Approaches toward enhancing survival probability following deep anterior lamellar keratoplasty

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***Abstract*:** The greatest advantage of deep anterior lamellar keratoplasty over full-thickness corneal transplantation is the elimination of graft failure caused by endothelial rejection. Despite this advantage, a deep anterior lamellar keratoplasty graft can fail because of several factors, such as complications related to the donor–recipient interface, graft epithelial abnormalities, graft vascularization, stromal graft rejection, and recurrence of herpetic keratitis. Increased deep anterior lamellar keratoplasty graft survival is mainly built upon optimization of the ocular surface to provide a hospitable environment for the graft. Any predisposing factors for graft epithelial abnormalities, corneal neovascularization, and preexisting vernal keratoconjunctivitis should be identified and treated preoperatively. Prompt recognition and appropriate treatment of interface-related complications and stromal graft rejection usually result in good anatomic outcomes, with no detrimental effects on vision.

Keywords: complications related to the donor–recipient interface, deep anterior lamellar keratoplasty, epithelial abnormalities, graft failure, graft rejection, graft survival, herpetic keratitis, vascularization, vernal keratoconjunctivitis

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Introduction

Until recently, full-thickness penetrating kerato-plasty (PK) was the first-line keratoplasty technique for the management of corneal pathologies. There is already a substantial body of literature to suggest good long-term clinical outcomes of PK for various indications that enjoys a very high success rate.[1] Immunologic rejection, mainly in the form of endothelial rejection, is a major risk factor for PK graft failure.[1] Another important risk factor for graft failure includes nonimmunologic conditions including ocular surface disorders, infectious keratitis, trauma, and glaucoma.[1] After the introduction of deep anterior lamellar keratoplasty (DALK), PK is no longer the default technique of keratoplasty in corneal pathologies with normal endothelium. DALK has gained popularity due to the elimination of complications encountered with PK, such as suprachoroidal hemorrhage, and it enjoys a less troublesome postoperative course due to the absence of endothelial rejection.[2] In addition, the technique requires less stringent criteria for the selection of donor tissue.[2] These features, along with the lower postoperative endothelial cell loss, are the greatest advantage of DALK over PK, especially in patients who are at high risk of graft rejections. Despite these advantages, a DALK graft can fail because of nonimmunologic factors, such as persistent postoperative double anterior chamber, haziness of surgical interface, graft epithelial abnormalities, infectious keratitis, recurrence of primary pathology in graft including corneal dystrophies, graft vascularization, and scarring. Furthermore, subepithelial and stromal graft rejection may still occur postoperatively and if left untreated, can lead to lamellar graft failure. In contrast to PK in which increased graft survival is generally built upon immunosuppressive therapy to reduce the risk of endothelial graft rejection, the graft survival in DALK mostly depends upon optimization of the ocular surface to provide a

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Table 1. Treatable Etiologies of Graft Failure After Deep Anterior Lamellar Keratoplasty as Presented in Text.

Complications associated with donor–recipient interface • Intraoperative Descemet's membrane perforation • Postoperative Descemet's membrane nonattachment • Interface wrinkling • Interface haziness
Postoperative graft epithelial abnormalities • Donor-related factors • Surgical factors • Recipient-related factors
Vernal keratoconjunctivitis
Corneal graft neovascularization
Graft rejection
Recurrence of herpes simplex keratitis

hospitable environment for the graft. In addition, appropriate management of interface-related complications and stromal graft rejection is essential for achieving good visual and anatomic outcomes. In this review article, we aim to discuss the treatable etiologies of graft failure after DALK and provide measures that can improve graft longevity in this type of surgery.

Review

This article aims to discuss the treatable etiologies of graft failure after DALK (Table 1) and highlights measures that can improve graft longevity. Other causes of graft failure that cannot be prevented (i.e. recurrence of corneal stromal dystrophy) are not discussed in this review. A review of the literature was performed in PubMed, including all English articles published from January 2004 to October 2019. Search terms were 'deep anterior lamellar keratoplasty' with 'graft failure', 'interface-related complications', 'epithelial abnormalities', 'vernal keratoconjunctivitis', 'vascularization', 'angiogenesis', 'graft rejection', and 'herpetic keratitis'. The ethical board approval was not required for this review article.

Complications associated with donor–recipient interface

Although DALK eliminates many complications that are seen in full-thickness PK, there are a few complications that are due to the presence of surgical interface between the donor graft and recipient bed in this lamellar keratoplasty technique.

These complications which can cause graft failure include intraoperative Descemet's membrane (DM) perforation, postoperative double chamber formation, interface wrinkling, and interface haziness (Figure 1). DM perforation can take place during different steps of surgery, including trephination, needle insertion, bubble puncturing, deep stromal excision, and graft suturing. The rate of intraoperative DM perforation is between 4% and 50%, depending on surgeon experience, indications for corneal transplantation, the presence of corneal scarring near the DM, and surgical techniques.[3–6] This complication is more frequently encountered in eyes with keratoconus as compared with other conditions requiring corneal transplantation.[7] Advanced ectasia with corneal thickness less than 250 μm increases this risk.[8] The ratio of scar depth to minimal corneal thickness can predict perforation rates during pneumatic dissection.[9] The risk of DM perforation is lowest with the big-bubble technique (6%) and highest with manual dissection technique (26%).[10]

Intraoperative DM perforation can result in postoperative DM detachments and graft edema, endothelial cell loss, and interface opacity (Figure 1(a)).[11–13] The size of perforation and the stage at which it happens are crucial for successful completion of DALK. Perforations that occur during the early stage of the surgery lead to slower visual recovery secondary to the retention of posterior corneal stroma. A large DM perforation leads to a flat anterior chamber intraoperatively necessitating several air injections, which is associated with a greater extent of endothelial cell loss.[14]

Interface haze may result from incomplete stromal dissection and can cause a reduction in visual acuity.[5] Factors that are associated with failure to achieve pneumatic dissection in big-bubble DALK include shallow trephination, small trephination size, and presence of corneal scar.[15,16] Strong adhesions between the corneal stroma and DM, which is present in corneal scar, make it difficult to achieve a bare DM during big-bubble DALK.[17] Interface wrinkling is due to a mismatch between the size of recipient bed and donor graft (Figure 1(b)); it is often located peripherally and has no impact on vision. Interface wrinkling is usually transient, and it tends to improve 1 year after surgery. Eyes with advanced keratoconus (mean keratometry >60 D), however, may develop persistent interface wrinkling in the central cornea that may affect vision by inducing higher order aberrations.[18]
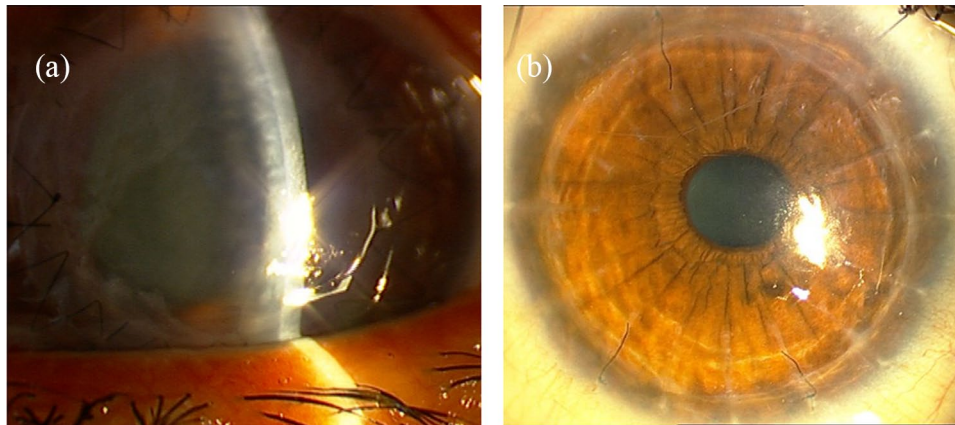
Figure 1. Complications related to donor–recipient interface after deep anterior lamellar keratoplasty. (a) The formation of double anterior chamber that is characterized by graft stromal edema and recipient Descemet's membrane nonattachment and (b) multiple folds are evident in the surgical interface.

Management

Big-bubble technique has become the most popular surgical technique for DALK. The main challenge associated with this technique is the placement of the cannula through recipient cornea at an appropriate depth and as close as possible to the DM. This maneuver often requires mastery through a long learning curve, leading to an initial success rate of only 50% for novice cornea-trained surgeons.[3,19] Performing an initial deep trephination maximizes the chances of achieving pneumatic dissection during DALK.[16] Several surgeons have adopted modifications to the original technique to increase the rate of big-bubble formation. Feizi and colleagues[20] introduced peripheral air injection in which a 27-G needle is inserted into the corneal stroma from the trephination site toward the limbus. They found that the rate of successful big-bubble formation is 81.3% with this modification.[20] Peripheral air injection has a shorter learning curve, and it is more successful in the hands of less-experienced surgeons.[21] In addition, in case of DM perforation during peripheral air injection, it is possible to change the site of needle insertion to the opposite limbus or even inside the trephination. In this condition, the perforated DM will not interfere with big-bubble formation.[20,21]

Accurate evaluation of the needle depth is difficult by conventional en face microscopy. Therefore, different intraoperative instruments, including corneal pachymetry and anterior-segment optical coherence tomography, have been used to insert the needle into deep stroma and increase the likelihood of big-bubble formation.[22–24]

Different measures can be used for the management of intraoperative DM perforation depending on the step of surgery at which the perforation takes place as well as the location and size of the defect. These measures include suturing of perforation, intraoperative stromal patching, use of fibrin glue, and conversion to a manual dissection technique.[25] Perforations that occur during trephination is closed by tight sutures, followed by manual dissection of the corneal stroma. Afterward, donor graft is fixed to the recipient bed using full-thickness sutures in the site of perforation. If perforation occurs during posterior stromal removal, that area should be excised last, and a thin layer of stroma should be left in place covering it. At the end of surgery, the anterior chamber is partially filled with air or expansile gas. If a perforation occurs during the suturing step, air injection into the anterior chamber at the conclusion of procedure will be sufficient.

Postoperatively, shallow DM detachments are often self-limited and resolve spontaneously. Surgical intervention, however, is required for the management of large pseudoanterior chambers, including fluid drainage and air or expandable gas injection. This procedure can be repeated if a single injection fails to attach DM.

Interface wrinkling, another complication exclusively encountered after DALK, can be prevented by oversizing the donor graft by 0.25 or 0.50 mm because mismatch between the size of donor graft and recipient bed is responsible for the development of this complication.[3] Interface-related complications such as failure of DM to attach,
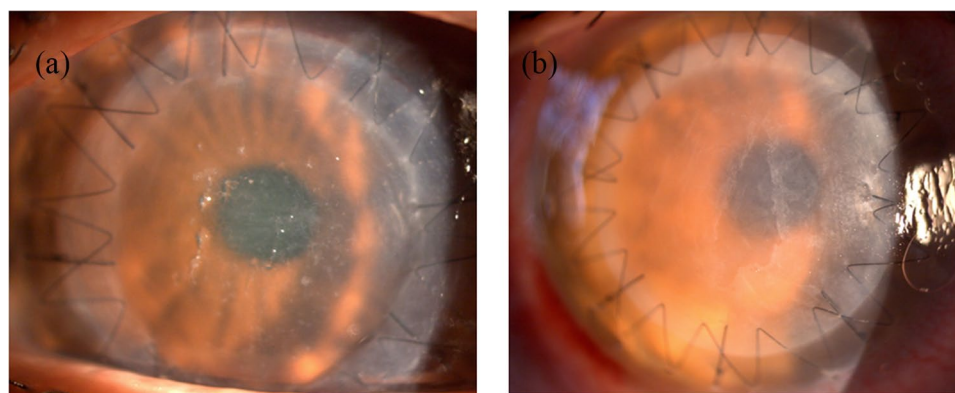
Figure 2. Epithelial graft abnormalities after deep anterior lamellar keratoplasty. (a) Filamentary keratitis characterized by the presence of multiple filaments in a background of severe dry ocular surface and graft epithelial irregularities and (b) A persistent epithelial defect with characteristic heaped-up edges. The regenerated surface epithelium in other areas appears irregular and hazy. A bandage contact lens is placed on the eye.

haziness, and wrinkling that persist postoperatively and affect the vision may necessitate a full-thickness PK.

Graft epithelial abnormalities

The integrity of the graft epithelium after DALK is an imperative factor in graft clarity. Graft epithelial abnormalities after DALK include punctate epithelial keratopathy, filamentary keratitis, and epithelial defects (Figure 2). Epithelial defects which are present in 93.3% of grafts on postoperative day 1 may persist longer than 14 days in 0.8–6.0% of DALK cases performed to treat keratoconus.[26–29] Graft epithelial defects can lead to subepithelial and stromal opacities, infectious keratitis, corneal melting, and perforation, which may delay visual rehabilitation and result in graft failure in 25% of patients.[30–32] Epithelial instability after DALK is caused by donor-, surgery-, and recipient-related factors. It is crucial to recognize the perioperative ocular surface abnormalities and take the appropriate measures to resolve them to enhance the chances of graft longevity after DALK.

Donor-related factors

Donor-related factors that can influence graft epithelium during the early postoperative period after DALK include those related to diabetes in the donor, death-to-preservation time, storage time, the storage media, and donor quality. History of diabetes in the donor is an independent risk factor for presence of graft epithelial

defects postoperatively.[30] The prevalence of epithelial defects on the first postoperative day varies depending on the type of storage media; it ranges from as high as 80% with organ culture medium to as low as 31% with cold storage medium.[30,33] The impact of death-to-preservation time and storage time on the corneal graft surface early postoperatively is controversial.[30,33] Chou and colleagues[30] found that the postmortem time before enucleation is more important than the storage time in the development of graft epithelial abnormalities. Similarly, a DALK study found that the likelihood of graft epithelial defects is significantly increased with increased death-to-preservation time.[34] Although some investigators failed to establish an association between storage time and an increased odds of postoperative graft epithelial abnormalities, others reported a positive correlation.[30,33,35–41] Some damage to the graft epithelium might occur due to antibiotics used in the storage media.

Other donor features such as the assigned 'graft rating' can influence the rate of postoperative graft epithelial abnormalities. Naturally, a tissue with higher quality exhibits a lower rate of epithelial defects after DALK.[42] Feizi and colleagues[42] revealed that the presence of graft epithelial defects on the first day after DALK has a significant association with graft rating reported by the eye bank and storage time. Since the introduction of DALK, many surgeons have been using less stringent criteria for selecting tissue for DALK surgery as compared with PK, leading to the use of corneal tissues of less-than-ideal quality and

with longer preservation times. This explains the higher rates of epithelial defects after DALK than those reported after PK in the immediate postoperative period.[33,35,43,44]

Surgical factors

Further damage to the graft epithelium can occur intraoperatively during donor preparation for DALK. Because of the way the donor tissue is oriented while DM is being stripped off; the epithelium may suffer multiple injuries from being against the donor punch block. Other surgical factors that have detrimental effects on graft epithelium postoperatively are longer surgical duration and intraoperative graft desiccation.[30] A proper surgical technique with a perfect alignment of the graft and host edges is crucial in ensuring adequate epithelial growth over the donor cornea postoperatively; for example, an overriding margin will impede migration of the epithelial cells to the donor tissue. Sutures that are placed too tight prevent uniform distribution of tear film over the corneal surface, hindering adequate graft epithelialization.[33,36]

Recipient-related factors

An intact graft epithelium on the first postoperative day provides a 'jump start' for maintaining a healthy graft surface, meanwhile the importance of the status of the recipient's ocular surface should not be overlooked. Epithelial regeneration in graft depends on the interaction among multiple factors such as the presence of healthy eyelids, tear film, limbal stem cells, and nerve fibers. Several neurotrophic factors, including insulin growth factor, nerve growth factor, substance P, and acetylcholine, are secreted by corneal nerves and direct epithelial cell division and maturation.[45–47] All superficial and deep corneal nerve fibers are cut during trephination. The process of graft re-innervation is slow and incomplete with an abnormal pattern and can further be delayed in vulnerable patients with preexisting conditions, such as fifth nerve palsy and previous episodes of herpes simplex keratitis, leading to severe neurotrophic keratopathy.[48]

Furthermore, graft epithelial abnormalities can be exacerbated by the preexisting dry eye and limbal stem cell deficiency and pathologic process in the eyelids and conjunctiva. Eyelid abnormalities including trichiasis, keratinized lid margins, and cicatricial- or involutional-related eyelid malpositionings can cause microtrauma to the graft.[49,50] Conjunctival fibrosis, symblepharon, and fornix foreshortening can destabilize the tear film and interfere with normal blinking.[51,52] Dry eye syndrome can be caused by aqueous tear deficiency or lipid tear abnormality. In severe cases, dry eye syndrome ultimately leads to corneal pannus, persistent corneal epithelial defects, epithelial keratinization, and damage to the limbal stem cells.[36,53,54] The limbal stem cells can be severely damaged following chemical and thermal injuries. Placing corneal transplants into eyes with limbal stem cell deficiency can result in persistent epithelial defects, vascularization, and scarring of the graft, leading to graft failure.[55]

Management

Preoperative measures. Thorough evaluation of eyelids and ocular surface, including slitlamp examination, conjunctival and corneal staining with Lissamine green and fluorescein, and impression cytology, is critical to improve the graft prognosis in cases with ocular surface disorders.[56] Coexisting ocular surface diseases, including exposure keratitis, dry eye, meibomian gland dysfunction, and limbal stem cell deficiency, should be preoperatively diagnosed and properly managed. Surgical correction of lid margins as well as diseases of the tarsal plate is among the most vital preoperative measures to enhance graft survival. Treatment plans for dry eye must be tailored to the underlying disease and its severity. Artificial tears and lubricants are commonly used to facilitate corneal epithelialization.[57] Severe cases require more intense treatment, including topical anti-inflammatory agents or more invasive procedures such as punctual occlusion and tarsorrhaphy.[57] Meibomian gland dysfunction should be treated with lid hygiene, topical antibiotic, short course of topical corticosteroid, as well as oral doxycycline in selected cases.[58,59] Patients with limbal stem cell deficiency have notoriously poor outcomes if keratoplasty is performed as a solo procedure; in these cases, limbal stem cell transplantation, including keratolimbal allograft, living-related conjunctival limbal allograft, conjunctival limbal autograft, and cultivated limbal stem cell transplants, should be performed simultaneously to restore ocular surface. A great advantage of DALK is that it allows both corneal and stem cell transplantation to be performed at the same time in cases with limbal stem cell deficiency that have a normal endothelium.[60,61]

Intraoperative measures. Although the corneal graft is eventually resurfaced by the recipient's epithelial cells, an intact donor epithelium on day 1 predicts a smoother postoperative course for the corneal graft. This is the rationale for using a graft with intact epithelium in patients with preexisting ocular surface disorders. The donor epithelium should not be removed intraoperatively, and desiccation of the ocular surface should be prevented by frequent irrigation with balanced salt solution.[30] In addition, donor DM should be removed very gently to minimize damage to the graft epithelium. Other important issues are perfect apposition of donor and recipient edges and proper suturing technique. These factors are crucial for the smooth migration of recipient epithelial cells to corneal graft and for the maintenance of a normal tear meniscus.[33,36]

Postoperative measures. Postoperative care aims to promote healing of the graft epithelial defect and prevent a progression to graft ulcer. In the case of persistent epithelial defects, patients should be monitored frequently and all eye drops associated with graft epithelial toxicity should be discontinued. The prolonged use of preservatives in an already-compromised ocular surface can damage the epithelial surface, resulting in worsening of the ocular surface disorders.[62] Antibiotic eye drops are recommended in the presence of graft epithelial abnormalities to prevent infections. Topical steroids may inhibit the epithelial healing process and should be used with caution. Removal of tight sutures at the areas with surface irregularities can solve epithelial healing problems. Other therapeutic approaches are frequent nonpreserved artificial tears, lubricants, punctal occlusion, moist inserts, treatment of meibomian glad dysfunction, and topical vitamin A.[63–65] Bandage soft contact lenses have been used for the management of epitheliopathy, as they facilitate reepithelialization by protecting the advancing epithelial cells from being sloughed off by the blinking eyelids, maintaining a tear layer in constant contact with the cornea, as well as providing anesthetic relief.[66,67] Large-diameter scleral contact lenses are recommended for the prevention of microtrauma to the cornea caused by lid margin pathologies.[68,69]

Autologous serum drops (20%) have been advocated in patients with persistent epithelial defects. It harbors a wide variety of growth factors which are found in serum, including epidermal growth factor, vitamin A, transforming growth factor-beta, and neurotrophic factors.[49,70,71] These substances are essential in wound healing and promote migration, proliferation, and differentiation of the corneal epithelial cells.[70] Autologous serum is contraindicated in cases with some concomitant conditions, including blood dyscrasias. Alternatively, allogeneic serum obtained from healthy donors can be used. Umbilical cord blood serum is an allogeneic serum which is rich in epitheliotrophic growth factors, such as insulin-like growth factor, transforming growth factor-beta, epidermal growth factor, and vascular endothelial growth factors (VEGFs).[72,73]

Surgical intervention is usually indicated for persistent corneal epithelial defects not responding to medical treatment. Several options are available, such as punctual occlusion, amniotic membrane transplantation (AMT), and tarsorrhaphy. Tarsorrhaphy is most commonly used in the management of persistent corneal epithelial defects; however, the unacceptable cosmetic result is usually a major concern for patients.[74] AMT, in addition, is a widely used method to promote corneal epithelial healing. AMT, which can be used as a graft or patch, restores an intact basement membrane, suppresses T-cell proliferation and decreases surface inflammation, facilitates surface epithelialization, and prevents corneal neovascularization and scarring.[75,76] All of these features provide a favorable stromal microenvironment for better epithelial cell adhesion and proliferation.

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a bilateral chronic inflammatory disease of the conjunctiva. This condition frequently affects young male patients, but in tropical regions of the world it may affect both sexes equally.[77] The pathomechanism of VKC involves both chronic immunoglobulin E (IgE)-mediated mast cell degranulation and immune reactions mediated by T-helper 1- and T-helper 2-lymphocyte derived cytokines, as well as other inflammatory cells.[78,79]

Itching is the most characteristic symptom and may be accompanied by watering, mucous discharge, injection, blurred vision, pain, and photophobia. Itching and other symptoms may be continuous or more pronounced in certain seasons. Clinical signs include conjunctival hyperemia, giant papillae on the upper palpebral conjunctiva, Horner-Trantas dots, and limbal

gelatinous infiltrates. Significant vision loss in VKC is usually associated with certain corneal findings with punctate epithelial keratopathy being the most common. Keratoconus, which is caused by frequent eye rubbing in some atopic pediatric patients, is also frequently accompanied by VKC leading to reduced visual acuity.[77]

Patients with VKC may require corneal transplantation to treat their keratoconus, corneal scarring, or corneal vascularization. Although no significant differences were reported in visual acuity or graft survival rates after corneal transplantation for keratoconus in eyes with or without VKC, there are concerns that the outcomes might be worse in VKC patients with keratoconus; several factors such as chronic inflammation, ocular surface abnormalities, and peripheral corneal vascularization are the likely culprits (Figure 3).[80–83] Feizi and colleagues[83] reported an excellent visual outcome following DALK in keratoconus-affected eyes with VKC, with 88.5% of eyes attained final best-corrected visual acuity (BCVA) $\geqslant$ 20/40 as compared with 91.6% in eyes with only keratoconus. They observed no difference between the study groups in spherical equivalent refractive error and mean keratometric value. However, suture-related complications, including peripheral vascularization and abscess formation, were more frequently encountered in the VKC group, resulting in a significantly larger amount of keratometric astigmatism.[83] In addition, the rate of second or more graft rejection episodes was significantly higher in the VKC group.[83] A report of reactivation of VKC and shield ulcer after DALK in pediatric patients with keratoconus exists.[84] Shield ulcers may result in graft failure due to graft opacification, vascularization, and rejection.[84]

Management

DALK should be performed only after good medical control of VKC and any exacerbation of ocular inflammation should be aggressively treated after the surgery. In addition, it is advisable to defer surgery to the cooler seasons when the disease becomes more quiescence. Postoperatively, the patient should be observed closely to timely diagnose the reactivation of the disease and to initiate appropriate treatment regimen. This regimen includes topical short-term pulsed steroids, with a topical antihistamine and mast cell stabilizer. After the inflammation is brought under control, topical steroids are discontinued and patients are maintained on topical antihistamines
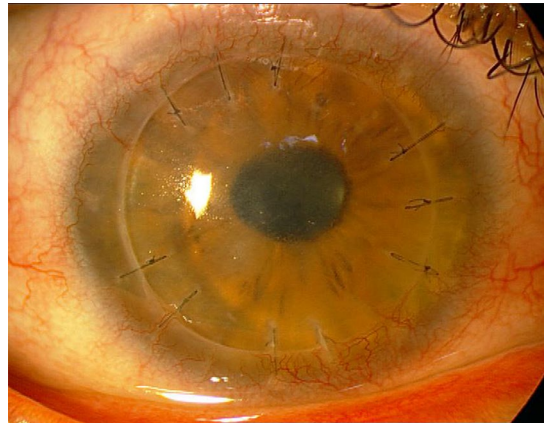

Figure 3. Reactivation of vernal keratoconjunctivitis in a patient with keratoconus who underwent deep anterior lamellar keratoplasty. The photograph shows an injected eye with peripheral corneal vascularization involving both host and donor in addition to the presence of suture abscesses and graft epithelilal haziness.

and mast cell stabilizers throughout the warm seasons of the year.

Since topical corticosteroids have extensive side effect profiles, initial treatment should begin with low potent steroids such as fluorometholone or loteprednol. More potent steroids such as prednisolone acetate or dexamethasone should be used in more resistant cases.[85] Supratarsal injection of triamcinolone acetonide constitutes a safe option for recalcitrant cases and significantly reduces ocular symptoms and signs and the frequency of recurrences.[86]

Mast cell stabilizers, such as cromolyn sodium and lodoxamide, are a mainstay for prophylaxis and frequently used as first-line therapy. These drugs should be applied four to six times per day and it may take up to 2 weeks for them to show a clinical response.[87] Lodoxamide is superior to cromolyn sodium in reducing symptoms and signs of the disease.[87] Antihistamines are usually used in mild VKC; but they have limited effects in the more severe form of the disease. Some antihistamines can exacerbate symptoms because they have a drying effect. Ketotifen and olopatadine have both antihistamine and mast cell stabilization properties, and can effectively reduce the symptoms and signs of VKC, with evidence favoring ketotifen as being more effective.[88]

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to be a useful

therapeutic option in VKC.[89,90] Ketorolac or diclofenac can be used in combination with abovementioned antihistamine drugs to provide rapid relief of symptoms.[91] Their use, however, should be limited to short-term treatment because they can cause corneal melting and perforation.[92]

Drug-resistant VKC can be effectively treated with topical cyclosporine 0.05% in conjunction with topical corticosteroids.[93,94] The immunophilin cyclosporine A is a calcineurin inhibitor that inhibits T-lymphocyte activation by inhibiting the expression of the interleukin (IL)-2 receptor, and the activation of mast cells and eosinophils, thereby decreasing tear cytokine concentration.[95,96] Topical cyclosporine 0.1% has a good efficacy and 30% of patients with VKC are able to discontinue topical steroid use.[97] This drug has an excellent side-effect profile.[98] The most common side effect is eye irritation (12%), and >1% of patients may develop infectious complications (e.g. herpetic keratitis or bacterial corneal ulcer).[97] Higher concentrations of 1–2% have been reported to be effective and safe for severe form of VKC.[99,100]

Tacrolimus, another calcineurin inhibitor, inhibits the activation of T lymphocytes and prevents the release of inflammatory mediators.[101] Chatterjee and Agrawal[102] evaluated the effect of 0.03% tacrolimus ointment on patients with steroid-refractory VKC. The majority of patients did not require additional steroid therapy after 4 weeks of treatment with tacrolimus.[102] Miyazaki and colleagues[103] reported that 0.1% topical tacrolimus is effective in VKC patients with corneal complications, including epitheliopathy or shield ulcers.

Patients with refractory VKC may require oral corticosteroids or other immunomodulatory agents such as omalizumab.[104] Allergen-specific immunotherapy may also be effective and can prevent the side effects often encountered with topical therapies.[105] Surgical intervention, ranging from scraping to superficial keratectomy, may be required for the management of complications such as nonhealing corneal plaques or shield ulcers. Early diagnosis of shield ulcer, debridement of the plaque, and initiation of topical medications are essential to maintain the graft clarity in patients with VKC who undergo DALK and develop this complication.[84]

Corneal graft neovascularization

Corneal neovascularization is induced during several conditions, including active blepharitis, limbal stem cell deficiency, persistent epithelial defects, infectious keratitis, allergy, trauma, chemical burns, corneal graft rejection, and autoimmune diseases.[106,107] These pathologies result in disequilibrium between proangiogenic and antiangiogenic factors that can lead to the migration and proliferation of vascular endothelial cells into the corneal stroma.[108] Corneal vascularization is a significant sight-threatening complication because the newly formed vessels lack structural integrity and leak fluid and can lead to persistent inflammation, stromal edema, intrastromal lipid and protein deposition, and opacification.[106,107]

Corneal neovascularization predisposes transplanted corneas to rejection by facilitating both the presentation of donor antigens to the recipient immune system and the entrance of recipient activated immune cells to the corneal graft.[109] Therefore, the survival of corneal allografts, including DALK grafts, transplanted in a vascularized recipient bed is low (Figure 4). Treatment of corneal neovascularization either preoperatively or postoperatively is crucial for enhancing corneal graft survival and improving visual outcomes. Intraoperatively, an interrupted suturing technique with the placement of suture knots in the donor is indicated when DALK is performed in a vascularized recipient bed.[110] Postoperatively, these patients should be followed up closely to allow for selective suture removal when corneal vessels reach the graft. This approach prevents aggravation of angiogenesis.

Management

Several measures, including corticosteroid medications, laser photocoagulation, photodynamic therapy, and fine needle diathermy (FND), have been used to treat corneal neovascularization. Corneal new vessel formation is usually associated with an inflammatory process. Therefore, topical corticosteroids can effectively diminish inflammation and consequent corneal angiogenesis.[111] Nevertheless, chronic use of corticosteroids may cause prominent adverse effects, including superinfection, cataract formation, and secondary glaucoma.[111] Moreover, these medications have limited antiangiogenic properties and cannot effectively decrease preexisting vessels.[112]
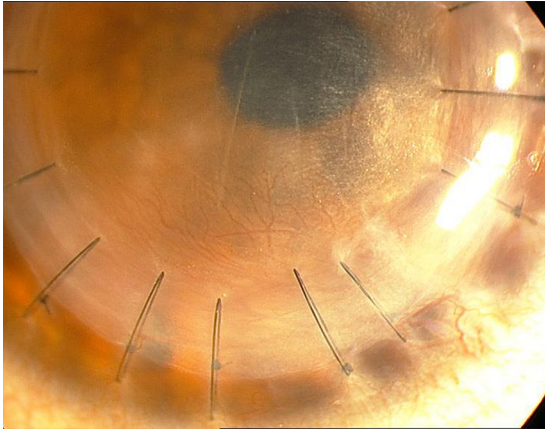
Figure 4. Corneal graft vascularization after deep anterior lamellar keratoplasty. This late complication is characterized by invasion of blood vessels deep in the donor–recipient interface. Leakage of fluid, lipid, and proteinaceous materials from these vessels causes the interface haze as seen here.

VEGF plays a key role in pathologic neovascularization and lymphangiogenesis in the eyes.[113–115] Subconjunctival, perilimbal, and intrastromal anti-VEGF monoclonal antibodies such as bevacizumab have been used successfully for the management of corneal vascularization.[113–115] These agents can prolong the survival of corneal allograft transplanted in a vascularized recipient bed. Foroutan and colleagues[116] found that perilimbal injection of bevacizumab resulted in partial regression of newly formed vessels at the donor–recipient interface after DALK. All patients had an increase in visual acuity, which was secondary to improved corneal clarity.[116] The majority of patients, however, required repeated injection as obvious regression of blood vessels did not take place within a month after the first injection.[116] The drawback of this treatment is that mature blood vessels do not respond to anti-VEGFs, necessitating surgical approaches including laser photocoagulation and FND.[117]

The 577-nm yellow dye laser and argon laser has been used to effectively obliterate corneal vascularization.[118,119] The drawback of this treatment is that laser photocoagulation obliterates corneal efferent vessels and has limited effects on afferent vessels because these deeply located vessels have a fast blood circulation.[118] Other complications include damage to the other structures, including corneal endothelium, iris, or crystalline lens.[120]

FND is an inexpensive and useful procedure which can equally obliterate afferent and efferent

vessels at different corneal planes. Multiple treatments may be required to achieve the desired result.[121] Corneal perforation is a possible serious complication that usually occurs during passing of the needle in corneas with thin stroma.[121] Other potential complications which are reversible include intrastromal hemorrhages, transient opacification of the cornea, and striae.[121] Intrastromal hemorrhage is the most common complication and may occur intraoperatively or immediately after surgery. This complication resolves over a few weeks but can leave behind crystalline deposits in corneal stroma.[121]

Graft rejection
Although DALK eliminates the possibility of endothelial graft rejection, there is still a risk of other types of graft rejection postoperatively.[122] The rate of graft rejection following DALK varies from 0% to 20%, with an average follow-up period range from 12 to 77 months.[123,124] Overall, the incidence of graft rejection after DALK is 50% less than that observed after PK.[125] There are three types of graft rejection following DALK, including epithelial, subepithelial, and stromal rejection (Figure 5). The clinical features of these rejection reactions after DALK are similar to those observed in rejection after PK. Stromal rejection is defined as diffuse or sectoral graft stromal infiltrates/edema, vascularization crossing the donor–recipient junction, or both involving the previously clear graft or surgical interface (Figure 5(b)).[126] Stromal graft rejection should be differentiated from other etiologies of graft stromal inflammation, including herpetic keratitis (see below).[127]

The majority of episodes of stromal graft rejection occur within the first year after keratoplasty with sutures still in place, although it has been reported as long as 3 years after DALK.[123,128–130] Risk factors for DALK graft rejection are younger recipient age, African American race, corneal neovascularization, loose sutures, suture infiltrate, and VKC.[3,16,131]

Injection, reduced vision, and photophobia are main complaints in symptomatic patients.[130] Rejection episodes, however, can be identified in the absence of symptoms during a routine follow-up examination.[130] Therefore, high-risk patients need to be warned of this potential late complication and its symptoms and signs so they can return to clinic promptly. Surgeons also need to
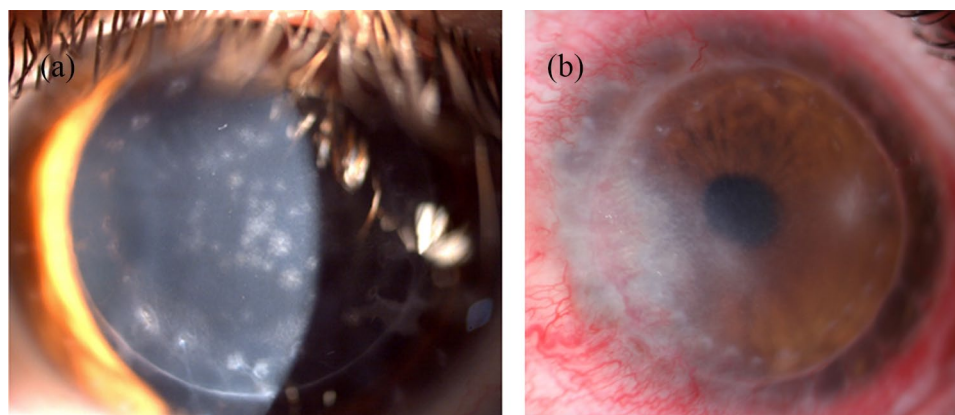
Figure 5. Graft rejection after deep anterior lamellar keratoplasty. (a) Subepithelial rejection characterized by multiple patches of subepithelial infiltrates throughout the graft resembling those seen in viral epidemic keratoconjunctivitis and (b) stromal rejection characterized by sectoral stromal edema and infiltration in addition to vascular invasion of the peripheral graft.

be aware that more frequent follow-up examinations are required in high-risk patients to diagnose rejection episodes gone unnoticed. Early diagnosis of stromal rejection after DALK and its prompt treatment is essential to prevent the late sequel of graft rejection including interface vascularization and opacification of the graft, and eventually graft failure.

Management

It has been assumed that one of the advantages of DALK over PK is a relatively short-term corticosteroid regimen. However, subsequent studies have found substantial rates of stromal rejection after DALK, particularly with a relatively short topical corticosteroid dosing regimen.[125,126] Therefore, extending the steroidal treatment for up to 1 year after DALK, similar to those used in PK, can significantly reduce stromal rejection episodes.[126] The advantages and disadvantages of long-term steroidal treatment, however, should be considered for every single patient. Another measure which can reduce the risk of allograft rejection after DALK is the use of long-term preserved corneal tissues that lack live cells, including keratocytes and antigen-presenting cells.[132]

Graft rejections after DALK tend to be successfully treated with frequent topical corticosteroids that are tapered off over several weeks as symptoms regress.[126,133] Timely recognition and aggressive treatment usually results in good visual and anatomic outcomes.[128] Although intravenous pulse steroid in combination with topical steroid therapy was used for the treatment of stromal graft rejection after DALK,[123] all patients reported in the literature responded to topical steroids such as betamethasone, dexamethasone, and prednisolone.[5,13,16,134] Steroids with low intraocular penetration, such as loteprednol, rimexolone, or fluorometholone, may be used if steroid-induced glaucoma develops.[135]

Recurrence of herpes simplex keratitis

Herpes simplex keratitis (HSK) is the most common etiology of corneal blindness in industrialized countries.[136] It is characterized by a high risk of recurrence that increases over time and results in corneal scarring and neovascularization. One sequel of HSK is neurotrophic keratitis, which is caused by damage to the corneal nerves. Neurotrophic keratitis can result in persistent corneal epithelial defects and corneal stromal melts as a consequence of excessive degradation of stromal collagen.[137] Despite advances in antiviral therapy in the last three decades, corneal transplantation is still required in a large number of cases to restore visual acuity.

PK has traditionally been the technique of choice for HSV-related corneal scarring. Recently, DALK has become an increasingly preferred surgical treatment in such patients which can achieve satisfactory vision, less recurrence of keratitis, less drug-induced complications, less allograft rejections, and a higher long-term graft survival rate.[138] The graft survival rate has been reported in 72% after DALK for herpetic keratitis.[139] Despite these
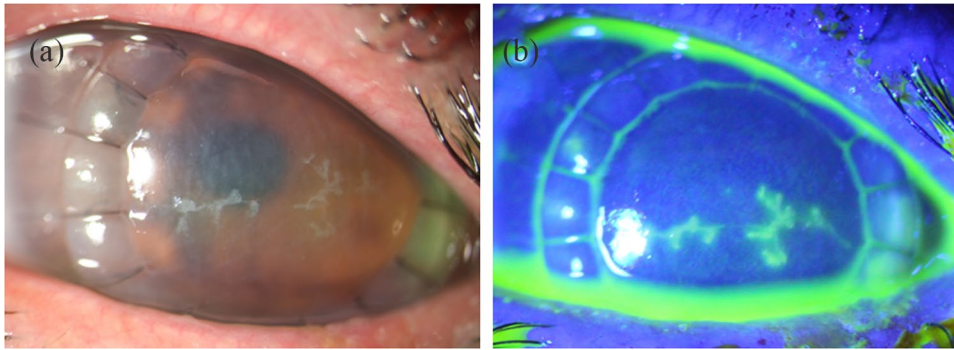
Figure 6. Recurrence of herpes simplex keratitis after deep anterior lamellar keratoplasty. (a) A classic epithelial lesion in a corneal graft with a characteristic linear branching corneal ulcer (dendritic ulcer). (b) The epithelial lesion is examined after staining with fluorescein dye.

advantages, there is a substantial risk of recurrence of HSV keratitis (Figure 6) and graft failure, making the graft prognosis relatively poor compared with other indications for DALK, including keratoconus and corneal stromal dystrophies.[140,141]

Management

Performing corneal transplantation during the active stage of the disease leads to higher rates of graft failure.[142] Therefore, DALK should be performed in the inactive stage of the disease after a period of quiescence.[143] Prophylactic oral acyclovir (400 mg twice a day) is advisable for at least 12 months after DALK to reduce the recurrence of HSK.[144] Despite this prophylactic measure, episodes of recurrence have been reported both within and after this time period with a rate of 33%.[139] These findings suggest the prophylactic measure may minimize the recurrence of HSV keratitis but does not completely eliminate this risk. Therefore, close follow-up examinations are required after keratoplasty for the early diagnosis of recurrence of HSV keratitis and its related complications such as corneal epithelial problems, vascularization, and graft rejection.[139] In addition, these patients should undergo routine kidney function examinations every 3 months to monitor the adverse effects of oral acyclovir.

Conclusion

Main advantage of DALK over PK is the complete absence of endothelial graft rejection which dramatically increases the graft survival. Despite this advantage, DALK transplant faces many issues, including complications related to the donor–recipient interface, graft epithelial problems, corneal neovascularization, stromal rejection, and recurrence of herpetic keratitis, which may lead to its failure postoperatively. Appropriate patient selection is vital for a successful outcome in DALK. Younger patients are more likely to experience frequent rejection episode due to their robust immune system. Therefore, in young patients with corneal pathologies sparing the endothelium such as keratoconus, stromal scars, and corneal dystrophies, DALK is clearly advantageous over PK. Active inflammation increases the risk of graft failure and must be treated before transplant. In patients with mental disabilities, such as Down's syndrome, DALK has clear advantage over PK as it reduces the risk of rejection. In addition, it minimizes the possibility of ocular damage secondary to self-induced trauma, such as eye rubbing. Increased DALK graft survival is mainly built upon optimization of the ocular surface to provide a hospitable environment for the graft. Any predisposing factors for graft epithelial abnormalities and preexisting VKC should be identified and treated preoperatively. In addition, maintaining appropriate measures are crucial when any epithelial problems or recurrence of VKC is encountered postoperatively. Medical or surgical treatment of corneal neovascularization either preoperatively or postoperatively is critical for enhancing DALK graft survival. Prompt recognition and aggressive treatment of stromal graft rejection usually result in good results, with no detrimental effects on the anatomical and visual outcomes. In patients with a history of HSK, DALK should be performed in the inactive stage of the disease after a period of quiescence, and prophylactic oral acyclovir is recommended for at least 12 months postoperatively to reduce the recurrence of keratitis.

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