which is subjected to the prolonged use of topical corticosteroids to prevent immune rejection, and there is decreased risk of cataract progression and less compromised local ocular surface immunity.

Traumatic rupture of PK wounds months to decades after surgery is a potential complication[35] that can be catastrophic. There is a theoretic advantage of DALK wounds over PK wounds, and there are clinical reports of traumatic dehiscence of DALK wounds that suggest that the injuries are less severe than might have been expected of PK eyes.[36] It is difficult to prove this assertion at this time because of the smaller numbers and shorter postoperative follow-up available on DALK eyes. However, an incidence of globe rupture of 1.8% (36/1962), of which 35 received PK (2.0%) and one was a DALK eye (0.5%), was reported in a series of 1962 consecutive keratoplasties (PK, 1776 eyes; DALK, 186 eyes) between 1998 and 2006.[35]

Sutures can be removed earlier on DALK eyes. Unless permanent sutures are used, PK eyes do not have a stable refraction until all sutures have been removed, which in some cases may not occur until several years after surgery. Although early reports suggested that sutures could be removed in DALK eyes as early as 3 months postoperatively because of the lower burden of corticosteroid use and better wound anatomy, 6 to 12 months seems more the norm. However, once sutures are removed, further refractive surgery can be performed earlier and presumably with less concern of wound rupture in DALK eyes. One study suggests that astigmatic keratotomy incisions behave somewhat differently in DALK eyes than in PK eyes.[37] Penetrating keratoplasty eyes often do not have a stable refraction for years after surgery; wound strength is always of concern when performing refractive procedures such as LASIK because of the wound stressing effects of the IOP-increasing suction ring required for surgery.

The advantages of PK over DALK are as follows:

- Penetrating keratoplasty can be used to treat corneal conditions that involve the endothelium, such as Fuchs' endothelial corneal dystrophy, pseudophakic and aphakic corneal edema, posterior polymorphous corneal dystrophy, and congenital hereditary corneal endothelial dystrophies, although EK (DSEK or DSAEK) may now be preferred.
- Penetrating keratoplasty can treat penetrating corneal trauma, especially if there is loss of corneal tissue.
- Penetrating keratoplasty can be used if there is scarring down to the level of DM, such as postacute hydrops in keratoconus, old penetrating central corneal injuries, and severe postinfectious corneal ulcers. In the presence of an adequate ECD, the non-DM–baring DALK techniques may be used as an alternative to PK.
- Penetrating keratoplasty can be used if DM is not exposed in the visual axis, and vision in those with PK may be superior.
- Penetrating keratoplasty is a more familiar operative procedure for most corneal surgeons.

There are geographic and social differences in the indications for corneal surgery, but many corneal diseases are associated with compromised corneal endothelium, which means that PK, or EK, will account for most requests for donor corneal tissue directed to any given eye bank. Also, in keratoconus eyes that have had previous hydrops, traumatic penetrating injuries to the central cornea, or severe microbial infections with residual scarring down to DM, the big-bubble technique for DALK will not usually be successful. Other direct dissection DALK techniques, which leave some residual cornea, can be considered in these cases, although final vision may not be as good as after PK. If corneal hydrops complicating keratoconus has occurred and DALK without DM exposure is performed, pressure-dependent stromal edema after surgery has been described that cleared with IOP-lowering medication and time.[38] However, MD-DALK has been reported for a patient with a history of hydrops-complicating keratoconus.[39] If DM is exposed in the visual axis, and there are no DM folds in the visual axis, then visual acuity is similar for DALK and PK. If a significant amount of pre-Descemet's stroma is left in the recipient bed, then visual acuity in DALK eyes may be compromised.[19,22,26,32,40] In these cases, removal of the DALK graft followed by excimer laser photoablation or the big-bubble technique to remove the remaining stromal tissue and replacement of the DALK graft can improve visual acuity[26,40] and prevent the need for a subsequent PK.

Alió[40] managed 4 eyes with poor vision after DALK using the Melles technique, lifted the DALK donor graft as long as 2 years postoperatively, and exposed DM with a big-bubble technique, improving 6-month BSCVA to 20/25 in 3 patients and 20/32 in one patient. However, when DM cannot be exposed, or if there is significant scarring of the deep corneal stroma, many surgeons may choose to use PK as the primary procedure.

There is a definite learning curve for both PK and DALK procedures, although most corneal surgeons already possess the acquired skills for PK surgery. The operative time for DALK is usually longer than for PK, and both procedures require more operative time than DSEK surgery because of the extensive suturing of the DALK or PK donor graft.

The complications unique to DALK are as follows:

- Ruptures of DM.
- Large lamellar splits in DM.
- Microperforations of DM.
- Double anterior chamber.

- Endothelial cell loss secondary to air/synthetic gas.
- Interface haze or irregularity if all stroma is not removed in the visual axis.
- Interface debris, hemorrhage, vascularization, microbial infections, and epithelial ingrowth.
- Wrinkles of DM or the residual stroma and DM layer.
- Sequestered OVD in the interface.
- Mydriasis from air block glaucoma usually complicating anterior chamber gas injection to treat DM detachment.
- Recurrence of stromal cornea dystrophy in the residual bed.
- Occasional re-epithelialization problems.

The most common complication involves puncturing DM with either small perforations of 1 mm or less, or macroperforations that usually lead to immediate operative conversion to PK. This can occur with either big-bubble techniques using air, OVD, or fluid injection, or micro or macro DM perforation during direct dissection using a surgical blade with or without the injection of fluid, air, or OVD injection. Conversion to a conventional PK may be advisable unless the perforation is small.

Lamellar splits in DM with stromal pressure dissection using air, fluid, or OVD are uncommon and may not be recognized by the operating surgeon, but they do increase the risk of DM perforation because of the thinness of the remaining DM. If a perforation occurs, but a DALK is completed, then air or other gas placement in the anterior chamber to tamponade the perforation may lead to additional ECD loss, gas pupillary block with a fixed dilated pupil,[41,42] or eventual failure of the DALK graft and the need for a delayed conversion to PK. Although perforations are common at an average rate of 11.7%, intraoperative PK conversions of 2.0% and delayed PK conversions of 0.4% suggest that most DALK cases will be completed as planned. If a DM perforation occurs before DM has been exposed in the central optical zone of 5 mm or so, residual stroma may be left and the donor graft placed on top, with possible reduced visual acuity from residual stroma in this situation.

Microperforations of DM that do not preclude a lamellar onlay graft can occur during DALK, although there is a risk of postoperative DM detachment and pseudo double anterior chamber formation. Double anterior chamber is usually a consequence of DM perforations, but has also been described in the absence of known perforations. This also may persist if the endothelium has not been removed from the donor graft and may complicate subsequent cataract surgery with DM detachment.[43] Endothelial cell loss secondary to air/synthetic gas after anterior chamber injection to manage intraoperative DM tears or postoperative double anterior chamber may occur.[44]

Interface haze is rarely a problem with DM-baring procedures and sometimes even experienced observers cannot distinguish between a PK and a DALK eye if DM has been exposed in the entire recipient bed. Interface haze may cause glare or decreased visual acuity. Interface debris, hemorrhage from host stromal vascularization, interface vascularization, microbial infections, and interface epithelial ingrowth are rare complications.[22,45,46] Wrinkles of DM are more common in keratoconus eyes with advanced cones, presumably from compression of the cone when placing the donor graft.[47] Wrinkles may also contribute to glare or decreased vision. If noted at the time of surgery, manipulating the donor graft may displace the wrinkles out of the visual axis and decrease their effect on vision.

Retained OVD can complicate the Melles or limbal pocket techniques where an OVD is used to expand the limbal entrance pocket dissection to enable safe trephination.[48] Often OVD is also used to reexpand the collapsed air bubble in the big-bubble techniques before removing the remaining stroma. In any case, the surgeon needs to be diligent in gently irrigating OVD from the lamellar bed before placing the donor graft to avoid potential donor graft edema or donor failure.

Postoperative DM detachment or a double anterior chamber leads to poor vision from an edematous graft and the need to inject air or another gas into the anterior chamber to tamponade the tear. Larger or inferior tears are more difficult to tamponade with gas and may require suture reattachment or delayed conversion to PK. Complications of a large gas bubble in the anterior chamber include loss of endothelial cells; air block glaucoma, which, in its most severe form, can result in permanent pupillary mydriasis due to iris ischemia, iris peripheral anterior synechiae, and glaucomflecken because of anterior lens epithelial/lens cortical infarcts (a group of complications usually referred to as "Urrets–Zavalia syndrome");[49] and, rarely, ischemic damage to the optic nerve or retina. These complications are related to elevated IOP and are likely also related to the duration of the IOP elevation. Prompt diagnosis of the pupillary block glaucoma and management with pupil dilation or paracentesis to reduce the size of the gas bubble, deepen the anterior chamber, and eliminate the pupillary block will often prevent these complications.

Recurrence of the corneal stromal dystrophies in the anterior portion of a corneal graft is expected for PK or DALK. However, recurrence in the interface has been a problem with LASIK surgery and can also occur with DALK. It is suspected that recurrence of a stromal dystrophy such as lattice dystrophy in the deep lamellar bed is due to retained host stroma and would be unlikely with the DM-baring techniques.

Occasional re-epithelialization problems can occur if cryolathed or lyophilized donor lamellar tissue is used, although re-epithelialization can also complicate PK when the epithelium is often not viable after longer corneal donor storage times.

Complications unique to PK are as follows:

- Immune rejection of donor corneal endothelium.
- Prolonged topical corticosteroid use necessary in some cases.
- Microbial endophthalmitis.
- Trephine complications (iris damage, damage to the crystalline lens, and retained DM).
- Open eye complications (positive vitreous pressure, expulsive choroidal hemorrhage, and damage to the iris and/or lens).

- Penetrating wound complications (flat anterior chamber from wound leak, iris synechiae to wound, and poor vertical wound apposition).
- Elevated IOP from retained OVD.
- Anterior chamber epithelial ingrowth.
- Primary donor graft endothelial failure.
- Accelerated donor graft endothelial cell loss (instrument trauma to the donor endothelium, trauma to the endothelium at surgery from iris or lens contact, and postoperative biphasic accelerated loss).

Immune corneal endothelial rejection can be a major problem with high-risk corneal transplant recipients, usually involving significant corneal stromal vascularization, inflammation, and anterior segment abnormalities. These eyes are occasional candidates for DALK if the host endothelium is normal, as it might be in ocular surface chemical injuries, ocular mucous membrane pemphigoid, Stevens–Johnson syndrome, inactive interstitial keratitis with corneal scarring from varicella zoster virus or herpes simplex virus, and vascularized corneas after treatment for microbial keratitis. Deep anterior lamellar keratoplasty or even a therapeutic LK would be the preferred procedure if ocular surface problems can be managed. However, for keratoconus, immune rejection is not a major problem, because in keratoconus a graft rarely fails as the result of immune endothelial rejection if treated promptly and appropriately. Whether the accelerated long-term loss of ECD in PK is related to subclinical immune endothelial rejection or other causes has not yet been determined.

Prolonged topical corticosteroid use may be needed in some cases with recurrent immunologic graft reactions. Corticosteroid-induced IOP increases may require use of topical glaucoma medications or filtration surgery to control the IOP. There may be loss of vision from secondary glaucoma, and the patient may not be able to wear contact lenses during times of significant immunosuppression of the ocular surface with topical corticosteroids because of the increased risk of infectious keratitis. There is also an increased cost associated with prolonged use of topical corticosteroid or glaucoma medications.

Some of the complications unique to PK, such as microbial endophthalmitis, expulsive choroidal hemorrhage, and epithelial downgrowth, can be devastating. These severe complications are fortunately rare, particularly for phakic PK surgery that would usually be the alternative to DALK surgery (because most eyes with keratoconus, nonpenetrating corneal scars, herpes simplex virus, corneal scars, and so forth are phakic).

Complications related to the anterior chamber penetrating nature of PK surgery are also uncommon in experienced hands, although when they do occur, they can result in compromised visual outcomes.

Complications common to PK and DALK include the following:

- Ametropias, astigmatism of excessive amount, irregular astigmatism.
- Suture-related problems (sterile inflammation, microbial abscess, problems with epithelialization, premature loosening, induced astigmatism, delayed absorption, and unpredictable breakage).
- Immune donor epithelial and stromal rejection.
- Recurrence of corneal dystrophies.
- Corneal ectasia (recurrent keratoconus) of the graft, progressive host ectasia in keratoconus eyes.
- Donor endothelial cell loss in PK and loss of host ECD in DALK, especially with DM perforations or anterior chamber injection of air or gas.
- Decreased resistance to globe rupture from blunt ocular trauma; usually the transplant wound remains the weakest part of the eyeball tunic.
- Ocular surface disease.
- Donor-to-host transmission of infection.

Sutures can be removed much earlier in DALK procedures than in PK, potentially leading to fewer suture-related problems after DALK. Stromal and epithelial immune rejection cannot occur in those DALK procedures where cryolathed or lyophilized donor corneal tissue has been used to prepare the lamellar donor tissue because all keratocytes and epithelial cells are killed in the processing of the donor tissue. However, most surgeons use corneal tissue preserved in short- or intermediate-term corneal preservation media, which usually preserves stromal keratocytes and, to a variable degree, donor corneal epithelium. Stromal graft rejections, which are uncommon in the first place, become more rare as postoperative time increases.

In general, low-risk PK eyes with a diagnosis such as keratoconus are usually tapered off topical corticosteroids by 6 months after surgery, and corticosteroid-related glaucoma is rarely a major management problem. However, for a few patients with repeated immune graft rejections, the required use of corticosteroids for immunosuppression can result in corticosteroid-induced glaucoma and posterior subcapsular cataract formation. The need for topical corticosteroids in DALK eyes is unusual after 6 months postoperatively. Even if corticosteroids are needed to treat subepithelial infiltrates or stromal graft rejection in DALK eyes, topical corticosteroids rarely have to be used for extended periods of time if there is no other source of inflammation.

Corneal dystrophies are known to recur after PK, usually involving the anterior part of the graft, and they would be expected to recur in similar fashion after anterior lamellar corneal procedures including DALK.

Late postoperative corneal ectasia after DALK has been reported.[50] This was a true keratoconus recurrence in a DALK cornea from lyophilized donor tissue in a schizophrenic patient with habitual eye rubbing, an apparent cause of recurrent keratoconus,[51] and a repeat DALK was successful. Late-onset keratoconus has also been reported for PK in keratoconus eyes. True keratoconus as a complication of a PK has been documented,[52] although most cases described as late-onset keratoconus are probably due to continued ectasia of a portion of the residual host cornea, usually inferiorly, and is not true keratoconus where the graft itself undergoes central thinning and ectasia. It remains to be determined whether keratoconus after a PK or a DALK graft is due to undiagnosed keratoconus in the donor cornea, patient factors such as biochemical abnormalities of host epithelium, stromal keratocytes, or behavior such as eye rubbing and contact lens wear. The more common cause of so-called recurrent keratoconus, continued thinning of the host cornea, is not easily addressed, but sometimes resection of a crescent of ectatic host cornea can reduce astigmatism to acceptable levels. Late ectasia of graft–host junction, especially inferiorly, is not uncommon after PK for keratoconus. This may reflect incomplete removal of ectatic tissue at the time of PK. A theoretic advantage of DALK is the freedom to use larger grafts that approach the limbus to help avoid this late complication. A 2-step, 2-diameter technique has been described to obtain DALK diameters of 9.5 to 11.0 mm if the initial diameter of 7.75 mm is successful.[53]

Ocular surface disease, such as dry eye, neurotrophic, neuroparalytic, epithelial stem-cell dysfunction, or other diseases, can be a problem with either procedure, although LK procedures generally are less difficult to manage because immune endothelial rejection is not a factor and anti-rejection medication is generally less crucial.

Conclusions and Future Research

The objective of this review was to compare DALK with PK for the outcomes of BSCVA, refractive error, rejection, and graft survival. One level II study and level III evidence indicate that DALK and PK have similar outcomes in terms of BSCVA and refractive error. Exposure of DM or minimization of residual stroma seems to be associated with better visual outcome in DALK. If residual stroma in the surgical bed is minimal ($<$25–65 μm), vision may be comparable between the groups: If residual stroma is thicker, or if DM wrinkles or haze is present, vision may be less in the DALK eyes as a group, but not less than 1 line of Snellen visual acuity on average. Astigmatism and ametropia remain a problem for both PK and DALK. Epithelial and stromal immune rejection reactions of the donor tissue can occur with either procedure and are usually easily managed with topical corticosteroids. However, immune rejection reactions against donor graft endothelium cannot occur with DALK surgery, but they are a definite risk for PK and may occur any time during the lifetime of the graft. Each donor endothelial rejection reaction may result in decreased ECD or failure of the graft. The immune rejection reactions themselves and the immunosuppressive treatment for the acute rejection reactions or the prevention of rejection may lead to corticosteroid-associated IOP elevation in susceptible patients, acceleration of cataract changes, decreased wound healing, and compromised local immunity, thereby providing an advantage of DALK over PK. Sufficient evidence remains to be gathered before a definitive conclusion can be reached about improved graft survival after DALK compared with after PK.

If ECD is used as a proxy for graft survival, there are substantial data from level III studies and a level II study that at any postoperative point in time DALK eyes have higher ECD than PK eyes. Because keratoconus is the disease most commonly treated using 1 of these 2 procedures and keratoconus recipients tend to be young and healthy with a long life expectancy, the preservation of endothelial cells in DALK surgery may provide a major advantage that will only become apparent within time frames more relevant to these patients, that is, decades. As DALK procedures increase in number and extended follow-up becomes available, data on ECD and graft survival can be compared with existent data on populations with PK.

Randomized clinical trials comparing DALK and PK are needed, but they are difficult and costly to implement. The Dutch Lamellar Corneal Transplantation Study has enrolled 28 patients in each arm of a randomized clinical trial that is currently being conducted to compare DALK with PK and posterior LK with PK.[54] The primary outcome measure is the discard rate of donor corneas, with secondary outcome measures of visual acuity, astigmatism, stray-light evaluation, contrast sensitivity, endothelial cell loss, incidence of endothelial rejection, vision-related quality of life, and patient satisfaction. Surgeons or patients who believe that the visual and refractive results of PK and DALK are the same but the rate of endothelial cell loss over time is significantly different might view a randomized prospective study comparing the 2 techniques as unacceptable, and it could be difficult to enroll patients. It is difficult to conduct a trial large enough to evaluate the secondary outcome measures listed above. An observational study with well-standardized outcome assessment may be more feasible. Any future DALK trials should include imaging techniques to measure residual posterior cornea stroma in the donor bed when DM exposure has not been fully obtained to more fully elucidate the relationship between BSCVA and residual corneal stroma.

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