Minimally Invasive Corneal Neurotization With Acellular Nerve Allograft: Surgical Technique and Clinical Outcomes

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Same text as above.
Marking for contralateral transfer of the either a supraorbital or supratrochlear nerve. A higher crest is marked on the donor side (left upper eyelid) and the approximate location of the sensory donor nerves is marked with small vertical lines. Natural eyelid crease is marked on the recipient side (right upper eyelid).

cotton or Cochet–Bonnet esthesiometer was performed to determine viable donor nerve sites. During all visits, patients were asked to report their dry eye symptoms (e.g., ocular irritation, foreign body sensation, etc.), ability to feel eye drops in the operative eye, symptoms of anesthesia, and sensibility in the donor dermatome. Careful ocular surface evaluation using fluorescein staining was performed to note changes in corneal appearance and integrity, and health of the donor nerve fascicles. Postoperatively, patients were given topical antibiotic ointment to apply to the incision and topical antibiotic drops four times daily to the operative eye for 2 weeks following surgery. Patients with usually significant corneal injury due to NK (e.g., dense punctate epithelial erosions, persistent corneal epithelial defect or ulceration, corneal scarring or neovascularization, etc.), and viable donor sensory nerves were deemed to be candidates for the procedure. Patients with active ocular inflammatory or infectious conditions (e.g., microbial keratitis, ocular cicatricial pemphigoid, uveitis, etc.), poor systemic health, bleeding diathesis, and those with limbal stem cell deficiency were excluded from the study. Informed consent and preoperative medical clearance for general anesthesia were obtained in all patients.

Operative Approach. All procedures were performed under general anesthesia. After infiltrating the surgical sites with 1% lidocaine with 1:100,000 epinephrine, the procedure was initiated by making an incision in the recipient and donor site(s) (Fig. 1). For supraorbital or supratrochlear nerve transfers, bilateral eyelid crease incisions were performed for contralateral transfer (in cases of ipsilateral trigeminal neuropathy) and unilateral crease incision was performed if the ipsilateral sensory nerves were intact. The supraorbital and supratrochlear nerves were then exposed through the eyelid incision. Given the innate anatomic variability in caliber of the potential donor pedicles and allograft, the final determination to use either the supratrochlear or supraorbital donor pedicle was based on intraoperative best fit assessment. Once identified, the donor nerve was severed 1 to 2 cm distal to the supraorbital rim (Fig. 2). For the infraorbital nerve, a transconjunctival fornix incision was used to access the orbit where the orbital floor was removed to unroof the infraorbital groove. Next, processed acellular nerve allograft (Avance Nerve Graft) measuring 70 mm × 1–3 mm was coapted to the donor nerve (Fig. 3). A nerve connector, wrap, or an amniotic membrane graft derived from umbilical cord was used, based on surgeon’s preference, to protect the neurorrhaphy for all the end to end coaptations. For the end to side coaptation, no material was used to protect the neurorrhaphy based on technical preference. In cases of contralateral supraorbital or supratrochlear nerve transfer, the graft was

FIG. 1. Marking for contralateral transfer of the either a supraorbital or supratrochlear nerve. A higher crest is marked on the donor side (left upper eyelid) and the approximate location of the sensory donor nerves is marked with small vertical lines. Natural eyelid crease is marked on the recipient side (right upper eyelid).

FIG. 2. Isolated supraorbital nerve segment severed ~2 cm from the supraorbital notch.

Any preexisting tarsorrhaphy was severed to allow for wide exposure of the ocular surface. In cases where supraorbital or supratrochlear nerves were transferred, a blepharotomy medial to the medial horn of the levator aponeurosis was then performed through the medial portion of the eyelid incision using Westcott scissors. The nerve graft was then tunneled through the blepharotomy incision into the superior medial conjunctival fornix with a hemostat (Fig. 5A). In patients who underwent ipsilateral transfer, the excess nerve graft tissue was then sharply trimmed to the desired length. For the patient in whom the infraorbital nerve was used, the nerve graft was directly brought from the inferior orbit into the inferior bulbar subconjunctival space. The epineurium was then incised, and nerve fascicles were released along the graft segment just distal to the conjunctival fornix (Fig. 5B).

The nerve fascicles were then tunneled in the subconjunctival space to the corneoscleral limbus (Fig. 5C). Additional conjunctival incisions were made at the terminal ends of the fascicles adjacent to the limbus, and an 8-0 vicryl suture on a spatulated needle was used to secure the perineurium of the fascicle to the sclera (Fig. 5D). The conjunctival incisions were then closed with 8-0 vicryl sutures. Either a temporary or permanent tarsorrhaphy depending on particular patient’s risk for corneal decompensation was performed or reformed (if one was already in place prior to surgery) to protect the cornea during early postoperative period. Postoperatively, an eye patch was placed

FIG. 3. Coaptation between nerve allograft (long arrow) and supraorbital nerve (short arrow).
over the affected eye for 24 hours, and the patients were instructed to place topical antibiotic drops 4 times daily into the affected eye for 1 week. Strenuous activity and heavy lifting were restricted for 2 weeks postoperatively. Timing of tarsorrhaphy removal was based on corneal examination. Patients resumed all preoperative ocular medications after the eye patch was removed.

RESULTS

A total of 7 patients underwent corneal neurotization with nerve allograft at the Duke University Medical Center (5 patients), Baylor College of Medicine (1 patient), and Penn State University Medical Center (1 patient). Average age of the patients was 46 years (range: 6–75 years). Average postoperative follow up was 6 months (range: 3–10 months). Successful end-to-end coaptation of the acellular nerve allograft to the deep division of the supraorbital nerve was performed in 5 patients, side-to-end coaptation of the allograft to the infraorbital nerve in 1 patient, and end-to-end coaptation to the supratrochlear nerve in 1 patient. All patients showed improvement in corneal sensibility. Central improvement was seen in 5 patients and peripheral improvement in all patients at their last follow-up examination. Patient characteristics and postoperative results are summarized in Table. Description of each patient is detailed below.

Patient 1. A 45-year-old Caucasian female with history of left vestibular schwannoma resected 15 years ago was referred for management of NK in her left eye. She also had partial facial paralysis on her left side with secondary lagophthalmos. Her ocular examination demonstrated dense central corneal opacity due to corneal ulceration and perforation 2 years ago for which she had undergone corneal gluing, tarsorrhaphies, and gold weight placement. Preoperative Cochet–Bonnet esthesiometry revealed decreased corneal sensation in the left eye (Table).

Following corneal neurotization with the nerve allograft coapted to the contralateral supratrochlear nerve, she reported more ocular surface comfort, improvement in dry eye symptoms, and subjective improvement in vision at 4 months postoperatively. Objectively, she had improvement in corneal sensibility in the inferior and superior quadrants by Cochet–Bonnet testing at 4 months follow up (average 0.5 cm) with full restoration of sensation within the donor nerve dermatome. In vivo confocal microscopy at 4 months postoperatively demonstrated increased density of the corneal anterior stromal nerves (Fig. 6). Her visual acuity improved from 20/150 to 20/40 at 10-month follow up at the outside institution. She did not have her corneal sensibility measured at 10-month follow up but continued to subjectively experience improvement in her ocular surface symptoms. No complications were noted during the follow-up period.

Patient 2. A 62-year-old Caucasian male with medical history significant for hyperthyroidism, ulcerative colitis on immunosuppression, was referred for management of NK with persistent corneal epithelial defect in his right eye despite maximal medical therapy and multiple tarsorrhaphies. His ocular history was notable for stable thyroid eye disease with moderate proptosis, advanced open-angle glucoma on maximal medical therapy, and recent pars plana vitrectomy with endolaser for rhegmatogenous retinal detachment in the affected eye. On dilated fundoscopic examination, he had evidence of dense chorioretinal scarring from retinal laser treatment in the 3 and 9 o’clock meridians (in the locations of long posterior ciliary nerves). Preoperative Cochet–Bonnet esthesiometry measured 0 cm in the right eye (Table).

The patient underwent corneal neurotization using nerve allograft coapted to the ipsilateral supraorbital nerve and aggressive tarsorrhaphy in attempts to avoid further corneal deterioration and potential Gundersen flap. At 1-month follow up, his corneal epithelial defect was completely healed, but no return of corneal sensibility was
## Patient characteristics and outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Denervation time</th>
<th>Etiology</th>
<th>Comorbidities</th>
<th>Follow up</th>
<th>Epithelial defect pre/ postoperatively</th>
<th>Donor nerve</th>
<th>Preoperative corneal sensibility*</th>
<th>Postoperative corneal sensibility</th>
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<th>BCVA (postoperatively)</th>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>F</td>
<td>20 years</td>
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<td>No/no</td>
<td>Cont ST</td>
<td>2.3 cm</td>
<td>3.0 cm IVCM confirmed corneal nerve regeneration†</td>
<td>20/150</td>
<td>20/40</td>
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<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>1 year</td>
<td>TED, UC, glaucoma, RRD, HTN</td>
<td>Amblyopia, Goldenhar syndrome</td>
<td>10 months</td>
<td>Yes/no</td>
<td>Ipsi SO</td>
<td>0 cm</td>
<td>3.4 cm</td>
<td>HM</td>
<td>HM</td>
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<tr>
<td>3</td>
<td>6</td>
<td>M</td>
<td>6 years</td>
<td>Agenesis of CNV DM, retinal laser, ocular surgery</td>
<td>Amblyopia, Goldenhar syndrome</td>
<td>6 months</td>
<td>Yes/no</td>
<td>Cont SO</td>
<td>None</td>
<td>Improved</td>
<td>LP</td>
<td>CF at 5 feet</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>F</td>
<td>3 months</td>
<td>PDR, TRD, IDDM I, CP</td>
<td>PVD, smoking, CAD, CM</td>
<td>4 months</td>
<td>Yes/no</td>
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<td>9 months</td>
<td>HZO</td>
<td>HZO, IDDM</td>
<td>6 months</td>
<td>No/no</td>
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<tr>
<td>6</td>
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<td>Central trigeminal nerve injury</td>
<td>Smoking</td>
<td>4 months</td>
<td>Yes/no</td>
<td>Ipsi IO</td>
<td>1 cm</td>
<td>5.0 cm</td>
<td>HM</td>
<td>20/200</td>
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<tr>
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<td>F</td>
<td>3 years</td>
<td>Smoking</td>
<td></td>
<td>3 months</td>
<td>Yes/no</td>
<td>Cont SO</td>
<td>0 cm</td>
<td>0.4 cm</td>
<td>20/40</td>
<td>20/30</td>
</tr>
</tbody>
</table>

*Cochet–Bonnet measurements are reported in centimeters. Measurements were taken in 4 quadrants and centrally with the average value reported. For those patients uncooperative with measurement, presence of corneal sensibility is reported as either “none” or “improved” by testing the cornea with a wisps of cotton.

†Cochet–Bonnet and IVCM measurements were obtained at 4 months postoperatively.

BCVA, best-corrected visual acuity; CAD, coronary artery disease; CM, cardiomyopathy; CN, cranial nerve; CN V, cranial nerve 5; Cont, contralateral; CP, cerebral palsy; HTN, hypertension; HZO, herpes zoster ophthalmicus; IDDM, insulin-dependent diabetes mellitus; IO, infraorbital; Ipsi, ipsilateral; IVCM, in vivo confocal microscopy; PDR, proliferative diabetic retinopathy; RRD, rhegmatogenous retinal detachment; SO, supraorbital; ST, supratrochlear; TED, thyroid eye disease; TRD, tractional retinal detachment; UC, ulcerative colitis.
Corneal Neurotization With Acellular Nerve Allograft

FIG. 6. Representative in vivo confocal micrographs showing paucity of the corneal anterior stromal nerves before corneal neurotization and their increased density 4 months after corneal neurotization. White arrows point to the stromal nerves.

FIG. 7. Appearance of the nerve allograft and ocular surface at postoperative month 6 after corneal neurotization using contralateral supraorbital nerve in primary gaze (A) in infraduction (B).

noted at that time. By 3 months, he started feeling eye drops in his right eye and noted dry eye symptoms. He did note symptoms of synesthesia at 3 months (i.e., he felt the eye drops placed in the affected eye in his ipsilateral scalp). He also had initial symptoms of bulbar conjunctival hyperesthesia on testing with Cochet–Bonnet. Both of these symptoms resolved over the subsequent 7 months. At 10-month follow up, he continued to demonstrate corneal epithelial integrity and improvement in corneal sensitivity in all 4 quadrants and centrally (average of 3.4 cm). His visual acuity remained stable limited by posterior segment pathologic factors. His scalp sensation was completely restored. His postoperative period was complicated by recurrence of the corneal epithelial defect at 3 months postoperatively during a flare up of his ulcerative colitis. After initiating a short taper of oral prednisone, his corneal epithelial defect healed within 1 week. No recurrence of the epithelial defect or any other postoperative complications were noted during the follow-up period.

Patient 3. A 6-year-old Caucasian male with Goldenhar's syndrome and right-sided agenesis of trigeminal nerve was referred for management of NK complicated by persistent corneal epithelial defect in his right eye despite intensive medical management (i.e., preservative-free artificial tears every 1 hour, nighttime lubricant eye ointment, and moxifloxacin eye drops 4 times daily) and lateral tarsorrhaphy. His ocular history was significant for dense amblyopia in his right eye due to corneal opacification and tarsorrhaphy. Preoperative corneal sensitivity testing with a wisp of cotton revealed absent corneal sensation in the left eye. Accurate measurement of corneal sensitivity with Cochet–Bonnet esthesiometer was not possible due to patient's poor cooperation.

He underwent corneal neurotization on the right side with nerve allograft coapted to the contralateral supraorbital nerve. His corneal epithelial defect was healed at 1-month follow up with no apparent return of corneal sensitivity. At 6-month follow up, he continued to demonstrate corneal epithelial integrity and blink reflex upon testing his corneal sensitivity with a wisp of cotton in all 4 quadrants and centrally. He was noted to have improvement in his best-corrected visual acuity from light perception to counting fingers at 5 feet. No postoperative complications were noted during the postoperative period. His scalp sensation on the donor side returned at 6 months postoperatively.

Patient 4. A 33-year-old Caucasian female with cerebral palsy, cognitive impairment, and diabetes mellitus type I was referred for management of NK complicated by persistent corneal epithelial defect and stromal scarring in her left eye following pars plana vitrectomy and en-dolaser for tractional retinal detachment. Her ocular history was notable for proliferative diabetic retinopathy with tractional retinal detachments and multiple vitreoretinal procedures. Preoperative corneal sensitivity testing with a wisp of cotton revealed absent corneal sensation in the left eye. Accurate measurement of corneal sensitivity with Cochet–Bonnet esthesiometer was not possible due to patient's poor cooperation.

She underwent corneal neurotization with nerve allograft coapted to ipsilateral supraorbital nerve. Her ocular surface exam and corneal sensitivity started improving at 1 month demonstrating withdrawal and blink when testing corneal sensation with a wisp of cotton in 4 quadrants and centrally. Her corneal epithelial defect was healed, but she still demonstrated punctate keratopathy. She also demonstrated superior bulbar conjunctival hyperesthesia on testing with a wisp of cotton. Her ipsilateral scalp sensation returned at 1 month postoperative. At 4 months postoperatively, she continued to demonstrate improvement in corneal sensitivity as tested by a wisp of cotton in all 4 quadrants and centrally, and resolution of corneal opacification and punctate keratopathy. Her conjunctival hyperesthesia resolved, and visual acuity remained stable limited by her retinal pathology. She had no postoperative complications during the follow-up period.

Patient 5. A 68-year-old male with medical history significant for smoking and coronary artery disease was referred for management of NK 9 months after suffering from herpes zoster ophthalmicus in his right eye. Despite intensive ocular lubrication, he continued to have severe punctate keratopathy and decreased visual acuity. He had paresthesia and decreased sensitivity to light touch in the ipsilateral V1 dermatome. Preoperative average Cochet–Bonnet esthesiometry revealed decreased corneal sensation in the right eye at 1.3 cm.

He underwent corneal neurotization with nerve allograft coapted to the contralateral supraorbital nerve. After he completed his standard postoperative topical ocular regimen, he continued to use artificial tears every 1 hour, nighttime lubricant eye ointment, and moxifloxacin eye drops 4 times daily and multiple vitreoretinal procedures. Preoperative corneal sensitivity testing with a wisp of cotton revealed absent corneal sensation in the left eye. Accurate measurement of corneal sensitivity with Cochet–Bonnet esthesiometer was not possible due to patient’s poor cooperation.

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drops on as needed basis. At 2 months postoperatively, he showed improvement of corneal sensibility in all 4 quadrants and centrally (average 3.5 cm). His best-corrected visual acuity also improved from 20/70 to 20/40. He noted improving sensation of the scalp on the donor side. His ocular examination was notable for decreased keratopathy and improved corneal clarity (Fig. 7). By 6 months postoperatively, his average corneal sensibility improved to 6.0 cm and visual acuity to 20/20 in the affected eye. On slit-lamp examination, he had mild punctate corneal staining with fluorescein but denied any dry eye symptoms. The patient had full restoration of scalp sensation on the donor side. He stopped using ocular lubricants. He had no complications during the postoperative period.

**Patient 6.** A 75-year-old Hispanic male with insulin-dependent diabetes mellitus and a history of herpes zoster ophthalmicus presented with an 8-month history of nonhealing corneal epithelial defect and microbial keratitis of the right eye. He had previously undergone treatments with topical fortified antibiotics, topical and oral antivirals, topical antifungals drops, topical corticosteroids drops, bandage contact lens, amniotic membrane grafts (twice), and lateral tarsorrhaphy (twice). On presentation, he was noted to have a persistent corneal epithelial defect with corneal thinning, and a neurotrophic cornea was diagnosed with Cochet–Bonnet sensation measured at 1 cm on the right eye. A global decrease in right V1 sensation and symmetric V2 sensation was noted. The patient underwent corneal neurotization with nerve allograft co-apted to the ipsilateral infraorbital nerve (Fig. 8A,B) in a side-to-end fashion. At 4 months postoperatively, corneal sensation improved to 5 cm with the Cochet–Bonnet esthesiometer in all 4 quadrants and centrally. Visual acuity improved from hand motions preoperatively to 20/200 postoperatively with Cochet–Bonnet esthesiometry revealed diffuse loss of corneal sensation with readings of 0 cm in all quadrants and centrally. Following desensitization, the cornea undergoes structural changes, including decreased levels of both epithelial and endothelial cells, as well as increased number of hyper-reflective keratocytes. These innervation-dependent anatomic changes provide a potential pathophysiologic framework for the clinical manifestations of NK. There are 3 stages of NK with increasing severity of disease. Stage I involves punctate keratopathy, stromal scarring, and corneal neovascularization. Stage II is characterized by a persistent epithelial defect with stromal opacification. Stage III involves severe corneal ulceration with stromal thinning and perforation potentially leading to loss of the eye.

Treatment for NK depends on the stage of the disease. Stage I disease is usually treated with ocular lubrication. As the disease progresses to stages II and III, antibiotic drops and ointments are used for prevention of secondary infectious complications. Contact lenses can be placed to protect the corneal epithelium. New topical treatments, such as autologous serum drops, have been used to replace the proteins and molecules usually found in tears. Prokera lenses or dried amniotic membrane with a bandage contact lens can be used to temporarily treat the ocular surface and help heal the epithelial defect.

Surgical treatment is employed for severe cases. Tarsorrhaphy and amniotic membrane grafts are commonly performed for this disease with variable success in achieving closure of the persistent epithelial defects. Botulinum toxin has also been used to induce temporary ptosis to protect the corneal epithelium. These measures are preventative to ensure no further damage to the eye, but they do not address the underlying problem of insensate cornea.

New surgical approaches have been studied that would restore sensation to the cornea, thus preventing further damage and improving wound healing. Terzis et al. first described corneal neurotization in 2009. Six patients in their study with ipsilateral trigeminal nerve palsy underwent reinnervation of the cornea via a coronal approach, with the contralateral supraborital and supratrochlear branches of the ophthalmic division of the trigeminal nerve. Subsequently, Elbaz et al. described a technique of using a sural nerve autograft anastomosed to either an ipsilateral or contralateral supratrochlear nerve and tunneled through the upper eyelid incision avoiding a coronal incision. The most recent report by the authors of this study described an endoscopic technique for corneal neurotization. All of these techniques allowed for successful transfer of the nerves and return of corneal sensation.

All studies to date have focused on direct nerve transfers or use of a nerve autograft. We describe the largest case series to date of corneal neurotization and the first case series of successful corneal neurotization with the use of nerve allograft. The technique for supraorbital and supratrochlear nerve transfers is similar to that described by Elbaz et al., but instead of her central corneal scarring, was noted. Her best-corrected visual acuity had improved from 20/40 to 20/30 at 3-month follow up (Table). No postoperative complications were noted during the follow-up period.

**DISCUSSION**

The ophthalmic division of the trigeminal nerve controls the sensation of the cornea, providing protection and lubrication of the ocular surface through its role as the afferent pathway for the blink reflex. In addition, sensory corneal innervation supplies local neurotrophic factors believed to play a role in the regenerative capacity of the corneal epithelium, which is crucial for normal wound healing.

When the trigeminal nerve is impaired, these protective mechanisms are deficient, leading to ocular morbidity. Following desensitization, the cornea undergoes structural change, including decreased levels of both epithelial and endothelial cells, as well as increased number of hyper-reflective keratocytes. These innervation-dependent anatomic changes provide a potential pathophysiologic framework for the clinical manifestations of NK. There are 3 stages of NK with increasing severity of disease. Stage I involves punctate keratopathy, stromal scarring, and corneal neovascularization. Stage II is characterized by a persistent epithelial defect with stromal opacification. Stage III involves severe corneal ulceration with stromal thinning and perforation potentially leading to loss of the eye.

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harvesting a nerve autograft, the authors use a nerve allograft avoiding donor site morbidity while maintaining the minimal invasive nature of surgery. Similar to the technique described by Elbaz et al., the reported technique avoids risks of alopecia, injury to the frontal branch of the facial nerve, scalp incisions, and extensive dissection needed with a coronal approach. In the authors’ experience, the recovery of sensory dermatome of the donor nerve is faster with the current technique compared with either endoscopic or coronal approaches. In addition, the operative time required to execute the procedure is shorter (~<90 minutes) compared with all the previously described techniques. Although all of the procedures were conducted under general anesthesia, it may be feasible to safely perform this procedure with local and topical anesthesia under conscious sedation in selected patients.

Determination of the optimal donor nerve pedicle for corneal neurotization relies on a combination of preoperative and intraoperative assessment, as well as surgeon’s preference. During preoperative evaluation, both ipsilateral and contralateral sensation in the supraorbital, supratrochlear, and infraorbital nerve distribution is performed. This allows the surgeon to identify viable donor sites, while eliminating those with suboptimal function. Patients with NK stemming from a local ocular process may have unaffected nerve function within the remainder of the V₁ dermatome, while those with a central cause are more likely to have diminished function in V₁ and potentially V₂ dermatomal distributions. When using a nerve graft, one attempts to minimize the graft length, to decrease the required distance of axonal regeneration and match donor and graft nerve caliber to aid in anastomosis formation. The ideal donor is close to the site of interest, easily accessible, and carries minimal donor site morbidity. Based on these principles, the authors prefer to use intact ipsilateral supraorbital or supratrochlear nerves as primary donors. When used, the final determination between supratrochlear and supraorbital nerve donor sites is made intraoperatively based on the best donor-graft size match for anastomosis creation. Generally, the authors have found that the deep division of the supraorbital nerve has a more reliable anatomy and provides a larger diameter with robust structure for successful neurorrhaphy. If the ipsilateral supraorbital/supratrochlear donor sites are unavailable, the next options are the ipsilateral infraorbital and contralateral supraorbital/supratrochlear nerves. Using the ipsilateral infraorbital nerve maintains a limited graft length but requires more extensive and intricate dissection into the orbit including bone removal. Given that the infraorbital nerve is coapted in a side-to-end fashion to the nerve allograft, the postoperative sensory recovery in the donor nerve dermatome is expected to be faster compared with end-to-end coaptation. Using a contralateral supraorbital/supratrochlear donor pedicle requires a longer graft length but can be achieved through a more straight forward and universally employable dissection technique. In the authors’ experience, transection of the supratrochlear or supraorbital nerves carries less morbidity compared with transection of the infraorbital nerve. Therefore, a side-to-end coaptation was performed when infraorbital nerve was used. If both of these options are available, the final determination is based on the surgeon’s familiarity with pertinent anatomy and required technique. In instances when both ipsilateral nerves are compromised, a contralateral donor is necessary.

Avance Nerve Graft is an off-the-shelf processed human nerve allograft intended for the surgical repair of peripheral nerve discontinuities. Through a proprietary cleansing process for recovered human peripheral nerve tissue, the graft preserves the essential inherent structure of the extracellular matrix while cleansing away cellular and noncellular debris.17-25 The graft is currently used for peripheral nerve repair following trauma, tumor resection, and other causes of peripheral nerve injury.17-25 Clinical studies have demonstrated that nerve allografts hold promise as successful alternatives to the current standard treatment of autogenous nerve grafting.26 Regardless of the material used, the ideal nerve repair should be tension free, with no additional scarring or nerve entrapment and enhanced neural regeneration. Nerve repair methods include epineurial repair, group fascicular repair, and combination of the 2.27 Due to the small caliber of the coapted nerves in this study (1–3 mm), epineurial technique was used. During anastomosis between the donor nerve and the graft, care must be taken to avoid tension on the repair and to engage only epineurium to avoid fascicular damage and possible neurroma formation.28 The suture line can be protected by nerve conduits, wraps, and umbilical cord-derived amniotic membrane grafts but can also be shielded by grafts of healthy muscle or fat. Protection of the anastomotic site, theoretically, decreases the rate of axonal escape, reduces scarring with ultimate neuroma formation, and improves the success of axonal regeneration. After coaptation, it takes on average 2 to 4 weeks for initiation of axonal regeneration into the graft that serves as a conduit for axons to reach their target.29 After this latency period, the axons then grow on average 1 mm per day, which corresponds to the rate of slow transport of the neurofilament protein, although this is almost certainly faster in children.30 The axons then invade the anterior corneal stroma as evidenced by our postoperative in vivo confocal microscopic evaluation in patient 1 as well as other recently published reports.27,28 Given the rate of axonal regeneration, there is an expected delay of at least 2 to 3 months or longer in re-establishment of sensitivity following neurotization. This is consistent with our experience and that of other authors.3,27,28 In patient 4, improvement in corneal sensitivity was noted as early as 1 month postoperatively. Her slit-lamp biomicroscopy at the same follow-up visit demonstrated resolved corneal epithelial defect and improved corneal clarity, implying either accelerated axonal regeneration compared with the expected rate or neurotrophic factor support of her corneal epithelium. The lag in re-establishment of corneal sensitivity seen in other patients may also be due to delay in dermatomal remapping by the brain as noted by synesthesia described by patient 2 in this cohort and by some of the patients in the study by Elbaz et al.3 Two out of 6 patients (Patients 2 and 4) were found to have initial conjunctival hyperesthesia likely related to axonal ingrowth into the conjunctiva from the underlying nerve fascicles. This has resolved at their last follow up. We have also noted improvement of the ocular surface (e.g., closure of epithelial defects, decreased corneal epithelial fluorescein staining) and subjective improvement in ocular surface symptoms as early as 1 month postoperatively (patients 2 and 4 who underwent ipsilateral transfers). This occurred in patients 2 and 3 before any objective re-establishment of corneal sensitivity. This phenomenon may be due to release of neurotrophic factors by the axonal terminals that nourish corneal epithelium that occurs before any clinical detection of improved corneal sensitivity.

Although all patients in the study demonstrated improvement in ocular surface and corneal sensibility, there are potential limitations to this technique. First, additional neurorrhaphy may increase the risk of neuroma formation and axonal sprouting failure to reach the cornea. Permanent numbness and paresthesia in the area of the sensory donor nerve dermatome are also potential complications. Also, nerve coaptation can be a technical challenge requiring specialized training in microneurovascular surgery and precision in technique. In addition, the maximum length of nerve allograft is 7 cm, which may limit its use in patients with widely spaced orbits or in those with more distal donor nerves. Finally, nerve regeneration and outcomes


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in nerve repair and grafting are not always predictable and need further studies to examine their efficacy.29

The practical drawbacks of the acellular nerve allograft include those of cost, necessity to store the grafts in the freezer for immediate use, and availability.30 However, these shortcomings may be offset by shorter operating time and absence of donor site morbidity from autograft harvest. The primary theoretical limitation of acellular nerve allograft is the dependence on in situ Schwann cell migration into the graft. This migration process is restricted by a gradual quiescence of the Schwann cells, which theoretically may limit the ultimate effective length of the allograft.31 However, the acellular nerve allograft has been shown to have similar functional success rate compared with nerve autograft in both sensory and motor reinnervation at gap lengths as long as 7 cm and with a variety of nerve caliber.17,31,32

In summary, the use of nerve allograft allows for a successful and minimally invasive strategy to reinnervate patients with corneal anesthesia. Long-term postoperative follow up and prospective studies with a large number of patients are needed to establish long-term safety and efficacy of this technique.

REFERENCES