Surgical Management of the Ocular Surface in Neurotrophic Keratopathy: Amniotic Membrane, Conjunctival Grafts, Lid Surgery, and Neurotization

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Purpose: To review the surgical modalities available to treat Mackie stage 2 and stage 3 neurotrophic keratopathy.
Methods: Literature review and technique descriptions.
Results: The following procedures are described in detail with accompanying videos: temporary, permanent, and botox-assisted tarsorrhaphy; amniotic membrane transplant; keratoplasty with amniotic membrane and tarsorrhaphy augmentation; Gunderson and conjunctival pedicle flaps; buccal graft transplantation; and neurotization.
Conclusion: A variety of surgical options exist to manage neurotrophic keratopathy when medical treatments alone fail to resolve epitheliopathy. Ongoing protection and optimization of the ocular surface health remains crucial to prevent recurrent epithelial breakdown.

Key Words: Neurotrophic cornea—Neurotrophic keratitis—Neurotrophic keratopathy—Herpetic keratitis—Keratitis—Trigeminal nerve disease—Ocular surface disease.

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Neurotrophic keratopathy (NK) is defined as "corneal epitheliopathy leading to frank epithelial defect with or without stromal ulceration associated with reduced or absent corneal sensations".[1] Moderate and severe NK can lead to profound visual disability and poor quality of life. The condition is relatively rare, classified as an orphan disease (ORPHA137596) affecting 5 individuals or fewer per 10,000 patients[2] and poorly understood. Complications include persistent epithelial defect, secondary infection, stromal thinning, scarring, vascularization, perforation, and even loss of the eye.

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Neurotrophic keratopathy causes can be genetic, systemic, involving the central nervous system, postherpetic infection, chemical and physical burns, keratitis medicamentosa, chronic ocular surface injury, and many more. Neurotrophic keratopathy is difficult to treat as the underlying cause may not be clear and is often multifactorial.[1]

Initial treatment of NK is medical, including removal of offending agents that is, preservatives, preservative free lubricants, treating infection and concurrent surface problems, punctal occlusion, lid abnormality correction, topical recombinant human growth factor, serum eye drops, therapeutic contact lenses, and anti-inflammatory therapies.[3] Once medical therapies are exhausted, surgical treatments are required. Even after successful surgical therapy, the ocular surface environment must be continually optimized. This review will summarize the surgical treatments used in neurotrophic corneas.

TARSORRHAPHY—TEMPORARY, PERMANENT, AND BOTOX-INDUCED OPTIONS

Tarsorrhaphy is a surgical procedure in which the superior and inferior eyelids are brought together to decrease the exposure of the ocular surface, hence protecting the cornea in cases that present with neurotrophic involvement. Tarsorrhaphies have been shown to promote corneal healing in multiple scenarios.[4–6] The success rate in the treatment of such corneal epitheliopathy has been reported to be up to 90%.[7] Tarsorrhaphies can be central or peripheral and also temporary or permanent. The decision of where to place the tarsorrhaphy sutures and its duration depends on the extent and severity of corneal involvement. Given the need for regular follow-up, it is important to remember to leave an opening, allowing one to evaluate the progress of the corneal condition.

Temporary tarsorrhaphies are usually performed under local anesthetic and can be placed centrally or laterally (see Video 1, Supplemental Digital Content 1, http://links.lww.com/ICL/A145). One of the more commonly used techniques consists of passing a double armed nonabsorbable suture (e.g., Nylon 5-0) through the inferior and superior eyelids (see Video 2, Supplemental Digital Content 2, http://links.lww.com/ICL/A146). Each pass should include the eyelid skin and tarsal plate and should exit in the grey line of the eyelid margin. The use of a plastic bolster (cannulation plastic tubing) has been described to protect the skin, avoid cheese-wiring of the suture through tissue and allow for easy opening and closing of the tarsorrhaphy during follow-up.[8] This technique allows for a large area of temporary apposition and is usually placed

centrally; once the condition improves it can be easily removed in the clinic setting and does not permanently affect vision. A temporary tarsorrhaphy with cyanoacrylate has also been suggested as a short-term alternative to surgical tarsorrhaphy;[9] however, the short duration of the eyelid closure (nine-day average) and potential complications of glue entering the eye are potential drawbacks.

Permanent tarsorrhaphies are normally used when there is a greater severity of the neurotrophic condition and the ocular surface health cannot be maintained with the pre-existing interpalpebral fissure for example, those affected by lesions of the trigeminal nerve. One of the more popularized techniques requires the eyelid margin to be dekeratinized to be able to generate permanent scaring between the superior and inferior tarsal surfaces; absorbable sutures are used to create a surgical closure of the two denudated margins.[10] A more invasive technique denominated "internal fixation" includes the division of the posterior and anterior lamella to generate a stronger union and scarring between the two eyelids. This technique requires the closure to be performed in two different planes with absorbable 6-0 sutures. Once the two tarsal surfaces have scarred together, the apposition is permanent. This technique is normally placed temporally in the eyelid so that the visual axis remains clear. Studies have compared the effectiveness of the different tarsorrhaphy techniques; internal fixation technique has demonstrated a higher success rate than bolster suture techniques.[11]

As an alternative to surgical tarsorrhaphy, botulinum toxin has been used to induce ptosis of the upper eyelid. The toxin is injected through the superior eyelid skin directly into the levator palpebral superioris. The effective dose found has been reported to be 5 to 15 international units[12,13] and may need to be repeated in 48 hrs if the induced ptosis is inadequate.[14] After administration, ptosis is usually obtained after 2 to 8 days and lasts a mean of 46 days.[12] This technique successfully addresses corneal exposure, allows for complete evaluation of the surface during follow-up and facilitates application of medical treatment. Reported side effects have included diplopia which resolved.[12]

AMNIOTIC MEMBRANE TRANSPLANT

Amniotic membrane (AM) is a semitransparent tissue generated from the innermost layer of the placenta and contains a thick basement membrane with an epithelial and stromal side of similar composition to that of corneal and conjunctival epithelium.[15] The mechanical (support and protect epithelial cells), biological (promotes adhesion and migration of epithelial cells), and anti-inflammatory (antifibrosis and anti-angiogenesis) properties of AM render it an elementary part of ocular surface reconstruction.[16] The AM can be placed so that the epithelial side or stromal side faces up (away from the host cornea). After application of AM, the re-epithelialization by the host epithelium occurs preferentially on the basement membrane side of the epithelium although re-epithelialization can occur on the stromal side as well.[17] The stromal side is a more potent down regulator of inflammation and therefore in the presence of acute inflammation (e.g., chemical burn or Stevens Johnson Syndrome), the membrane may be placed so that the stromal side faces the palpebral aperture.[18] Multiple layers of AM can be placed and can integrate into the corneal stroma with resulting increase in corneal thickness at the expense of potential degradation in tissue transparency.[19] However, for the indication of NK with good visual potential, we advocate that when using fresh frozen AM, it is preferential to place the tissue epithelial side down because of the aforementioned haze which may affect vision, although it is noted that much of the literature discusses placing AM stromal side down.

Guidelines propose AMT as a treatment for stage 2 and 2 NK (moderate and severe); however, low resolutions rates mean that it should be considered in emergent cases only.[1] During the amnion membrane transplant (AMT) fresh frozen AM which is typically thicker and heavier, can be anchored to the cornea with nonabsorbable sutures (nylon 10-0 for corneal sutures)[20] (see Video 3, Supplemental Digital Content 3, http://links.lww.com/ICL/A147), absorbable sutures (vicryl 9-0 or 10-0 for conjunctiva),[21] or fibrin glue.[22] The authors advocate anchoring to the bulbar conjunctiva with small episcleral bites with sutures with or without fibrin glue below the AM to secure it in place (Fig. 1).

Different types of AM are harvested in a similar fashion: placenta is washed with sterile antibiotic solution, the AM is separated from the chorion and then spread on nitrocellulose filter paper stromal side down and cut into appropriate size pieces.[23] The tissue can be cryopreserved, freeze dried, or air-dried. Dehydrating processes were originally speculated to reduce tissue biological functions although similar clinical outcomes have been reported.[24] The advantage of dehydrated tissue is that it can be stored in room temperature for immediate use and has a shelf life of 1 to 6 months.

Cryopreserved

Most AM supplied by eye banks are cryopreserved (fresh frozen in glycerol). In addition, there are several commercial products that contain cryopreserved AM tissue including Prokera (Bio-Tissue, Doral, FL) and AmnioGraft (Bio-Tissue). The former includes a solid plastic ring that encompasses the cornea and sits on the conjunctiva and the latter is the tissue only. The advantage of the Prokera is that it can be applied as an in-office procedure at the slit-lamp using topical anesthetic drops. After removing the device from its pouch, it is rinsed with sterile saline. Topical anesthesia is applied, the upper eyelid is held and the patient is asked to look downward. The Prokera is inserted into the superior fornix, slid under the lower eyelid and centration is checked at the slit lamp. In general, it is best to avoid using the Prokera in glaucoma patients who have a trabeculectomy or glaucoma drainage device as the bleb may rub against the device.

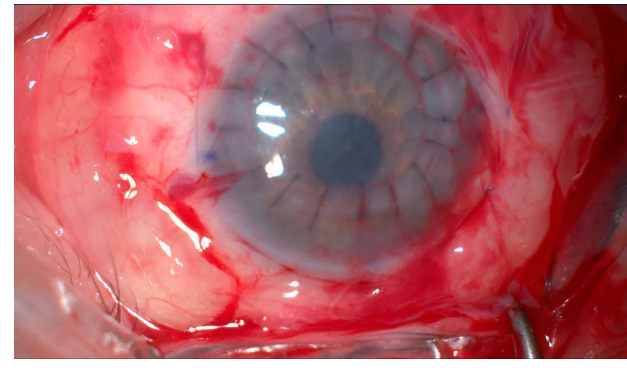

FIG. 1. Amniotic membrane sutured in a continuous purse-string fashion around the limbal periphery with episcleral bites.

Dehydrated

Dehydration preservation methods vary but usually involve vacuum combined with low temperature heat to maintain structural and biological tissue properties. There are several commercial dehydrated AM available: AmbioDisk (Katena, Parsippany, NJ), BioDOptix (Labtician, Oakville, ON, Canada) and Aril (Seed Biotech, Dallas, TX). All products are applied in a similar fashion. First, topical anesthesia is applied and a lid speculum placed. The area is carefully dried where the AM will be placed with a sponge spear. The AM package is opened with care as the thin, small, transparent dry tissue is easily misplaced or dropped. A nontoothed sterile forceps is used to apply the AM to the dried corneal surface and then gently smoothed flat (Fig. 2).

The authors recommend allowing the graft a full minute to stick to the corneal surface and then applying a relatively dry (with the aid of sponge eye spears) bandage contact lens on top of the AM tissue. After careful removal of the speculum, centration of the AM, and the bandage contact lens should be checked at the slit lamp.

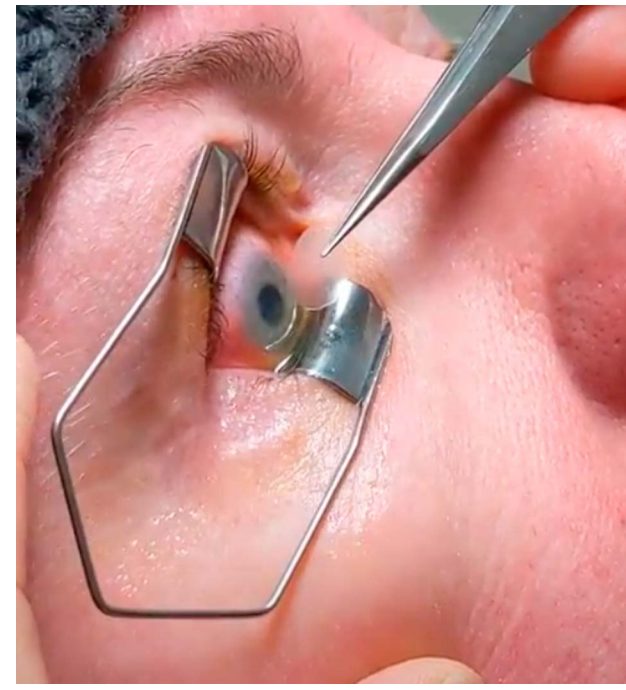

FIG. 2. Placement of the BioDOptix dehydrated amnion requires meticulous attention to centration and smoothness of the laying process.

KERATOPLASTY—DEEP ANTERIOR LAMELLAR KERATOPLASTY AND PENETRATING KERATOPLASTY WITH AMNIOTIC MEMBRANE AND TARSORRHAPHY AUGMENTATION

Corneal surgery in eyes with dry ocular surfaces and reduced sensation are at high risk of failure. Neurotrophic corneas undergoing deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PKP) often develop a postoperative epithelial defect that may become persistent. Contributing factors include donor epithelial loss during preservation, intra-operative corneal exposure and drying, neurotrophic status, and keratitis medicamentosa. Persistent epithelial defects in this setting often give rise to secondary infection, vascularization, stromal thinning, ulceration, and can threaten graft survival.

The augmentation of DALK/PKP with tarsorrhaphy or tarsorrhaphy in conjunction with amniotic membrane transplantation can be used to promote faster and more complete epithelial healing. The procedure comes with two relative drawbacks—the temporary cost of obscuring sight (so the patient should be functionally sighted in the other eye or have adequate supports at home in order to recuperate safely) and the cosmetic concern of the patient. Discussions about esthetics versus healing of the ocular surface should be addressed pre-operatively, especially if the tarsorrhaphy is permanent.

After the DALK/PKP has been performed, a layer of fresh amniotic membrane is sutured into place. Our preferred technique is as follows: the amniotic membrane is draped over the ocular surface and over the bulbar conjunctiva to incorporate a good margin of amnion to account for retraction that occurs post-operatively. A continuous 9-0 vicryl or 10-0 nylon suture is used to suture the amnion into place in a circumferential fashion 1 to 2 mm away from the limbus. A double layer of amniotic membrane may also be used. Fibrin glue can be used as an adjunct to sutures to adhere to the cornea and is placed underneath the membrane. A bandage contact lens can also be placed.

Tarsorrhaphy is then performed. Depending on the sight in the other eye, a lateral or centrally placed tarsorrhaphy can be performed on top of the amnion. If the patient is likely to have exposure issue long-term, a permanent tarsorrhaphy is considered. Our preferred technique for a bolster tarsorrhaphy is described earlier in this article.

Patients should be warned that the amniotic membrane may take a few weeks to dissolve and reassured that small chunks of amnion may break off from time to time as it naturally disintegrates and is completely normal. Care should also be taken not to rub the eyes, which would risk dislodging the amnion.

GUNDERSON AND CONJUNCTIVAL PEDICLE FLAPS

Conjunctival flaps were first described by Gundersen in 1958[25] in the use of treatment of nonhealing epithelial defects, involving the use of a 360° peritomy, complete corneal de-epithelialization, and superior conjunctiva mobilization to encompass the entire corneal surface. Because of retraction and difficulty in fashioning, the technique fell by the wayside and gave rise to modern techniques to decrease complication rates. However, for eyes with a poor visual prognosis, this technique is beneficial to know.

The general principles of the technique of the Gundersen flap are summarized as follows: local anesthesia is applied subconjunctival, although retrobulbar, subtenons, or peribulbar blocks have been used. General anesthesia is not necessary. Care should therefore be exercised not to perforate where the portion of conjunctiva will cover the cornea. A traction suture of 7.0 silk is placed at the superior limbus to place the globe in downward gaze, exposing the superior conjunctival bed. Because the distance from the upper limbus to apex of the superior fornix is 16 mm, there is usually sufficient tissue to cover a 12-mm corneal diameter in its entirety. The cornea is de-epithelialized and any

necrotic stromal tissue is debulked. Subconjunctival 2% lignocaine with epinephrine 1:50,000 (1–2 mL) is applied to the superior conjunctiva. A 3-cm long horizontal incision is made where the conjunctiva reflects at the superior fornix. Underlying tenons are then dissected in the direction heading toward the limbus to ensure a very thin flap is created. When the limbus is reached, the conjunctiva is incised horizontally in a peritomy-like fashion to free the inferior edge of the flap. This creates a "bridge" of conjunctiva anchored by two lateral and medial broad-based flaps with intact blood supply. The flap is placed onto the surface of the cornea and assessed for traction (it should sit without traction on the corneal surface), then sutured into place with 8.0 vicryl such that the superior conjunctiva is bare and the inferior edge of the Gundersen flap is anchored to the inferior limbus with episcleral bites. The patient is then given a combination of antibiotic and steroid drops four times a day on a slowly reducing regimen over a period of 8 weeks as it heals.

Conjunctival flaps are used to promote epithelialization, halt inflammation, reduce or eliminate need for frequent medication instillation, and prevent progression to perforation. They can aid in replacement of deficient stroma by replacing it with healthy basal tissue on which epithelium may grow and provide access to blood vessels and blood supply to the diseased cornea, thereby permitting access to serum-based growth factors and nutrients and assistance in infection resolution. In general, smaller peripheral or bridging flaps may be considered for small or peripheral ulcers (see Video 4, Supplemental Digital Content 4, http://links.lww.com/ICL/A148), whereas total flaps are generally used in eyes with significant stromal damage and limited visual prognosis.

Conjunctival flaps generally require a pedicle to ensure a continuous blood supply. Pre-operative assessment of suitability is therefore important to ensure that mobilization and advancement of conjunctiva is possible, which is often difficult where there is coexistent scarring from chemical burns or forniceal obliteration from Stevens Johnson Syndrome for example, limiting mobilization. Alternatives if no local conjunctiva was available were proposed by Dua in 2012[26] where a free autologous conjunctival graft from the opposite eye (or distal site in ipsilateral eye) was sutured onto the affected cornea and the peripheral graft margin was sutured to viable tissue with an intact blood supply. This permitted blood vessels to connect with the graft vessels and carrying blood to the cornea to aid healing. Because of the lack of abundant tissue supply, it is imperative that the procedure is conducted meticulously and accurately as the opportunity for repeated reoperation is extremely limited if not impossible.

Disadvantages of conjunctival flaps are iatrogenic limbal stem cell deficiency, limitation of cornea and anterior chamber visualization, inaccuracy of intraocular pressure measurements, potential for perforation under the flap, retraction, altered cosmesis, limited reversibility, potential scarring disrupting potential for future glaucoma surgery, and the need for an operating room.[27]

BUCCAL GRAFT TRANSPLANTATION TECHNIQUE

One of the challenges of ocular surface reconstruction is the reconstitution of the conjunctival and forniceal space to maintain a moist ocular surface environment conducive to healing. Although amniotic transplantation is a reasonable choice, autologous oral mucosa is also an excellent choice in periorbital reconstruction[28] because of similar biological properties to conjunctiva. Secretions released by oral mucous are predominantly mucous or seromucinous and similar in composition to natural tears. This contributes to increased mucin production that coats the corneal surface and stabilizes the tear film and reduces tear film break up time. Furthermore, labial secretions contain growth factors including epidermal growth factor and transforming growth factor-ß to promote normalized growth and differentiation of the ocular surface epithelium and re-epithelialization. Finally, the density of mucin secreting glands is high and produces constant spontaneous secretion even when sleeping, essential to maintaining the integrity of ocular surface lubrication and preventing breakdown.

Benefits include minimal cost, ease of accessibility of oral mucosa, technical simplicity of harvest, good oral regeneration with potential for repeat harvest and a longstanding history of use in periocular reconstruction. Autologous oral mucosa avoids the risks of allogeneic immune rejection and need for immunosuppression. Additional benefits include easy vascularization, greater structural integrity, and sparing of the bulbar conjunctiva to provide a viable source of tissue where distant conjunctiva is in short supply or required for other procedures that is, glaucoma filtration in future.[29]

This technique has been published in several studies[30–32] initially in the reconstruction of late leaking trabeculectomy blebs or glaucoma drainage devices. The oral mucosa is harvested from the inside of the lower oral labia, which is prepped with povidone iodine solution 10% followed by sterile draping. Gripped by gauze, the lower labia is everted and infiltrated with xylocaine 1% in 1/100,000 epinephrine into the submucosa of the intended harvest area approximately 1.5 cm from the vermilion border. A Castroviejo 10-mm trephine is first used to ink mark an outline then used to trephine through the mucosa to a depth of 2 mm into the submucosa. The circular harvested tissue is then grasped with toothed forceps and the base of the tissue is undermined and dissected using Westcott scissors. Hemostasis is achieved with bipolar cautery and a 5.0 rapid absorption suture is used to close the wound with three sutures (center bisecting the circle, then halving the residual gaps on either side). The donor tissue is flipped mucosa side down, stretched, and the excess fat is trimmed until the tissue is as thin as possible without buttonholing (see Video 5, Supplemental Digital Content 5, http://links.lww.com/ICL/A149). The final mucosal graft is then placed in balanced salt solution while awaiting use.

The healing of oral mucosa on the ocular surface gives a different clinical picture than free amniotic grafting. It initially appears thick, congested, and vascularized as vascular infiltration from the adjacent conjunctiva occurs. Over the course of 12 months, however, the "bulkiness" of the tissue smooths out over time and becomes less noticeable.

Complications are rare and usually self-limiting but include postoperative discomfort, hemorrhage or hematoma of the harvest site, infection, neurosensory deficit, wound dehiscence, and poor cosmesis, although the latter does improve over time. Wound contracture can result in tightness and limitation of jaw opening. An alternative to the lower oral labia is the inner cheek which gives less postoperative pain and neurosensory deficit but is more challenging to access.

NEUROTIZATION

Corneal neurotization is a relatively new development in the treatment of neurotrophic cornea initially developed in 2009[33] and directly addresses the underlying problem of deficient corneal innervation. The technique involves the surgical reinnervation of a severely hypoesthetic or anesthetic cornea using a fully functioning

sensory nerve from an alternate location. Two main approaches have been described—direct, where the normal nerve is transferred directly to an anesthetic cornea and indirect, where an interpositional nerve graft is placed as a link between the anesthetic cornea and normal nerve. The first modern corneal neurotization approach described by Terzis et al in 2009 used direct supraorbital and supratrochlear nerve transfer, which has been replicated by others since.[34] Other direct approaches involve ipsilateral supraorbital nerve transfer and hemicoronal incision, ipsilateral infraorbital nerve transfer and endoscopic ipsilateral or contralateral supraorbital nerve transfer.

Caution is advised with respect to pre-operative planning. Conjunctival scarring or glaucoma drainage device placement can limit the choice of donor nerve selection. Nerve damage during donor harvest may contribute to re-innervation failure. Patients should be made aware of postoperative neurosensory deficits although most resolve with time. Pain, neuromas, and scars have also been reported.

In conclusion, the surgical treatment options for managing NK are varied and are aimed at optimizing the ocular surface and promoting epithelial healing. Surgical options should be targeted according to stage of NK. Amniotic membrane and lid procedures are useful in emergent situations but may significantly affect vision and cosmesis. Medical treatments alone are often not enough to resolve the epitheliopathy. Ongoing protection and maintenance of the ocular surface is of paramount importance in the prevention of epithelial breakdown.

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