NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of nerve graft for corneal denervation

Blinking helps prevent infection and keeps the eye healthy by spreading a film of tears across the clear layer at the front of the eye (cornea). When nerves to the cornea are damaged (denervation), feeling is lost, and blinking happens less often. This makes the cornea vulnerable to infection and ulcers, which can result in poor vision. In this procedure, under general anaesthesia, one end of a piece of another nerve (the nerve graft) is attached to a healthy nerve, usually above the eye. The other end is passed under the skin and inserted around the damaged cornea. Over several months, new nerve endings grow into the cornea from the graft. The aim is to protect the cornea by improving healing, to reduce infections and the need for eye drops.

Contents

Abbreviations

Word or phrase	Abbreviation
Best-corrected visual acuity	BCVA
National Eye Institute visual function questionnaire−25	NEI VFQ-25
Standard deviation	SD

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2021 and updated in February 2022.

Procedure name

- Nerve graft for corneal denervation.

Professional societies

- Royal College of Ophthalmologists
- The Bowman Club.

Description of the procedure

Indications and current treatment

The cornea is innervated by the ophthalmic branch of the trigeminal nerve. This innervation maintains the health of the cornea. It does this by providing trophic factors to the corneal cells, activating protective blink reflexes, and stimulating tear production.

Damage to the trigeminal nerve can result in a decrease or loss of corneal sensation. The trigeminal nerve can be damaged by various diseases, chemical burns, physical injuries, or by surgery. Loss of innervation to the cornea can

result in neurotrophic keratitis (also known as neurotrophic keratopathy). People with neurotrophic keratitis typically have corneal epithelium defects, poor corneal healing, and can develop sight loss. They are also prone to corneal infections. Neurotrophic keratitis is often defined by 3 stages of severity (Mackie classification). See Outcome measures for a description of the Mackie classification.

Current treatment for neurotrophic keratitis aims to stop progression to later stages of the disease and promote regeneration of the epithelium. This can include topical lubricants and artificial tears. Antibiotic tear drops may be needed to prevent infections. Options for severe disease include lateral tarsorrhaphy (using sutures to partially or fully close the eyelids), topical nerve growth factor, topical collagenase inhibitors, and amniotic membrane grafting.

What the procedure involves

Nerve graft to restore corneal sensation is done under general anaesthesia. This overview presents evidence on autografts, when the graft is taken from the person having the procedure, and allografts, when the graft is a processed nerve from a deceased donor. This overview presents evidence for 4 different graft types:

- Autografts:
  - Sural nerve, harvested from the lower leg.
  - Lateral antebrachial cutaneous nerve, harvested from the forearm.
  - Great auricular nerve, harvested from below the ear.
- Allograft: processed nerve from a deceased donor.

The nerve graft is harvested or prepared. At the same time, an incision is made on the contralateral side. This is to access an orbital nerve (the supratrochlear, supraorbital, or infraorbital nerve) of the eye that still has normal sensation (the 'donor' nerve). In some people, the ipsilateral supratrochlear, supraorbital, or infraorbital nerve, or the ipsilateral great auricular nerve is used as a donor nerve. The nerve graft is attached to the donor nerve and then subcutaneously tunnelled to the perilimbal area of the affected eye. The nerve fascicles can either be placed around the entire limbal circumference and secured to the sclera or are inserted into corneoscleral tunnels. The nerve fascicles are secured with sutures or fibrin glue, or both. The conjunctiva is closed and a temporary lateral tarsorrhaphy may be placed. A patch and topical lubricants may be prescribed after surgery. Over time, new nerve endings grow into the cornea. A corneal transplant may be needed to fully restore sight in people with loss of corneal clarity.

This procedure is distinct from 'direct' corneal neurotisation, where the supratrochlear, supraorbital, or infraorbital nerve is dissected and directly transferred to the affected eye without the use of an interpositional nerve graft.

Outcome measures

Mackie classification

The Mackie classification grades neurotrophic keratitis as follows:

- **Stage 1**: punctate keratopathy, positive Bengal staining of the inferior palpebral conjunctival surface (indicative of damage to the corneal epithelium), a decrease in tear breakup time, and an increase in tear viscosity.
- **Stage 2**: epithelial breakdown with recurrent or persistent epithelial defects surrounded by loose hazy epithelium.
- **Stage 3**: corneal ulceration that can progress to melting and perforation.

Corneal sensation

Corneal sensation is typically measured using a handheld Cochet-Bonnet aesthesiometer that contains a thin, retractable, nylon monofilament. Variable pressure can be applied by the device by adjusting the monofilament length (up to 60mm). The filament is first fully extended and applied to the cornea. The filament is then incrementally reduced until the person being tested can feel it. The shorter the length of the filament, the greater the pressure applied on the cornea, and the lower the sensation of the cornea.

Best-corrected visual acuity (BCVA)

BCVA is the measurement of the best visual acuity achieved through use of corrective lenses (that is, glasses or contact lenses). Visual acuity is often measured by a Snellen chart. The Snellen chart consists of multiple lines of letters. The letters in each line are smaller than the letters in the previous line. Standing at 6 metres (20 feet) and covering 1 eye, the participant reads from the top of the chart downwards. The smallest row that can be read accurately indicates the visual acuity of the eye being tested. Visual acuity is expressed in relation to 'standard' vision. For example:

- 6/6 or 20/20 – 'standard' vision.
- 6/12 or 20/40 – the participant sees the same level of detail at 6 metres (20 feet) as someone with 'standard' vision sees at 12 metres (40 feet).

- 6/60 or 20/200 – the participant sees the same level of detail at 6 metres (20 feet) as someone with 'standard' vision sees at 60 metres (200 feet).

A newer test of visual acuity is the Logarithm of the Minimum Angle of Resolution (LogMAR) chart. This chart uses similar principles to the Snellen chart but is more accurate. Higher LogMAR visual acuity scores indicate worse vision. A person with 'standard' vision can resolve 1 minute of visual angle and scores LogMAR 0. A person with 6/12 vision on the Snellen chart would score approximately LogMAR 0.3.

Efficacy summary

Efficacy and safety summaries are split by type of graft and donor (that is, the nerve to which the graft is attached) nerve.

Autograft: sural nerve graft with orbital nerves as donor

Corneal sensation

In a before-and-after study of 16 people (14 aged 18 or under), there was a statistically significant increase in central corneal sensation. It increased from a mean of 0.8 mm (SD 2.5 mm) before surgery to 49.7 mm (standard deviation [SD] 15.5 mm) at a mean follow up of 24.0 months ($p<0.0001$; Capatano, 2019).

In a non-randomised controlled trial of 10 people, there was a statistically significant increase in corneal sensation. It increased from 2.5 mm (SD 5.4 mm) before surgery to 22.5 mm (SD 18.3 mm) after 1-year follow up ($p=0.002$). In the comparator group, 16 people had direct neurotisation. At 3 and 6 months follow up, people who had direct neurotisation had a statistically significantly higher change from baseline corneal sensation than people who had indirect neurotisation ($p=0.042$ and $p=0.048$, respectively). However, this difference was not seen at 1-year follow up ($p=0.579$; Fogagnolo, 2020).

In a case series of 11 people, corneal sensation improved in 9 people and did not change in 2 people at a mean follow up of 14.5 months. There was no statistical analysis done (Elalfy, 2021).

In a case series of 6 people, corneal sensation was regained in all people at a final follow up of 6 to 17 months. There was no statistical analysis done (Weis, 2018).

Visual acuity

In the before-and-after study of 16 people (14 aged 18 or under), there was no statistically significant change in BCVA before and after surgery. The authors

note that this is 'due to the presence of corneal stromal scarring in all the eyes in our cohort' (Capatano, 2019).

In the non-randomised controlled trial of 10 people, there was no statistically significant change in decimal BCVA from 0.42 (SD 0.23) before surgery to 0.48 (SD 0.27) at 1-year follow up (p=0.054). This study reported decimal BCVA in which higher scores indicate better visual acuity. In the comparator group, 16 people had direct neurotisation. There was no statistically significant difference in the improvement of BCVA between the 2 techniques (p=0.089; Fogagnolo, 2020).

In the case series of 11 people, visual acuity improved in 6 people, stabilised in 3 people, and deteriorated in 2 people at a mean follow up of 14.5 months. There was no statistical analysis done (Elalfy, 2021).

In the case series of 6 people, 5 people had improved visual acuity after neurotisation. There was no statistical analysis done (Weis, 2018).

Corneal damage

In the before-and-after study of 16 people (14 aged 18 or under), there was a statistically significant decrease in the number of people with persistent epithelial defects from 17 people (89%) before surgery to 4 people (21%) after surgery (p<0.0001; Capatano, 2019).

In the non-randomised controlled trial of 10 people, there was a statistically significant decrease in the area of the epithelial defect from 12.40 mm^2 before surgery to 0.10 mm^2 after surgery (p=0.006). In the comparator group, 16 people had direct neurotisation. There was no statistically significant difference in the change in epithelial defect area between the 2 techniques (p=0.120; Fogagnolo, 2020)

In the case series of 11 people, no one developed any further corneal ulcers after the procedure at a mean follow up of 14.5 months. Additionally, there was a decrease in corneal and conjunctival staining in 10 people, and no change in 1 person. There was no statistical analysis done (Elalfy, 2021).

In the case series of 6 people, 4 people had improved corneal epithelial status after neurotisation. There was no statistical analysis done (Weis, 2018).

Corneal reinnervation

In the case series of 11 people, in 4 of 5 people assessed, nerve fibre density, nerve branch density, nerve fibre length, and total branch density generally increased over a mean follow up of 14.5 months. There was no statistical analysis done (Elalfy, 2021).

In the non-randomised controlled trial of 25 people, there was an increase in the mean corneal nerve fibre length from 1.8 mm/mm^2 (SD 0.15 mm/mm^2) before surgery to 14.67 mm/mm^2 (SD 7.92 mm/mm^2) at 1-year follow up. Data was not provided separately for the indirect and direct neurotisation groups. However, the change in corneal nerve fibre length from before to after surgery did not differ significantly between the groups (p=0.833; Fogagnolo, 2020)

Mackie stage

In the before-and-after study of 16 people (14 aged 18 or under), before surgery, 3 eyes had Mackie stage 1 neurotrophic keratitis, 7 eyes had grade 2, and 9 eyes had grade 3. After surgery 15 eyes had Mackie stage 1 neurotrophic keratitis, 4 eyes had grade 2, and 9 eyes had grade 3. There was no statistical analysis done (Capatano, 2019).

Tear outcomes

In the case series of 11 people, the following tear outcomes were reported at a mean follow up of 14.5 months. No statistical analysis was done (Elalfy, 2021):

- Tear film breakup time increased in 10 people, decreased in 1 person.
- Tear meniscus height increased 7 people, no change in 4 people.
- Schirmer's test (tear production) increased in 4 people, no change in 7 people.
- Tear film osmolarity decreased 7 people, no change in 2 people, increased in 2 people.

Use of conservative treatments

In the case series of 11 people, reduction in lubricant use after surgery was reported by 3 people, with 8 people reporting no change. No statistical analysis was done (Elalfy, 2021).

Quality-of-life outcomes

In the case series of 11 people, 6 people completed the before and after surgery NEI VFQ-25. In general, there were improvements in overall vision, ocular discomfort, and reading, and a reduction in limitation of activities and psychosocial impact of the disease. No statistical analysis was done (Elalfy, 2021).

Autograft: sural nerve graft with great auricular nerve as donor

Corneal sensation

In a case series of 2 people, corneal sensation improved from absent to 47 mm in 1 person over 8 months follow up, and from between 0 and 15 mm to 37 mm in 1 person over 5.5 months follow up. There was no statistical analysis done (Jowett, 2019).

Visual acuity

In the case series of 2 people, visual acuity improved from 20/125 to 20/80 in 1 person over 4.5 months follow up, and from 20/300 to 20/80 in 1 person over 5.5 months follow up. There was no statistical analysis done (Jowett, 2019).

Autograft: great auricular nerve graft with orbital nerves as donor

Corneal sensation

In a case report of 1 person, corneal sensation improved from absent before surgery to 10 mm at 12 months follow up (Benkhatar, 2018).

Visual acuity

In the case report of 1 person, BCVA did not change from below 20/200 before surgery to below 20/200 at 6 months follow up (Benkhatar, 2018).

Corneal appearance

In the case report of 1 person, corneal appearance did not improve after surgery (Benkhatar, 2018).

Corneal reinnervation

In the case report of 1 person, there was an absence of corneal nerve fibres before surgery. At 6 months after surgery, nerve fibres were present at high density in both nasal and temporal sectors (Benkhatar, 2018).

Autograft: lateral antebrachial cutaneous nerve graft with orbital nerves as donor

Corneal sensation

In a case report of 1 person, corneal sensation improved from absent before surgery to 40 mm at 12 months follow up (Bourcier, 2019).

Visual acuity

In the case report of 1 person, BCVA improved from 20/200 before surgery to 20/80 at 12 months follow up (Bourcier, 2019).

Allograft: acellular nerve allograft with orbital nerves as donor

Corneal sensation

In a before-and-after study of 17 people, there was a statistically significant increase in mean corneal sensation from 3.6 mm (SD 8.4 mm) before surgery to 44.2 mm (SD 16.2 mm) after surgery ($p<0.01$). The mean final follow up in this study was 17.7 months. However, the follow up time for the assessment of corneal sensation is not clearly described. There were no statistically significant differences in time to first gain of corneal sensation, time of maximum gain of corneal sensation, or before-after surgery improvement in corneal sensation when comparing end-to-end with end-to-side coaptation, supraorbital with infraorbital donor nerves, and ipsilateral with contralateral donor nerves (Sweeney, 2020).

In a case series of 7 people, all had improved corneal sensation after surgery. Follow up ranged from 3 to 10 months. There was no statistical analysis done (Leyngold, 2019).

Visual acuity

In the before-and-after study of 17 people, there was no statistically significant change in BCVA from 20/500 before surgery to 20/300 after surgery ($p=0.22$; BCVA measurements were converted into LogMAR for analysis). The mean final follow up in this study was 17.7 months. However, the follow up time for the assessment of visual acuity is not clearly described. The authors state that visual acuity gains were limited by pre-existing conditions (Sweeney, 2020).

In the case series of 7 people, 6 of 7 had improved BCVA after surgery. Follow up ranged from 3 to 10 months. There was no statistical analysis done (Leyngold, 2019).

Corneal damage

In the case series of 7 people, of the 5 people who had an epithelial defect before surgery, all were resolved after surgery. Follow up ranged from 3 to 10 months. There was no statistical analysis done (Leyngold, 2019).

Safety summary

Autograft: sural nerve graft with orbital nerves as donor

Persistent epithelial defects

The before-and-after study of 16 people (14 aged 18 or under) reported 5 episodes of persistent epithelial defects in 4 eyes of 4 people after surgery. All happened over 24 months after neurotisation, 3 were after corneal transplant. All resolved within 4 weeks after presentation with antibiotics, with or without a bandage contact lens (Capatano, 2019).

Facial oedema

The non-randomised trial of 10 people reported 10 cases of oedema of the upper third of the face (Fogagnolo, 2020).

Suture exposure

The before-and-after study of 16 people (14 aged 18 or under) reported 5 cases of suture exposure. This did not happen after switching to absorbable polyglactin sutures (Capatano, 2019).

Referred sensation

The non-randomised trial of 10 people reported that all people who regained corneal sensation developed misperception of the corneal tactile stimulation in the contralateral forehead. This complication happened in the first 3 to 6 months after surgery, regardless of the technique employed. Then, the sensation shifted from the forehead to the cornea about 6 to 9 months after surgery (Fogagnolo, 2020).

Donor site morbidity

Numbness

The non-randomised trial of 10 people reported 10 cases of partial numbness of the frontal region on the leg where the sural nerve was harvested (Fogagnolo, 2020).

Autograft: sural nerve graft with great auricular nerve as donor

Referred sensation

The case series of 2 people reported that 1 person had referred sensations to the ipsilateral earlobe. This was relieved by ocular irrigation (Jowett, 2019).

Autograft: great auricular nerve graft with orbital nerves as donor

Donor site morbidity

Paraesthesia

The case report of 1 person reported that the person had mild paraesthesia of the earlobe that resolved over 6 months (Benkhatar, 2018).

Autograft: lateral antebrachial cutaneous nerve graft with orbital nerves as donor

Donor site morbidity

Numbness

The case report of 1 person reported 1 case of numbness of the forearm and contralateral forehead that resolved over 6 months (Bourcier, 2019).

Allograft: acellular nerve allograft with orbital nerves as donor

Dry eye

The case series of 7 people reported 2 cases of dry eye symptoms (Leyngold, 2019).

Recurrent epithelial defect

The case series of 7 people reported 1 case of recurrent epithelial defect. This was treated with oral prednisone and healed in 1 week (Leyngold, 2019).

Altered sensation

The case series of 7 people reported 2 cases of bulbar conjunctival hyperesthesia (Leyngold, 2019).

The case series of 7 people reported 1 case of synaesthesia that resolved over 7 months (Leyngold, 2019).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: small bony excrescence, haematoma, disconnection of anastomosis, scarring, graft scarring or shortening. They considered that the following were theoretical adverse events: persistent pain at donor site, injury due to reduced sensation to foot or arm.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to nerve graft for corneal denervation. The following databases were searched, covering the period from their start to 4th February 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	People with neurotrophic keratitis.
Intervention/test	Indirect (use of a nerve graft) corneal neurotisation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 71 people from 1 non-randomised controlled trial, 2 before-and-after studies, 4 case series, and 2 case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on autograft: sural nerve graft with orbital nerves as donor for corneal denervation

Study 1 Capatano J (2019)

Study details

Study type	Single arm, single centre, non-randomised, before-and-after study
Country	Canada
Recruitment period	2012 to 2017
Study population and number	n=19 eyes in 16 people All people who had corneal neurotisation for neurotrophic keratitis at a hospital for children and young people.
Age and sex	Mean 12.5 years (SD 8.3 years) with 88% of people aged 18 years or younger; 56% female
Patient selection criteria	Inclusion criteria: all people who had corneal neurotisation for neurotrophic keratitis at a hospital for children and young people. Further details of patient selection are not described.
Technique	Sural nerve graft coapted to the ipsilateral or contralateral supratrochlear, supraorbital, or infraorbital nerves. In 14 people, the graft was coapted to the supratrochlear nerve, in 1 person to the supraorbital, and in 1 person to the infraorbital. Coaptation was performed using sutures and/or fibrin glue. In the first 7 eyes (6 people), the fascicles of the sural graft were laid in the perilimbal subconjunctival space. In the following 12 eyes, the ends of nerve fascicles were inserted into the peripheral corneal stroma via a partial-thickness corneoscleral tunnel incision. The authors state that this was to replicate the normal innervation of the cornea and shorten the distance between the donor nerve end and the cornea. After surgery, a temporal permanent tarsorrhaphy was constructed. A central temporary tarsorrhaphy was also placed for 1 week.
Follow up	Mean 24.0 months (SD 16.1 months)
Conflict of interest/source of funding	Conflict of interest: the authors declared no conflict of interest. Source of funding: Supported in part by grants from the Plastic Surgery Foundation and American Society of Peripheral Nerve; Moorfields Eye Charity; and HCA International Foundation.

Analysis

Follow up issues: Reliable testing of corneal sensation was not possible in 1 person due to young age and developmental delay, and this person was excluded from corneal sensory analysis.

Study design issues: This single arm, single centre, non-randomised, before-and-after study evaluated the outcomes of people with neurotrophic keratitis treated with corneal neurotisation. The primary outcome was

central corneal sensation, as measured by Cochet-Bonnet aesthesiometry with sensation ranging from 0 mm (absent sensation) to 60 mm (full sensation). Other outcomes included BCVA (reported using LogMAR), episodes of persistent epithelial defect (PED, defined as non-infected corneal ulceration that failed to resolve within 2 weeks of commencing treatment), adjunctive medical treatments and any side effects or complications from MICN were documented.

Differences in continuous variables were assessed with Wilcoxon signed-rank test, while categorical variables were assessed with Fisher's exact test. A p value <0.05 was considered statistically significant. The authors do not report adjustment for multiple comparisons.

Study population issues: Three eyes had Mackie stage 1 neurotrophic keratitis, 7 eyes had grade 2, and 9 eyes had grade 3. The most common aetiology of neurotrophic keratitis was congenital corneal anaesthesia (14 eyes, 74%). Amblyopia was present in 5 eyes (26%), facial nerve palsy in 5 (26%), cataracts in 2 (11%), glaucoma in 1 (5%), and microphthalmia in 1 (5%).

Key efficacy findings

Number of people analysed: 16 people, 19 eyes
Follow up at time of assessment: mean 24.0 months (SD 16.1 months)

- **Central corneal sensation:** Statistically significant increase from a mean of 0.8 mm (SD 2.5 mm) before surgery to 49.7 mm (SD 15.5 mm) after surgery (p<0.0001; Table).
    - At 3 months after surgery, central corneal sensation in the perilimbal subconjunctival group was 2.5 mm (SD 6.1 mm), and 19.4 mm (SD 23.1 mm) in the corneoscleral tunnel group (p=0.08). Central corneal sensation at other time points was comparable between the groups.
- **BCVA:** No change in BCVA from before surgery to after surgery (Table). The authors note that this is 'due to the presence of corneal stromal scarring in all the eyes in our cohort'.
- **History of PED:** Statistically significant decrease in the number of people with PEDs from 17 (89%) before surgery to 4 (21%) after surgery (p<0.0001; Table).
- **Neurotrophic keratitis grade:** Before surgery, 3 eyes had Mackie stage 1 neurotrophic keratitis, 7 eyes had grade 2, and 9 eyes had grade 3. After surgery 15 eyes had Mackie stage 1 neurotrophic keratitis, 4 eyes had grade 2, and 9 eyes had grade 3 (Table).

Summary of outcomes

Outcome	Before surgery	After surgery	p value
CCS (mm)			
Mean (± SD)	0.8 ± 2.5	49.7 ± 15.5	<0.0001
Median (range)	0 (0 to 0)	60 (40 to 60)	<0.0001
BCVA (LogMAR)			
Mean (± SD)	1.01 ± 0.68	0.89 ± 0.73	Not significant
Median (range)	0.7 (0.3 to 2.28)	0.7 (0.0 to 2.28)	Not significant
History of PED			
Total vs. after surgery	17 (89%)	4 (21%)	<0.0001
1 year prior vs. after surgery	10 (53%)	4 (21%)	Not reported
NK grade (eyes)			
Grade 1	3 (16%)	15 (79%)	Not reported
Grade 2	7 (37%)	4 (21%)	Not reported

Outcome	Before surgery	After surgery	p value
Grade 3	9 (47%)	0	Not reported

Abbreviations: BCVA, best-corrected visual acuity; CCS, central corneal sensation; LogMAR, logarithm of the minimum angle of resolution; NK, neurotrophic keratitis; PED, persistent epithelial defect; SD, standard deviation.

Key safety findings

Number of people analysed: 16 people, 19 eyes
Follow up at time of assessment: mean 24.0 months (SD 16.1 months)

- There were no intraoperative complications.
- After surgery complications:
    - Persistent epithelial defects, n=5 episodes in 4 eyes of 4 people.
        - All occurred over 24 months after neurotisation, 3 were following corneal transplant.
        - All resolved within 4 weeks after presentation with antibiotics with or without a bandage contact lens.
    - Suture exposure, n=5
        - Did not occur after switching to absorbable polyglactin sutures.

Study 2 Fogagnolo P (2020)

Study details

Study type	Multicentre, non-randomised controlled trial
Country	Italy
Recruitment period	2014 to 2019
Study population and number	n=26 eyes in 25 people; 10 eyes by indirect neurotisation (with sural nerve graft), 16 eyes by direct neurotisation Adults with neurotropic keratitis
Age and sex	Mean 45.4 years; 80% female
Patient selection criteria	Inclusion criterion: chronic neurotropic keratitis (reduced or abolished corneal sensation measured by Cochet-Bonnet aesthesiometer with a duration time from the onset of >3 months) because of central nervous denervation despite conventional treatment. Exclusion criteria: presence of any active corneal disease other than neurotropic keratitis and diagnosis of polyneuropathy or other types of disorder affecting the peripheral nervous system.
Technique	Indirect neurotisation or direct neurotisation was chosen according to the person's clinical characteristics and preferences. For indirect neurotisation, a sural nerve graft was coapted end-to-end to the supratrochlear and/or supraorbital nerves. The nerve graft was tunnelled subconjunctivally to the perilimbal area of the cornea. A scleral-corneal tunnel for each fascicle was made into the anterior corneal stroma to help nerve growth toward the centre of the cornea. The nerves were then fixed in the desired position with fibrin glue, and the conjunctiva was repaired with 8-0 Vicryl suture.
Follow up	Mean 18.76 months; data at 1 year follow up was used for the main analysis
Conflict of interest/source of funding	Conflict of interest: the authors report 'no proprietary or commercial interest in any materials discussed in the article'. Source of funding: supported by a grant from the Italian Society of Ophthalmology.

Analysis

Follow up issues: Of people who had indirect neurotisation, 2 were followed up for less than 12 months.

Study design issues: This multicentre, non-randomised controlled trial assessed the comparative efficacy and safety of indirect corneal neurotisation (using a sural nerve graft) versus direct corneal neurotisation in people with neurotrophic keratitis. Consecutive people with neurotropic keratitis who attended the corneal service of the 3 centres were screened for eligibility. Outcomes included neurotrophic keratitis healing, corneal sensation (measured by a Cochet-Bonnet aesthesiometer), BCVA (reported as a decimal), and *in vivo* confocal microscopy.

The Wilcoxon test was used to compare the continuous variables before surgery and at 1 year follow up in overall people and separately in the 2 groups. The Chi-squared test was used to compare the proportion of people with neurotrophic keratitis in severity stages 1, 2, and 3 in the 2 groups. The Mann-Whitney U test was

used to compare the changes in continuous variables between the 2 groups. A p value <0.05 was considered statistically significant. The authors do not report adjustment for multiple comparisons.

Study population issues: There were statistically significant differences in the baseline values of BCVA and neurotrophic keratitis severity stage between the 2 groups. Decimal BCVA was significantly lower in the direct neurotisation group (0.19 [SD 0.23] vs. 0.42 [SD 0.28]; p=0.044). Mackie stage was significantly higher in the direct neurotisation group (0% vs. 40% had stage 1, 31.25% vs 40.00% had stage 2, and 68.75% vs 20.00% had stage 3; p=0.009).

Key efficacy findings

Neurotrophic keratitis healing

Number of people analysed: 10 eyes in 10 people
Follow up at time of assessment: 1 year

- Neurotrophic keratitis healed in all people after a mean period of 3.9 (SD 1.5 months; range: 2 to 6 months) (healing rate 100%). There was no statistically significant difference in the healing time of the 2 techniques.
- In people treated with indirect corneal neurotisation, there was a statistically significant decrease in the area of the epithelial defect from 12.40 mm^2 before surgery to 0.10 mm^2 after surgery (p=0.006). There was no statistically significant difference in the change in epithelial defect area between the 2 techniques (p=0.120).

Corneal sensation

Number of people analysed: direct neurotisation = 16 eyes in 16 people; indirect neurotisation = 10 eyes in 10 people
Follow up at time of assessment: 1 year

- In people treated with indirect neurotisation, there was a statistically significant increase in corneal sensation from 2.5 mm (SD 5.4 mm) to 22.5 mm (SD 18.3 mm; p=0.002). Note that there are discrepancies in the data provided in the text (2.5 mm to 22.5 mm) and the table below (2.5 mm to 17.5 mm). It is not clear from the publication whether the differences in data represents different analysis sets.
- At 3 and 6 months follow up, people treated with direct neurotisation had a statistically significantly higher change from baseline corneal sensation than people treated with indirect neurotisation (p=0.042 and p=0.048, respectively). This difference was not seen at 1 year follow up (p=0.579).

Aesthesiometry data over time according to the type of neurotisation

Visit (months)	DCN Group, mean mm ± SD (range)	ICN Group, mean mm ± SD (range)	p-value, DCN vs. ICN as compared to baseline
Baseline	4.0 ± 8.9 (0 to 30)	2.5 ± 5.3 (0 to 15)	0.867
After 1	6.5 ±11.6 (0 to 40)	5.0 ± 10.1 (0 to 20)	0.785
After 3	15.2 ± 20.3 (0 to 60)	6.5 ± 7.5 (0 to 20)	0.042
After 6	19.8 ± 17.1 (0 to 60)	9.3 ± 19.1 (0 to 40)	0.048
After 9	23.0 ± 25.1 (0 to 60)	16.2 ± 22.9 (0 to 45)	0.432
After 12	22.3 ± 20.4 (0 to 60)	17.5 ± 17.3 (0 to 45)	0.579

Abbreviations: DCN, direct corneal neurotisation; ICN, indirect corneal neurotisation; SD, standard deviation.

Visual acuity

Number of people analysed: direct neurotisation = 16 eyes in 16 people; indirect neurotisation = 10 eyes in 10 people
Follow up at time of assessment: 1 year

- In people treated with indirect corneal neurotisation, there was a numerical increase in decimal BCVA from 0.42 (SD 0.23) before surgery to 0.48 (SD 0.27) after surgery. This was not statistically significant (p=0.054). There was no statistically significant difference in the improvement of BCVA between the 2 techniques (p=0.089), however, there was a statistically significant difference in the before versus after surgery BCVA of people treated with direct neurotisation (p=0.004).

In vivo confocal microscopy findings

Number of people analysed: 26 eyes in 25 people
Follow up at time of assessment: 1 year

- In all but 1 person, corneal sub-basal nerve plexus was not detectable before surgery. After surgery, all people had new nerve fibres appear which gradually formed a regenerated corneal sub-basal nerve plexus that reached near-normal features 1 year after surgery.
- Mean corneal nerve fibre length increased from 1.8 mm/mm^2 (SD 0.15 mm/mm^2) before surgery to 14.67 mm/mm^2 (SD 7.92 mm/mm^2) after surgery. The change in corneal nerve fibre length from before to after surgery did not differ significantly between the people who had direct or indirect neurotisation (p=0.833).

Key safety findings

Number of people analysed: 10 eyes in 10 people
Follow up at time of assessment: Up to 21 months

In people who had indirect neurotisation, the following safety findings were reported:

- Oedema of the upper third of the face, n=10
- Partial numbness of the frontal region on the leg where the sural nerve was harvested, n=10
    - This deficit of sensation gradually reduced in size and intensity within the first year after surgery.

In all people who regained corneal sensation (with either direct or indirect neurotisation), the following safety findings were reported:

- Misperception of the corneal tactile stimulation in the contralateral forehead.
    - This complication occurred in the first 3 to 6 months after surgery, regardless of the technique employed. Then, the sensation shifted from the forehead to the cornea about 6 to 9 months after surgery.

Study 3 Elalfy M (2021)

Study details

Study type	Single arm, single centre, non-randomised, prospective, consecutive case series
Country	UK
Recruitment period	2016 to 2018
Study population and number	n=11 eyes in 11 people People with neurotrophic keratitis undergoing corneal neurotisation surgery
Age and sex	Median 43 years; 73% Female
Patient selection criteria	Inclusion criteria: All people included in the study had episodes of recurrent persistent epithelial defects or corneal ulceration aggressively treated with conventional therapy including temporary tarsorrhaphy, with corneal neurotisation procedure performed once their ocular surface was stabilised. All people had 0 corneal sensation on Cochet–Bonnet aesthesiometer before surgery and full corneal sensation in the contralateral eye.
Technique	Sural nerve graft, end-to-end coapted to the ipsilateral or contralateral supratrochlear or supraorbital nerve (or both). Four to five sural nerve fascicles were each inserted into corneoscleral lamella tunnels around the entire limbal circumference, with 2 further fascicles laid in the perilimbal area. Coaptation was performed using 10-0 Nylon sutures and fibrin glue (Tisseel). In 3 cases amniotic membrane was also wrapped around the coaptation.
Follow up	Mean 14.5 months
Conflict of interest/source of funding	Conflict of interest: The authors declared that no financial or non-financial conflicting interests exist for any author. Source of funding: The authors report no source of funding.

Analysis

Follow up issues: 6 people did not complete in vivo confocal microscopy. Eight people completed the pre-neurotisation questionnaire, and 6 people completed both pre- and post-neurotisation questionnaire.

Study design issues: This single arm, single centre, non-randomised, prospective, consecutive case series reported the functional, anatomical, and subjective outcomes of people with neurotrophic keratitis who had corneal neurotisation surgery. Functional outcomes included bilateral assessment of visual acuity; slit-lamp examination of corneal and conjunctival staining using fluorescein 1% eye drops (increased staining is indicative of worsening keratitis); tear production (Schirmer's 1 test); tear film break-up time; tear film meniscus height, quality and osmolarity; central corneal thickness; and measurement of corneal sensation using Cochet–Bonnet aesthesiometer. Structural outcomes included changes in corneal nerve density and morphology by in vivo confocal microscopy. Subjective outcomes were collected using the NEI VFQ-25. This questionnaire includes items on general health, vision, difficulties with activities (near, distance, driving) and responses to vision problems (levels of disability, discomfort, and psychosocial impact). Further subjective outcomes included frequency of eye lubricants, visits to the hospital up to 6 months after surgery and the frequency of corneal ulcers 2 years before and up to 6 months after surgery.

No statistical analysis was performed.

Study population issues: Person 4 had corneal neovascularisation, person 2 had corneal scarring and people 7, 8 and 11 had superficial corneal scarring preoperatively. No other ocular comorbidities that could affect the final visual outcome were detected in any of the people.

Key efficacy findings

Functional outcomes

Number of people analysed: 11 eyes in 11 people
Follow up at time of assessment: mean 14.5 months

- **Vision (Snellen acuity):** improved in 6 people, stabilised in 3 people, and deteriorated in 2 people at the last follow up compared to before surgery.
- **Corneal and conjunctival staining:** decreased in 10 people, no change in 1 person.
- **Tear film breakup time:** increased in 10 people, decreased in 1 person.
- **Tear meniscus height:** increased 7 people, no change in 4 people.
- **Schirmer's test (tear production):** increased in 4 people, no change in 7 people.
- **Tear film osmolarity:** decreased 7 people, no change in 2 people, increased in 2 people.
- **Central corneal thickness:** increased in 9 people, no change in 1 person, decreased in 1 person.
- **Corneal sensation** improved in 9 people, no change in 2 people.
    - Late recovery of corneal sensation was noted in 1 person, from 0 at 6 and 12 months after corneal neurotisation, to 10 mm at 24 months.

Structural outcomes

Number of people analysed: 5 eyes in 5 people
Follow up at time of assessment: 9 to 36 months

- Apart from 1 person, nerve parameters including nerve fibre density, nerve branch density, nerve fibre length, and total branch density generally increased over the follow up period.

Subjective outcomes

Number of people analysed: 11 eyes in 11 people
Follow up at time of assessment: not reported

- **Use of lubricants:** reduction in lubricant use after surgery in 3 people; no change in 8 people.
- **Frequency of hospital visits**: reduced after surgery in 5 people; no change in 5 people; increased after surgery in 1 person.
- **Corneal ulcers**: No person developed any further corneal ulcers following the procedure.

Number of people analysed: 8 (pre-neurotisation questionnaire); 6 (pre- and post-neurotisation questionnaire).
Follow up at time of assessment: not reported

- **NEI VFQ-25 results**
  - Overall vision: 1 person reported that vision remained poor after surgery, 5 people reported fair or good vision.
  - Ocular discomfort: all had moderate ocular discomfort before surgery. Four people improved to mild discomfort, 3 people continued to experience moderate discomfort. The source of this data is unclear, as only 6 people were reported to have completed both before and after surgery questionnaires.
  - Reading: improved from extremely or moderately difficult to no or mild difficulty in 4 people, no change in 2 people.
  - Distance vision: 4 people reported no or mild difficulty with distance vision after surgery. The before surgery outcomes are not reported.
  - Limitation of activities: all people reported limitation of activity most of the time before surgery, all reported none or some limitation of activity after surgery.
  - Psychosocial impact of the disease: all people reported psychosocial impact of the disease most of the time before surgery, all reported none or some psychosocial impact of the disease after surgery.

Key safety findings

No during or after surgery complications were observed in any people at either donor or recipient sites.

Study 4 Weis E (2018)

Study details

Study type	Single arm, single centre, non-randomised, prospective, consecutive case series
Country	Canada
Recruitment period	Not reported
Study population and number	n=6 eyes in 6 people Adults with neurotrophic keratitis
Age and sex	Mean 57 years (SD 19 years); 83.3% male
Patient selection criteria	Inclusion criteria: consecutive people with neurotrophic keratitis who had corneal neurotisation.
Technique	Sural nerve graft coapted to the ipsilateral or contralateral supratrochlear or supraorbital nerves. Coaptation was performed either end-to-end or end-to-side, using 10-0 Nylon sutures and fibrin sealant. Each nerve fascicle was sutured to the sclera at the limbus with 9-0 Vicryl sutures. After surgery, a temporary suture tarsorrhaphy was performed on the affected anaesthetic eye.
Follow up	Mean 12 months
Conflict of interest/source of funding	Conflict of interest: the authors declared 'no proprietary or commercial interest in any materials discussed in this article.' Source of funding: not reported.

Analysis

Follow up issues: follow up ranged from 6 to 17 months.

Study design issues: This single arm, single centre, non-randomised, prospective, consecutive case series reported this centre's early experience with corneal neurotisation for neurotrophic keratitis. Outcomes included corneal sensation, visual acuity, and epithelial condition. Corneal sensation was measured by gently pressing a pieces of tissue paper against the cornea in 4 peripheral quadrants of the eye as well as centrally. If light touch was present, this was recorded as positive. If no light touch was noted, then harder pressure was evaluated with a Schirmer strip. This method of evaluation of corneal sensation is likely less accurate than use of an aesthesiometer. Visual acuity was measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

No statistical analysis was described.

Key efficacy findings

Number of people analysed: 6 eyes in 6 people
Follow up at time of assessment: 6 to 17 months

- All people regained corneal sensation at the last follow up and 5 of 6 people had improved visual acuity.

Corneal neurotisation outcome summary

Person	Follow up (months)	Visual acuity		Epithelial status		Regained corneal sensation
		Before surgery	At follow up	Before surgery	At follow up	
1	6	20/60	20/40	Intact, central dense scarring	Intact, central dense scarring	Yes
2	9	20/800	20/160	Ulcer	Intact	Yes
3	13	Hand motion	20/25	Ulcer	Intact	Yes
4	16	20/300	20/70	Intact, central scarring	Intact	Yes
5	11	20/50	20/70	Dense corneal scar and peripheral punctate epithelial defects	Dense corneal scar and inferior Punctate epithelial defects	Yes
6	17	20/100	20/80	Ulcer	Corneal scarring, intact epithelium	Yes

Key safety findings

No complications were reported.

Summary of key evidence on autograft: sural nerve graft with great auricular nerve as donor for corneal denervation

Study 5 Jowett N (2019)

Study details

Study type	Single arm, single centre, non-randomised, prospective, case series
Country	USA
Recruitment period	2017
Study population and number	n=2 eyes in 2 people Adults with neurotrophic keratitis
Age and sex	28 and 31 years old; 100% male
Patient selection criteria	People with grade 3 neurotrophic keratitis.
Technique	Sural nerve graft coapted to the ipsilateral great auricular nerve. Scleral-corneal tunnel incisions were used to expedite neurotisation of the corneal stroma. Fibrin glue and 10-0 Nylon sutures were used to coapt the nerve. A temporary lateral suture tarsorrhaphy was placed after surgery.
Follow up	6 to 8 months
Conflict of interest/source of funding	Conflict of interest: the authors declared that they have no conflicts of interest. Source of funding: the authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Analysis

Study design issues: This single arm, single centre, non-randomised, prospective, case series reported a novel corneal neurotisation technique to treat neurotrophic keratitis. Outcomes included corneal sensation, as measured by Cochet-Bonnet aesthesiometry, and BCVA.

No statistical analysis was described.

Key efficacy findings

Number of people analysed: 2 eyes in 2 people
Follow up at time of assessment: 6 to 8 months

- Both people had improved corneal sensation and BCVA at final follow up.

Summary of people treated

Person	Corneal sensation	BCVA

	Before surgery	Follow up	After surgery	Before surgery	Follow up	After surgery
1	Absent	8 months	47 mm	20/125	4.5 months	20/80
2	0 to 15 mm	5.5 months	37 mm	20/300	5.5 months	20/80

Abbreviations: BCVA, best-corrected visual acuity.

Key safety findings

One person noted referred sensations to the ipsilateral earlobe. This was relieved by ocular irrigation.

Summary of key evidence on autograft: great auricular nerve graft with orbital nerves as donor for corneal denervation

Study 6 Benkhatar H (2018)

Study details

Study type	Case report
Country	France
Recruitment period	Not reported
Study population and number	n=1 eye in 1 person Adult with neurotrophic keratitis.
Age and sex	58 years old; female
Patient selection criteria	Not reported
Technique	Great auricular nerve graft end-to-end coapted to the contralateral supratrochlear nerve. Each fascicle was secured under the conjunctiva with 10-0 Nylon sutures around the cornea. The procedure ended with lateral tarsorrhaphy.
Follow up	12 months
Conflict of interest/source of funding	Conflict of interest: the authors declare no conflict of interest. Source of funding: the authors declare no source of funding.

Analysis

Study design issues: This case report described the first use of corneal neurotisation using a great auricular nerve graft to treat neurotrophic keratitis. Outcomes included corneal sensation (measured by Cochet-Bonnet aesthesiometry), corneal innervation (measured by confocal microscopy), and an assessment of the status of the corneal epithelium (measured by slit-lamp examination).

Key efficacy findings

Number of people analysed: 1 eye in 1 person
Follow up at time of assessment: up to 12 months

- Over 12 months follow up, there was a return of corneal sensation and reinnervation of the cornea. There was no improvement in visual acuity or corneal appearance.

Outcomes of corneal neurotisation over time

Assessment time	Corneal sensation (aesthesiometry)	BCVA	Slit-lamp examination (corneal appearance)	Confocal microscopy findings (corneal innervation)
Before surgery	Absence of sensation	Below 20/200	-	Absence of nerve fibres
3 month follow up	Absence of sensation	Not reported	Not reported	Clear nerve regeneration through the corneal subbasal and stromal layers
6 month follow up	Absence of sensation	Below 20/200	No improvement in corneal appearance	Nerve fibres were present at high density in both nasal and temporal sectors
9 month follow up	10 mm	Not reported	Not reported	Not reported
12 month follow up	10 mm	Not reported	No improvement in corneal appearance	Not reported

Abbreviations: BCVA, best-corrected visual acuity.

Key safety findings

Number of people analysed: 1 eye in 1 person
Follow up at time of assessment: 12 months

- Mild paraesthesia of the earlobe, n=1
    - Progressively resolved over a period of 6 months.

Summary of key evidence on autograft: lateral antebrachial cutaneous nerve graft with orbital nerves as donor for corneal denervation

Study 7 Bourcier T (2019)

Study details

Study type	Case report
Country	France
Recruitment period	Not reported
Study population and number	n=1 eye in 1 person Adult with neurotropic keratitis caused by chronic herpes simplex viral infection
Age and sex	32 years old; male
Patient selection criteria	Not reported
Technique	Lateral antebrachial cutaneous nerve graft end-to-end coapted to the contralateral supraorbital nerve. The 4 branches of the graft were sutured to the scleral limbus positions using 10/0 Nylon sutures.
Follow up	12 months
Conflict of interest/source of funding	Conflict of interest: The authors declared no conflicts of interest. Source of funding: funded by Les Hôpitaux Universitaires de Strasbourg, Strasbourg, France.

Analysis

Study design issues: This case report described the first use of the lateral antebrachial cutaneous nerve for corneal neurotisation in an adult with herpes-related neurotrophic keratitis. Outcomes included corneal sensation, measured by Cochet-Bonnet aesthesiometry, and visual acuity.

Key efficacy findings

Number of people analysed: 1 eye in 1 person
Follow up at time of assessment: Up to 12 months.

- Over 12 months follow up, there was a return of corneal sensation and improvement in BCVA cornea.

Outcomes of corneal neurotisation over time

Assessment time	Corneal sensation (aesthesiometry)	BCVA

Before surgery	Absence of sensation	20/200
3 month follow up	10 to 15 mm	20/200
6 month follow up	Not reported	20/100
12 month follow up	40 mm	20/80

Abbreviations: BCVA, best-corrected visual acuity.

Key safety findings

Number of people analysed: 1 eye in 1 person
Follow up at time of assessment: Up to 12 months.

- Numbness of the left forehead and forearm, n=1
    - Resolved over 6 months.

Summary of key evidence on allograft: acellular nerve allograft with orbital nerves as donor for corneal denervation

Study 8 Sweeney AR (2020)

Study details

Due to the similarity in authors, technique, and recruitment centres, this study may include 2 people who are also described in Leyngold (2019). However, this is not explicitly stated.

Study type	Single arm, multicentre, non-randomised, before-and-after study
Country	USA
Recruitment period	Not reported
Study population and number	n=17 eyes in 17 people People with neurotrophic keratitis who had corneal neurotisation
Age and sex	Mean 42.6 years (range 4 to 69 years); 53% female
Patient selection criteria	Not reported
Technique	Acellular nerve allograft, end-to-end or end-to-side coapted to either the ipsilateral or contralateral supraorbital or infraorbital nerves. All surgeons approximated the donor nerve fascicles to the limbus without corneoscleral tunnelling. Further description is provided in Leyngold (2019).
Follow up	Mean 17.7 months
Conflict of interest/source of funding	Conflict of interest: the authors declared no conflict of interest. Source of funding: supported in part by an unrestricted departmental grant from Research Prevent Blindness, Inc.

Analysis

Follow up issues: Follow up ranged from 7 to 31 months.

Study design issues: This single arm, multicentre, non-randomised, before-and-after study assessed the outcomes of corneal neurotisation using an acellular nerve allograft for people with neurotrophic keratitis. Outcomes included corneal sensation (as measured by Cochet-Bonnet aesthesiometry), BCVA, and time until maximum corneal sensation. These outcomes were also assessed in subgroups stratified by coaptation technique, donor nerve, and ipsilateral vs. contralateral donor nerve.

Statistical analysis included statistical summaries and 2-sample t-tests assuming equal variance. Statistical significance was set at $p<0.05$. The authors do not report adjustment for multiple comparisons.

Study population issues: The cause of corneal anaesthesia was prior infection in 8 people, trigeminal nerve palsy in 8 people (6 of which were secondary to intracranial surgery) and ocular trauma in 1 person. Pre-

existing eye conditions included corneal scars in 8 people, amblyopia in 2 people, optic neuropathy in 2 people, cataract/uveitis in 1 person, and proliferative diabetic neuropathy in 1 person.

Key efficacy findings

Corneal sensation

Number of people analysed: 17 eyes in 17 people
Follow up at time of assessment: Unclear, the mean final follow up was 17.7 months

- There was a statistically significant increase in mean corneal sensation from 3.6 mm (SD 8.4 mm) before surgery to 44.2 mm (SD 16.2 mm) after surgery ($p<0.01$).
    - The time to first gain of corneal sensation occurred at a mean of 3.7 months (SD 2.7 months).
    - The time to maximum gain of corneal sensation occurred at a mean of 6.6 months (SD 3.5 months)
- There were no statistically significant differences in time to first gain of corneal sensation, time of maximum gain of corneal sensation, or before-after surgery improvement in corneal sensation when comparing end-to-end vs. end-to-side coaptation, supraorbital vs. infraorbital, and ipsilateral vs. contralateral donor nerve sites

BCVA

Number of people analysed: 17 eyes in 17 people
Follow up at time of assessment: Unclear, the mean final follow up was 17.7 months

- There was no statistically significant change in BCVA from 20/500 before surgery to 20/300 after surgery ($p=0.22$; BCVA measurements were converted into LogMAR for analysis).
    - The authors state that visual acuity gains were limited by pre-existing conditions.

Key safety findings

No complications reported.

Study 9 Leyngold IM (2019)

Study details

Due to the similarity in authors, technique, and recruitment centres, this study may include 2 people who are also described in Sweeney (2020). However, this is not explicitly stated.

Study type	Single arm, multicentre, non-randomised, retrospective, case series
Country	USA
Recruitment period	Not reported
Study population and number	n=7 eyes in 7 people People with neurotrophic keratitis who had corneal neurotisation with nerve allograft.
Age and sex	Mean 46 years (range 6 to 75); 57% male
Patient selection criteria	Not reported
Technique	Acellular nerve allograft, end-to-end or end-to-side coapted to either the ipsilateral or contralateral supraorbital, supratrochlear, or infraorbital nerves. Nerve fascicles were tunnelled in the subconjunctival space to the corneoscleral limbus.
Follow up	Mean 6 months (range 3 to 10 months)
Conflict of interest/source of funding	Conflict of interest: the authors declared no conflict of interest. Source of funding: not reported.

Analysis

Study design issues: This single arm, multicentre, non-randomised, retrospective, case series reported early results with a novel corneal neurotisation procedure using an acellular nerve allograft for people with neurotrophic keratitis. Outcomes included corneal sensation (as measured by Cochet-Bonnet aesthesiometry), BCVA, and an assessment of epithelial defects.

No statistical analysis was performed.

Study population issues: The cause of neurotrophic keratitis included vestibular schwannoma in 1 person, retinal laser and ocular surgery in 2 people (1 also had diabetes), agenesis of the trigeminal nerve in 1 person, central trigeminal injury in 1 person, and herpes zoster ophthalmicus in 2 people (1 also had diabetes).

Multiple comorbidities were reported, including amblyopia (1 person), cerebral palsy (1), cardiomyopathy (1), coronary artery disease (1), diabetes (2), glaucoma (1), Goldenhar syndrome (1), hypertension (1), proliferative diabetic retinopathy (1), rhegmatogenous retinal detachment (1), smoking (2), thyroid eye disease (1), tractional retinal detachment (1), and ulcerative colitis (1).

Key efficacy findings

Number of people analysed: 7 eyes in 7 people
Follow up at time of assessment: 3 to 10 months

- All people had improved corneal sensation after neurotisation, 6 of 7 had improved BCVA, and of the 5 people who had an epithelial defect before surgery, all were resolved after surgery.

Summary of people treated

Person	Follow up (months)	Epithelial defect		Corneal sensation (mm)		BCVA	
		Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
1	10	No	No	23	30	20/150	20/40
2	10	Yes	No	0	34	HM	HM
3	6	Yes	No	None*	Improved*	LP	CF at 5 ft
4	4	Yes	No	None*	Improved*	HM	CF at 3 ft
5	6	No	No	13	60	20/70	20/20
6	4	Yes	No	10	50	HM	20/200
7	3	Yes	No	0	4	20/40	20/30

*For those people uncooperative with measurement, presence of corneal sensibility is reported as either “none” or “improved” by testing the cornea with a wisp of cotton.
Abbreviations: BCVA, best-corrected visual acuity; CF, counting fingers; HM, hand motion; LP, light perception.

Key safety findings

Number of people analysed: 7 eyes in 7 people
Follow up at time of assessment: 3 to 10 months

- Dry eye symptoms, n=2
- Synaesthesia, n=1
    - Resolved over 7 months.
- Bulbar conjunctival hyperesthesia, n=2
- Recurrent corneal epithelial defect, n=1
    - Treated with oral prednisone and healed in 1 week.

Validity and generalisability of the studies

- The studies include adults, young people, and children. Corneal neurotisation may have a different efficacy/safety profile when performed in people of different ages.
- There were several differences in the type of technique used by the studies. It is unclear which technique provides the most favourable outcomes. The differences included:
  - Type of nerve graft. The sural nerve, great auricular nerve, lateral antebrachial nerve, and an acellular nerve allograft were all used.
  - Coaptation technique. End-to-end and end-to-side coaptation were both used.
  - Donor nerve. Multiple donor nerves were described, including the orbital nerves (supratrochlear, supraorbital, and infraorbital nerves), and the great auricular nerve. There were also differences in the laterality of the donor nerve.
  - Fascicle placement. Some studies used corneoscleral tunnel incisions.
- The studies that conducted statistical analyses did not report adjustment for multiple comparisons. Testing many hypotheses without adjustment for multiple comparisons increases the likelihood of finding a statistically significant difference between data that is only different due to chance.
- The studies had small sample sizes, with the largest, Sweeney (2020), including 17 people who had indirect corneal neurotisation.
- The maximum follow up was 2 years. All studies had a follow up of 6 months to 2 years. This is appropriate to the procedure as some level of corneal sensation is usually recovered after 6 months.
- One study, a non-randomised controlled trial (Fogagnolo [2020]), enrolled a concurrent control group. Two studies, Capatano (2019) and Sweeney (2020), had a quasi-experimental before-and-after design. The other studies were either case series or case reports and did not perform any comparative statistical analysis.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

Two Professional expert questionnaires for nerve graft for corneal denervation were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

Not required for this procedure.

Issues for consideration by IPAC

- No other issues.

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Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/02/2022	Issue 2 of 12, February 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/02/2022	Issue 2 of 12, February 2022
International HTA database (INAHTA)	04/02/2022	-
MEDLINE (Ovid)	04/02/2022	1946 to February 03, 2022
MEDLINE In-Process (Ovid)	04/02/2022	1946 to February 03, 2022
MEDLINE Epubs ahead of print (Ovid)	04/02/2022	February 03, 2022
EMBASE (Ovid)	04/02/2022	1974 to February 03, 2022
EMBASE Conference (Ovid)	04/02/2022	1974 to February 03, 2022

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

Number	Search term
1	exp Cornea/
2	exp Corneal Diseases/
3	Trigeminal Nerve Diseases/
4	Trigeminal Nerve/
5	Ophthalmic Nerve/
6	(cornea* adj4 (anaesthesia* or denervation* or dystroph*)).tw.
7	(neurotrophic adj4 (keratopathy* or keratiti*)).tw.

IP overview: Nerve graft for corneal denervation

8	((cornea* or ophthalmic or trigeminal or cranial nerve) adj4 (impair* or disease* or disorder* or neuropath* or dysfunction* or abnormal*)).tw.
9	(cornea* adj4 (endothelium or epithelium) adj4 (defect* or deficit* or abnormal* or breakdown or break-down or deteriorat*)).tw.
10	or/1-9
11	Nerve Regeneration/
12	Nerve Transfer/
13	Cornea* neuroti?ation.tw.
14	((innervation or sensation*) adj4 restor*).tw.
15	(reinnervation* or re-innervation* or re-epitheliali?ation or reepitheliali?ation).tw.
16	((Nerv* or neural) adj4 (graft* or transfer* or transplant* or crossover* or neurotization* or neurotisation* or donor* or regenerat* or re-generat* or recover* or repair*)).tw.
17	or/11-16
18	10 and 17
19	animals/ not humans/
20	18 not 19

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Mixed techniques			
Park JK, Charlson ES, Leyngold I et al. (2020) Corneal Neurotization: A Review of Pathophysiology and Outcomes. Ophthalmic plastic and reconstructive surgery 36(5):431-7	n=54 eyes	Corneal neurotisation can significantly improve corneal sensation and visual acuity and should be considered for the treatment of refractory neurotrophic keratitis, especially in paediatric populations. No significant differences found between techniques or donor nerves.	Pools data from people who had nerve graft neurotisation with people who had direct nerve transfer.
Acellular nerve allograft			
Kim JS, Rafailov L, and Leyngold IM. (2021) Corneal Neurotization for Postherpetic Neurotrophic Keratopathy: Initial Experience and Clinical Outcomes. Ophthalmic plastic and reconstructive surgery 37(1):42-50	n=2 FU=11.3 months	Corneal neurotisation can successfully reinnervate corneas previously devitalised by herpetic disease and halt the progressive nature of postherpetic NK. If utilised appropriately and early in the disease process, neurotisation may reduce morbidity and maximise visual potential in postherpetic NK.	One of the people included in this study is also included in Leyngold (2019). Statistical analysis is performed on the entire cohort, including 4 people who had direct neurotisation.
Rafailov L, Kim JS, Wisely CE et al. (2021) Clinical Outcomes and	n=29 eyes in 28 people FU=12 months	Corneal neurotisation provides improvement in corneal health and sensibility, with high	Outcomes for people who had indirect neurotisation are

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Patient Satisfaction After Corneal Neurotization. Cornea 40(11):1377-86.		patient satisfaction and minimal postoperative pain and morbidity.	not presented separately to people who had direct neurotisation.
Great auricular nerve			
Lau N, Osborne SF, Vasquez-Perez A et al. (2021) Corneal Neurotization Using the Great Auricular Nerve for Bilateral Congenital Trigeminal Anesthesia. Cornea	n=1 FU=9 months	Using the great auricular nerve technique for corneal neurotisation bypasses trigeminal innervation and has the potential to improve corneal sensation. This technique would be desirable for cases with bilateral congenital trigeminal anaesthesia, such as pontine tegmental cap dysplasia.	Study with longer follow up included.
Sural nerve graft			
Bains RD, Elbaz U, Zuker RM, et al. (2015) Corneal neurotization from the supratrochlear nerve with sural nerve grafts: a minimally invasive approach. Plastic and reconstructive surgery 135(2):397e-400e.	n=10 eyes FU=6 months	Establishment of protective corneal sensation in all people in this series using corneal neurotisation with sural nerve grafts.	Likely patient population overlap with Catapano, 2019. Technique publication, results insufficiently described.
Charlson ES, Pepper JP, and Kossler AL. (2022) Corneal Neurotization via Dual Nerve Autografting. Ophthalmic plastic and reconstructive	n=1 FU=6 months	This study describes a dual nerve grafting approach via simultaneous parallel sural nerve grafts from	Studies with more people or longer follow up included.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
surgery 38(1):e17-e19		both the supratrochelar and supraorbital nerves to the affected contralateral cornea with return of sensation by postoperative week 11.	
Ebner R, Fridrich G, Socolovsky M et al. (2020) In Vivo Corneal Confocal Microscopy: Pre- and Post-operative Evaluation in a Case of Corneal Neurotization. Neuro-Ophthalmology 44(3):193-6	n=1 FU=24 weeks	**Paediatric** Favourable trophic changes were observed at different levels of the person's cornea, particularly in the sub-basal nerve plexus; complete absence of these neurological structures was observed before neurotisation but appeared largely restored 6 months thereafter.	Case report. Studies with more people and longer follow up included. No new safety outcomes.
Elbaz U, Bains R, Zuker RM et al. (2014) Restoration of corneal sensation with regional nerve transfers and nerve grafts: a new approach to a difficult problem. JAMA ophthalmology 132(11):1289-95	n=3 people (4 eyes) FU=approx. 6 to 9 months	**Paediatric** Corneal sensory reconstruction provides corneal sensation in previously anaesthetic corneas. This can be achieved with minimal morbidity using sural nerve grafts, which surgeons commonly use to reconstruct nerve gaps elsewhere. This multidisciplinary approach restores an ocular defence mechanism and may enable subsequent corneal transplant in these people.	Long-term outcomes of these people are described in Catapano, 2019.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Fung SSM, Catapano J, Elbaz U et al. (2018) In Vivo Confocal Microscopy Reveals Corneal Reinnervation After Treatment of Neurotrophic Keratopathy With Corneal Neurotization. Cornea 37(1):109-12	n=2 FU=6 months/2.5 years	**Paediatric** In both cases, in vivo confocal microscopy showed corneal reinnervation following neurotisation.	Studies with more people and longer follow up included. No new safety outcomes.
Kolseth CM, Charlson ES, and Kossler AL. (2020) Corneal Neurotization: A Surgical Treatment for Neurotrophic Keratopathy. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 40(2):e11-2	n=1 FU=11 weeks	In this patient, a return of sensation of 60 mm in all quadrants of the cornea was seen by postoperative Week 11.	Case report. Studies with more people and longer follow up included. No new safety outcomes.
Lathrop KL, Duncan K, Yu J et al. (2020) Development of Corneal Sensation With Remodeling of the Epithelium and the Palisades of Vogt After Corneal Neurotization. Cornea 39(5):657-60	n=1 FU=2 years	**Paediatric** The patient tolerated the procedure well and noted subjective improvement in corneal sensation beginning at 16 weeks postoperatively, progressing over the next year. The patient's visual acuity improved to 20/60 in the left eye with no progression of his corneal scarring 12	Case report. Studies with more people and longer follow up included. No new safety outcomes.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
		months after the procedure.	
Peragallo JH, Weil NC and Behshad S. (2021) Conjunctival incision management for strabismus surgery in the post-corneal neurotization patient. Journal of AAPOS 25(1):40-3	n=2 FU=approx. 1 year	Corneal neurotisation was successful in both people with no complications reported. Strabismus surgery was performed at least 6 months after neurotisation for disease stabilisation.	Studies with more people and longer follow up included. No new safety outcomes.
Sepehripour S Lloyd MS, Nishikawa H et al. (2017) Surrogate Outcome Measures for Corneal Neurotization in Infants and Children. The Journal of craniofacial surgery 28(5):1167-70	n=1 FU=10 months	**Paediatric** Postoperatively there was evidence of improved corneal healing and function after 8 weeks. At 10 months postoperative, the cornea was completely free of vascularisation. This is the first time the procedure has been undertaken in a young child.	Case report. Studies with more people and longer follow up included. No new safety outcomes.
Steinemann A, Preiser D, Eggenschwiler L et al. (2021) Minimally Invasive Corneal Neurotization for Neurotrophic Keratopathy. Klinische Monatsblatter fur Augenheilkunde 238(4):365-6	n=1 FU=1 year	The results remained stable 1 year after the neurotisation, without any signs of corneal revascularisation. The patient was extremely pleased with the outcome and his newly improved quality of life.	Case report. Studies with more people and longer follow up included. No new safety outcomes.
Thomson DR, Nduka C, Kannan RY et al. (2021) The surgical	n=11 FU=10 months	There was evidence of significant improvement in protective corneal sensation and blinking	Identical or very similar patient population to Elalfy (2021) but

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
management of extra-cranial trigeminal nerve palsies: A retrospective case series. Journal of Plastic, Reconstructive and Aesthetic Surgery		frequency after corneal neurotisation.	shorter follow up and fewer reported outcomes.