REVIEW

Surgical management of herpetic keratitis

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Purpose of review
The purpose of this review is to discuss the options for, and recent developments in, the surgical treatment of herpes keratitis. Although the mainstay of treatment of herpetic keratitis is topical or oral antiviral agents, surgical intervention may be necessary for corneal melting or long-term complications such as scarring, lipid keratopathy, necrotizing keratitis, and neurotrophic keratitis.

Recent findings
There are a number of surgical therapies available for herpes keratitis. Preferred therapeutic modalities differ based on the size, causation, and location of the infection but consist of either replacement of the infected tissue or structural support of the tissue to allow healing. Incremental improvements in the existing treatment modalities have made them more effective, easier, and safer, whereas novel therapies such as corneal neurotization are starting to be described in ophthalmic literature.

Summary
Several options are available for surgically managing the complications of herpes keratitis. Ophthalmologists should select the optimal procedure based on the individual patient's situation.

Video abstract
http://links.lww.com/COOP/A28.

Keywords
amniotic membrane, conjunctival flap, corneal gluing, corneal neurotization, herpes keratitis, lamellar keratoplasty, penetrating keratoplasty

INTRODUCTION

Herpes keratitis includes two distinct diseases – herpes simplex keratitis (HSK) and herpes zoster keratitis (HZK). However, these two are often not distinguished in studies and literature, and a number of features are common to both. Therefore, unless specified, this section will use herpes keratitis to include both diseases. The treatment of active herpes keratitis is typically medical. Topical or oral antivirals are used to treat infectious viral keratitis, whereas steroids are used to treat stromal keratitis. Oral antiviral coverage is usually used in conjunction with steroids in HSK but may be used, in some cases, in HZK too. Necrotizing HSK, which can rapidly result in corneal ulceration and perforation, is treated with topical as well as oral antivirals, along with steroids. Neurotrophic keratitis can occur in both conditions and is treated with surface support such as artificial or serum tears, lubricating ointment, punctal occlusion, or bandage contact lenses.

Acute surgical treatment of herpes keratitis is seldom needed except in necrotizing HSK and severe neurotrophic herpes keratitis, where there is progressive corneal melting despite medical therapy. Other than these tectonic conditions, surgery is usually used to treat the complications of herpes keratitis such as scarring, persistent epithelial defects, chronic inflammation, or neurotrophic keratoconjunctivitis.

TEXT OF REVIEW

Herpes keratitis is the result of reactivation and replication of latent herpes simplex or zoster virus in the trigeminal ganglion. This causes loss of the nerve cell, and consequently, loss of sensation in the area of the cornea supplied by the neuron. Therefore, all forms of herpes keratitis cause a neurotrophic cornea with its resulting complications such as neurotrophic keratitis and dry eye [1,2]. Epithelial keratitis such as dendritic and geographic keratitis in HSK, and pseudodendrites in HZK are usually caused

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KEY POINTS

- Herpetic keratitis frequently requires surgical intervention to recondition the ocular surface, maintain vision, and in some cases, provide tectonic support.
- Outcomes of corneal transplants for herpes keratitis are universally poor.
- Corneal neurotization is a relatively novel procedure that offers potential to restore sensation in neurotrophic corneas.
- In many cases, a combination of medical and surgical treatment for herpetic keratitis is required to provide a favorable outcome.

by live virus and do not cause significant damage to the cornea other than mild underlying scarring. Repeated episodes may result in more extensive and visually significant scarring. Nonnecrotizing or interstitial keratitis occurs because of inflammation of the stroma with an intact epithelium and usually heals without scarring if treated with steroids. However, untreated interstitial keratitis can lead to stromal vascularization which can result in lipid exudation and rapid loss of vision. Necrotizing keratitis, however, results in rapid corneal ulceration and can lead to significant scarring and even perforation. Endotheliitis results in corneal edema, bullous keratopathy, and eventual subepithelial scarring. The devitalized and exposed cornea in neurotrophic keratitis may cause scarring, ulceration, and possible perforation. Surgical intervention is, therefore, needed for tectonic support, complications of corneal anesthesia, or for optical reasons because of scarring caused by herpes keratitis.

CORNEAL GLUING

The purpose of glue is to serve as a temporary plug for impending and small corneal perforations in herpes keratitis. However, this use is off-label, and not an FDA approved use for this product. Cyanoacrylate derived tissue adhesives are the oldest and most common synthetic glues, composed of cyanoacrylic acid with alkyl side chains of various lengths. The longer ester side chain cyanoacrylates are less toxic to the eye but require longer time to polymerize [3]. Direct application of the cyanoacrylate glue at the slit lamp (or on a supine patient) using a pipette, 30 gauge cannula, needle, or the plastic end of a cellulose sponge is effective in halting progression of corneal melting on perforations smaller than 3 mm diameter [4,5]. It does this through bacteriostatic activity against gram-positive

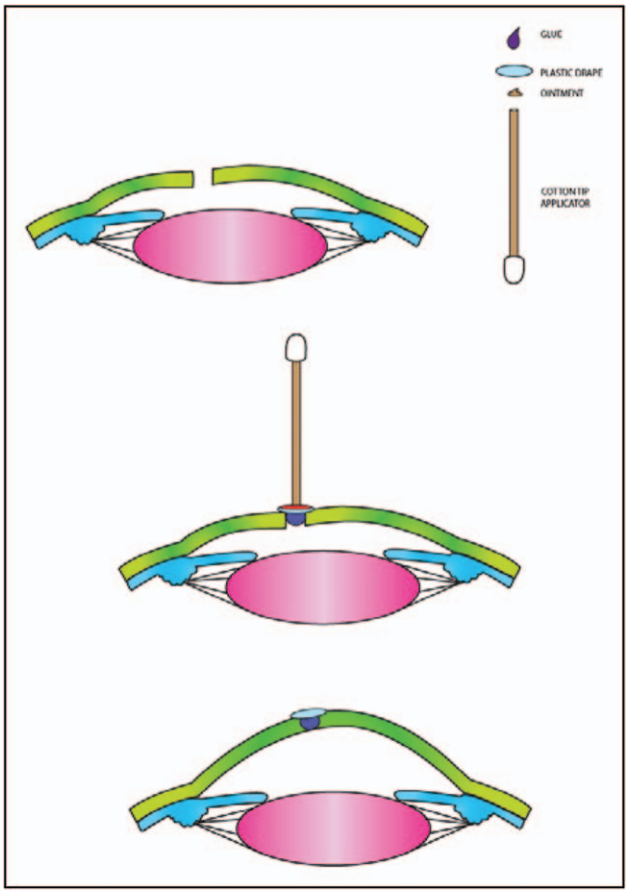

FIGURE 1. Application of cyanoacrylate glue using the drape method.

organisms, inhibition of polymorphonuclear leucocytes and reducing collagenolytic and proteolytic enzyme loads [6]. Once the glue has been applied and dried, a bandage contact lens is placed over it.

Several alternative techniques for application of cyanoacrylate glue have been described. In one, a sterile patch from a plastic surgical drape is trephined using a 3 mm dermal punch, picked up using a cotton tip applicator dipped in lubricating ointment; a drop of tissue adhesive is placed on the other side, and then inverted over the perforation to seal it (Fig. 1) [7]. In cases with large perforations with iris incarceration, a sandwich drape technique may be used where a smaller 2 mm sterile drape is placed directly over a defect. Cyanoacrylate glue is placed on it, and it is covered with a second 3 mm drape to avoid direct exposure of tissue adhesive to uveal tissue and mitigate inadvertent uveitis [8].

In blood-based tissue adhesives such as fibrin glue, fibrinogen is mixed with thrombin to convert it into networks of fibrin strands which bind to collagen [3]. In contrast to cyanoacrylate, which is proinflammatory, uncomfortable, and results in corneal vascularization, fibrin glue is flexible,

biodegradable, and noninflammatory [3,9▪]. Fibrin-based tissue adhesive assisted amniotic membrane transplant plug has been found to be successful in small corneal perforations [10]. The limitation of fibrin glue is that it has no significant bacteriostatic activity, has a half-life of seconds, and is less effective at sealing corneal incisions compared to cyanoacrylate [11]. However, a head to head randomized controlled comparison suggested that fibrin glue and cyanoacrylate tissue adhesive were comparable in the treatment of small corneal perforations, with fibrin glue providing faster healing and inducing less corneal neovascularization, at the expense of requiring a significantly longer time to act [12]. Both synthetic and blood born tissue adhesives are a time saving, temporary, and effective measure that can be used to seal small corneal perforations.

AMNIOTIC MEMBRANE TRANSPLANTATION

Human amniotic membrane is composed of three layers – an epithelial layer which is removed during processing, a basement membrane layer, and a stromal layer [6]. It provides structural support in the form of collagen types IV, V, and VII, laminin and fibronectin, and a variety of growth factors including nerve growth factor and epithelial growth factor, which help facilitate epithelial cell migration and adhesion. In addition, its stromal surface contains metalloproteinase and interleukin-1 receptor antagonists as well as anti-VEGF factors which suppress inflammation and angiogenesis [13–15].

The first documented use for eye disease was by de Rotth in 1940 when he used an amniotic membrane transplant (AMT) to treat a conjunctival defect [16]. AMT regained popularity after Tseng and Lee described its use to treat damaged rabbit corneas in 1995 [17,18]. Since then it has been widely used, with persistent epithelial defects in neurotrophic keratitis as one of the most common indications. In a prospective randomized controlled trial, AMT was compared with conventional treatment (tarsorrhaphy and bandage contact lens) in eyes with refractory neurotrophic keratitis. Both treatments were effective, with both groups showing median time to complete epithelialization of 21 days [19,20].

Epitheliopathy and ulcerations lacking depth or significant stromal thinning, where the goal is to maintain corneal clarity and help healing, may respond well to a single-layered AMT approach [21]. Single-layered AMT is available either as a self-retaining membrane, or as a free graft that is secured with sutures. Both cryopreserved (e.g. Prokera) and dehydrated (e.g. AmbioDisk) options are available.

AMT can be trimmed to fill in defects using the 'in-lay' technique, or placed limbus to limbus to act as a living bandage 'overlay'. The AMT is placed within the epithelial defect oriented basement membrane side up to provide a surface for epithelial cell migration and adhesion. It is secured with 10–0 monofilament nylon sutures and covered with a bandage contact lens [22]. When covering the entire cornea as an 'overlay', the membrane can be secured to the episclera with absorbable 8–0 Vicryl suture. It is advisable to remove the devitalized epithelial cells from the edges of the ulcer prior to AMT placement to promote regrowth of healthy epithelium.

For severe neurotrophic keratitis with stromal melting, a multilayered approach is necessary where several layers of amniotic membrane tissue are stacked to fill the stromal defect, taking care not to overlap the edges of the ulceration. A larger overlay membrane can then be placed over the entire corneal-limbal surface and secured. The technique described by Berguiga involves the use of a sutured AMT first and then sliding additional membranes beneath the overly to fill the stromal defect [23]. This not only provides a scaffold for epithelialization, but also provides structural support to the thinning cornea as demonstrated by Nubile *et al.* [24]. In this study, 20 of 22 eyes demonstrated a significant postoperative increase in corneal thickness on anterior segment optical coherence tomography, and confocal microscopy established evidence of stroma-derived cells populating the transplanted amniotic membrane inlay. This persisted for the follow up period of 12 months demonstrating a true assimilation of amniotic membrane tissue within the healing stroma.

CONJUNCTIVAL FLAP AND PEDICLE GRAFT

Gunderson *et al.* [25] first described the technique and role of conjunctival flaps in the treatment of refractory infectious keratitis in the 1960s. The standard conjunctival flap procedure aims to restore anatomical and ocular surface integrity by providing metabolic and mechanical support for corneal healing by translocating a flap or pedicle of the conjunctiva and suturing it on top of a nonhealing neurotrophic ulcer, an area of corneal melting, or a small frank perforation [20]. By physically bringing the conjunctival tissue and its associated lymphatic and blood vessels to the cornea, it promotes an environment to recruit vital growth factors and nutrients while allowing removal of pro-inflammatory proteases [26,27▪]. This allows for rapid epithelialization of the defect by conjunctival epithelial cells in as early as 24 h and by corneal epithelial cells

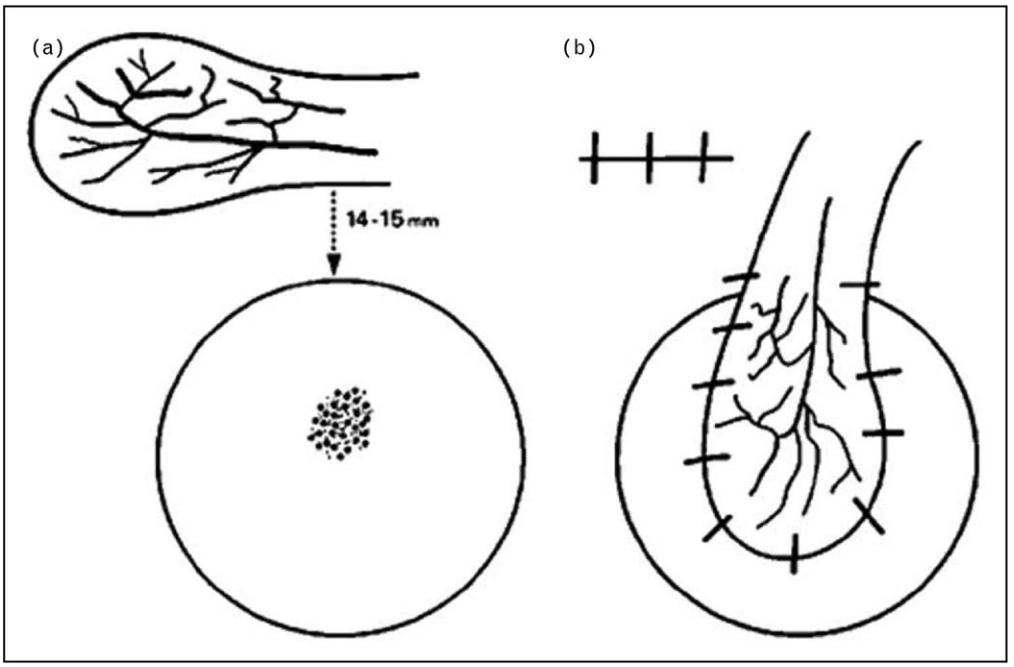

FIGURE 2. Superior forniceal conjunctival advancement pedicle graft technique. Adapted with permission [31].

as early as 4–6 weeks [28]. Once adequate healing has occurred with corresponding vascularization and scarring after several months, the conjunctival flap may be removed, and a transplant may be performed to improve vision in the eye. Alternatively, it could be a permanent option to reduce pain in blind eyes with refractory neurotrophic keratitis.

Surgical technique for conjunctival flap procurement varies depending on the location, size, severity, and extent of the defect. Central or paracentral neurotrophic ulcers may require a complete Gunderson flap, while peripheral ulcers can be adequately covered through the use of a pedicle or partial flap. In either case, the corneal area to be transplanted is de-epithelialized and the necrotic corneal tissue is debulked. A peritomy is performed and the conjunctiva without Tenon capsule is mobilized over the cornea and sutured into place using nonabsorbable sutures, which are subsequently removed [29]. Care is taken to limit traction on the flap, as retraction of the flap is a common cause for unsuccessful outcomes.

Limitations of conjunctival flaps include iatrogenic limbal stem cell deficiency, limited visualization of the cornea and anterior chamber, inaccurate intraocular pressure measurements, and the scarring may preclude future surgery requiring viable conjunctiva such as trabeculectomy [30]. The vascularization that accompanies these grafts decreases the chances of corneal transplant survival in the future. An alternative technique is a superior forniceal conjunctival advancement pedicle (SFCAP) technique which incorporates tenon fascia and a prominent blood vessel into a pedicle that is created by two parallel superior conjunctival incisions 4–5 mm apart in the forniceal recess, and attaching it to the diseased cornea with interrupted 10–0 nylon sutures. This thicker and smaller size of the pedicle not only preserves the conjunctiva and limbal stem cells, but also allows for visualization of the peripheral cornea and anterior chamber (Fig. 2) [31]. Another partial pedicle technique described by Khodadoust *et al.* [30] incorporates a limited peritomy adjacent to the corneal defect, followed by a crescent shaped pedicle flap incorporating underlying tenon fascia sutured over the defect. In both thicker flaps are used with deep corneal ulcers or perforations.

Conjunctival flaps are underutilized because of the complex and meticulous surgery, and the fact that the procedure tries to maintain globe integrity at the expense of a poor cosmetic result and visual outcomes. However, it is a strong candidate in the repertoire of a corneal surgeon in neurotrophic ulcers that have progressed despite aggressive medical therapy.

TARSORRHAPHY

Permanent lateral tarsorrhaphy is another relatively underutilized procedure, but for persistent epithelial defects in the setting of an insensate cornea, it is very useful [32,33]. It is particularly helpful in cases of severe ocular surface disease not responding to

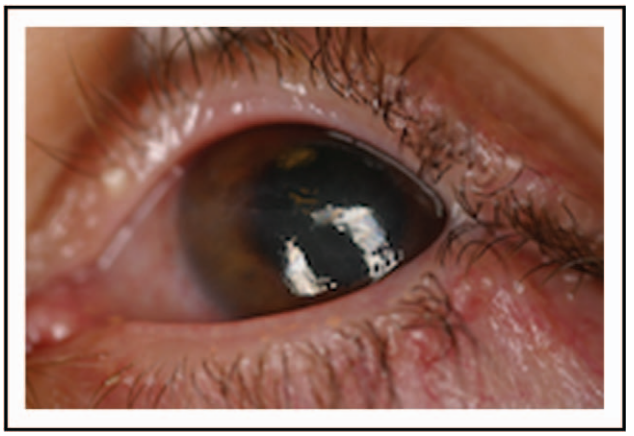

FIGURE 3. Temporal tarsorrhaphy for neurotrophic keratopathy.

other treatments. Cosar *et al.* [34] evaluated the healing time of epithelial defects following tarsorrhaphy and demonstrated that 90% of epithelial defects resolved within 18 days after placement of a tarsorrhaphy, whereas the mean duration of signs and symptoms prior to tarsorrhaphy was 90 days.

Tarsorrhaphies work by decreasing ocular surface exposure, thereby reducing tear film evaporation, and providing a more hospitable environment for epithelial healing. The degree of lid closure can be modified based on the severity of corneal disease. There are several variations in technique when performing a tarsorrhaphy. Our recommendation for permanent lateral tarsorrhaphy is to separate the anterior and posterior lamellae using an incision along the gray line and denuding the tarsal margin of the posterior lamellae of each lid. The lids are then approximated using 6–0 Vicryl sutures placed in a horizontal mattress configuration. The overlying anterior lamellae can then be closed with the use of interrupted 6–0 Vicryl sutures taking care to make sure that the lashes are oriented outward to prevent abrading the cornea (Fig. 3).

Lateral tarsorrhaphy is often used as an adjunct with other treatments. Penetrating keratoplasty in the setting of severe neurotrophic keratitis due to herpes keratitis has poor graft survival rates due to poor healing and possible recurrence of HSV. Partial closure of the lateral eyelid margin at the time of penetrating keratoplasty may provide an environment that better promotes epithelialization of the graft [35▪].

One of the main factors limiting the implementation of a tarsorrhaphy is the concern patients have regarding the cosmetic outcome. A discussion weighing the concerns of esthetics versus the preservation of the ocular surface must be addressed with the patient.

CORNEAL TRANSPLANTATION

It is difficult to determine exactly how many corneal transplants are done primarily for herpetic indications as studies do not often distinguish between ulceration or scarring caused by herpes versus other causes. In addition, the diagnosis of herpes keratitis is frequently missed as stromal and delayed manifestations are often mistaken for other causes. A review of recent studies that do distinguish herpetic indications for transplantation reveals that approximately 10–20% of all penetrating or anterior lamellar transplants are done for complications of herpes keratitis, especially overseas [36▪,37]. This is true even in the pediatric population and in cases of emergent transplantation where about 10 and 11% of all transplants were performed for herpes keratitis-related complications, respectively [38,39]. In the United States, the percentage of transplants done for HSK has declined substantially from a high of 25% in the 1950s. Initially, this change was because of a relative increase in the number of transplants for other reasons; however, more recently, there has been a decrease in the absolute numbers, presumably from improved treatment and prophylaxis [40].

Corneal transplants are typically performed in herpes keratitis for tectonic support in cases of uncontrolled ulceration, or for optical reasons as in cases of scarring or lipid keratopathy. Traditionally, they were full thickness (PKP), but increasingly, recent studies show a predominance of anterior lamellar transplants (DLK) [41▪▪,42]. A comparison of DLK versus PKP in China for herpetic indications showed that DLK had a lower rate of rejection, recurrence, and graft failure; however, none of these was statistically significant [43]. DLK was not possible with endothelial involvement or Descemet membrane scars or ruptures and, as the study was retrospective, there may have been self-selection of the patients for the procedures with PKP done in more severe cases. Another retrospective review of HSK grafts showed similar benefits to DALK with graft survival reaching statistical significance [44]. However, a report on the long-term outcomes of DLK for herpes simplex showed a rejection rate of 50% and a recurrence rate of 33% [45]. Nevertheless, DLK appears to be a good alternative to PKP in herpetic transplants as long as there is no deep scarring or endothelial dysfunction.

Corneal transplantation after herpes keratitis, even when the eyes are quiescent, with no active keratitis, has poor outcomes with 3-year survival rates of around 60% (Altay). The causes of this are manifold: most stromal keratitis is associated with deep vascularization which increases the risk of

rejection; recurrences of HSK are common after nerves regenerate in the graft; and distinguishing between recurrence and rejection can be difficult. In addition, the significant hypoesthesia that accompanies herpes keratitis can lead to recurrent trauma and exposure keratopathy [46]. However, transplantation in eyes with active inflammation has an even more dismal outlook with less than a quarter of eyes with active inflammation surviving compared to 85% of those with quiescent scars [47].

Corneal vascularization is a common complication of herpes keratitis stromal disease and is a major reason for the poor prognosis and high recurrence rate of herpetic corneal transplantation [48]. Angiogenesis is believed to occur because of the VEGF induced by the viral antigen in the corneal scar. Removing the scar containing the antigenic stimulus may help in reducing the corneal vascularization after penetrating keratoplasty. In fact, in high-risk keratoplasty in vascularized corneas, Altenburger found that herpetic corneas were more likely to have a postoperative reduction in corneal angiogenesis compared to other high-risk conditions such as acute keratoconus, and other forms of keratitis [49].

In summary, corneal transplantation in herpes keratitis has poor outcomes because of rejection and graft failure. DALK may have similar or superior outcomes in superficial scarring in herpes keratitis but cannot be performed in deeper scars or cases of perforation. Waiting until the eye is quiet for a few months, and removal of the entire scar, if possible, may improve the outcomes.

CORNEAL NEUROTIZATION

Although nerve transfers for neuropathic conditions are well established, corneal neurotization is a relatively novel procedure in the treatment of neurotrophic keratitis. First described by Terzis *et al.* this procedure allows restoration of innervation to the insensate cornea, thereby restoring sensation and nerve-derived trophic support of the corneal epithelium [50]. Using *in vivo* confocal microscopy, Fung *et al.* were able to demonstrate reinnervation of the corneal stroma and subbasal layers after performing corneal neurotization in two patients [51▪▪].

The most commonly described method is coaptation of a sural nerve graft to a contralateral branch of the ophthalmic division of the trigeminal nerve, usually the supratrochlear nerve [52]. The sural nerve graft is passed subcutaneously across the nasal bridge and through the upper eyelid of the affected eye. The fascicles of the nerve are carefully dissected, passed subconjunctivally and circumferentially around the cornea, and secured to the perilimbal region (Fig. 4). A temporary tarsorrhaphy is then placed to promote healing.

Following this procedure, return of corneal sensation may take 3 to 6 months and is thought to

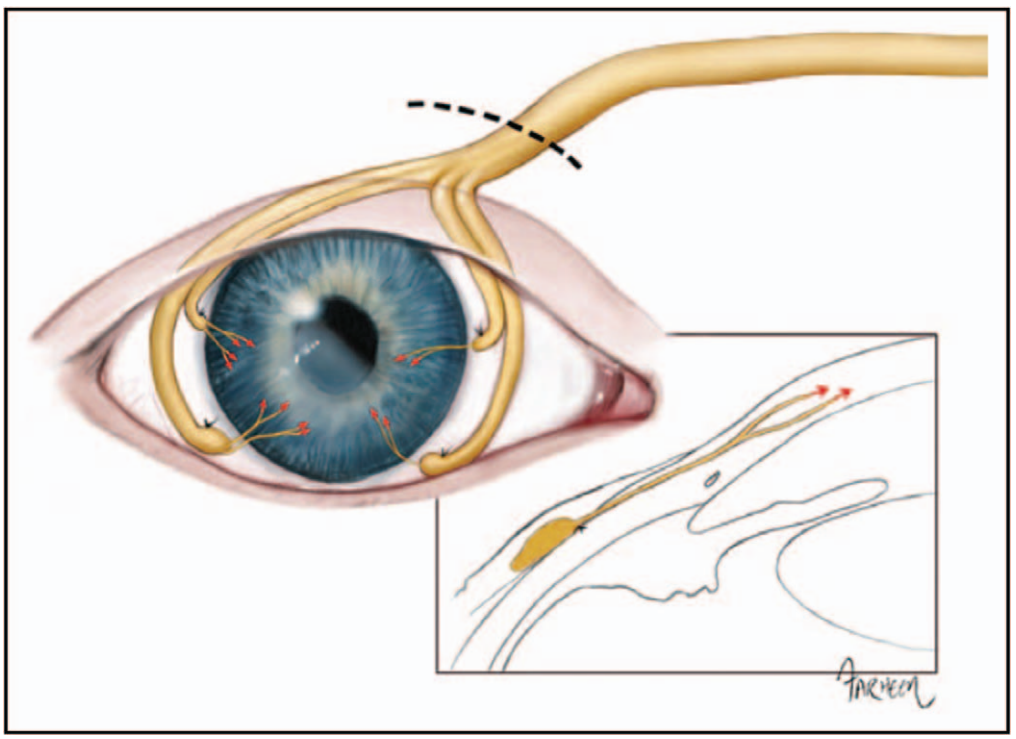

FIGURE 4. Technique of corneal neurotization. Adapted with permission [52].

occur as nerve axons from the branches of the trigeminal nerve traverse the scaffold supplied by the sural nerve graft. Initially, sensation of the cornea is referred to the contralateral forehead. With time this corrects to sensation originating from the eye. The return of corneal sensation can be monitored with the use of the Cochet-Bonnet esthesiometer as well as with confocal microscopy. This allows procedures to restore vision, such as penetrating keratoplasty, to have a greater chance of success.

CONCLUSION

Herpes keratitis is a debilitating and potentially devastating disease process that relies on early recognition and medical management to limit corneal scarring, ulcerating, vascularization, edema and perforation. When conservative measures fail, surgical management is needed for complications such as necrotizing keratitis, lipid keratopathy, scarring, and neurotrophic keratitis. The treatment plan should be patient centered as there is no single step-wise approach to treating patients, and there is often a need for multiple simultaneous procedures. Corneal transplantation is useful to treat all the manifestations of herpes keratitis, but it is preferable to do it in quiescent eyes to increase graft survival. Both PKP and DALK may be performed, but PKP is the procedure of choice in cases where the endothelium or Descemet membrane is involved. A partial tarsorrhaphy should be considered in conjunction with the transplant to improve outcomes. Acutely, in perforations, or impending perforations, the cornea may be glued for tectonic support until a more definitive transplant can be performed. AMT or conjunctival flaps are useful modalities for neurotrophic keratitis by decreasing inflammation and providing growth factors to aid healing. Novel surgical modalities such as corneal neurotization have the potential to decrease the long-term complications and poor prognosis of these eyes by replenishing the corneal sensation. Unfortunately, despite the enormous armamentarium of surgical options available, outcomes are poor in eyes with herpes keratitis.

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Conflicts of interest

There are no conflicts of interest.

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