Restoration of Corneal Sensation With Regional Nerve Transfers and Nerve Grafts
A New Approach to a Difficult Problem

Importance
Corneal anesthesia is recalcitrant to conventional treatment and can lead to permanent visual loss.

Objective
To assess the outcomes of a novel sensory reconstructive technique for the treatment of corneal anesthesia.

Design, Setting, and Participants
This prospective study evaluating a new technique was conducted at a tertiary referral center. Four eyes in 3 patients with corneal anesthesia underwent nerve transfers with nerve grafting to restore corneal sensation. Corneal sensory reconstruction was performed using a segment of the medial cutaneous branch of the sural nerve. Two patients with unilateral trigeminal nerve anesthesia—one following basal skull fracture and another following large posterior fossa tumor resection—underwent corneal sensory reconstruction using the contralateral supratrochlear nerve as the donor sensory nerve. One patient with a history of cerebellar hypoplasia and bilateral congenital corneal anesthesia underwent bilateral corneal sensory reconstruction using the respective ipsilateral supratrochlear nerves as the sensory donor nerves. Corneal anesthesia was evaluated preoperatively and postoperatively in the center of the cornea and in 4 corneal quadrants using a Cochet-Bonnet esthesiometer (Luneau). Complications of the procedure were also documented.

Main Outcomes and Measures
Esthesiometry scores.

Results
All eyes had prior complications of corneal anesthesia and had no measurable corneal sensation in the affected eye(s) preoperatively. Two patients—one with cerebellar hypoplasia and the other with posterior fossa tumor resection—had markedly improved corneal sensation 6 months postsurgery (3 eyes; mean [SD] central esthesiometry, 55 [5] mm). A third patient with a history of basal skull fracture underwent unilateral corneal neurotization and recovered 15-mm esthesiometry score centrally after 7.5 months of follow-up. None of the operated on eyes have developed corneal anesthesia–related complications since reconstruction.

Conclusions and Relevance
Corneal sensory reconstruction provides corneal sensation in previously anesthetic corneas. This can be achieved with minimal morbidity using sural nerve grafts, which surgeons commonly use to reconstruct nerve gaps elsewhere. This multidisciplinary approach restores an ocular defense mechanism and may enable subsequent corneal transplant in these patients.
The insensate cornea represents a difficult problem that has defied definitive management. Corneal sensation is critical in maintaining epithelial integrity and limbal stem cell function. Reduced corneal sensation renders the corneal surface prone to injury and decreased reflex tearing. In addition, the poor healing secondary to corneal sensory denervation favors the formation of nonhealing epithelial defects that ulcerate and perforate if not appropriately treated.

Corneal anesthesia can be categorized into acquired or congenital causes. Its acquired form arises from infectious, inflammatory, traumatic, neoplastic, and iatrogenic causes, all of which impair the function of the ophthalmic division of the trigeminal nerve and lead to neurotrophic keratopathy. The congenital form of this condition may be either isolated or syndromic. Furthermore, corneal anesthesia can be either confined to the ophthalmic nerve or alternatively associated with other ocular conditions, such as strabismus, lagophthalmos, or paralytic ectropion, depending on the etiology and the extent of involvement of other cranial nerves. Children may experience photophobia and decreased vision without pain or distress. Signs may vary from mild conjunctival injection to sight-threatening conditions, such as corneal ulceration or perforation, especially if the facial nerve is affected. Unfortunately, few treatment options preserve vision. Initial management seeks to maintain the integrity of the ocular surface. In cases where a nonhealing corneal epithelial defect is present, a tarsorrhaphy is mandatory. Ultimately, in the event of corneal perforation, cyanoacrylate gluing or tectonic corneal transplantation are required. However, because of the lack of sensation and the resultant substantial reduction in corneolimbal stem/progenitor cells, grafted corneas do not heal well and therefore graft longevity is limited with poor visual prognosis.

Neurotization involves the transfer of a healthy donor nerve segment into a tissue to reestablish either motor or sensory innervation. Neurotization is a well-established modality of treatment for different clinical conditions and the technique continues to evolve and gain popularity. Direct neurotization of the anesthetic cornea was previously reported by Terzis et al in adults with unilateral facial paralysis and corneal anesthesia. The technique involved the transfer of the contralateral supraorbital and supratrochlear nerves to the limbal area of the anesthetic cornea. Although successful in restoring sensation to the cornea, this approach denervates the contralateral forehead and scalp, requires a large bicoronal incision with subsequent scarring, and is not applicable in bilateral palsies wherein all branches of the ophthalmic division of the trigeminal nerve are affected.

The purpose of this study was to report early outcomes following a novel corneal neurotization technique in young patients. To our knowledge, this is the first report of restoration of corneal sensation using a sural nerve graft in unilateral and bilateral anesthetic corneas. This novel method reinnervates the cornea, avoids the cosmetically objectionable bicoronal scar, and is more versatile than the previous bicoronal approach.

Methods

This study was approved by the Research Ethics Board of the Hospital for Sick Children, Toronto, Ontario, Canada, and written informed consent was obtained from patients and/or parents/guardians. We included in the study 4 eyes of 2 consecutive patients who had undergone corneal neurotization surgery using a nerve graft. A surgical recommendation was rendered after mapping patients’ sensation over the face to ensure sensation in the territory of the donor supratrochlear nerve. The primary outcome measure was the degree of corneal sensation following surgery. Corneal anesthesia was evaluated preoperatively and postsurgical intervention centrally and in 4 quadrants using a Cochet-Bonnetesthesiometer (Luneau). Corneal sensation of 60 mm was considered normal.

Two patients underwent unilateral corneal neurotization and 1 patient underwent bilateral corneal neurotization. All surgical procedures were performed under general anesthesia. Harvesting of the median cutaneous branch of the sural nerve and dissection of the donor supratrochlear nerve were carried out simultaneously. The sural nerve was harvested proximal to distal using a nerve harvesting device (Figure 1A). The nerve harvesting device was placed around the nerve and passed distally to free the nerve from surrounding tissues. The nerve was then divided, yielding approximately 10 to 15 cm of nerve graft (Figure 1B). The peroneal component of the nerve was preserved but could be used through separate incisions, if required.

The supratrochlear nerve was found on the surface of the corrugator supercilii muscle passing cephalad from the supratrochlear notch. This was accessed through a transverse incision over the medial upper eyelid just inferior to the brow, deep to the origin of the frontalis (Figure 1C and D). An epineural window was then created in the side for end-to-side coaptation of the sural nerve graft. End-to-side coaptation was our preferred option to maximally preserve forehead sensation; however, in the bilateral case, the supratrochlear nerves were found to be small so we divided the nerve distally and performed the coaptation end to end. In unilateral cases, the opposite supratrochlear nerve was used, necessitating subcutaneous tunneling of the nerve graft over the nasal bridge (Figure 1E).

The distal nerve graft was reversed and tunneled subconjunctivally to the perilimbus area of the cornea using a medium-sized eyelet Wright needle (Figure 1F). Distally, the epineurium was removed and the individual fascicles were separated (Figure 1G). The fascicles were then placed around the entire limbal circumference to reinnervate all 4 quadrants (Figure 1H shows the separated fascicles prior to tunneling under the conjunctiva; Figure 1I) and secured to the sclera with 10-0 nylon sutures (Figure 1J). Proximally, coaptation of the graft to the cut surface of the supratrochlear nerve was performed under the operating microscope with 10-0 nylon sutures and fibrin glue (Tisseel; Figure 1K). The conjunctiva was closed (Figure 1L) and lateral tarsorrhaphy was performed in all eyes to optimize the ocular surface.
Results

Preoperatively, all eyes had complications of anesthetic cornea including corneal perforation and/or significant scarring from previous infectious keratitis. No eyes had detectable corneal sensation preoperatively. Figure 2 shows the time progression of the esthesiometry measurements. Postoperatively, no ocular complications were reported and, in particular, none of the operated on eyes developed complications related to corneal anesthesia during the postoperative follow-up.

Patient 1
A boy with cerebellar hypoplasia presented to our clinic at 14 months of age with a right corneal ulcer. Bilateral facial nerve paralysis with hearing loss and bilateral corneal anesthesia were noted. The right eye had poor lid closure and there was a large central corneal ulcer with neovascularization, cataract, and esotropia. The left eye was unremarkable except for a small paracentral opacity from a resolved chronic epithelial defect. The right cornea eventually perforated and a penetrating keratoplasty was carried out at the age of 19 months. This graft failed and the patient underwent a second transplant that also failed and opacified. Sensory mapping indicated that sensation was intact in the forehead region bilaterally. At age 9 years, he underwent bilateral corneal neurotization using the supratrochlear nerve and sural nerve grafts. He developed corneal sensation in his right and left eyes as depicted in Figure 2A and Figure 2B, respectively, within 6 months.

Patient 2
A girl was referred to our clinic for a preoperative assessment prior to excision of a large posterior fossa clear cell meningioma at age 10 years. Her sensation was diminished in the distribution of the left trigeminal nerve including reduced corneal sensation. Her eye examination findings were otherwise unremarkable. A week following her meningioma resection, she presented with a large central neurotrophic...
corneal ulcer in the left eye that decreased her visual acuity to counting fingers at 0.3 m. There was no corneal sensation in the left eye. This ulcer was recalcitrant to treatment and her cornea eventually developed deep central scarring. At age 16 years, she underwent left corneal neurotization using the contralateral supratrochlear nerve with sural nerve grafting. Additional sural nerve graft segments were used to reinervate her cheek and lips by placing grafts from the intact right mental and infraorbital nerves into the affected left mental and infraorbital nerves, respectively. She recovered corneal sensation as shown in Figure 2C within 8.5 months.

Three months after surgery, she said that ipsilateral corneal tactile stimulation felt as if the examiner was stroking the skin territory of the contralateral supratrochlear nerve just above the contralateral brow. By 6 months postoperatively, she said that ipsilateral corneal stimulation no longer elicited contralateral supratrochlear stimulation, and she instead perceived the tactile stimulus as originating from the ipsilateral cornea.

Patient 3
A 9-year-old boy sustained a basal skull fracture resulting in right trigeminal, abducens, and facial nerve palsies. He first presented to our clinic at the age of 11 years with infectious keratitis and corneal anesthesia in his right eye. The examination findings of the left eye were unremarkable. Despite all treatments, his cornea perforated, requiring a tectonic corneal graft, which eventually failed and scarred. At age 17 years, he underwent unilateral corneal neurotization from the contralateral supratrochlear nerve. Simultaneously, he underwent further sensory reconstruction like patient 2, in which sural nerve grafts were used side to end to reconstruct the infraorbital and mental nerve defects. In addition, he underwent cross-face sural nerve grafting for his facial paralysis. The ipsilateral stimuli were first perceived as arising from the contralateral forehead and after 3 months, as arising from the ipsilateral cornea in an identical manner to that seen in patient 2. After 6 months, he recovered protective sensation in all quadrants as shown in Figure 2D.

Figure 2. Cochet-Bonnet Esthesiometry Progression

Measured in millimeters, centrally, and in 4 corneal quadrant precorneal neurotization and postcorneal neurotization. The right eye (A) and left eye (B) of patient 1 with bilateral corneal anesthesia from cerebellar hypoplasia. C, The left eye of patient 2 with corneal anesthesia from previous posterior fossa tumor resection. D, The right eye of patient 3 with corneal anesthesia from basal skull fracture. The ranges on the right indicate the levels of corneal sensation in millimeters. POD indicates postoperative day.
Discussion

Corneal anesthesia requires close monitoring; threatens vision; and imposes medical, social, and economic burdens to the patient and society. Most treatments do not address the underlying cause and outcomes in these cases remain poor. We present a novel technique that restores corneal sensation in unilateral and bilateral corneal anesthesia using a sural nerve graft. This approach may be used to maintain ocular surface integrity (Figure 3), reduce the risk for infections, and maintain vision. It may also enable corneal transplantation in severely scarred corneas.

In unilateral neurotization cases, afferent signals arriving from the affected side travel to the contralateral healthy trigeminal ganglion and the patient learns to distinguish the stimulus location over time as was demonstrated in patients 2 and 3. In the patient with bilateral ophthalmic nerve damage, a different reconstructive strategy was chosen because sensation in the distribution of the ipsilateral supratrochlear nerves was intact.

In a previous study, the contralateral supratrochlear and supraorbital nerves were directly transferred to provide corneal sensation. The average (SD) reported time to reestablish corneal sensibility after direct neurotization was 2.80 (2.17) years in 6 eyes, with average (SD) denervation time of 7.00 (8.56) years. The resulting sensibility was high (≥50 mm) in 1 patient, moderate (>20–<50 mm) in 2 patients, low (≤20 mm) in 2 patients, and not available in 1 patient after a mean (SD) of 16 (2.4) years. In some of their patients, corneal scarring resolved and an improvement in visual acuity was observed. In our patients, the improvement in corneal sensibility was already noticeable after 3 months of follow-up in 3 of 4 eyes. It may be that the young population in our study partly accounted for this difference. Our approach might also conduct more sensory fibers into the cornea because we did not rely on the very wispy distal portions of the supratrochlear and supraorbital nerves; rather, we connected the nerve graft to the much larger-caliber proximal supratrochlear nerve. In our series, we noted no change in visual acuity during the study duration, which is not surprising given that 2 of the 4 eyes had significant scarring after failed previous corneal transplants and 1 eye had moderate amblyopia.

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The previously reported direct corneal neurotization technique is revolutionary but has some shortcomings; we have addressed some of these concerns with this new strategy. It can only be used in unilateral disease where the contralateral supratrochlear and supraorbital nerves have intact sensation. Moreover, it requires a large bicalcular incision and extensive dissection area to reflect the scalp over the forehead to expose and isolate the entirety of the delicate distal ends of the donor nerves. The bicalcular incision leaves a large scar over the top of the head from ear to ear, which can be cosmetically unappealing.

Unlike the direct neurotization technique, the sural graft/transfer approach enables management of bilateral corneal anesthesia. The harvested sural nerve segment is long enough to permit other nerves to serve as potential sources of innervation. In these instances, coaptation to branches arising from the maxillary division or even the mandibular division of the trigeminal nerves are possible as long as their function is normal. The grafted sural nerve enables the recipient nerve to extend its axons to reach the cornea. This donor nerve usually contains 4 to 8 fascicles, each of which may be separated to cover the entire corneal limbus.

The extent of growth of the axons into the cornea following coaptation depends on the time elapsed from surgery, the distance to the target organ, and the age of the patient. However, the exact mechanism of corneal reinnervation postnerve transfer is not completely understood especially in view of the fact that the distal donor nerve fascicles are laid around the limbus and not directly coapted to corneal nerves. Following peripheral nerve transection, Wallerian degeneration occurs in the distal transected segment, which creates a microenvironment for axonal regeneration. Similar processes take place following nerve graft coaptation. Furthermore, the ability of regenerating axons to penetrate the cornea has been demonstrated in several studies following laser in situ keratomileusis, photorefractive keratectomy, and penetrating keratoplasty. Transection of corneal nerves during penetrating keratoplasty occurs in the corneal tissue itself, after which spontaneous nerve regeneration takes place.
place. However, despite the short distance, nerve regeneration in corneal transplants is suboptimal because of misalignment of proximal and distal corneal Schwann cell channels, which is partly responsible for the reduced corneal sensation after penetrating keratoplasty. Following laser in situ keratomileusis, which involves transection of superficial stromal nerves, stromal reinnervation is achieved through the apposition of these channels as demonstrated in a rabbit model. In contrast, in posttraumatic or iatrogenic corneal anesthesia, the distance from nerve transection site to end organ is usually significantly larger. Therefore, the Schwann cell tubes that support spontaneous axonal regeneration degenerate and may atrophy by the time this process takes place. In congenital cases, the neuronal pathway to the cornea has never been established. By coapting a fresh nerve graft to the supratrochlear nerve, the new Schwann cells' basal laminae in the donor nerve graft support axonal regeneration. We surmised that regenerating axons find their way from the surrounding nerve graft fascicles to the corneal stroma or at least to the subepithelial level, thereby restoring sensation.

The sural nerve is purely sensory. Its removal results in a numb patch of skin over the anterolateral ankle and does not interfere with mobility. Postoperative sural nerve-donor site infection, untoward scarring, and neuropathic pain rarely occur following sural nerve harvest, and none of these complications arose in our patients. The incidence of these complications is low and therefore justifies the use of the sural nerve in corneal reinnervation.

The limitation of our study was that corneal reinnervation was only determined clinically. Despite the high correlation demonstrated between functional and morphologic findings in neurotrophic keratitis, evaluation of morphologic parameters pertinent for monitoring reversal of corneal anesthesia, such as an increase in nerve density, decreased density of hyperreflective keratocytes, or an increase in epithelial cell density, would provide anatomical validation of nerve regeneration and resumption of sensation in our patients. Further investigation with in vivo confocal microscopy before and after surgery or corneal histopathologic assessment of corneal buttons excised from patients undergoing corneal transplantation following neurotization surgery could therefore provide more robust evidence of nerve regeneration.

Conclusions

Corneal anesthesia poses a challenge to the ophthalmologist as conservative treatments are often inadequate and may not prevent visual loss. Corneal neurotization using a peripheral sensory nerve graft is a promising technique that gives hope to patients with this condition and expands our therapeutic armamentarium to restore corneal sensation.

REFERENCES


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**OPHTHALMIC IMAGES**

**Intrathecal Anesthesia After Retrobulbar Block, With Terson-Like Syndrome**

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Sagittal (A) and axial (B) computed tomographic images demonstrate anesthetic injected into the optic nerve during retrobulbar block. Images were obtained while the patient was intubated for apnea that developed approximately 5 minutes after retrobulbar injection. The patient was successfully extubated 6 hours later. One day later, the patient was noted to have retinal hemorrhages consistent with a Terson-like syndrome (C). No afferent pupillary defect was present, and Snellen visual acuity remained 20/25.