Elektrical Direct Stimulation of Peripheral Nerves to enhance Regeneration - Safety & Feasibility

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The primary objective of the present study is to explore the safety and feasibility of electrical stimulation in patients with diverse kinds of nerve lesions. The secondary objective is to make a reasonable estimation of clinical effect size, which...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON50763

Source
ToetsingOnline

Brief title
EDISON - Electrical DIrect Stimulation of Nerves

Condition

- Peripheral neuropathies

Synonym
Peripheral Nerve Lesion / Nerve Injury

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Brief Elektrical Stimulation, Nerve Regeneration

Outcome measures

Primary outcome

Primary outcome measures are 1) the occurrence of adverse effects 2) the feasibility of electrical stimulation, measured as the burden for the department and for the patient.

The burden of the department will be measured as: direct costs of the electrical stimulation (stimulation device, electrodes, extra operative time, time used by neurophysiology department) and costs of the postoperative extensive evaluation. The burden for the patient will be outlined in detail below.

Secondary outcome

Secondary outcome measures are the clinical effects of the electrical stimulation. It is not the aim of the current project to detect statistical differences in the stimulation and control group, but the goal is to make a reasonable estimation of effect size which can then be used for the design of a larger randomized trial in any of the patient categories. The following table summarizes the aimed outcome measures and the timing of follow-up.

Patient category; Follow-up; Outcome measure

1. brachial plexus; 6/12/18/24/36 months; Biceps force (quantitative), EMG/Mune, DASH

2. distal nerve transfers; 6/12/18/24 months; Biceps force (quantitative), EMG/Mune, DASH

3a. nerve grafting median nerve; 6/12/18/24 months; Thenar reinneration, EMG/MUNE, sensibility of the hand (quantitative), DASH

3b. nerve grafting radial nerve; 6/12/18/24 months; Recovery of wrist and finger extension, DASH

4. nTOS; 6/12/18/24/36 months; Thenar and hypothenar reinnervation, EMG/MUNE, DASH

5. distale zenuwtransfers: 6/12/18/24 mnd; kracht vingerextensie; EMG/MUNE, DASH

Physical examination:

The examiner will be blinded for the assigned stimulation or no stimulation.

The operative record will state that stimulation took place *according to study protocol*.

Quantitative biceps force will be assessed with a hand-held manometer, or with dumbbells.

Active external rotation will be assessed in degrees of active range of motion.

Sensibility of the hand will be quantitatively assessed with Semmes-Weinstein filaments and 2 point discrimination.

House-Brackmann score will be assessed testing active facial movements.

Recovery of wrist and finger extension will be assessed with the MRC grade of volitional force.

Questionnaires:

DASH - Disability of Arm / Shoulder / Hand

Ancillary investigation:

Needle EMG (electromyography) - assesses semi-quantitatively the number of

regenerated motor fibers

MUNE is a electromyography technique to assess quantitatively the number of

regenerated motor fibers (Gooch, Doherty et al. 2014)

Study description

Background summary

Despite efforts to enhance peripheral nerve regeneration, there has been little progress in improving clinical outcomes for patients with a peripheral nerve lesion. Many different methods were explored in laboratory settings, but until now, none of these methods were brought to the clinic successfully. Recently, a method of brief post*surgical low frequency electrical stimulation (ES) of surgically repaired nerves has been developed. Electrical stimulation was shown to accelerate axon outgrowth across the repair site and it hastened target reinnervation. The mechanistic insights and functional impacts of the post* surgical electrical stimulation have been gained through a large number of animal studies. Brain*derived neurotrophic factor, cyclic AMP and regeneration* associated genes play a vital role in expediting the outgrowth of axons across the injury site. (Gordon 2016)

Electrical stimulation has also been shown to be effective in patients. Until now, only a few patient series have been published or presented at meetings that explore the effects of brief electrical stimulation (1 hour 20 Hz) during or after nerve surgery. (Chan, Curran et al. 2016) These series will be summarized below.
1. Severe compressive neuropathy: carpal tunnel syndrome. (Gordon 2010)
In a randomized study, 11 patients underwent electrical stimulation of the median nerve after decompressive surgery. Results were compared to 10 controls. The stimulation group had significant axonal regeneration 6-8 months after carpal tunnel operation when the Motor Unit Number Estimation (MUNE, Gooch 2014) increased to 290+/-140 (mean+/-SD) motor units from 150+/-62 motor units at baseline ($p<0.05$). In comparison, MUNE did not significantly improve in the control group ($p>0.2$). Terminal motor latency significantly accelerated in the stimulation group but not the control group ($p>0.1$). Sensory nerve conduction values significantly improved in the stimulation group earlier than the controls. Other outcome measures showed a significant improvement in both patient groups.
2. Digital nerve repair. (Wong 2015)
Patients with complete digital nerve transection underwent epineurial nerve repair. After coaptation of the severed nerve ends, fine wire electrodes were implanted before skin closure. Postoperatively, patients were randomized to

receiving either 1 hour of electrical stimulation or sham stimulation in a double-blinded manner. Patients were followed monthly for 6 months by a blinded evaluator to monitor physiological recovery of spatial discrimination, pressure threshold, and quantitative small fiber sensory testing. Functional disability was measured using the Disability of Arm, Shoulder, and Hand questionnaire (DASH). A total of 36 patients were recruited, with 18 in each group. Those in the ES group showed consistently greater improvements in all sensory modalities by 5 to 6 months postoperatively compared to the controls. Although there was a trend of greater functional improvements in the ES group, it was not statistically significant (p*>*0.01).

3. Peroperative traction injury to the spinal accessory nerve. (Barber 2018)

Shoulder dysfunction is common after neck dissection for head and neck cancer, resulting from traction injury of the spinal accessory nerve. Adult participants undergoing neck dissection were recruited. Those in the treatment group received intraoperative electrical stimulation applied to the spinal accessory nerve (SAN) after completion of neck dissection, while those in the control group received no stimulation. The primary outcome measured was the Constant-Murley Shoulder Score, comparing changes from baseline to 12 months post-neck dissection. Fifty-four patients were randomized to the treatment or control group (1:1). Significantly lower shoulder scores were observed in the ES group at 12 months, indicating better preservation of shoulder function (p*=* 0.007). Only four patients in the ES group compared to 17 patients in the control groups had a relevant decrease in shoulder function post-operatively (p* =*0.023). It was concluded that peroperative stimulation had a positive effect of nerve recovery after stretch lesions.

4. Severe compressive neuropathy: ulnar nerve compression. (Morhart 2018, Power 2019)

In a study regarding decompressive surgery of the ulnar nerve 24 patients were enrolled to receive post-operative electrical stimulation or sham stimulation. The presented cohort comprised of 16 patient who received stimulation and 8 controls. Patients were followed 3 years after surgery. In the patients receiving electrical stimulation MUNE detected a larger number of motor units in the hypothenar muscle compared with controls (+/- 180 vs 90 respectively). It was concluded that ES stimulates nerve recovery after decompressive surgery.

5. Nerve transfer to restore biceps function. (Morhart 2018)

Nerve transfer from a fascicle of the ulnar nerve to the musculocutaneous nerve (Oberlin*s procedure) is applied in patients who have biceps muscle paralysis following a nerve traction injury. This procedure reliably results in biceps muscle recovery estimated at Medical Research Council (MRC) grade 4/4+, a semi-quantitative scale ranging from 0 to 5. The presented cohort included 9 patients who received post-operative stimulation and 9 controls. The median MRC score was 5 in the stimulation group versus MRC 4+ in the control group. The quantitative elbow strength was 12 kg (stimulation group) versus 6 kg (control group). The Disability of Arm Shoulder Hand questionnaire (DASH) decreased from 60 (pre-operatively) to 40 (stimulation group) versus 50 (control group).

In summary, a limited number of patient series have been presented that

describe the benefits of brief electrical stimulation during or after surgery in patients with compressive neuropathy, nerve repair, and nerve traction injury. A number of limitations exist on these series. 1) The number of patients is small in each of the studies 2) The published or presented series were reported from a single Canadian research consortium. 3) In patients with other types of nerve lesions were not investigated yet, for instance patients in whom surgical repair of larger peripheral nerves or repair of proximal spinal nerves (brachial plexus) was performed, patients with axonal nerve injury without surgical intervention, pediatric patients, and patients with lesions of cranial nerves (other than the spinal accessory nerve). The effects and safety of peri-operative electrical stimulation in these *new* patient categories are unknown. It is unsure whether the preliminary results in the describes studies justify to apply electrical stimulation in patients with other types of nerve lesions.

Barber, B., H. Seikaly, K. Ming Chan, R. Beaudry, S. Rychlik, J. Olson, M. Curran, P. Dziegielewski, V. Biron, J. Harris, M. McNeely and D. O'Connell (2018). "Intraoperative Brief Electrical Stimulation of the Spinal Accessory Nerve (BEST SPIN) for prevention of shoulder dysfunction after oncologic neck dissection: a double-blinded, randomized controlled trial." J Otolaryngol Head Neck Surg 47(1): 7.
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Power, H.A., Morhart M.J., Olson J.L., Chan K.M. (2019) "Postsurgical Electrical Stimulation Enhances Recovery Following Surgery for Severe Cubital Tunnel Syndrome: A Double-Blind Randomized Controlled Trial." Neurosurgery. 2019 [Epub ahead of print]
Wong, J. N., J. L. Olson, M. J. Morhart and K. M. Chan (2015). "Electrical stimulation enhances sensory recovery: a randomized controlled trial." Ann Neurol 77(6): 996-1006.

Study objective

The primary objective of the present study is to explore the safety and feasibility of electrical stimulation in patients with diverse kinds of nerve lesions. The secondary objective is to make a reasonable estimation of clinical effect size, which can then be used for the design of a larger randomized trial in any of the patient categories.

Study design

It concerns a prospective randomized trial that includes patients with nerve lesions that need to be surgically treated according to current standards of care. Patients will be randomized to receive brief electrical stimulation of the affected nerve (during or directly after surgery) or no stimulation.

Intervention

Brief electrical stimulation will be applied to the proximal nerve that was repaired or decompressed. This will be applied for one hour, with a frequency of 20 Hz, the same as in previous studies. In most cases the electrical stimulation will be applied during surgery. In control patients, there will be no stimulation. In case of compressive neuropathy, electrical stimulation will take in the recovery room for one hour using electrodes that can be removed afterwards. In these patients sham stimulation will be performed depending on the randomization, to guarantee the blinded study setup.

Study burden and risks

The risk of an adverse effect is estimated to be virtually zero. From a theoretical point of view, brief electrical stimulation of a nerve will not result in adverse effect. In the patient series that were published or presented, no adverse effects were reported. Electrical stimulation was well tolerated, and no adverse effects were encountered in the experience of the Canadian group with other patients that were not reported yet (personal communication with K.M Chan).
The burden of the patient can be divided in the burden of the electrical stimulation itself, and the burden of taking part in the thorough post-operative evaluation.
The burden of the electrical stimulation depends on the nature of the nerve lesion.
- In case the electrical stimulation is performed during their surgery, the duration of the surgery may be longer. In most cases the time of the electrical stimulation (one hour) will be used to perform parts of the surgery where the relevant nerve is not manipulated in the operative field. In many of the intended surgical procedures, it is necessary to harvest an autologous sural nerve graft from the patient*s leg, which usually takes the amount of time that is necessary to complete the electrical stimulation. In a minority of patients, it may be necessary to extend the time the patient is under general anesthesia.

- In case the electrical stimulation is applied after the surgery, this will take place in the recovery room. As a result of the electrical stimulation, the patient may experience a muscle twitch during the electrical stimulation. The discomfort of the patient will be measured using a Numerical Rating Scale. After the stimulation or sham stimulation, the fine wire electrodes that were inserted during surgery, will be taken out, which probably leads to less discomfort than taking out an intravenous line.
The postoperative follow-up of included patients is intended as more thorough than in current clinical practice. The patient is subject to a fixed schedule of postoperative follow-up (the number of visits will be the same as in current clinical practice), and during the postoperative visits a larger number of tests may be applied, either during physical examination (which will probably not exceed 10 minutes extra time during each visit), either with ancillary investigation (EMG/MUNE). Additionally, patient will be asked to answer a questionnaire.
The anticipated benefit for the patients who receive electrical stimulation is that they experience a better nerve regeneration. As such, this may result in a qualitatively better recovery or recovery earlier in time of biceps muscle force, hand function, or facial movement depending on the concerned nerve lesion and repair.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients eligible for enrollment are patients who are indicated for nerve surgery, eiter reconstructive or decompressive. This trial concerns patients in whom the nerve surgery is intended to improve symptoms of nerve degeneration.
The following patient categories are open for inclusion:
1. brachial plexus nerve grafting procedures in adults
2. distal nerve transfers in adults
3. distal nerve grafting procedures in adults of the
3a. median nerve
3b. radial nerve
4. severe compression of the brachial plexus - neurogenic thoracic outlet syndrome (adults)
5. distal nerve transfer in adults after spinal cord injury
In each of these categories a maximum of 20 patients can be included.

Exclusion criteria

Patients not fit to agree to informed consent due to linguistic barriers for adequate communication.
Patients who are not available for the designed follow-up schedule, for instance living abroad.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-03-2021
Enrollment:	100
Type:	Actual

Medical products/devices used

Generic name:	Intra-operative nerve stimulation and recording system.
Registration:	No

Ethics review

Approved WMO

Date:	10-02-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64844.058.18