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Corneal Neurotization: A Novel Surgical Procedure for Neurotrophic Keratopathy

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Purpose: The aim of this study is to describe techniques, results, and open issues of corneal neurotization (CN) for the treatment of neurotrophic keratopathy (NK).

Methods: An overview of the most important studies of CN is provided. The 2 main surgical approaches (namely, direct CN and indirect CN) with specific advantages and disadvantages are described. The results regarding changes of corneal sensitivity and clarity, visual acuity, and in vivo confocal microscopy metrics are summarized. Ex vivo studies with histopathology of the neurotized cornea are reported. Intraoperative and early and late postoperative complications are described along with current open issues to be further clarified.

Results: Corneal sensitivity improves after both direct and indirect CN. Corneal reinnervation allows the healing of NK in almost the totality of the operated eyes, determining a corresponding improvement of corneal clarity and visual acuity. Regeneration of corneal nerve fibers is confirmed by means of either in vivo confocal microscopy or ex vivo histopathology. Few self-limiting complications are reported during the postoperative course. Current open issues concern the identification of the technique of choice, the use of autograft or allograft, and the timing of CN either when performed alone or when combined with other surgeries.

Conclusions: CN represents a game-changing surgical procedure for NK, which has the potential to restore corneal sensitivity in all stages of the disease regardless of the mechanism of denervation. Further long-term results are needed to confirm its efficacy over time. The design of randomized clinical trials comparing CN with noninterventional therapies could further validate the adoption of this technique.

Key Words: neurotrophic keratopathy, corneal neurotization, corneal nerves, neurotrophic keratitis, corneal sensitivity

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The human cornea contains an extremely dense sensory innervation provided by the ophthalmic branch of the trigeminal nerve and by autonomic nerve fibers. Disruption of the corneal innervation at any level, from the nucleus to the distal terminations, may lead to a pathological condition named neurotrophic keratopathy (NK). This degenerative disease includes various ocular surface changes ranging from superficial punctate keratopathy (stage I according to Mackie classification), persistent epithelial defect (stage II) to, in more severe cases, stromal involvement leading to corneal ulcer, keratolysis, and perforation (stage III). Various ocular or systemic conditions can determine NK onset, such as herpetic keratitis, chemical injury, corneal surgery, dry eye disease, diabetes, neurosurgical procedures, intracranial tumors, and congenital conditions. The treatment of NK is chosen according to the severity of the disease: in early stages, supportive treatment with preservative-free tear film substitutes and lubricant ointments is used to prevent epithelial breakdown. As the severity of NK progresses, topical antibiotics, blood-derived eye drops, and therapeutic contact lens are indicated. The welcomed market introduction of recombinant nerve growth factor (NGF) (Oxervate; Dompè Farmaceutici, Milan, Italy) with specific target on the root pathology has determined a paradigm shift in medical management of NK. Although NGF has shown good efficacy in randomized clinical trials (RCTs), the high costs still limit its wide diffusion in the routine practice.

Traditionally, surgical treatments such as tarsorrhaphy, amniotic membrane transplantation, conjunctival flap, and tectonic keratoplasty were reserved for severe and refractory NK cases. Corneal neurotization (CN) has been recently introduced as a potentially curative surgical procedure, being able to restore corneal sensitivity and reverse corneal changes, thanks to the new neural terminations. Since the first report,[1] different surgical techniques have been described with specific pros and cons: direct CN (DCN) relies on the transfer of a healthy nerve branch to the anesthetic cornea, whereas indirect CN (ICN) involves the interposition of an autologous nerve graft or an acellular nerve allograft (ANA).

TECHNIQUES

Direct CN

This technique was first described by Terzis et al[1] in 2009. The contralateral supraorbital and supratrochlear nerves were harvested through a coronal incision, tunneled over the nasal bridge, and sutured to the corneal perilimbal area at the 4 cardinal points (Fig. 1A). Subsequently, others (including our group) proposed a sutureless approach for fixing transferred nerves, thanks to the use of fibrin glue, and the creation at the 4 cardinal points of a scleral–corneal tunnel incision where the fascicles are trimmed and bluntly inserted to help nerve growth toward the center of the cornea.[2]

In case of isolated injury of long ciliary nerves (eg, herpetic keratitis), ipsilateral supraorbital, and/or supratrochlear nerves can be used, thus allowing a smaller scalp incision and a shorter nerve dissection (Fig. 1B). Jacinto et al[3] reported this technique in a patient with NK owing to direct ciliary nerves damage transferring 3 branches of the ipsilateral supraorbital nerve to the perilimbal area.

Gennaro et al[4] described in 2019 a new variant of the technique by transferring the healthy ipsilateral infraorbital nerve in a patient experiencing NK with isolated damage of the first trigeminal branch (Fig. 1C). Leyngold et al[5] investigated the feasibility of a minimally invasive approach for DCN by transferring endoscopically the ipsilateral supraorbital nerve to the corneal limbus in a patient with postherpetic NK. This technique limits postsurgical alopecia and visible scar size, decreases surgical and healing time, and reduces the risk for facial nerve injury and hematoma with a minimal blood loss.

Indirect CN

The feasibility of ICN was reported by Elbaz et al[6] who used the reversed sural nerve graft to connect with an end-to-side coaptation the contralateral supratrochlear nerve (Fig. 2A). Distally, the proximal stump of the sural graft was divided into the individual fascicles, distributed in all the 4 quadrants of the perilimbal area in the subconjunctival space and then sutured with 10-0 nylon sutures. This technique is more conservative, preventing the denervation of contralateral or ipsilateral forehead, being feasible also in bilateral NK cases that can occur more commonly in children in association with congenital disorders. Our group used sural nerve graft during ICN to create an end-to-end coaptation with the contralateral supraorbital nerve aiming at inducing a higher axon growth (Fig. 2B).[2]

Benkahtar et al[7] described in 2018 the first case of ICN using the great auricular nerve. The harvesting of the graft was conducted as first stage, and the isolation of the supratrochlear nerve and the coaptation of the autograft were then performed. The use of this graft provided some advantages over the sural nerve, such as less donor site complications and the possibility to create a single surgical field. Bourcier et al reported a case of ICN using the lateral antebrachial cutaneous nerve graft connected to the contralateral supraorbital nerve through an end-to-end neurorrhaphy.[8]

In 2019, Leyngold et al[9] reported a series of 7 patients who underwent ICN with the use of ANAs. The technique was similar to that one previously described by Elbaz et al,[6] except for the use of an allograft instead of an autograft. This technique avoids the occurrence of visible scar, alopecia,

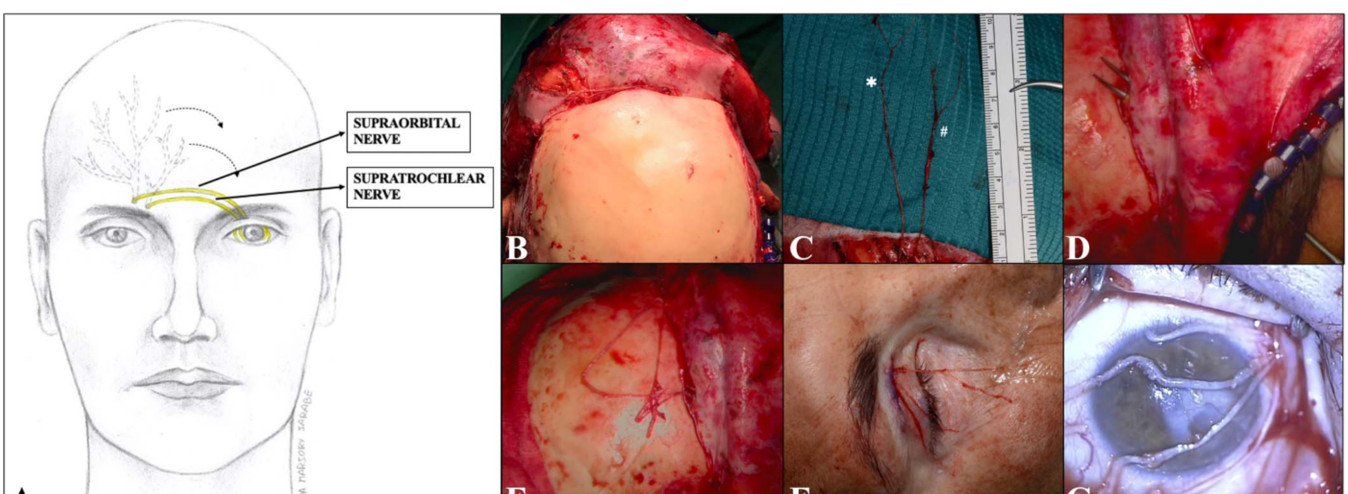

FIGURE 1. Diagram and intraoperative pictures of the DCN. A, Diagram of the DCN with the transposition of the contralateral supraorbital and supratrochlear nerves on the affected cornea. B–G, Intraoperative pictures showing the different steps of the DCN technique: coronal access (B); harvesting of the contralateral supraorbital (*) and supratrochlear nerves (#) (C); creation of a subcutaneous tunnel over the nasal bridge (D); transposition of the contralateral supraorbital and supratrochlear nerves from the contralateral forehead (E) to the anesthetic eye, through a small incision in the upper eyelid, along the lid crease (F); and microscopic view of the 4 donor nerve fascicles distributed over the affected cornea (G).

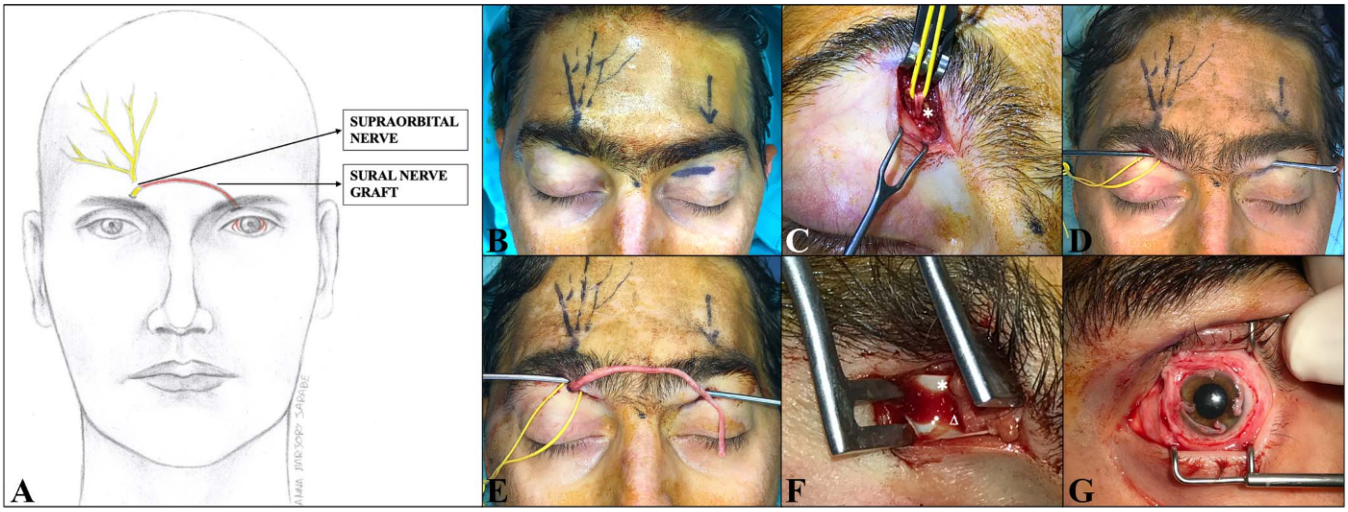

FIGURE 2. Diagram and intraoperative pictures of the ICN. A, Diagram of the ICN with an end-to-end neurorrhaphy between the reversed sural nerve graft and the contralateral supraorbital nerve. B–G, Intraoperative pictures show the different steps of the technique: surgical drawing (B); the contralateral supraorbital nerve (*) is isolated at its orbital exit through the supraorbital notch (C); creation of a subcutaneous tunnel over the nasal bridge for the reversed sural nerve graft (D–E); end-to-end neurorrhaphy between the distal stump of the sural nerve graft (Δ) and the contralateral supraorbital nerve (*), using 10-0 Prolene suture (F); microscopic view of the proximal stump of the sural nerve graft divided into the individual fascicles distributed over the affected cornea.

injury to the frontal branch of the facial nerve, and morbidity related to the sural nerve sacrifice with consequent numbness of calcaneus and foot posterolateral surface. Subsequently, other research groups applied the use of processed ANAs for ICN in the context of a large multicenter study involving 17 patients with NK.[10]

RESULTS

All the studies that tested corneal sensitivity by means of Cochet–Bonnet esthesiometer reported increased values after both DCN and ICN. The recovery of corneal sensitivity usually started from 6 to 12 months after surgery and then increased progressively over time. Interestingly, patients initially localized the corneal tactile stimulation in the cutaneous skin territory of donor nerves; after a period of neuronal plasticity lasting a few months, the sensation was shifted to the cornea.[2,6]

Postoperatively, corneal reinnervation allowed the healing of NK in almost the totality of the operated eyes by restoring the release of trophic agents (Figs. 3A–C). In parallel, a gradual recovery of the corneal clarity with a corresponding improvement of visual acuity was reported after CN in most of the available studies.

Regeneration of corneal nerve fibers after CN was documented by means of either in vivo confocal microscopy (IVCM) or ex vivo histopathology. Usually, the detection of regenerated nerves on IVCM scans preceded by a few months the recovery of corneal sensitivity.[2] Ex vivo histopathological examination of neurotized cornea was performed in eyes that underwent keratoplasty or evisceration after CN.[2,11] This analysis demonstrated abundant neurofilament-positive axonal profiles in the neurotized corneal button excised at the time of keratoplasty. On the contrary, Ting et al[12] evaluated an eye that was eviscerated 5 years after CN and found normal-sized central corneal nerves that were not in direct continuity with the transplanted perilimbal nerve bundles. If corneal reinnervation after CN is provided by the paracrine neurotrophic support of the transferred nerves or by the direct sprouting of the nerve themselves remains to be clarified.

Neurophysiological examination of the corneal reflex in the neurotized cornea was performed after CN, showing a partial recovery of threshold and latency values in the operated eyes.[2] Magnetoencephalography was also used to demonstrate an evoked response localized to the somatosensory cortex following corneal stimulation 8 months after CN.[11]

Overall, CN is considered a safe procedure, and few self-limiting complications were reported during the postoperative course. The large coronal incision of the traditional DCN can cause alopecia, frontal nerve damage, subcutaneous hematoma, and incision scar; sural nerve graft harvesting during ICN can determine loss of sensation, discomfort, and allodynia in the lower leg or foot. Terzis et al[1] reported a subgaleal hematoma (1 case) and an asymptomatic subconjunctival neuroma (1 case). In the study from Catapano et al, the first 5 patients developed exposure of the conjunctival sutures; a persistent epithelial defect recurred in 5 patients after CN but was successfully treated with topical antibiotics and bandage contact lens.[11] Ting et al[12] eviscerated 1 eye 5 years after CN due to persistent pain and poor cosmesis. However, in case of failed CN, surgery can be repeated using other donor nerves. In a previous study, we described the case of a patient who underwent 2 sequential CN surgeries performed 1 year apart: DCN was the first approach but, because of the lack of improvement of the clinical picture, ICN was subsequently performed and allowed the healing of NK.[2]

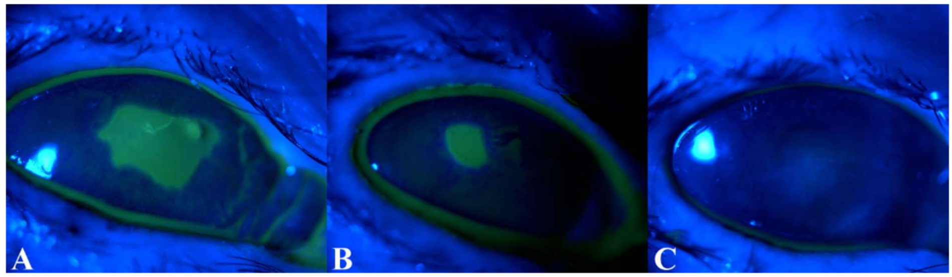

FIGURE 3. Representative slit lamp photographs of the cornea before and after surgery. A, Before direct corneal neurotization, the clinical picture showed a NK owing to fifth cranial nerve palsy secondary to acoustic neurinoma surgical removal with a large epithelial defect (5×3 mm). B, One month postoperatively, the area of the epithelial defect of the cornea was markedly reduced (1.5×1.5 mm). C, Three months postoperatively, the epithelial defect of the cornea completely healed.

OPEN ISSUES

Technique of Choice

Since the description of the initial surgical approach for CN from Terzis et al dated about 10 years ago,[1] different surgical techniques, variants, and refinements have been reported, and each of them has specific advantages and disadvantages. To date, there is a debate about the technique of choice, and it remains unclear whether one surgical approach is superior to the rest in both safety and efficacy. The complexity and frequent inhomogeneity of NK cases regarding patient's age, disease's history and stage, mechanism of denervation, and comorbidity make difficult a direct comparison between DCN and ICN; furthermore, the surgical techniques are not fully interchangeable. Our group conducted a prospective comparative study including patients with NK who underwent DCN with the transfer of the contralateral supraorbital and/or supratrochlear nerves or ICN with the interposition of sural nerve graft.[2] Although DCN allowed an earlier recovery of corneal sensitivity, the difference was not significant 1 year postoperatively. The data obtained from this comparative analysis were not conclusive also for visual acuity and IVCM metrics. It remains still unknown if the technique used for CN significantly affects its clinical outcomes.

Autografts Versus Allografts

To date there is no universal consensus supporting the use of ANAs for ICN. On one hand, the preference for surgeon of using ANAs is multifactorial: the convenience of a processed allograft ready at the time of surgery simplifies the procedure, reliably provides an untraumatized good-quality nerve graft of predictable caliber and length, eliminates time and coordination of second site surgery, and avoids scar or other possible complications of autograft harvesting.[9] On the other hand, in other surgeries, ANAs are usually used for nerve reconstruction when a short gap (2–3 cm) is present, suturing the allograft to the proximal and distal stumps of the recipient nerve. In ICN, the lack of the distal nerve stump along with the need for a nerve graft of a length up to 7 cm could theoretically reduce ANAs' efficacy. In fact, it has been recently showed that an increase in both allograft length and diameter yielded a significantly poorer outcome. However, a recent multicenter study reported the outcomes of ANAs of length up to 7 cm in CN and showed similar or better results of processed allografts compared with the autografts.[10] Further well-designed RCTs are needed to compare the outcomes of nerve autografts versus allografts in the setting of CN to establish the ideal graft.

Timing of CN

Given the presence of promising drugs that are coming down the pipeline (some of them such as recombinant NGF and regenerating agents are already on the market), there is a need for clear recommendation about the timing of surgery. On one hand, it is reasonable to advocate for early CN surgery in rapidly progressing NK to prevent permanent corneal scarring or complications such as corneal perforation, given the low complication rates and the remarkable improvement in visual acuity, corneal sensation, and NK staging. On the other hand, because of its invasiveness, CN could be considered a procedure of last resort reserved to end-stage NK cases or to patients unresponsive to medical therapies, particularly when the conventional technique of DCN with corneal approach is performed. It is reasonable to state that the continuous advances toward minimally invasive approaches will likely help the adoption of CN in earlier and less severe stages of NK.

The decision for the treatment of choice should be taken according to various parameters including, among others, patient's age, NK stage, mechanism of denervation, access to drugs, and surgeon's skills and preference. As a general rule, in NK cases owing to central nervous denervation with a complete damage to the trigeminal ganglion, CN is likely the only procedure that offers the chance to restore nerve function even if there has been an irreparable damage to the original location of innervation. Randomized clinical trials comparing CN with noninterventional therapies under various scenarios of NK are desirable to establish the treatment of choice for each NK severity stage.

Combined Surgeries

In patients with combined V and VII cranial nerve deficits, facial palsy acts synergistically with corneal anesthesia to increase the risk for corneal lesions that can lead to visual impairment, especially when an impairment of the Bell's phenomenon is present. Therefore, in these complex cases, facial reanimation should be performed as the first step to restore the eye closure that is essential for the protection of the cornea and the blinking reflex that is essential for effective eye lubrication. Subsequently, after ascertaining recovery of eyelid closure, the second surgical step is represented by CN to reestablish corneal sensitivity. Finally, if a significant corneal opacity persists, staged optical keratoplasty can be performed for visual rehabilitation. Unlike tectonic keratoplasty that is performed in the setting of NK only in emergency for the treatment of complications (eg, corneal perforation) with a poor prognosis, studies have reported successful outcomes for optical keratoplasty performed either in combination with CN or as a staged procedure after a variable amount of time (range 6–33 mo). In all studies, grafts achieved complete reepithelization, allowing a recovery of corneal sensitivity to preoperative values and a significant gain of visual acuity.

DISCUSSION

Until recently, NK therapy consisted of only supportive measures focused on lubrication and protection of the ocular surface, whereas surgery was limited to refractory cases to treat corneal complications. The recent advent on the market of recombinant human NGF allowed a paradigm shift in medical therapy. The results of the European and US trials confirmed the efficacy of this drug in the healing of NK; however, most of the treated patients had hypoesthesia due to herpetic eye disease or diabetes-related NK. CN represents a game-changing surgical procedure in the setting of NK, which has the potential to restore corneal sensitivity in all stages of the disease, regardless of the mechanism of denervation, even in cases of total anesthesia. Although the use of CN is still limited to a few research groups likely because of the long surgical time (especially for DCN) and the frequent need for a multidisciplinary team involving also maxillofacial/plastic surgeons, the promising results and the continuous advances in the technique toward minimally invasive approaches are contributing to increase its popularity among corneal surgeons. Long-term results confirming the efficacy of CN over time along with the design of RCTs comparing CN with noninterventional therapies could further validate the adoption of this technique.

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