Clinical Outcomes and Patient Satisfaction After Corneal Neurotization

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Purpose: The aim of this study was to assess clinical outcomes of corneal neurotization (CN) and determine patient perception of postoperative results.

Methods: This was a retrospective study involving 29 eyes in 28 patients who underwent CN. Chart review data included demographic and clinical history; ophthalmic examination including visual acuity, ocular surface quality, and corneal sensation; surgical technique; and postoperative course. Subjective self-reported patient outcomes of surgical success were also assessed. Only eyes with at least 6 months of follow-up were included in the statistical analysis.

Results: A total of 24 eyes and 23 patients were included in statistical analyses. The median postoperative follow-up time was 12.2 months (interquartile range 10.9–18.5 mo). Twenty-three eyes (92%) achieved improvement in ocular surface quality. Eleven of 13 (85%) demonstrated healing of persistent epithelial defects at their last follow-up. Patients gained a median of 2.3 cm in Cochet–Bonnet esthesiometry measurements of sensation. No significant difference was found between preoperative and postoperative visual acuity. All 17 patients who provided self-assessment of their surgical outcome indicated they would undergo CN again if given the choice. Most of the patients reported that the postoperative pain was tolerable, with a median pain score of 3.0 on a 10-point scale (interquartile range 0.0–4.0). Sixteen patients (94%) reported full or partial return of skin sensation along the donor nerve distribution.

Conclusions: CN provides improvement in corneal health and sensibility, with high patient satisfaction and minimal postoperative pain and morbidity.

Key Words: corneal anesthesia, corneal neurotization, neurotrophic keratopathy, patient satisfaction, neurotrophic cornea

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Neurotrophic keratopathy (NK) occurs from partial or complete loss of function of the ophthalmic branch of the trigeminal nerve. Since first described by Magendie in 1824 as "neuroparalytic keratitis,"[1] a number of etiologies have been attributed to NK, including herpetic keratitis, iatrogenic injury or trauma, chemical injury (eg, anesthetic abuse and burns), congenital diseases (eg, Riley–Day syndrome), intracranial compressive lesions, corneal surgery, radiation, diabetes mellitus, and multiple sclerosis. Herpetic keratitis is known to be the most common cause, accounting for 27% of cases in 1 study.[2] The blink and tear reflex elicited by intact corneal sensation is important in protecting the eye from irritants, preventing ocular surface desiccation, and providing tear flow to the eye, which contain nutrients vital to its maintenance. The pathophysiology of NK extends well beyond an impaired blink and tear gland reflex. The corneal nerves, which represent the highest concentration of sensory nerves in the body, are responsible for providing a number of trophic factors including cytokines, neuropeptides, and neuromediators that support corneal stem cells.[3,4] With injury to the trigeminal nerve, the densities of corneal epithelial cells and endothelial cells decrease with time.[5] The survival of the cornea is largely dependent on a 2-way communication between the epithelial cells, keratocytes, and corneal nerves.

Loss of sensory nerve function leads to compromised integrity of the corneal epithelium, potentiating injury to the stroma and sometimes leading to corneal perforation. The progression of injury is often graded on a 3-stage system first introduced by Mackie.[6] Stage 1 represents epithelial erosions with a cloudy appearance of epithelium and poor tear film quality. Stage 2 is defined by the presence of an oval persistent epithelial defects (PED) located in the paracentral cornea. Stage 3 is characterized by corneal erosion involving the stroma, often leading to severe corneal thinning and eventually perforation.

Traditionally, supportive nonsurgical treatments for NK included ocular lubrication, bandage contact lenses, autologous serum tears,[7] topical antibiotics, topical medroxyprogesterone, and oral tetracyclines. In 2018, a topical recombinant human nerve growth factor, cenegermin 0.002% (Oxervate; Dompé Farmaceutici SpA), was approved for the treatment of NK.[8] In one of the largest controlled trials with cenegermin, 65% of patients achieved complete PED closure after 8 weeks of treatment.[9] Although this treatment is well tolerated and may help improve corneal epithelial healing, it is unclear whether this treatment outcome is durable. In addition, the clinical trials did not demonstrate a

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statistically significant improvement in corneal sensation in the cenegermin groups over vehicle.

Before the introduction of corneal neurotization (CN), surgical treatments typically focused on protecting the eye in the later stages of NK when epithelial defects become vision threatening. These treatments include tarsorrhaphy, corneal transplantation, amniotic membrane grafting,[10] paralysis of the levator palpebrae superioris with botulinum toxin injection,[11] and conjunctival flaps.

Since first described by Terzis et al,[12] the technique of CN has evolved significantly in the past decade.[13] The original technique described harvesting both the contralateral supraorbital nerve (SON) and supratrochlear nerve (STN) through a coronal approach and tunneling the nerves across the bridge of the nose to the limbus for direct neurotization of the affected cornea. This original study continues to have the longest reported average follow-up time after CN: 6 patients were followed up for an average of 16 years, and all 6 demonstrated improvements in corneal sensation. Since then, a number of variations in CN technique have been described. Many of these techniques have focused on eliminating the need for a coronal incision through the use of an interpositional nerve autograft or allograft. Elbaz et al[14] first reported use of the interpositional nerve graft for CN with the use of the sural nerve graft (SNG) coapted to the STN, with improved corneal sensation in all 4 eyes studied. This was followed by multiple reports using the great auricular nerve,[15] lateral antebrachial cutaneous nerve,[16] and processed nerve allograft (PNA)[17] as interpositional nerve grafts. Similarly, various sensory donor nerves have been described including infraorbital nerve (ION)[18–20] and great auricular nerve.[21] In an attempt to eliminate the need for an interpositional nerve graft, while still avoiding extensive facial dissection, minimally invasive direct CN (MIDCN) using only palpebral or subbrow incisions for donor nerve harvest and transfer has been described.[17,22–25] Recently, a study comparing outcomes between direct versus indirect CN using SNG demonstrated comparable outcomes between groups.[26]

Although several previously published studies have described long-term clinical outcomes of indirect minimally invasive CN (MICN) with interpositional nerve autograft[26] and direct CN using coronal approach,[12] there is a paucity of outcome data for MICN with interpositional PNAs and MIDCN. In addition, patient satisfaction after CN has not been well studied. This retrospective case series aimed to describe clinical outcomes of these latter techniques and the subjective patient experience for 28 patients.

MATERIALS AND METHODS

A retrospective analysis on all consecutive patients who underwent CN at Duke University Medical Center by senior author (I.M.L) and University of South Florida Morsani College of Medicine by I.M.L and E.M.E. from March 2013 to December 2019 was performed. The study was approved by the Duke University Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. The processing of all protected patient health information was performed in a manner that was compliant with the Health Insurance Portability and Accountability Act.

This study encompasses all consecutive patients presenting for CN including children and adults. Patients were considered for surgery after demonstrating corneal hypoesthesia for at least a period of 6 months to allow for potential spontaneous nerve regeneration. Six months was considered an appropriate amount of time as spontaneous nerve regeneration would be unlikely to occur after this period[27] and patients risked further corneal injury without timely intervention. Patients with no available donor nerve, significant immunosuppression, poor systemic health, severe conjunctival scarring, and those with active ocular or periocular inflammatory, neoplastic, or infectious conditions were excluded from the study. Patients were also excluded if they were expected to undergo subsequent orbital radiation or chemotherapy after surgery. Patients with herpetic causes of NK had to demonstrate stable disease without flares for at least 6 months before surgery. In addition, those patients with herpetic etiologies of NK who were already on maintenance acyclovir or valacyclovir had their dose increased to 1 additional administration per day from baseline before and after surgery to reduce the risk of flare associated with surgery.[28] Patients who were on topical steroids preoperatively did not have their steroid dose or frequency increased postoperatively.

All patients underwent comprehensive ocular examination with slit lamp biomicroscopy during each preoperative and postoperative visit. Visual acuity (VA) was measured at every visit using a Snellen chart. Corneal sensation was measured with a Cochet–Bonnet (CB) esthesiometer in 5 locations of the cornea, including 4 peripheral quadrants (eg, superior, medial, lateral, and inferior) and centrally. The CB measurement analyzed in this study was a mean of all 5 locations. In cases where access to the cornea was limited by patient's anatomy, such as in cases where the patient had a tarsorrhaphy, a mean measurement of the available quadrants was recorded. Given the extent and location of the tarsorrhaphy in 2 patients included in this study, some of the corneal surface was not accessible for CB measurement despite full ductions of the eye. Corneal sensation was measured in all patients by first extending the CB monofilament to 6 cm, then progressively decreasing the length by 0.5-cm increments until the patient indicated sensation or blink was elicited. Patients who were not able to feel 0 cm of the CB monofilament were considered to have no sensation in that section of their cornea. In cases involving corneal transplants, corneal sensation was measured along the outer edge of the host cornea and central sensation was measured in the center of the donor cornea.

Patients were also tested for sensation along their bilateral V1 and V2 sensory distributions to allow for selection of a donor nerve. Skin sensation was tested with light touch using a cotton wisp, and patients were asked to compare their right and left sides. Patients with symmetrical sensation along V1 or V2 sensory distributions were selected to have their ipsilateral SON or ION to be used as a host nerve, with preference to the SON.

Other data collected for use in this study included medical and ophthalmic history, etiology of NK, denervation time, slit lamp photographs, in vivo confocal microscopy in selected patients, preoperative and postoperative ophthalmic surgery, and Mackie stage. Mackie[6] stage was determined based on previously described guidelines at the time of the latest preoperative and postoperative examinations using slit lamp biomicroscopy in clinic. For the purposes of this study, PED was defined as a sterile corneal epithelial defect visible by slit lamp biomicroscopy, which was present for more than 2 weeks despite treatment. Patients were examined postoperatively at approximately 1, 3, 6, 12, and 24 months after surgery. Many patients who traveled long distances for surgery were followed up less frequently in coordination with their referring ophthalmologist. Patients who were described in previous studies (Table 1) were included in the analysis to reflect updated and longer-term clinical data.

Patients were also verbally asked a series of questions at least 6 months after their surgery regarding their subjective outcomes and experience with a final free-form question asking them for any comments or concerns they had regarding surgery. Specifically, patient satisfaction with surgery, level of postoperative pain, return of skin sensation along the donor nerve distribution, and any additional commentary regarding surgery were assessed. Subjective experiences of patients who were unable to be reached after 2 attempts, lacked the capacity or desire to answer all questions, and children were excluded.

Surgical Technique

A customized approach to surgical technique was instituted for all patients following a previously described algorithm.[29] Patients in this study underwent CN by either direct transfer of SON or indirect transfer of SON, STN, or ION with the use of interpositional PNA (1–3 × 50 mm or 70 mm Avance Nerve Graft; AxoGen, Inc, Alachua, FL). The caliber and length of the PNA was selected based on the caliber of the host nerve and its approximate distance from the corneoscleral limbus, respectively. In some cases, the grafts had to be shortened for optimal inset at the corneoscleral limbus, especially in ipsilateral nerve transfers. Care was taken to ensure tension-free neurorrhaphy and fascicle coaptation at the corneoscleral limbus to maximize axonal regenerative capacity. The host nerve was selected based on its function and proximity to the cornea, with preference for the ipsilateral SON whenever possible. The SON has been found to have greater than double the number of axons found in the STN and less donor site morbidity on transection compared with ION.[30] Therefore, end-to-end coaptation was performed for SON and STN and end-to-side neurorrhaphy for ION. In all but 1 case, the host nerve was harvested using minimally invasive techniques with or without endoscopic guidance as previously described.[17,22–25] One case was performed through a hemicoronal incision because this was the first CN performed by the senior author before the development of minimally invasive techniques. In general, patients were offered direct ipsilateral neurotization whenever feasible to minimize the gap length and surgical complexity. In cases when the gap length was long enough to hinder tension-free coaptation to the corneoscleral limbus, a PNA was used as an interpositional nerve graft. A nerve connector (Axoguard Nerve Connector; AxoGen, Inc) was used for tubular repair in most cases where PNAs were used with the end-to-end coaptation. Endoscopic visualization was used to aid in harvesting the maximal length of donor nerve in some cases of minimally invasive direct transfer, as described previously.[17] A temporary suture tarsorrhaphy was placed in all patients to provide immediate postoperative protection of the fascicles, but a small portion of patients also underwent permanent lateral tarsorrhaphy if there was significant corneal erosion with risk for impending corneal perforation. Postoperatively, patients were asked to return for follow-up within the first week of surgery, at which point their temporary tarsorrhaphy was released. Permanent lateral tarsorrhaphy was severed postoperatively in most cases when the corneal surface demonstrated durable stability (over 6 mo). Postoperatively patients were prescribed ophthalmic antibiotic drops placed in the operative eye and ophthalmic antibiotic ointment placed on the eyelid incision twice daily after the eye patch removal on postoperative day 2 for the first 2 weeks after surgery. The rest of patients' preoperative ophthalmic medications were continued postoperatively and tapered based on the clinical improvement.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY). Characteristics of the study population are summarized with descriptive statistics, where continuous variables are expressed as median values and reported with an interquartile range (IQR), whereas categorical variables are expressed as frequencies and reported with a percentage. For each patient, Snellen VA was converted to logMAR VA.[31] Differences between preoperative and postoperative logMAR VA were analyzed by the Wilcoxon signed-rank test. The same type of analysis was performed for differences between preoperative and postoperative corneal sensation by CB esthesiometry. When stratifying differences in logMAR VA and corneal sensation by CN technique (ie, direct vs. indirect CN), the Mann–Whitney U test was performed. The level of statistical significance was set at $P < 0.05$.

RESULTS

Clinical and demographic data were available for all 29 eyes of 28 patients (Table 1). Of the 28 patients, 15 were male patients, and 13 were female patients. There were 2 pediatric patients included in this study. The most common etiology for NK was herpetic disease in 7 patients. Patient 27 was suspected of having herpetic disease after developing NK from an episode of keratouveitis but was seronegative and was, therefore, categorized as having idiopathic keratouveitis. Treatments before CN noted in the chart review included the following: antibiotic drops or ointments (19 patients), bandage contact lens (12), tarsorrhaphy (11), autologous serum tears (7), amniotic membrane graft (6), penetrating

TABLE 1. Clinical and Demographic Data of all Patients Undergoing Corneal Neurotization

Patient	Age (y) and Sex	Etiology	Denerv-Ation Time (mo)	Mackie Stage Preop	Mackie Stage Postop	PED Preop	PED Postop	Host Nerve	Allograft	Follow-Up Time After CN (mo)	Subsequent Surgery	Complications
1*	61 F	Retinal surgery	6	1	0	No	No	Ipsilateral SON	None	74	None	None
2*	62 M	Retinal surgery	Unknown	3	1	Yes	No	Ipsilateral SON	1 × 7 mm	26	None	None
3*	45 F	Schwannoma resection	237	3	1	Yes	No	Contralateral STN	1 × 7 mm	4	Platinum weight placement	None
4*	86 F	HZO	10	3	1	Yes	No	Contralateral SON	None	23	None	None
5*	6 M	Goldenhar syndrome with agenesis of CN V	67	3	1†	Yes	No†	Contralateral SON	1 × 7 mm	1†	None†	None
6*	33 F	DM1, endolaser, PRP	Unknown	2	1	Yes	No	Ipsilateral SON	1 × 7 mm	13	Severing of tarsorrhaphy	None
7*	67 M	HZO	6	1	0	No	No	Contralateral SON	1 × 7 mm	24	Entropion repair	Dermatome anesthesia
8*	59 M	HSV	20	3	1	Yes	No	Ipsilateral SON	None	19	Same d PKP, also CEIOL POM12	None
9	58 M	Schwannoma resection	238	3	3	Yes	Yes	Contralateral SON	1 × 7 mm	9	Gunderson flap	Treatment failure
10*	82 F	Multiple ocular surgeries	14	2	1	Yes	No	Ipsilateral SON	None	14	Upper eyelid recession	None
11*	79 F	HSV	57	1	1	No	No	Ipsilateral ION	1 × 7 mm	10	None	Transient exposure of 1 nerve fascicle
12	33 F	Schwannoma resection	Unknown	1	1†	No	No†	Contralateral SON	1 × 7 mm	3†	Severing of tarsorrhaphy†	None
13OD*	5 M	Idiopathic	Unknown	1	0	No	No	Ipsilateral SON	None	11	None	Asymptomatic bony excrescence at the SO notch
13OS*	5 M	Idiopathic	Unknown	2	0	Yes	No	Ipsilateral SON	None	11	None	None
14	26 M	Schwannoma resection	6	2	3	Yes	Yes	Contralateral SON	1 × 7 mm	14	None	Treatment failure, K ulcer
15	66 M	Trigeminal nerve decompression	38	1	0	No	No	Contralateral SON	2 × 7 mm	12	None	None
16	47 F	Trigeminal nerve decompression	120	1	0	No	No	Contralateral SON	1 × 7 mm	11	CDCR	None
17*	78 M	HSV	11	2	0	Yes	No	Ipsilateral SON	None	10	PKP for traumatic fungal keratitis	None
18	74 M	HZO	29	1	0†	No	No†	Ipsilateral SON	None	12†	CEIOL†	None
19‡	43 F	Trigeminal nerve decompression	34	2	0	Yes	No	Contralateral SON	1 × 7 mm	12	None	None
20	57 F	Retinal surgery	33	1	1	No	No	Ipsilateral SON	None	12	Severing of tarsorrhaphy	None

TABLE 1. (*Continued*) Clinical and Demographic Data of all Patients Undergoing Corneal Neurotization

Patient	Age (y) and Sex	Etiology	Denerv-Ation Time (mo)	Mackie Stage Preop	Mackie Stage Postop	PED Preop	PED Postop	Host Nerve	Allograft	Follow-Up Time After CN (mo)	Subsequent Surgery	Complications
21	59 F	Multiple ocular surgeries	Unknown	3	1	Yes	No	Ipsilateral ION	1 × 7 mm	14	AMT POM3 for PED, resolved at the final visit	None
22	66 M	Acoustic neuroma resection	396	1	1	No	No	Contralateral SON	1 × 5 mm	12	None	None
23	57 F	AVM resection	19	2	1	Yes	No	Contralateral SON	2 × 7 mm	7	Severing of tarsorrhaphy	None
24	66 F	Idiopathic	Unknown	2	1	Yes	No	Ipsilateral SON	1 × 7 mm	2	None	Lethargy
25*§	76 M	HZO	13	1	0†	No	No†	Ipsilateral SON	None	12†	CEIOL†	None
26	58 F	LASIK, DM2	28	2	0	Yes	No	Ipsilateral SON	None	10	None	None
27	79 M	Idiopathic keratouveitis	47	1	1	No	No	Ipsilateral ION	2 × 7 mm	7	None	Delayed presentation of maxillary molar tooth abscess
28	21 M	GSW to CN V	27	1	1	No	No	Contralateral SON	2 × 7 mm	1	None	None

*Patients previously described in previous publications.[17,23,24,32,37]

†Data provided by outside referring physician.

‡Patient treated with cenegermin in the postoperative period.

§Patient treated with cenegermin in the preoperative period.

AMT, amniotic membrane transplantation; AVM, arteriovenous malformation; CDCR, conjunctivodacryocystorhinostomy; CEIOL, cataract extraction and insertion of intraocular lens; CN V, cranial nerve V; DM; diabetes mellitus; F, female; GSW, gunshot wound; HSV, herpes simplex virus; HZO, herpes zoster ophthalmicus; ION, infraorbital nerve; K, cornea; LASIK; laser in situ keratomileusis; M, male; POM, postoperative mo; postop, postoperatively; preop, preoperatively; PRP, panretinal photocoagulation; SO, supraorbital.

keratoplasty (PKP) (5), eyelid gold weight (4), cenegermin (1), and ProKera (Bio-Tissue, Inc, Miami, FL) (1). Of the 29 eyes, 18 had undergone indirect CN with use of PNA. The donor nerves used in order of frequency were contralateral supraorbital (13/29, 45%), ipsilateral supraorbital (12/29, 41%), ipsilateral infraorbital (3/29, 10%), and contralateral supratrochlear (1/29, 3%). Nearly all patients underwent minimally invasive CN as previously described, with the exception of the first patient who underwent a hemicoronal approach.[32]

Corneal integrity and epithelial injury were also recorded preoperatively and postoperatively using the Mackie[6] classification system. Of the 24 eyes with at least 6 months of follow-up data for Mackie staging, 5 patients had Mackie stage 3, 8 had Mackie stage 2, and 11 had Mackie stage 1 disease preoperatively. Of the 5 patients with stage 3 disease preoperatively, 1 patient remained with stage 3 disease and 4 improved to stage 1 disease. Of the 8 patients with stage 2 disease before surgery, 1 patient progressed to stage 3 disease, 3 patients improved to stage 1 disease, and 4 had shown resolution of their epitheliopathy after CN. Of the 11 patients with stage 1 disease preoperatively, 4 remained at stage 1, and 7 had shown resolution of their epitheliopathy postneurotization. Of the 13 eyes with preoperative PEDs, 11 (85%) demonstrated durable PED closure through their last follow-up visit. Some of these patients were also noted to have improved corneal clarity and regression of corneal neovascularization. One patient who underwent contralateral MICN with SON and use of PNA had no improvement in corneal integrity or corneal sensation on his last follow-up visit, with a recurrent corneal ulcer that required a permanent tarsorrhaphy. Another patient who underwent the same procedure because the first did not show any improvement in corneal sensation or epithelial integrity and required a Gunderson flap approximately 2 years postneurotization.

Of the 29 eyes in this study, 24 had at least 6 months of follow-up data. Of these 24 patients, the median age at time of surgery was 60.2 years (IQR 49.6–76.2 yrs). The median duration of follow-up was 12.2 months (IQR 10.9–18.5 mo), with the longest follow-up period being approximately 6 years. The median denervation time that was available for 22 patients was 28.5 months (IQR 12.5–59.5 mo). The median preoperative logMAR VA was 1.41 (IQR 0.70–2.83; Snellen equivalent 20/500, IQR 20/100–hand motion), which did not significantly improve postoperatively (median postoperative logMAR VA 0.88, IQR 0.42–2.90; Snellen equivalent 20/150, IQR 20/50–hand motion; $P = 0.103$ by Wilcoxon signed-rank test). When comparing the postoperative change in logMAR VA between patients who had direct versus indirect CN, there was no significant difference between groups ($P = 0.057$).

Postoperative changes in corneal sensation were also studied when both the preoperative and at least 6 months of postoperative CB data were available for 22 of 29 eyes (Fig. 1). The median preoperative corneal sensation was 0.6 cm (IQR 0.0–1.7 cm), which significantly improved to a median postoperative value of 2.9 cm (IQR 1.6–5.5 cm, $P < 0.001$ by Wilcoxon signed-rank test). When comparing the postoperative change in corneal sensation between patients who had direct versus indirect CN, there was no significant difference ($P = 0.152$ by Mann–Whitney U test). All patients who manifested improvement in corneal sensation and had postoperative in vivo confocal microscopy demonstrated corneal reinnervation in the anterior stroma and subbasal region of the cornea postoperatively (Figs. 2A, B). We found that 13 patients, of both direct and indirect CN groups, experienced subjective improvement in ocular sensation on eye drop instillation before demonstrating any reliable improvements in CB measurements. Three patients in both groups also reported feeling the eye drops first in the distribution of the sensory donor nerve before feeling them in the surgical eye. This allesthesia occurred at around 3 to 6 months postoperatively and lasted for a few weeks until proper localization of tactile stimulus to the cornea.

Surgical complications and postoperative ocular surgeries are listed in Table 1. No intraoperative complications were noted. Two patients underwent PKP after CN, with atient 8 undergoing PKP at the time of CN because of impending corneal perforation. He demonstrated good recovery and had a sufficiently clear graft to allow for successful cataract surgery 12 months after CN. Patient 17 developed fungal keratitis from a tree branch injury to his previously (ie, before CN surgery) failed corneal graft 8 months after CN and required urgent repeat PKP. Although his previous 2 corneal grafts failed within months of transplantation, this graft remained clear without infection or recurrent PED at his last follow-up 2 years after CN. Postoperatively, 1 patient developed an exposed nerve fascicle at the corneoscleral limbus, which eventually epithelialized over several weeks without affecting the success of the procedure. A pediatric patient who underwent MIDCN with SON developed a small bony excrescence at the supraorbital notch, which was not bothersome to the patient and did not affect his outcome. There was a case of a maxillary tooth abscess with delayed presentation due to temporary postoperative hypoesthesia in the ION distribution. The abscess was treated successfully by tooth extraction and antibiotics with no long-term sequela. Patient 24 had described lethargy for 1 week after surgery that self-resolved and was believed to have been a consequence of general anesthesia rather than the procedure itself. Finally, 1 patient continued to have persistent hypoesthesia in the distribution of the donor SON.

Seventeen of 28 patients were able to provide subjective evaluation of their surgical results. Of the 7 patients who were unable, 3 could not be reached to answer questions, 2 were underage and unable to reliably answer questions, 1 had limited ability to communicate due to mental incapacity, and 1 patient was deceased because of sepsis associated with thoracic spine surgery. Four patients were excluded because of having less than 6 months of clinical follow-up. When patients were asked for their highest level of postoperative pain on a 0–10 scale, with 10 being the worst possible pain, the median pain score was 3.0 (IQR 0.0–4.0). When asked about postoperative numbness in the sensory distribution of the donor nerve, 29% (5/17) and 65% (11/17) had reported that their numbness had partially or completely resolved, respectively. Only one patient (6%) reported that their donor site numbness had not improved at all since the surgery.

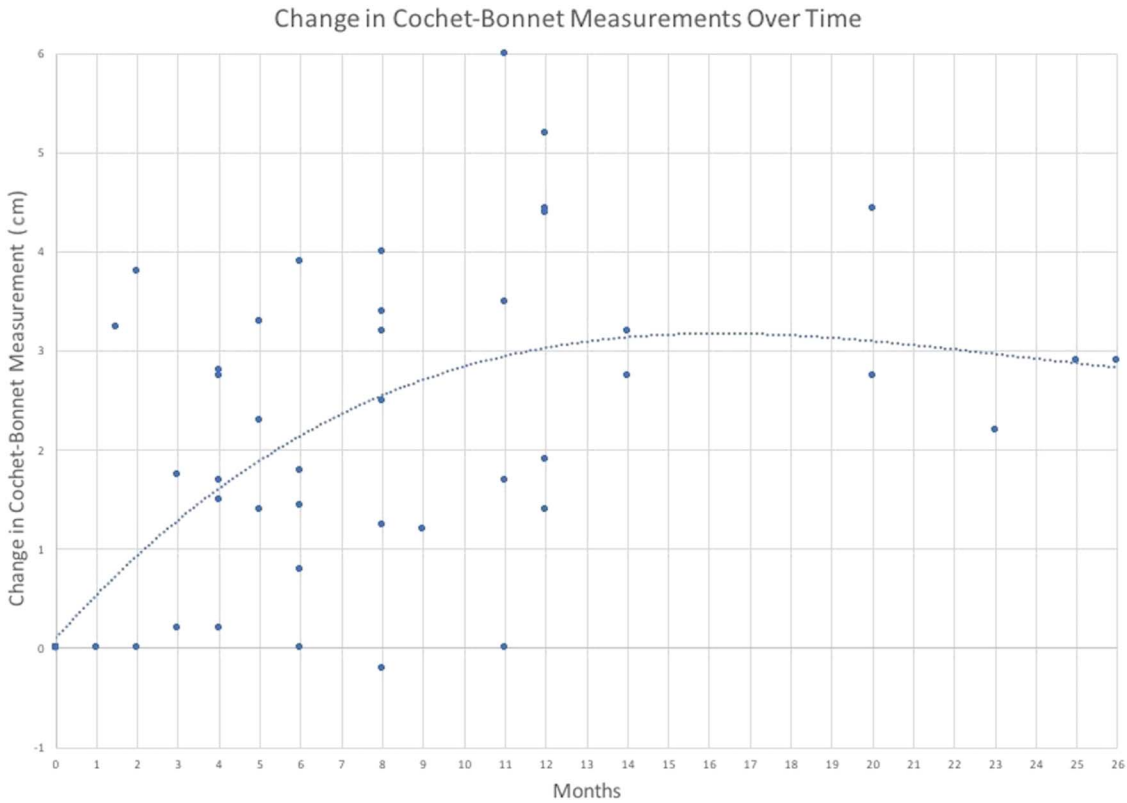

FIGURE 1. Scatterplot demonstrating change in individual corneal Cochet–Bonnet esthesiometry measurement from preoperative baseline over time with a polynomial third-order trend line reflecting the average trend. (The full color version of this figure is available at www.corneajrnl.com.)

When asked about pain or paresthesia along the distribution of the sensory donor nerve, 18% (3/17) reported mild or moderate discomfort or pain; all others (82%) reported no postoperative pain in the area.

Patients were also asked to evaluate their level of overall satisfaction with the surgery. Most patients reported that they were very satisfied (14/17, 82%) and 1 (17%) reported satisfied with the outcomes of CN, whereas 2 (12%) reported that they were dissatisfied, and none were very dissatisfied (0%) with surgery. When asked whether they would undergo the surgery again if given the choice, all patients had responded yes.

DISCUSSION

This study represents a retrospective review of both objective and subjective CN outcomes with long-term (ie, greater than 6 mo) data available for 24 of 29 eyes. Results demonstrated a high success rate with all but 2 patients achieving stabilization of ocular surface. The 2 eyes that were found to have treatment failure underwent contralateral MICN with PNA. This may suggest that an increased gap length between the donor nerve and the cornea may reduce surgical success. Although accounting for these 2 failures, MICN with the use of PNA yielded an 89% success rate of 18 eyes. These results are in line with other recently published studies on PNA use in CN[33] and peripheral nerve reconstruction throughout the body[34] and a similar study of MICN with interpositional nerve autograft.[35] An 85% closure of PEDs was found to occur at a better rate than those published for topical cenegermin, which demonstrated only 65% PED closure rates at 8 weeks.[8] However, the methods for qualifying PEDs differed between studies, with our study defining PED as a defect visible on slit lamp examination with fluorescein staining, whereas Bonini et al[8] required the defect to be at least 0.5 mm in size with fluorescein staining.

This study also examined the gain in corneal sensation by CB esthesiometry over time as a surrogate measure of corneal reinnervation. The longest follow-up time examined in this group was 26 months for 1 patient. As demonstrated in Figure 1 and in a similar study by Catapano et al,[35] most gain in corneal sensation was noted to occur within the first 6 months after surgery. The improvement in corneal sensation over time seems to follow a rectangular hyperbola function, approaching the maximum value at around 1 year. Six patients were noted to have regained full corneal sensation (mean CB measurement greater than 5 cm) at last follow-up. Although most patients had not recovered full corneal sensation, we found that even partial recovery of corneal sensation sufficiently improved corneal integrity and arrested the underlying disease process. It is interesting to note that subjective improvement in corneal sensation occurred before any measurable improvement by CB esthesiometry in some patients. This may be due to subthreshold improvement in

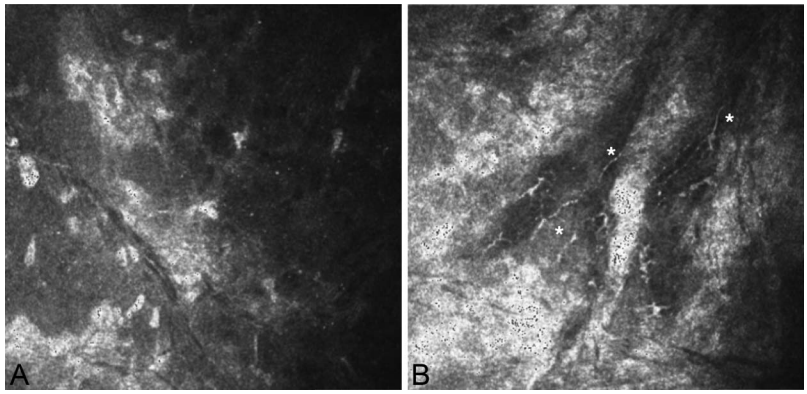

FIGURE 2. A, Corneal IVCM of patient 3 at 4 months before CN showing paucity of corneal nerves in the anterior stroma. B, Corneal IVCM of patient 3 at 4 months postoperatively showing presence of corneal nerves (*) in the anterior stroma. IVCM, in vivo confocal microscopy.

corneal sensation from regenerating but still poorly functional nerve endings within the cornea relative to the sensitivity of CB esthesiometer. Given that the donor nerves are implanted in the subconjunctival space, it is also plausible that the eye first regains some conjunctival sensation before corneal sensation due to proximity, and this is responsible for the subjective sensation associated with drop usage and foreign body sensation in the first 3 months. In addition, the reported allesthesia in some patients, with eventual correct stimulus localization, may represent a process of cortical remapping and plasticity.[26]

Overall, patients reported a high rate of satisfaction, with 88% of patients reporting that they were very satisfied or satisfied with the surgery. Patients also reported minimal discomfort during postoperative recovery with 94% reporting no to mild difficulty and partial to complete return of sensation with minimal-to-no pain or paresthesia in the distribution of the donor nerve. Because of the use of a minimally invasive approach for all but 1 of the patients in this study, none of the patients developed complications more likely to occur with a coronal approach such as alopecia, facial nerve injury, hematoma, or noticeable scarring.[36]

Lack of VA improvement is consistent with larger trials for treatment of NK, including phases 2 and 3 clinical trials for topical cenegermin. Both the phase 2 REPARO trial[8] and the NGF0214 study[9] did not demonstrate statistically significant improvements in VA measures despite successful PED closure in most patients. VA also did not significantly improve in other studies of CN.[26,35] This is because CN is often performed in later stages of NK, when dense central corneal scarring may limit final VA despite PED closure. As noted in a study by Kim et al,[37] patients with earlier CN are found to benefit from a greater degree of absolute corneal sensory recovery. The reasons for this are likely multifold, possibly because of diminished axonal regeneration and function within the stromal scar. Therefore, the authors recommend CN at earlier Mackie stages because the potential for preserving VA, without the need for subsequent corneal transplantation, may be higher. This approach is especially critical in children because of concerns of amblyopia development from corneal opacification.

Symptomatic postoperative complications for CN were rare; however, 1 patient developed an ipsilateral maxillary tooth abscess within the first 6 months of surgery, which was not initially noticed because of hypoesthesia from CN using the ipsilateral ION. Because the ION provides sensory innervation to maxillary dentoalveolar structures, patients who have undergone CN with ION might be at higher risk for delayed presentation of maxillary dentoalveolar pathology in the initial postoperative period. Although end-to-side neurorrhaphy may minimize this risk owing to avoidance of axonal transection, dentoalveolar complications can still occur as seen in 1 of our patients. Because of this risk, our preferred choice for donor nerve is a V1 branch.

Use of PNA for CN has been considered controversial by some.[38] To date, there have been no prospective studies comparing PNAs and nerve autografts in CN. Retrospective studies recently published by Leyngold et al[39] and Sweeney et al[33] had demonstrated that CN with PNAs is safe and effective, with a reinnervation timeline and gain in sensation that was comparative with autograft studies.[26,35] Numerous retrospective studies have demonstrated that PNAs compare favorably with nerve autografts for sensory, mixed, and motor reinnervation surgery at various gap lengths.[40–42] Recently, the largest study to date examining the use of PNAs as interpositional nerve grafts for peripheral nerve repairs throughout the body in 624 procedures in 385 patients demonstrated safe, efficacious, and durable reinnervation with sensory, mixed, and motor nerves.[34] The study demonstrated similar rates of meaningful sensory and motor recovery and adverse events when compared with nerve autograft repair. This was further confirmed by a recent systematic review that showed similar sensory outcomes and safety profiles between nerve autografts and PNAs for peripheral nerve surgery.[43] When comparing our PNA results with those of Catapano et al[35] who used interpositional SNG, both studies showed similar timelines in corneal sensory improvement and demonstrated similar PED closure rates, with both sets of patients sustaining most of their gain in corneal sensation within the first 6 months (Fig. 1). It should be noted that the study by Catapano et al did demonstrate a higher degree of corneal sensory gain compared with our study, but their study cohort included a larger proportion of children, with a mean age at time of surgery of 12.5 years.[35] Children have been previously found to have more robust responses in CN surgeries when measuring final corneal sensation and VA, presumably because of higher abilities of healing and neuroplasticity.[44] The median gain in corneal

sensation across all groups in our study was 2.3 cm, with a final median sensation of 2.9 cm. When comparing our corneal sensation results with the recent study by Fogagnolo et al,[26] who reported a gain of corneal sensation from 0.3 cm to 2.2 cm with MICN using interpositional nerve autograft and coronal approach with direct donor nerve transfer, our gain in sensation was very similar, likely because of similar age distribution of the studied patients. Fogagnolo et al reported a mean age of 45 years compared with our group that had a mean age of 54 years. Furthermore, it remains unclear what degree of corneal sensory recovery is required for durable improvements in corneal epithelial integrity. Because nerve autografts require additional anesthesia time and separate and often distal donor site surgery, with potential for painful neuroma formation, scarring, and loss of protective skin sensation, the authors continued to use PNAs over nerve autografts for indirect CN without an adverse effect on postoperative outcomes.

Because of the small sample sizes, we were unable to determine whether a difference in gap length could affect the rate of corneal healing or change in corneal sensation. Previous studies have noted that increased gap length may reduce the rate and chance of surgical success in peripheral nerve surgery, but only when comparing extremes such as subgroups of gap length of <15 mm with subgroups with gap lengths of 50 to 70 mm.[34] Furthermore, a recent study found no statistically significant difference in either corneal healing time or change in corneal sensation when comparing direct and indirect CN, similar to our findings.[26]

A number of limits to the scope of this study should be noted. One limitation to this study was the use of cenegermin in 2 patients. Patient 19 was started on cenegermin 2 months after CN although having stable Mackie stage 2 disease. Patient 25 was started on cenegermin in the week immediately before surgery. Both patients were started on cenegermin independently by outside cornea specialists. It is, therefore, difficult to elucidate whether the improvement of their ocular surface health was in response to CN and/or cenegermin. Although this was a relatively large case series, subgroup analyses by etiology, age, technique, and gap length were not possible because of small sample sizes within each group. Children have been previously found to have more robust responses with CN, presumably because of greater inherent abilities in overall healing and neuroplasticity,[44] but only 2 pediatric patients were included in this study. The etiologies of denervation in this study were widely varied in mechanism and anatomic location. However, a separate study on outcomes of CN for herpetic NK of patients in this study cohort has been previously published, which demonstrated similar outcomes with complete closure of PED in all 6 patients and gain in mean corneal sensation of 20 mm.[37] Patient self-evaluation of their surgical outcomes was limited by recall bias and a unmasked interviewer, although the interviews were conducted confidentially without the presence of the surgeon to encourage patient candor. Finally, because of the nature of CN and need for a customized approach for each patient, the study was limited by the heterogeneity of the surgical approaches used.

In summary, CN provides a safe and effective treatment for NK, a disease that has been historically very difficult to treat. Our study examined the use of CN for different etiologies of NK and postoperative patient satisfaction. Patients were found to have a high rate of success, regardless of surgical technique, allowing for PED closure and improved corneal integrity in most patients. As with previous studies, patients were not found to have a statistically significant improvement in VA often because of preexisting corneal scarring. Postoperative patient self-assessment of surgical outcomes indicated that most were satisfied with their results. Further studies will be necessary to understand how the relationships of gap length, etiology, denervation time, patient age, and technique may influence the success of CN.

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