Corneal Neurotization: A Novel Solution to Neurotrophic Keratopathy

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Background: This study was designed to evaluate the efficacy of direct corneal neurotization using contralateral supraorbital and supratrochlear nerves in patients with unilateral facial palsy and corneal anesthesia. A novel surgical procedure in which these donor nerve branches are inserted at the contralateral anesthetic corneal limbus for sensory neurotization is described.

Methods: The charts of six patients were reviewed thoroughly to evaluate changes in corneal sensibility following surgery for direct corneal neurotization. Visual acuity, blink reflex, donor deficit, synesthesia, long-term corneal health, and several psychosocial measures and overall patient satisfaction with the procedure are reported.

Results: Six patients with an average denervation time of 7.00 ± 8.56 years before surgery were followed for an average period of 16.3 ± 2.42 years. All six eyes showed improvement of corneal sensibility, visual acuity, and corneal health and remained free of ulcers or other signs of advancing neurotropic keratopathy. Average corneal sensibility improved from 2.00 ± 4.47 mm before surgery to 278.00 ± 226.00 mm following corneal neurotization ($p < 0.016$).

Conclusions: Direct neurotization of the cornea using the contralateral supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve appears to be an effective method of restoring the corneal sensibility in patients with unilateral facial palsy and anesthetic cornea. This technique preserves ocular anatomy and cosmesis and restores function by improving corneal health and visual acuity. (*Plast. Reconstr. Surg.* 123: 112, 2009.)

Corneal sensibility is provided by innervation from the ophthalmic nerve, which is the first division of the trigeminal nerve, and is essential for preserving the structure and function of the eye by initiating the blink reflex and by maintaining the health of the corneal epithelium.[1] Anesthesia resulting from any of a number of different causes leads to a clinical condition known as neurotrophic keratopathy, which affects corneal health over a wide spectrum of degenerative changes in the cornea and conjunctiva.[2–4] Patients who also suffer from facial palsy are at even greater risk for corneal disease, as lid laxity and the inability to completely close the eyelids leads to chronic exposure, dry eye, keratitis, and loss of corneal clarity. Various medical and surgical means of protecting the anesthetic eye have been implemented, yet corneal anesthesia remains troublesome to treat.

In this article, the authors evaluate the results of a novel procedure that attempts to provide direct corneal neurotization in cases of unilateral facial palsy with corneal anesthesia and determine the effectiveness of this procedure. This method, in combination with cross-facial nerve grafting and reanimation of the orbicularis oculi muscle, holds promise for restoring function, preserving ocular cosmesis, and promoting ocular health in these patients. To the best of our knowledge, this technique has not been described previously.

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PATIENTS AND METHODS

The charts of six patients with unilateral facial palsy and anesthetic corneas of varying causes were reviewed. Each had undergone surgery for direct corneal neurotization using branches of the ophthalmic division of the contralateral trigeminal nerve. All patients who had undergone the procedure in our center were included in the study; in all cases, corneal neurotization was part of a staged procedure for reanimation of the affected half of the face, including functional restoration of the orbicularis oculi muscle. Each of the six patients was randomly assigned a patient number for the purposes of this study. This cross-sectional retrospective chart review was conducted in accordance with the principles set forth in the Declaration of Helsinki and was approved by the Institutional Review Board of Eastern Virginia Medical School in Norfolk, Virginia.

Selection of Donor Nerves

The supratrochlear and supraorbital nerves are the two branches of the frontal nerve, the largest branch of the ophthalmic division of the trigeminal nerve. They exit from the supraorbital foramen and rise beneath the corrugator and frontalis muscles for a distance before piercing the muscle bellies en route to their targets. The supratrochlear nerve, which is the smaller of the two nerves, supplies the skin of the lower forehead and is partly responsible for supplying the conjunctiva; the supraorbital nerve is larger and its two terminal branches reach nearly as far back as the lambdoidal suture to supply the integument of the scalp.[5] Thus, the contralateral intact supraorbital and supratrochlear nerve branches are ideal donor nerves for the corneal neurotization procedure. These nerves can be dissected under magnification from their original anatomical position with reasonably little risk and are long enough to reach their new intended target (Fig. 1).

Surgical Technique

Dissection of the donor nerves, preparation, and tunneling across the bridge of the nose to the anesthetic eye was carried out by a single, experienced surgeon (J.K.T.) in all cases. Likewise, a single, experienced ophthalmologist (B.I.B.) performed the nerve fiber insertion for the neurotization procedure in all cases.

Through a bicoronal incision, the supratrochlear and supraorbital nerves were identified and carefully dissected under high magnification proximally to the supraorbital margin. Then, the nerve branches were tunneled over the nasal bridge to a small incision along the lid crease of the upper lid of the contralateral anesthetic eye (Fig. 2). Using the operating microscope, a fine

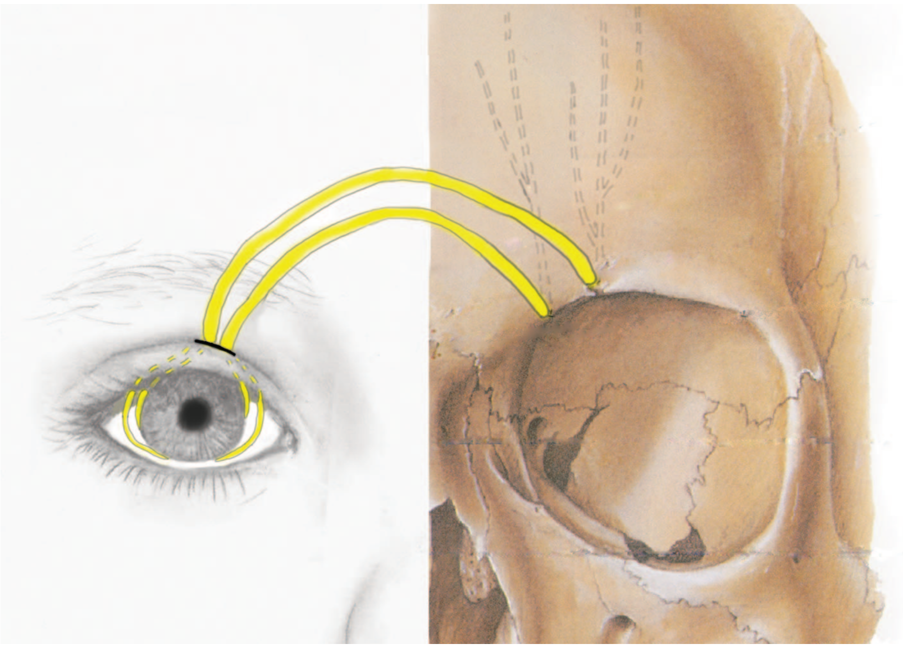

Fig. 1. The contralateral supraorbital and supratrochlear branches are harvested and tunneled across the bridge of the nose and inserted around the limbus of the contralateral anesthetic eye.

Fig. 2. Intraoperative view shows the contralateral supratrochlear and supraorbital nerve branches emerging from an incision in the upper lid crease after being tunneled over the nasal bridge. Small sutures mark the end of each branch for ease of identification.

hemostat inserted through a tiny incision under the upper lid from the superior conjunctival fornix carefully retrieved the distal nerve branches. Once this was completed, attention was turned to the eye to prepare the area around the limbus to receive the dissected sensory branches.

The eye was directed downward using a superior rectus tendon traction suture of 4-0 silk. Then, using blunt Westcott scissors, an incision was created through the superior bulbar conjunctiva 7 mm behind the superonasal position of the corneal limbus. In the potential space between where the sclera and Tenon's capsule are juxtaposed to the anatomical corneal limbus, a tunnel was created by blunt dissection using curved scissors around the circumference of the corneal limbus both temporally and nasally to the points of planned insertion of the prepared nerves.

Passing of the distal nerve branches into the prepared perilimbal space was accomplished by suturing each tiny distal branch with 10-0 suture to the eyelet of a blunt, round, abdominal guide needle that was inserted in reverse fashion through the prepared tunnel to the desired limbal position. Finally, the tiny nerve fanned and was sutured into place in the conjunctival sac next to the corneal limbus with 10-0 monofilament nylon sutures under direct high magnification. The conjunctiva was repaired in a similar fashion with a buried knot. Subsequently, the transposed nerves themselves were fixed into position at the supratarsal fold with 8-0 nylon suture (Fig. 3).

Donor nerves were approximated to their new targets in the described fashion to minimize manipulation of the anesthetic eye, which would prolong what was already anticipated to be impaired wound healing. Also, because normal corneal subepithelial nerves are measured on the order of nanometers, it would have been impractical if not impossible to perform any direct nerve-to-nerve suture.

Patient Examinations

In addition to ophthalmologic care, patients were seen at our center specifically for evaluation of corneal sensibility, synesthesia, donor deficit, and ocular cosmesis. Routine visual acuity testing was performed using a Snellen eye chart. Patients were also evaluated for infection or other adverse effects following the procedure. Average follow-up duration for the six patients was 16.3 $\pm$ 2.42 years from the date of surgery. This reflects ongoing follow-up for five of the six patients from the time of surgery to the time of the study; one patient died during follow-up before the study because of a recurrence of their brain tumor.

Patient Follow-Up Questionnaire

A written psychosocial questionnaire was mailed to the home of each patient as part of routine follow-up for our center. Each questionnaire was mailed with a postage-paid return enve-

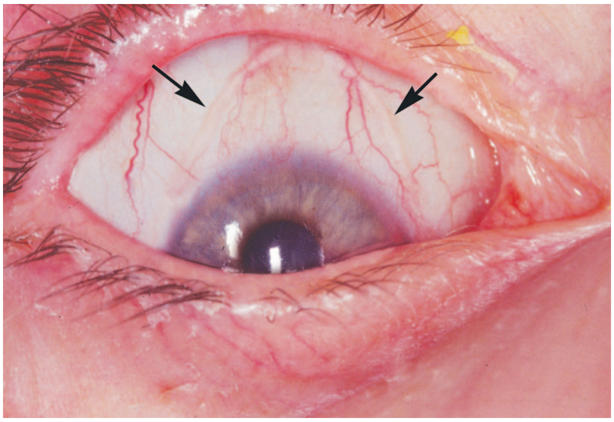

Fig. 3. This postsurgical photograph of transposed nerves taken during a follow-up visit shows branches of the contralateral supraorbital and supratrochlear nerves underlying the bulbar conjunctiva following direct corneal neurotization.

lope to encourage participation in providing information for follow-up, but no other incentives were offered.

Four questions sought the patient's subjective assessment of postprocedure corneal health, including sensibility, blink reflex, adaptation, and overall wellness. Another four were related to psychosocial issues following surgery, including home acceptance, workplace acceptance, self-consciousness, and symmetry compared with the nonaffected eye. Overall satisfaction was also assessed. Adaptation changes were meant to reveal cerebral plasticity and the course of possible synesthesia experienced by the patient.

Assessment of Corneal Sensibility

In our center, a Cochet-Bonnet esthesiometer was used throughout the follow-up period to measure corneal sensibility, except for a single visit when the instrument was being repaired and a von Frey hair was used instead. The esthesiometer consists of a single nylon filament, 0.12 mm in diameter, that can be adjusted to varying lengths to apply variable intensities of mechanical pressure, ranging from 973 to 17,699 mg/mm^2.

Testing began with the nylon filament fully extended to 60 mm, its most sensitive threshold, which is near the expected normal level of approximately 62 mm.[6] The instrument was held perpendicular to the corneal surface and moved toward the cornea within the desired quadrant until contact was confirmed once the filament began to bend. Testing continued in this manner by decreasing the length of the filament to 50, 40, 30, 20, 10, and 0 mm, until a positive response was elicited from each of the four quadrants or until the 0-mm setting was reached.

In this study, esthesiometry measurements from the entire cornea have been averaged to allow the data to be interpreted by grouping patients into four groups: complete anesthesia, or low, moderate, or high corneal sensibility. Readings of 20 mm or less were considered to be low, readings of 30 and 40 mm were considered moderate, and readings of 50 mm and greater were considered to be indicative of high corneal sensibility. To include the readings of the von Frey hair, measurements of 6.0 mbar and greater were considered low corneal sensibility, measurements less than 6.0 mbar and greater than 2.7 mbar were considered to be moderate, and measurements of 2.7 mbar and less were considered to be high corneal sensibility. For both instruments, if a positive response was not elicited at any setting over any part of the cornea, the sensibility was considered to be zero or completely anesthetic.

Statistical Analysis

The data were analyzed using descriptive statistics and the chi-square distribution test by the software Statistics to Use.[7] For interval data, results are given in the form of means ± SD; for ordinal data, medians are given. Although the small sample size limits the power of this study, analysis of the quantitative esthesiometry data were included to provide a method for objectively assessing the results, which were considered significant at $p < 0.05$.

RESULTS

Objective Data

After corneal neurotization, all six eyes healed well and showed improvement of corneal health and sensibility (Table 1). Clarity also improved, as clouding of the cornea was observed to resolve (Fig. 4) and best corrected visual acuity recovered (Table 2). Also, numbness of the contralateral forehead, called donor deficit, resolved over a median of 3 months; apart from patients' complaints of transient discomfort and itching at this site, no other problems or long-term complications were observed.

Although patients reported subjective sensibility between 6 months and 1 year, the average time to objective sensibility was 2.80 ± 2.17 years; this difference was likely the result of the infrequency of follow-up. The average postoperative corneal sensibility did not appear to be influenced by the number of nerve bundles used during the corneal neurotization procedure (Fig. 5) but improved for all patients following surgery from a mean of 2.00 ± 4.47 mm to 278.00 ± 226.00 mm after corneal neurotization ($p < 0.016$) (Fig. 6). It is unknown why a direct relationship was not observed between the number of nerve bundles inserted and resulting sensibility. This raises the question of whether additional unrecognized factors influenced reinnervation.

Two postsurgical complications were noted: in one case, during the immediate postoperative period, a subgaleal hematoma required drainage and pressure dressing; in later follow-up, another patient developed a neuroma that did not require any intervention (Fig. 7). Although all patients continued to have symptoms of dry eye requiring daily topical lubrication, no patient suffered a corneal ulcer or other signs of advancing neurotrophic keratopathy at any point during follow-up.

Table 1. Esthesiometry after Cornea Neurotization

Patient	Eye Laterality	No. of Nerve Terminals Used	Time From Neurotization (yr)	Sensibility of Cornea Quadrant (Filament cm)* I	II	III	IV
1	Right	3	2.0	3	2	3	6
			0.75	†	2	2	†
			2.0	1	2	3	1
2	Right	5	6.0	2	1	6	6
			7.0	3	5	6	5
			12.0	4	4	6	6
			14.0	5	6	2	1
			0.25	†	†	†	†
3	Left	5	4.0	3	†	†	3
			17.6	†	6	†	†
4	Left	3	—	—	—	—	—
5	Left	5	0.25	1	†	†	†
6	Left	4	5.0‡	600	1400	300	600

*Quadrants are from the examiner's point of view as if looking at a clock, with 12-o'clock being most superior point of the patient's cornea: I, 12 to 3 o'clock; II, 3 to 6 o'clock; III, 6 to 9 o'clock; and IV, 9 to 12 o'clock. Greater numbers of centimeters and lesser numbers of millibars correspond to a more sensitive cornea at the measured point.
†No sensibility.
‡Measurements from this visit in millibars.

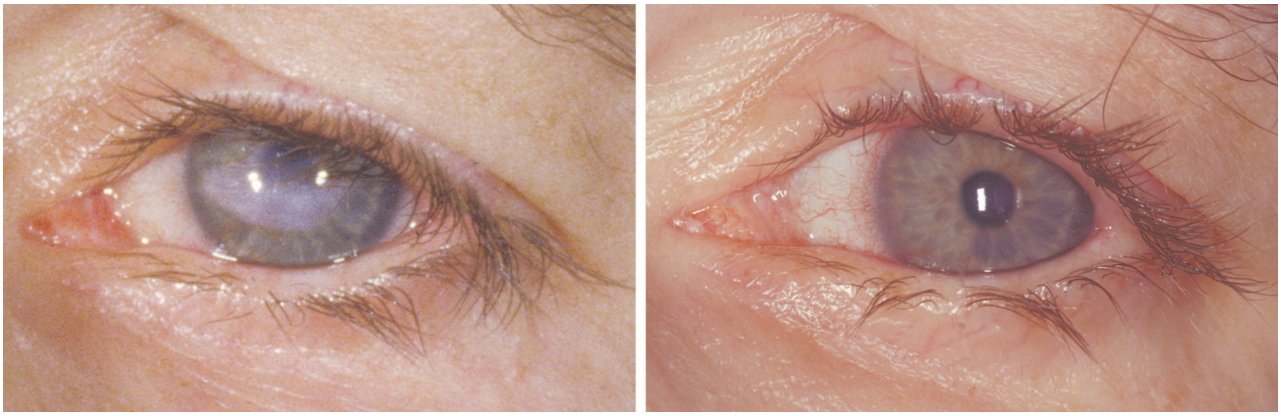

Fig. 4. The left eye of patient 3 preoperatively (*left*) and postoperatively (*right*) shows resolution of the corneal scar after direct neurotization using five branches of the contralateral supraorbital and supratrochlear nerves.

It remains unclear whether corneal clarity and best corrected visual acuity improved because of the supply of chemical neuromediators, which could have been supplied by the donor nerves, or because of recovered health of the cornea and epithelium secondary to an ingrowth of sensory nerves. Although the presence of newly grown nerves into the cornea is not known with certainty because confocal microscopy was not used, it is assumed to be the case because of the increase in corneal sensibility in all patients who underwent the procedure.

Patient Questionnaire Responses

Of five patients living at the time the questionnaire was distributed, three voluntarily completed and returned it (Table 3); it is unknown why the other two patients elected not to participate. The average time from the date of surgery to completion of the questionnaire was 16.3 ± 2.42 years.

Considered together, the median response was 5.5 for questions regarding eye health and 7.0 for questions regarding psychosocial aspects. The overall median response to all parameters regarding the outcomes of the corneal neurotization procedure was 6.0.

Patients' free written responses regarding the immediate postoperative period included complaints of itching and pain in the area of the forehead from which the donor sensory nerves were taken, but they denied eye pain. All patients agreed that they could feel a bump under the upper lid following surgery, and patient 2, who

Table 2. Demographic Data*

Patient	Affected Eye Laterality	Age at Denervation (yr)	Denervation Time (yr)	Follow-Up (yr)	Sex	Cause	Mackie Stage		Visual Acuity		Average Sensibility	
							Preop	Postop	Preop	Postop	Preop	Postop
1	Right	50	3	12	Female	Meningioma†	1	1	20/50	20/25	CA	Moderate
2	Right	40	1	16	Female	AN†	1	1	Tarsorrhaphy‡	20/100	Low	Moderate
3	Left	44	4	18	Female	AN†	3	1	20/400	20/60	CA	Low
4	Left	20	7	17	Male	AN†	1	1	20/200	‡	CA	‡
5	Left	34	3	19	Male	Trauma	2	1	LP	‡	CA	Low
6	Left	20	24	16	Female	AN†	1	1	20/100	20/80	CA	High

AN, acoustic neuroma; CA, complete anesthesia; LP, light perception.
*Throughout follow-up, complete records could not be obtained. Results of testing performed by our surgeon when out of the country using a different esthesiometer were not included. Subjectively, all patients' visual acuity and sensibility improved; no corneal ulcers were reported for any patient following neurotization.
†Extirpation of tumor.
‡Data not available.

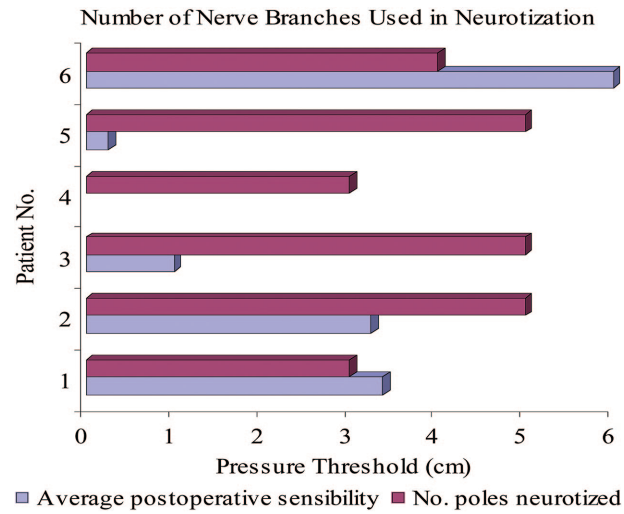

Fig. 5. Bar chart shows the relationship between nerve branches used in neurotization and average postoperative corneal sensibility. Although an attempt was made during surgery to use the available nerve branches to give each corneal quadrant a maximum and equal nerve supply, no clear trend was seen correlating the number of branches used to the resulting sensibility following surgery.

eventually developed a neuroma, noted that her eye always felt dry, even with the use of topical lubrication, and that it frequently felt "uncomfortable" and appeared "red." All three patients reported having normal sensation in the area of the forehead from where the donor nerves had been taken; two reported that it returned within a few months and one never noticed any numbness over the area at all. The only complaint relating to donor deficit was from one patient who noted that periods of "severe itching" were sometimes felt over that part of the forehead.

When asked what they wished they had known before surgery, patients listed that they wanted more information on possible complications and clear explanation that having this procedure would not eliminate the need for therapy with eye drops or ointment for lubrication. Nevertheless, in response to the question "Would you ever have this surgery again?" patients agreed, "Definitely yes," and commented that "[surgery was] more successful than I could have hoped."

DISCUSSION

Corneal Sensibility and Esthesiometry

Normal corneal sensation is essential for maintenance of the structure and function of the corneal epithelium both by means of neural mediators of epithelial cell mitosis and migration and by initiation of the blink reflex.[1,8,9] Even in the ab-

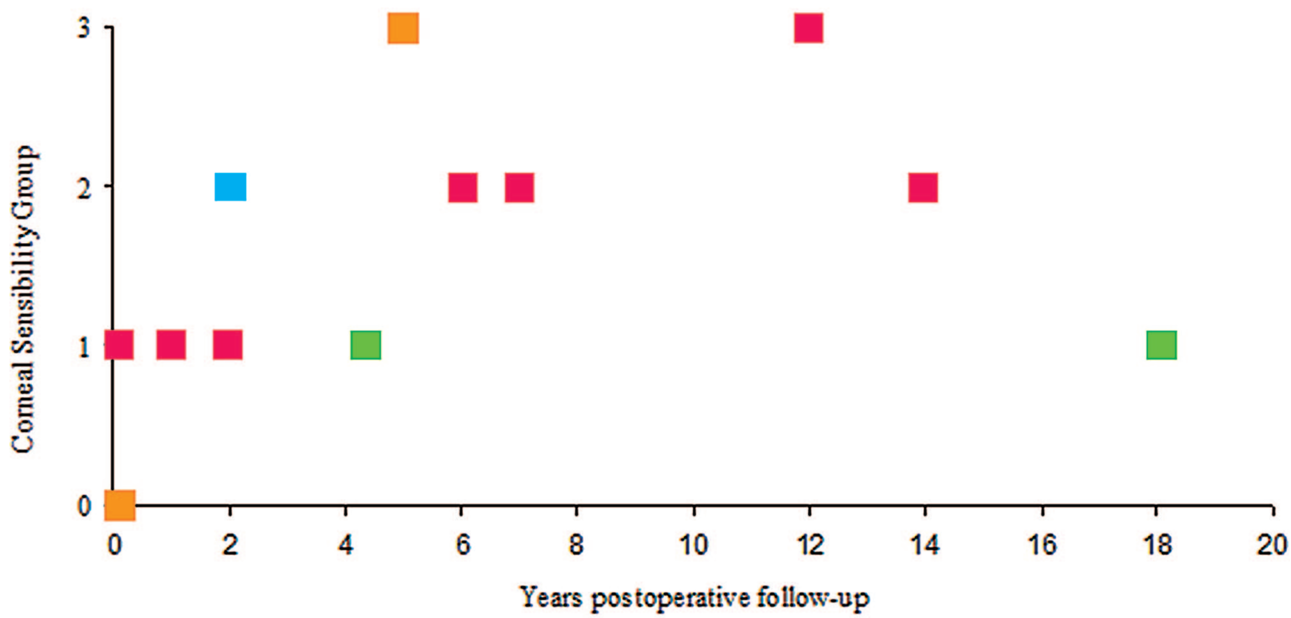

Fig. 6. Dot plot shows the trends in average corneal sensibility following direct cornea neurotization. This figure demonstrates that all patients' corneal sensibility improved after surgery and that such improvement was maintained throughout follow-up. Corneal sensibility groups correspond in the following manner: *0*, complete anesthesia; *1*, low sensibility; *2*, moderate sensibility; *3*, high sensibility. Each color corresponds to an individual patient.

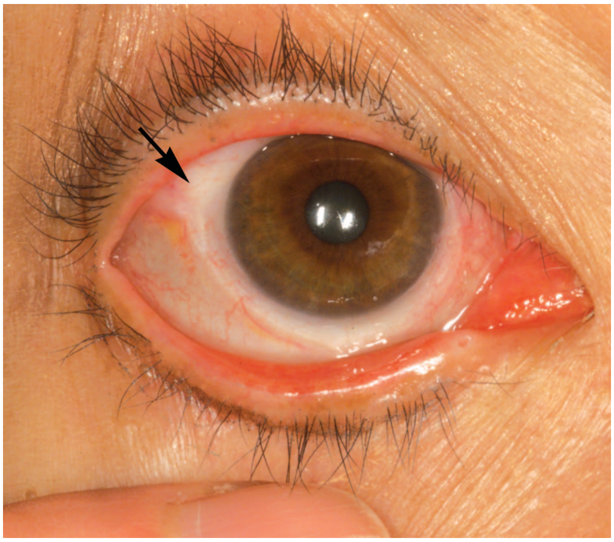

Fig. 7. The *arrow* indicates the presence of a neuroma that developed on one of the sensory nerve branches following direct corneal neurotization.

Table 3. Responses to Follow-Up Questionnaire

	Responses*		
Parameter	Patient 2	Patient 3	Patient 6
Sensibility	2.5	6	8
Wellness	5	3	6
Blink reflex	1.5	2	8
Workplace acceptance	6	†	10
Home acceptance	7	†	10
Self-consciousness	1.5	6	8
Symmetry	4	2	10
Adaptation	7.5	†	9
Satisfaction	8	5	9.5

*The maximum score for patient's ratings for each aspect was 10, where 1 = low and 10 = high.
†Question left unanswered.

sence of noxious stimuli, corneal nerves may initiate a blink reflex for maintenance of corneal health, such as in response to the cooling that occurs during evaporation.[10–12] This reflex is mediated by the trigeminal and facial nerves that interact by means of polysynaptic connections in the brainstem and is not only able to initiate the protective blink reflex but directly determines the speed with which the lids close to protect the eye.[13] Because corneal sensibility is so integral to corneal health, investigative esthesiometry can be used as an indicator of corneal health. Accurate measurement of corneal sensitivity can be a reliable test of long-term corneal compromise, and strong correlations exist between sensibility and the number and density of nerves and between numbers of nerves and the number of superficial corneal epithelial cells.[14,15]

As the traditional standard method of assessing corneal sensibility, use of the Cochet-Bonnet esthesiometer allows data to be compared with previous studies. Also, although newer devices such as the noncontact gas esthesiometer provide greater versatility and repeatability, this traditional testing method remains highly sensitive and cost efficient.

Corneal Reinnervation

An understanding of corneal reinnervation in eyes with normal sensibility has been achieved by observing the healing process in healthy patients following procedures such as penetrating keratoplasty, photorefractive keratectomy, and laser-assisted in situ keratomileusis, which destroy the patient's original corneal neural anatomy.[16] Reinnervation in this setting follows a predictable timeline, with neurotization of the cornea near the limbus visible at 8 weeks postoperatively, neurotization of the superficial central corneal seen at 3 to 7 months postoperatively, and complete neurotization including the basal layers of the central cornea seen between 6 months and 2 years postoperatively. Although this timeline is affected by factors such as the patient's age and health before surgery, levels of sensibility achieved in patients of all ages are adequate to sustain a healthy epithelium and to initiate the blink reflex by all stimulus types to protect the eye.[16–18]

Compared with this predictable healing timeline in relatively healthy eyes, our patients' reinnervation time was lengthened. Although it is hypothetically possible that we observed the result of spontaneous reinnervation from surrounding tissues rather than an ingrowth of nerve fibers from the transposed donor nerves, this seems unlikely to have occurred after such long periods of denervation before surgery. However, if the long donor axons were unknowingly injured during the surgical procedure, regrowth following Wallerian degeneration might have taken longer. Future studies may use nerve blocks to clarify the nerve supply for any corneal reinnervation.

Importance of Medical Management of Neurotrophic Keratopathy

Neurotrophic keratopathy encompasses the spectrum of consequences that result from a lack of neural support for normal epithelial physiology, including epithelial dysfunction caused by a decreased ability for epithelial cell mitosis and migration.[19] This is evidenced by recurrent epithelial breakdowns, impaired healing leading to persistent epithelial defects, and neurotrophic ulcers.[1]

This clinical entity presents in those with anesthetic corneas regardless of cause and requires vigilant care even at the earliest stages if progression to the globe-threatening complications of later stages is to be avoided. The Mackie classification is used in grading the condition and can be useful in guiding decisions for therapy (Table 4).[3,20] Assiduous therapy is important even in the early stages because the corneal epithelium is subject to breakdown even without the assaults of dehydration, infection, or trauma.[4,21]

CONCLUSIONS

The data show that direct neurotization can improve sensibility in previously anesthetic corneas and over time can lead to improved corneal health and restoration of function of the eye. These results are significant objectively and subjectively over many years and suggest that this procedure can prevent many common complications of neurotrophic keratopathy. That these achievements were made without requirements for additional surgical therapy indicates that this management approach provides a possible permanent surgical solution for those with unilateral anesthetic cornea and could be the first definitive treatment for neurotrophic keratopathy in these patients.

Although we realize the limitations of this type of study, we suggest that this new approach to treating corneal anesthesia holds promise for a group of patients who have been notoriously difficult to treat and who have suffered greatly with little hope of a solution to their malady. We propose that this procedure be investigated in a larger, controlled trial to validate the results we have shown.

Table 4. The Mackie Classification of Neurotrophic Keratopathy

Stage	Characteristics
1	Rose bengal staining of the inferior palpebral conjunctiva Decreased tear breakup time Increased mucous viscosity Punctate epithelial fluorescein staining Dellen Gaule spots Superficial vascularization Stromal scarring Epithelial hyperplasia Hyperplastic precorneal membrane
2	Epithelial defect, usually oval and in the superior cornea Defect surrounded by rim of loose epithelium Edges may become smooth and rolled Stromal swelling with folds in Descemet membrane Rare anterior chamber inflammatory action
3	Corneal ulcer Stromal lysis/melting Possible perforation

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