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Corneal Neurotization in Elderly Patients with Multimorbidity

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ABSTRACT

Purpose: Corneal neurotization (CN) is a surgical technique to improve corneal sensitivity and the ocular surface in eyes with neurotrophic keratopathy. It has been predominantly advocated in patients with congenital corneal hypesthesia. Neurotrophic keratopathy is however much more frequent at an older age and in often multimorbid patients. We report our experience with corneal neurotization in patients with multimorbidity.

Methods: Seven eyes of 5 patients (f:m=2:3, median age 70±12 years) suffering from neurotrophic keratopathy due to Diabetes mellitus ($n=3$), post Herpes Zoster keratitis (1) and drug use (1) were treated with direct CN using the supraorbital nerve ($n=5$) or indirect CN ($n=2$, with sural nerve interponate) and followed for a median of 7 months. In one case, a femtosecond laser was used to create peripheral intrastromal corneal pockets. Documented parameters included corneal sensitivity tested with a Cochet Bonnet aesthesiometer in four quadrants and the corneal center pre- and postoperatively, stage of NK, and duration of surgery.

Results: Corneal sensitivity was 0 mm in all areas tested of all corneas prior to neurotization (stage 3 NK). Mean surgical time was 247±53 min. At 3 months, it was improved in 63% of all areas tested (5/7 eyes). In two eyes, severe neurotrophic keratopathy recurred (stage 3 NK). Three out of the five patients died of general conditions during follow-up.

Conclusion: Corneal neurotization is a resource intensive technique, which successfully can improve corneal sensitivity. We also for the first time used a femtosecond laser to create peripheral intrastromal corneal pockets. When offering CN to elderly patients the long time to more profound corneal reinnervation, required to prevent corneal perforation, and generally potential fatal comorbidities should be considered carefully. Given the good results reported for younger patients the procedure should be indicated probably earlier in the course of the disease.

Introduction

Neurotrophic keratopathy (NK) is a rare corneal disease that results from impaired corneal innervation.[1,2] It leads to spontaneous recurrent epithelial defects and possibly corneal ulceration and perforation. The causes of NK are diverse. They include genetic disorders such as familial corneal hypesthesia, as well as systemic diseases such as diabetes mellitus, multiple sclerosis, or amyloidosis.[3] In addition, pathologies of the central nervous system, such as tumors, strokes, degenerative diseases, or surgical procedures, especially in the brainstem, can cause NK. Locally, infections, mostly by herpes simplex or varicella zoster viruses, but also chemical burns can be causative for this disease. NK has been categorized in three stages by Mackie as well as Dua: stage 1 with punctate epithelial fluorescein staining, stage 2 with an epithelial defect and stage 3 with stromal lysis possibly resulting in perforation.[3,4] Mastropasqua et al. propose a different grading of NK that *via* in-vivo confocal microscopy and anterior segment optical coherence tomography (semi)quantifies the severity of subbasal nerve fiber damage and the level of stromal ulceration.[5]

The therapeutic management of NK consists of several possible approaches, many of which, however, do not directly improve corneal sensitivity, but only represent a symptomatic treatment.[1] In mild NK, local therapy must be adjusted due to potential epithelial toxicity, and the side effect profile of systemic medications such as neuroleptics should be evaluated. Consistent lubrication and antimicrobial treatment in case of infection by bacteria, viruses or fungi is essential. In case of insufficient healing or recurrent epithelial defects even under bandage contact lenses, treatment with autologous serum drops is advisable.[6] Since 2017, Cenegermin, a recombinant human nerve growth factor has been approved for moderate and severe stages of NK,[7] but was withdrawn from the German market in March 2020. These medical options must be weighed individually against surgical measures such as temporary or permanent tarsorrhaphy, amniotic membrane transplantation or conjunctival flaps, which are often associated with either temporary visual loss and/or cosmetic impairment.

The principle of neurotization refers to the transposition of an autologous donor nerve into recipient tissue for the purpose of motor or sensory reinnervation. Corneal neurotization (CN) can be performed by direct transposition of locally available nerve tissue or by transplantation of an interposition graft, for which the sural nerve is often used. Direct corneal neurotization (DCN) was successfully performed by Terzis et al. by dissecting the contralateral supraorbital and supratrochlear nerve in a patient with facial paralysis.[8] In addition to this approach, direct neurotization using the ipsilateral supraorbital nerve has already been described in a patient with iatrogenic damage to the long ciliary nerve.[9] Terzis et al. also described the option of indirect corneal neurotization (ICN) using a sural nerve graft to the contralateral supratrochlear or supraorbital nerve *via* an end-to-side or end-to-end anastomosis.[8] In this approach, a subcutaneous tunnel across the nose is created to allow passage of the nerve graft to the affected eye. The time until reinnervation regardless of the surgical method ranges from 3 months to several years.[10] Most of the published CN cohorts include relatively young (<60 years of age) patients with isolated pathologies (e.g. congenital nerve damage or due to tumors, infection/herpes, and after neurosurgical procedures).[11–14] So far, there is only limited data on the outcome of corneal neurotization in elderly multimorbid patients. Therefore, the aim of this work was to analyze the outcome of corneal neurotization in a patient cohort with higher age and multiple systemic morbidities.

Material and methods

In this cohort study, a retrospective chart review was performed of all patients who had received CN at a tertiary referral center NK between 2018 and 2022. The patients were either treated with direct or indirect CN. The preoperative assessment included a verification of sensory function in the donor nerve area, e. g. the forehead, using a Cochet Bonnet aesthesiometer. For DCN sensitivity of the forehead (frontal branches of the trigeminal nerve) was tested and for ICN additionally the sensitivity of the heel/the lateral edge of the left foot (sural nerve). All surgical procedures were performed under general anesthesia by a multidisciplinary team of oculoplastic and corneal surgeons as well as a neurosurgeon. Direct CN was performed with the patients in a supine position using a coronal incision from the auricular helix of one ear to the median forehead just below the hairline. The subgaleal space was bluntly dissected and the periosteum incised just above the orbital rim to access the branches of the supraorbital nerve, which were carefully dissected. A tunnel was then created from a medial upper lid crease incision to the superior orbital rim to pass the nerve bundle with the aid of a Wright needle to the superior fornix of the conjunctiva with minimal manipulation. After careful removal of the epineurium, the branches were separated into several fascicles, partially shortened as required and placed along the limbal circumference. Subsequently, the conjunctiva was opened 2 to 4 mm from the limbus at several clock hours. Limbal intrastromal pockets were prepared with a crescent blade in five eyes and in two eyes using a

femtosecond laser (Ziemer Z8®, intraoperative parameters: incision site 45°/135°/315°, distance to limbus 1.7 mm, width 3 mm, angle of entry 0°, angle of curvature -30°). The ends of the fascicles were then placed in the stromal pockets and fixed adjacent to the sclera at the limbus with nylon 10.0 single sutures. This was followed by conjunctival and tenon closure using Vicryl 9.0 single sutures.

Indirect CN was performed using an autologous sural nerve graft of about 30 cm length (for bilateral ICN split in 2 fascicles). The lower leg wound was sutured with Vicryl 4.0 sutures, which were removed 10 days postoperatively. The sural nerve graft was divided in two halves of 15 cm each to allow a tension free anastomosis to the supraorbital nerve, which was severed at the superior orbital rim through a brow incision. The following surgical steps were identical to the direct corneal neurotization. The patient received an intraoperatively single shot antibiotic treatment with 1 gram of cefazoline intravenously as well as topical postoperative antibiotic treatment with gentamycin and dexamethasone eyedrops (5q) and ointment at night.

The primary outcome parameter of this cohort study was the degree of corneal reinnervation at final follow-up as measured using a handheld Cochet-Bonnet esthesiometer (Luneau®). The nylon filament was incrementally advanced in whole 1 cm steps until the patient sensed its contact and the length was recorded. This was obtained centrally as well as in the superior, temporal, inferior and nasal quadrant of the cornea. Additional documented parameters included age, gender, coexisting morbidities, previous eye surgeries, best corrected visual acuity (BCVA) pre- and postoperatively (obtained with a Snellen chart), stage of NK, duration of surgery, time to development of corneal reinnervation.

Statistical analysis was performed using Microsoft Excel for Windows 2018 (Microsoft Corporation, Redmond, Washington, USA). A p-value 0.05 was considered as statistically significant.

Results

Seven eyes (4 right and 3 left eyes) of 5 patients (f:m = 2:3, median age 70 ± 12 years) were included in the cohort. All had previously developed stage 3 NK at the time of surgery, either due to Diabetes mellitus ($n = 2$), status post Zoster keratitis ($n = 1$), polyneuropathy of unknown cause ($n = 1$) and multiple systemic drug use (including chemotherapy) ($n = 1$). Documented systemic comorbidities included gait disorder requiring walking aid (4) renal insufficiency (2), rheumatoid arthritis (2), CREST syndrome (1), Sjoegrens syndrome (1), and Lichen ruber (1).

Corneal neurotization was performed using DCN with the supraorbital nerve ($n = 5$) and ICN ($n = 2$), with a sural nerve interponate in an end-to-end anastomosis to the ipsilateral supraorbital nerve. Mean surgical time was 247 ± 53 min. Median follow-up was 7.6 ± 5.0 months. Corneal sensitivity was 0 mm in all areas tested of all corneas prior to corneal neurotization. At 3 months, corneal sensitivity was improved in 63% of all areas tested (22/35) to a median of 3 (0/4 min/max) (Figure 1). Reinnervation was detected from 3 months postoperatively in 5 eyes. Three eyes regained

sensitivity in all 5 areas tested. In two eyes, sensitivity remained 0 in the superior quadrant. Mean BCVA remained unchanged from 1.8±0.6 preoperatively to 1.9±0.5 at last postoperative follow-up.

Three out of the five patients died of general conditions (urosepsis 4 months postop, metastatic cancer 3 months postop, heart failure 3 months postop) early during follow-up. In two eyes, stage III NK recurred, requiring immediate perforating keratoplasty because of a descemetocele/perforation (Tables 1 and 2). Patient No. 2 presented with a corneal perforation 18 months post-neurotization despite a sensitivity of 4/6 cm in all quadrants tested 12 months postoperatively. In patient No. 3, the corneal perforation occurred 8 months postoperatively. At 6 months follow-up the patient had a sensitivity of 1/6 centrally and superiorly and 4/6 in the remaining quadrants. He subsequently developed a choroidal hemorrhage and a retinal detachment requiring vitrectomy

and silicone oil tamponade, resulting in a recurrent descemetocele and redo-keratoplasty 12 months post-neurotization.

Case 1

A 64-year-old, male patient with long standing (20 years) diabetes mellitus type 2-related stage 3 NK in both eyes had already required lamellar horseshoe KP and AMT on the right side due to a deep limbus parallel ulcer (Figure 2). He was scheduled for DCN surgery due to recurrent epithelial defects on the transplant despite repeat AMT. His left eye required emergency KP due to a perforated corneal ulcer prior, but subsequently remained stable. He also suffered from renal insufficiency and a gait disorder. Preoperative BCVA was 1.0 logMAR on the right eye due to a central corneal scar. Preoperative Schirmer's test was 5 mm in the right eye and 6 mm in the left eye. Intraoperatively, five branches of the
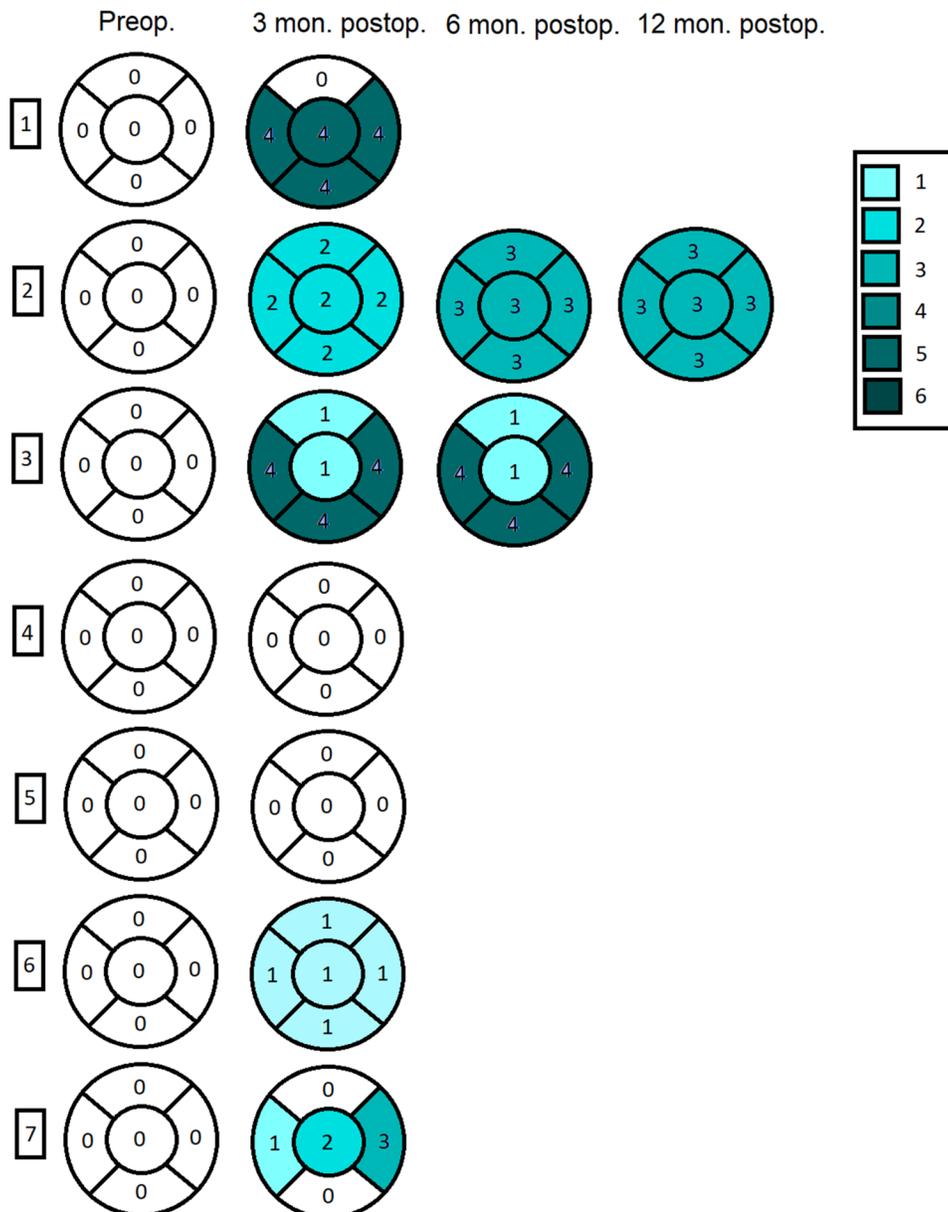
Figure 1. Graphic description of corneal sensitivity as tested with the Cochet-Bonnet aesthesiometer in 4 quadrants and the corneal center in all five patients (seven eyes) preoperatively and during follow-up of up to 1 year.

Table 1. Patient characteristics and outcome.

Patient	Age (y)	Etiology	Comorbidities	Prior ophthalmic surgery
1	64	Diabetes mellitus type 2	Renal insufficiency, gait disorder	st.p. multiple AMT, st.p. Horseshoe-keratoplasty
2	78	st.p. Herpes zoster	Rheumatoid arthritis and a CREST syndrome	st.p. 4x keratoplasty, st.p. multiple AMT, st.p. botulinum toxin induced ptosis, st.p. DCR
3	77	Unknown	Peripheral neuropathy, gait disorder	st.p. multiple AMT, st.p. 2x keratoplasty
4R	80	Drug side effect	Sjörgens syndrome, lichen ruber, rheumathoid polyarthritis etc. *	st.p. 7x AMT, st.p. 3x keratoplasty
4L	80	Drug side effect	#	st.p. 5x AMT, st.p. 4x keratoplasty
5R	55	Diabetes mellitus type 1	Renal insufficiency, gait disorder, partial amputation of extremities	st.p. 3x AMT, st.p. medial kanthoplasty + lateral tarsorrhaphy
5L	55	Diabetes mellitus type 1	#	#
			* see text; # same comorbidities (fellow eye)	# same comorbidities (fellow eye)

*See text; # same comorbidities (fellow eye), BCVA in logMAR, †patient died during follow-up.
AMT: amniotic membrane transplantation; KP: keratoplasty.

Table 2. Patient characteristics and outcome.

Patient	Follow-up (m)	Time to sensitivity (m)	BCVA preop	BCVA postop	Complications
1	4	3	1	0.9	†
2	15	2	1.3	2.3	Corneal perforation with IOL tamponade
3	14	2	1.3	1.9	2x keratoplasty, choroidal hemorrhage, retinal detachment
4R	7	–	2.3	2.3	†
4L	7	–	2.3	2.3	†
5R	1	3	1.9	2.3	†
5L	1	3	2.3	2.3	†
			BCVA in logMAR		† patient died during follow-up

BCVA in logMAR, † patient died during follow-up.
AMT: amniotic membrane transplantation; KP: keratoplasty.
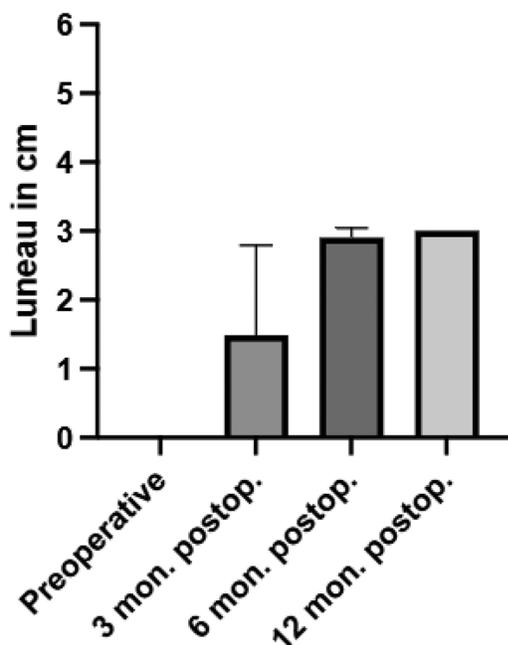
Figure 2. Mean sensitivity pre- and postoperatively.

supraorbital nerve were isolated and transposed in corneal pockets at 12h, 2h, 4h, 8h, and 10h (Figure 3). At the final follow-up 3 months after surgery, corneal sensitivity was 4/6 in all quadrants and centrally except in the superior quadrant and BCVA 0.9 logMAR. The patient died 4 months postoperatively due to urosepsis of unknown cause.

Case 2

A 78-year-old female patient with post-herpetic NK in the right eye had a total of four KPs due to perforations, twice in combination with an AMT and protective botulinum

toxin induced ptosis. Due to a persistent epithelial defect despite the mentioned procedures, this patient was planned for DCN. Comorbidities included rheumatoid arthritis and CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility sclerodactyly and telangiectasia). Before DCN her BCVA was 1.3 logMAR in the right and Schirmer's test 0 mm in both eyes. Four branches of a thin supraorbital nerve were transposed into peripheral corneal pockets at 2h, 4h, 8h, and 10h. At the final follow-up one year after surgery, corneal sensitivity was 3/6 in all quadrants and in the center. The patient then was lost to follow-up and returned 18 months later with a corneal perforation. Emergency keratoplasty was performed and the explanted perforated transplant was sent to pathology. On histology, no signs of a regenerated corneal nerve plexus could be found. After discharge (with BCVA 2.3), the patient refused further follow-up due to the COVID pandemic.

Case 3

A 77-year-old male patient presented with a perforated corneal ulcer requiring emergency keratoplasty in the left eye. A general diagnostic workup including a neurology consult revealed a generalized peripheral neuropathy with a mild progressive gait disorder. Prior to neurotization corneal sensitivity (tested in all four quadrants and centrally) was 0 in that eye, while the fellow eye had full corneal sensitivity (6/6). He was scheduled for DCN surgery due to persisting epithelial defects on the transplant. Preoperative BCVA was 1.3 logMAR on the left eye. Preoperative Schirmer's test was 11 mm on the right eye and 0 mm on the left eye. During neurotization, three supraorbital nerve branches were isolated and transposed into corneal pockets at 12h, 4h, and 8h. Three months after surgery, corneal sensitivity was improved to 4/6 in the nasal, temporal and lower quadrants and 1/4 in the center and the

upper corneal quadrant. This was unchanged at 6 months. Eight months after surgery, the patient presented with a recurrent descemetocele in the left eye, requiring another penetrating KP, during which a choroidal hemorrhage developed. A subsequent retinal detachment required vitrectomy and silicone oil tamponade. Two weeks later another descemetocele developed requiring again with an emergency penetrating keratoplasty, after which the corneal epithelial surface remained stable. BCVA at last follow-up (12 months) was 1.9 logMAR.

Case 4

An 80-year-old female patient was referred for left keratoplasty by her ophthalmologist because of bilateral corneal scars due to superinfected rheumatoid corneal ulcers. She had been treated with bilaterally with topical antibiotics and several AMTs. Her medical history included primary Sjörgens syndrome, Lichen ruber, rheumathoid polyarthritis, arterial hypertension, coronary stents, previous myocardial infarction and most recently a metastatic recurrence of a squamous cell carcinoma of the right heel, which required extensive chemotherapy and subsequently resulted in polyneuropathy and stage 3 kidney failure. The patient had non-healing epithelial defects on both eyes with substantial corneal thinning, which lead to the indication of bilateral DCN. Before surgery BCVA was 2.3 logMAR in both and Schirmer's test 13 mm in the right eye and 0 mm in the left eye. Intraoperatively, five fascicles of the supraorbital nerve were isolated and transposed to corneal pockets at 2h, 4h, 8h and 10h. At the final follow-up 3 months after surgery, corneal sensitivity remained 0 in all areas tested and BCVA 2.3 logMAR in both eyes. The patient died shortly after due to the metastatic cancer.

Case 5

A 55-year-old male patient presented with bilateral NK due to severe diabetes mellitus type I. He also suffered from severe diabetic peripheral neuropathy resulting in severe gait disorder and partial amputation of toes and fingers. This patient also had non-healing epithelial defects on both eyes with substantial corneal thinning, which lead to the indication of bilateral ICN. Preoperative BCVA was 1.9 logMAR in the right and 2.3 logMAR in the left eye and Schirmer's test 0 mm in both eyes. Because of the anticipated wound healing issues, ICN, avoiding a large coronal incision, was performed. The nerve sural nerve was harvested from the left leg and divided into two halves of approximately 15 cm each, which were each split into three fascicles. A femtosecond laser (Ziemer Femto LDV Z8) was used to create three intrastromal corneal pockets with the following parameters: incision site 45°/135°/315°, distance to limbus 1.7 mm, width 3 mm, angle of entry 0°, angle of curvature -30° (Figure 4).
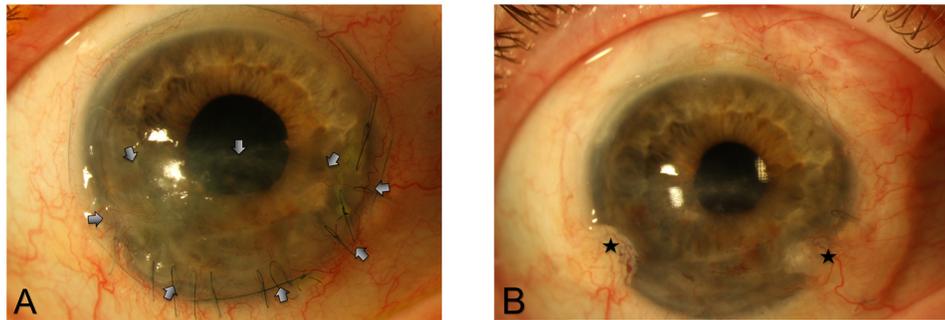
Figure 3. (a) Preoperative image of the right eye with a lamellar horseshoe KP (outline with grey arrows); (b) Anterior segment 3 months postoperatively. Intrastromal nerve fascicles are visible at 4h and 8h in the peripheral corneal stroma (black star).
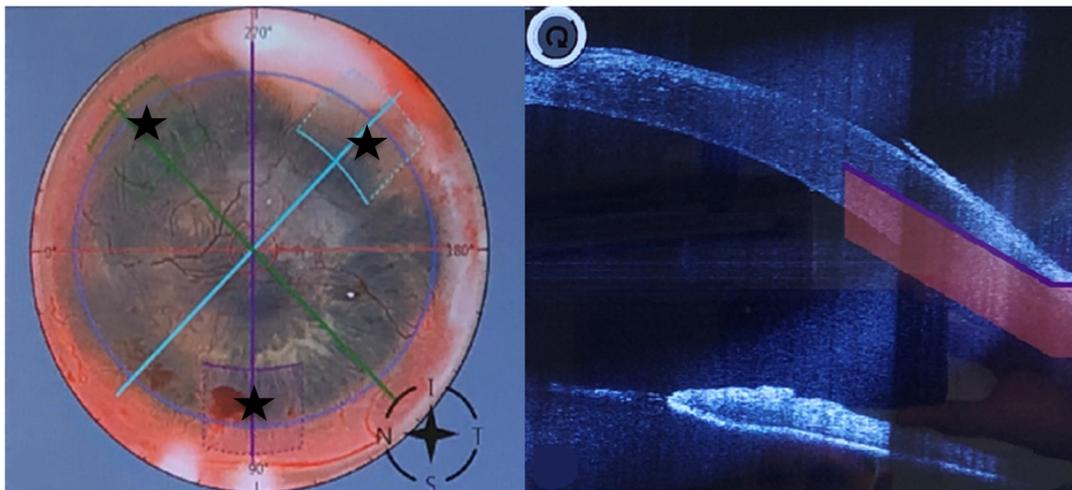
Figure 4. Intraoperative image of the femtosecond laser when cutting corneal pockets at 12h, 4h and 8h (left). Digital intraoperative image of the depth of the pocket within the corneal stroma (right).

At final follow-up 3 months after surgery corneal sensitivity was 1/6 in all areas in the right and 1/6 in the nasal quadrant, 2/6 centrally and 3/6 in the temporal quadrant in the left eye. BCVA remained at 2.3 logMAR in both eyes. The patient died shortly after due to acute heart failure.

Discussion

Corneal neurotization is a surgical approach for the treatment of moderate-to-severe neurotrophic keratopathy. Corneal sensation can be restored by transposing sensory facial nerve branches either directly (DCN) or by a nerve interponate (ICN) healthy to an anesthetic cornea.[15,16] The procedure usually requires an interdisciplinary surgical collaboration and substantial surgical time for each case, in our cohort 247 ± 53 min (Min/Max 190–345 min). So far little is known about factors limiting the success of this lengthy surgical approach. Here we analyze factors potentially limiting the outcome in our cohort.

So far, 20 studies with a total of 109 patients have been published.[11,13,15,17] In the largest meta-analysis by Swanson et al. 64 eyes showed a significant improvement in NK stages from a mean of 2.46 preoperatively to 0.84 postoperatively at a mean follow-up of 13 months.[11] In our cohort, corneal sensitivity improved in 63% of all areas tested (22/35) to a median of 3 (0/4 min/max) after a median follow-up of 7.6 months.

Many factors can potentially influence the results of CN. Besides length of follow-up these can be divided into patient-related parameters or surgical technique. Patient-related factors that can influence outcome include patient age, ocular surface status (e.g. dry eye, limbal stem cell deficiency, scarring), and systemic comorbidities. Surgical variations include the principal technique of reestablishing sensory innervation to the cornea, by either direct transposition (DCN) of a facial nerve or by indirect neurotization (ICN) using a nerve interponate.[18–20]

Most of the published cohorts tend to have a young mean patient age, e.g. Sweeney et al. 42.6 years,[13] Rathi et al. 15.6 years,[15] and Fogagnolo et al. 45.4 years.[17] Swanson et al. in their meta-analysis found no association between age and reinnervation after CN. The median age of the cohorts analyzed was 36 compared to 77 in our study. While a more substantial improvement in visual acuity was observed in older patients (> 20 years old), corneal reinnervation was superior in younger patients (< 20 years old).[11,17]

In younger patients NK is often due to an isolated etiology (e. g. post-herpetic, post-traumatic or post-surgical) and with a rather short duration of NK. In contrast to that, in our cohort the etiologies in four out of five patients were systemic long-standing diseases leading to NK (Table 1). Furthermore, 3 out of our 5 patients died within 4 months. This seems to confirm that young patients with an isolated etiology of NK tend to have a better outcome after CN. A recent case report by Ting et al. described an unfavorable outcome in two cases with advanced age (65/58 years) and a long history of NK due to microvascular decompression for trigeminal neuralgia and gamma knife radiosurgery for an

acoustic neuroma 10 and 16 years prior to CN.[21] Rathi et al. described seven cases with a mean age of 14.9 ± 10 years with NK due to an isolated etiology (post-herpetic (4), post-traumatic (2), and neurological disease (1)) and a duration of NK of only 2.3 ± 5.2 years.[15] The surgical outcome was considered to be successful in all these patients as all of them had improved corneal sensitivity at last follow-up. However, the degree of esthesiometric improvement was not specified.

Rafailov et al. report the outcome in an elderly patient population with a median age at time of surgery of 60.2.[14] Corneal sensation improved significantly from the median preoperative corneal sensation of 0.6 cm (IQR 0.0–1.7 cm) to a median postoperative value of 2.9 cm (IQR 1.6–5.5 cm) at a minimum of 6 months follow-up. In contrast to our cohort, the etiology of NK in their cohort however was mostly isolated (herpetic disease (7), ocular surgery (5), neurosurgery (9)). Only two of their 28 patients in their cohort had type 1 diabetes mellitus as the only systemic comorbidity. The most frequent indication for neurotization is surgical nerve damage after neurosurgery (62 cases), followed by NK after Herpes simplex virus or Varicella zoster virus infection.[22,23] While in our cohort, only one case of NK (case no. 2) was due to Herpes simplex virus, this patient in addition also suffered from rheumatoid arthritis and CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility sclerodactyly, and telangiectasia).

Our cohort is too small to allow for any meaningful comparison of direct and indirect CN, as only 1 case (2 eyes) underwent ICN. However equally high rates of corneal recovery and reinnervation have been reported for direct and indirect CN.[11,17] for which autografts, e.g. a sural nerve graft, or acellular cadaveric nerve (allo-graft) can be used.[22] Due to neurotrophic factors and vascular supply, the autografts in ICN may be superior to a cadaveric nerve graft, while the donor site morbidity in harvesting autografts is reportedly low.[24,25]

The nerve endings can be fixed at the recipient site using fibrin glue or sutures. They have been placed in intrastromal corneal pockets or simply the subconjunctival space.[10,20,21,23,24,26] In our cohort we fixed the fascicles in intrastromal corneal pockets and secured them with a limbal single suture of the epineurium to the sclera. In one of our bilateral cases (Case No. 5), these corneal pockets were cut with a femtosecond laser, allowing to design length and width, but more importantly the depth of the corneal pocket to provide a more precise location for the subbasal nerve plexus to reform. Unfortunately, the patient passed away before the 6 months follow-up, too short to make any meaningful conclusions about longterm benefits of this approach. Although the use of a femtosecond laser allowed precise lamellar pocket creation, its clinical benefit in this surgery remains speculative, particularly when balanced against the associated costs and equipment.

The time to corneal reinnervation after surgery varies. One review of pathophysiology and outcomes reported a median time of 8 months required for the maximum reinnervation (range 6–10 months).[12] However, in a pediatric cohort, the maximum reinnervation was only observed after 9 months.[25] With a human nerve allograft, the onset of

corneal reinnervation was observed at a mean of 3.7 (range 1–8 months) and the maximum effect at 6.6 months (range 3–15 months).[13] In a recent comprehensive review and an interim report on corneal neurotization, a return of corneal sensation was observed at a mean of 11.8 ± 13.8 months.[15] In our cohort, five out of seven eyes showed improved corneal sensation as early as 3 months postoperatively, but only 2 out of 7 eyes could be followed for 6 and 12 months respectively, as the remaining three patients had died.

In our cohort, direct corneal neurotization (DCN) using the supraorbital nerve was feasible and effective in five out of seven eyes. However, in patients with severe systemic disease or anticipated wound healing difficulties, indirect CN (ICN) with sural nerve grafts may be preferred due to the shorter surgical time and less invasive incision. This reflects our institutional preference in elderly or frail individuals.

In all of these patients, severe ocular surface comorbidities—including previous perforations, scarring, and ocular surface failure—were present even before CN. In patients with advanced cicatricial or ischemic damage, simpler procedures such as tarsorrhaphy or conjunctival flap coverage may serve as safer alternatives with lower perioperative stress, albeit without addressing loss of sensation.

Conclusion

While our study is limited by the retrospective design and the small sample size, it provides some important learnings to ensure good success rates and make appropriate use of this resource intensive technique. Our results suggest that extensive ocular comorbidities and chronicity of neurotrophic keratopathy, rather than chronological age per se, were major limiting factors in achieving optimal outcomes after CN. When offering it to multimorbid patients the long time for more profound corneal reinnervation required to prevent corneal perforation and general, potentially fatal comorbidities should be considered carefully. Given the good results reported for younger patients the procedure should be indicated probably earlier in the course and in cases with an isolated etiology of NK. Beyond this we here for the first time report the use of a FS-laser to create intrastromal pockets for implantation of the nerve endings immediately in the corneal stroma.

Disclosure statement

Due to the nature of the research, supporting data is not available. The authors received no funding for this work. The authors confirm that the data supporting the findings of this study are available within the article. As part of the university program for medical education and scientific research, consent to publish these findings and images were gathered. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Heinrich-Heine-University Duesseldorf and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No specific ethics approval was required for this study because corneal neurotization is an established procedure that all patients were thoroughly informed about the risks and benefits of this procedure and provided consent. According to Section 6, Paragraph 2 of the Law on the Protection of Personal Data in Healthcare (North Rhine-Westphalia state law), patient consent for data analysis is not required when study personnel only use patient data to which they already have access through their regular activities, the research purpose cannot be achieved by other means and there is a legitimate public interest in conducting the research.

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References

1. Alder J, Mertsch S, Menzel-Severing J, Geerling G. Aktuelle und experimentelle Therapieansätze bei neurotropher Keratopathie. Ophthalmologe. 2019;116(2):127–137. doi: 10.1007/s00347-018-0843-5.
2. Roth M, Dierse S, Alder J, Holtmann C, Geerling G. Incidence, prevalence, and outcome of moderate to severe neurotrophic keratopathy in a German tertiary referral center from 2013 to 2017. Graefes Arch Clin Exp Ophthalmol. 2022;260(6):1961–1973. doi: 10.1007/s00417-021-05535-z.
3. Dua HS, Said DG, Messmer EM, Rolando M, Benitez-del-Castillo JM, Hossain PN, Shortt AJ, Geerling G, Nubile M, Figueiredoet FC, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018;66:107–131. doi: 10.1016/j.preteyeres.2018.04.003.
4. Mackie IA. Neuroparalytic keratitis. In Roy FH, Meyer SM, Fraunfelder F (Ed). Current Ocular Therapy (pp. 452–454), 1995. Philadelphia: WB Saunders.
5. Mastropasqua L, Nubile M, Lanzini M, Calienno R, Dua HS. In vivo microscopic and optical coherence tomography classification of neurotrophic keratopathy. J Cell Physiol. 2019;234(5):6108–6115. doi: 10.1002/jcp.27345.
6. Schrader S, Wedel T, Moll R, Geerling G. Combination of serum eye drops with hydrogel bandage contact lenses in the treatment of persistent epithelial defects. Graefes Arch Clin Exp Ophthalmol. 2006;244(10):1345–1349. doi: 10.1007/s00417-006-0257-y.
7. Bonini S, Lambiase A, Rama P, Filatori I, Allegretti M, Chao W, Mantelli F; REPARO Study Group. Phase I trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology. 2018;125(9):1468–1471. doi: 10.1016/j.ophtha.2018.03.004.
8. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel solution to neurotrophic keratopathy. Plast Reconstr Surg. 2009;123(1):112–120. doi: 10.1097/PRS.0b013e3181904d3a.
9. Jacinto F, Espana E, Padilla M, Ahmad A, Leyngold I. Ipsilateral supraorbital nerve transfer in a case of recalcitrant neurotrophic keratopathy with an intact ipsilateral frontal nerve: a novel surgical technique. Am J Ophthalmol Case Rep. 2016;4:14–17.
10. Lueke JN, Holtmann C, Beseoglu K, Geerling G. Corneal neurotization. Ophthalmologe. 2020;117(3):248–252. doi: 10.1007/s00347-019-00980-y.
11. Swanson MA, Swanson RD, Kotha VS, Cai Y, Clark R, Jin A, Kumar AR, Davidson EH. Corneal neurotization: a meta-analysis of outcomes and patient selection factors. Ann Plast Surg. 2022;88(6):687–694. doi: 10.1097/SAP.0000000000003117.
12. Park JK, Charlson ES, Leyngold I, Kossler AL. Corneal neurotization: a review of pathophysiology and outcomes. Ophthalmic Plast Reconstr Surg. 2020;36(5):431–437. doi: 10.1097/IOP.0000000000001583.
13. Sweeney AR, Wang M, Weller CL, Burkat C, Kossler AL, Lee BW, Yen MT. Outcomes of corneal neurotisation using processed nerve allografts: a multicentre case series. Br J Ophthalmol. 2022;106(3):326–330. doi: 10.1136/bjophthalmol-2020-317361.
14. Rafailov L, Kim JS, Wisely CE, Espana EM, Soifer M, Leyngold IM. Clinical outcomes and patient satisfaction after corneal neurotization. Cornea. 2021;40(11):1377–1386. doi: 10.1097/ICO.0000000000002759.
15. Rathi A, Bothra N, Priyadarshini SR, Achanta DSR, Fernandes M, Murthy SI, Kapoor AG, Dave TV, Rath S, Yellinedi R, et al.

Neurotization of the human cornea—a comprehensive review and an interim report. Indian J Ophthalmol. 2022;70(6):1905–1917. doi: 10.4103/ijo.IJO_2030_21.

16. Malhotra R, Elalfy MS, Kannan R, Nduka C, Hamada S. Update on corneal neurotisation. Br J Ophthalmol. 2019;103(1):26–35. doi: 10.1136/bjophthalmol-2018-312104.

17. Fogagnolo P, Giannaccare G, Bolognesi F, Digiuni M, Tranchina L, Rossetti L, Dipinto A, Allevi F, Lozza A, Rabbiosi D, et al. Direct versus indirect corneal neurotization for the treatment of neurotrophic keratopathy: a multicenter prospective comparative study. Am J Ophthalmol. 2020;220:203–214. doi: 10.1016/j.ajo.2020.07.003.

18. Domeshek LF, Hunter DA, Santosa K, Couch SM, Ali A, Borschel GH, Zuker RM, Snyder-Warwick AK. Anatomic characteristics of supraorbital and supratrochlear nerves relevant to their use in corneal neurotization. Eye (Lond). 2019;33(3):398–403. doi: 10.1038/s41433-018-0222-0.

19. Tung TH, Mackinnon SE. Nerve transfers: indications, techniques, and outcomes. J Hand Surg Am. 2010;35(2):332–341. doi: 10.1016/j.jhsa.2009.12.002.

20. Wolkow N, Habib LA, Yoon MK, Freitag SK. Corneal neurotization: review of a new surgical approach and its developments. Semin Ophthalmol. 2019;34(7-8):473–487. doi: 10.1080/08820538.2019.1648692.

21. Ting DSJ, Pradhan SP, Barnes E, Ahmed OA, Figueiredo FC. Minimally invasive corneal neurotization for neurotrophic kera-

topathy: the potential effect of age, denervation chronicity and lesion location. Am J Ophthalmol Case Rep. 2023;29:101804. doi: 10.1016/j.ajoc.2023.101804.

22. Wu Y, Zhang J, Ding W, Chen G, Shao C, Li J, Wang W, Wang W. Clinical outcomes of minimally invasive corneal neurotization after cerebellopontine angle neurosurgical procedures. Curr Eye Res. 2022;47(5):670–676. doi: 10.1080/02713683.2022.2025843.

23. Dragnea DC, Krolo I, Koppen C, Faris C, Van den Bogerd B, Ní Dhubhghaill S. Corneal neurotization—indications, surgical techniques and outcomes. J Clin Med. 2023;12(6):2214. doi: 10.3390/jcm12062214.

24. Catapano J, Fung SSM, Halliday W, Jobst C, Cheyne D, Ho ES, Zuker RM, Borschel GH, Ali A. Treatment of neurotrophic keratopathy with minimally invasive corneal neurotisation: long-term clinical outcomes and evidence of corneal reinnervation. Br J Ophthalmol. 2019;103(12):1–8. doi: 10.1136/bjophthalmol-2018-313042.

25. Catapano J, Shafarenko M, Ho ES, Ont OTR, Zuker RM, Borschel GH. Sensory and functional morbidity following sural nerve harvest in paediatric. J Plast Reconstr Aesthet Surg. 2018;71(12):1711–1716. doi: 10.1016/j.bjps.2018.07.020.

26. Leyngold IM, Yen MT, Tian J, Leyngold MM, Vora GK, Weller C. Minimally invasive corneal neurotization with acellular nerve allograft: surgical technique and clinical outcomes. Ophthalmic Plast Reconstr Surg. 2019;35(2):133–140. doi: 10.1097/IOP.0000000000001181.