Commentary: Corneal neurotization

Neurotrophic keratopathy is a degenerative disease characterized by corneal denervation leading to hypoesthesia and depletion of nerve-derived growth factors. It results from the impairment of trigeminal nerve function either due to congenital (e.g., familial dysautonomia and Goldenhar syndrome) or acquired causes (herpetic keratitis, surgery, tumors, trauma, medication-induced, metabolic).[1]

Conventional treatment for neurotrophic keratopathy is mainly palliative and aims at promoting corneal epithelial regrowth. Medical management is prescribed in the early stages and comprises preservative-free lubricants, topical antibiotics, and blood-derived eye drops, whereas surgical interventions such as tarsorrhaphy, amniotic membrane transplantation, and tectonic keratoplasty are reserved for the more severe cases.[1] Recently, topical recombinant human nerve growth factor (rhNGF) has been approved by the United States Food and Drug Administration (FDA) as a treatment for neurotrophic keratopathy. rhNGF directly targets the underlying deficits of neurotrophic keratopathy; however, it does not restore corneal sensitivity and its cost remains prohibitive to patients.[2]

Corneal neurotization has emerged as a potentially curative treatment for neurotrophic keratopathy by facilitating the reinnervation of the cornea, establishing neuromodulator homeostasis, and promoting corneal wound healing. It essentially involves the transfer of a healthy nerve segment to the anesthetic cornea. The supraorbital nerve is the preferred donor nerve; other donor sites include the supratrochlear, infraorbital, and greater auricular nerve.[3] The donor nerve may be transferred directly to the corneal surface or indirectly by using an interposition nerve graft. Direct neurotization involves the transfer of ipsilateral or contralateral donor sensory nerves from the surrounding tissue tunneled to the limbus of the anesthetic cornea. The technique has evolved over the years from the more invasive approach requiring coronal incisions to the minimally invasive endoscopic procedure.[4] The indirect approach uses an autologous or allogenic interposition nerve graft to link the sensate branch of the donor trigeminal nerve to the anesthetic cornea. It is less invasive and can be performed using an eyelid crease incision or inferior fornix transconjunctival incision.[5] Both direct and indirect approaches have their pros and cons. The advantages of the direct approach include a single location of postoperative hypoesthesia and presumed direct sprouting of the transferred nerves to reinnervate the cornea.[2] When performed via a coronal incision, the direct approach has the disadvantages of being more invasive and requiring a longer surgical time. The advantages of the indirect technique include the ability to access the donor nerve proximally where more axons are available for regeneration and greater surgical flexibility to deal with the anatomical constraints. Disadvantages of the indirect approach include potential complications at the neurorrhaphy site, increased distance for nerve regeneration, and numbness at the secondary harvest site.[3,5]

While corneal neurotization is typically performed in cases of chronic recalcitrant neurotrophic keratopathy that are unresponsive to conventional treatment, some authors recommend the intervention early on in the disease course before irreversible damage occurs.[6]

The choice of direct versus indirect approach is determined by patient-related factors, availability of infrastructure, and surgeon's preference. An indirect approach may be better suited in children as it is less invasive, and also in patients with bilateral involvement and those with past cranial surgeries. A second surgical team is usually required to harvest the nerve graft in this approach.[7]

The choice of the donor site, that is, ipsilateral or contralateral, is based on the availability and condition of sensate nerves, which is determined by preoperative sensory assessment of the region. In select cases where the nerve damage is limited to the distal nerve branches (long ciliary nerve) and ipsilateral sensations are intact, the use of ipsilateral trigeminal nerve branches as donor nerves may be feasible.[8]

When using an indirect approach, the type of nerve graft may be autologous or an acellular allograft. A sural nerve autograft is most commonly used. Commercially available processed acellular nerve allograft is emerging as a promising alternative, where the graft acts as a scaffold to direct the regenerating donor nerve fibers to the target cornea. It does not require graft harvesting and thus eliminates graft site morbidity.[8]

Numerous studies have reported favorable outcomes after corneal neurotization in terms of objective improvement in corneal sensitivity, visual acuity, and increase in sub-basal nerve fiber density observed on confocal microscopy.[3,7] In this issue, Rathi *et al*.[9] report favorable outcomes in seven cases of neurotrophic keratopathy that underwent corneal neurotization by using an indirect approach. While subjective improvement in corneal sensations may be perceived earlier, objective changes using esthesiometry are usually documented approximately 5–6 months after surgery.[2] Younger patients (<18 years) have demonstrated greater improvement in corneal sensation with better visual outcomes.[3] At present, there is no conclusive evidence to suggest the superiority of any particular surgical approach.[7] Interestingly, outcomes of indirect corneal neurotization with acellular nerve grafts of up to 7 cm have been reported to be comparable to those with autografts.[2]

While the technique of corneal neurotization has shown notable advances in recent years, certain questions remain unanswered, including the long-term durability of corneal sensation and the superiority of the procedure over topical rhNGF therapy. At present, corneal neurotization is being performed at a select few ophthalmic set-ups owing to the surgical complexity, longer operative time, and frequent need for a multidisciplinary team. Coordinated efforts to train more surgeons in set-ups with the requisite infrastructure are required to facilitate its widespread adoption. This shall further help us validate the favorable outcomes that have been reported with the procedure to date.

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