**Use of Electric Stimulation to Enhance Functional Outcomes after Peripheral Nerve Injury**

**BACKGROUND**

Functional outcomes of peripheral nerve injury using standard surgical repair alone are poor and limited by the slow regeneration process. There is ample evidence showing that electric stimulation therapy accelerates nerve regeneration. In this randomized controlled trial, patients with median nerve injury(mixed sensory and motor nerve) will undergo brief low frequency electric stimulation of the nerve after surgery which is expected to reduce the nerve regeneration time from 56-70 to 21 days.

Great amount of research has been done on adjuvant therapies to increase axon regeneration in order to improve outcomes after peripheral nerve repair. There is ample evidence from animal studies and limited human studies that demonstrate that electric stimulation (ES) therapy accelerates nerve regeneration, both motor and sensory, as well as increasing gene expression related to nerve formation and regeneration. This effect translates in reduced time for motoneuron to regenerate their axons through the injured nerve(from 56-70 days to 21 days), shorter denervation time of target organs and therefore enhanced functional recovery. There is great amount of evidence from animal and human studies that support the positive effects of ES in sensory nerve injury. However, there is little experience in the use of electric stimulation in mixed nerves injuries (sciatic, femoral, median, common peroneal, tibial). No studies, to our knowledge, have yet be conducted to establish the pre-therapy/post-therapy clinical and neurophysiological effects of ES in both muscle and sensory recovery following surgical repair of a complete transected missed motor and sensory peripheral nerve in humans.

**AIM**

The aim of our study is to be able to quantify both motor and sensory regeneration post ES therapy following surgical repair of a mixed motor and sensory peripheral nerve. It is also imperative to establish a gold standard assessment tool kit for future clinical trials.

**HYPOTHESIS**

Enhancing the nerve regeneration process is considered a paramount therapeutic target for improving functional recovery after peripheral nerve injury. Great amount of research has been done on adjuvant therapies to increase axon regeneration in order to improve outcomes after peripheral nerve repair.

A primary cause of the poor outcomes following peripheral nerve injury is slow axon regeneration rate. ES accelerates the axon growth across the repair site in motor and sensory axons in both animal models and humans. It translates in less chronic denervation of target organs and better functional outcomes. The ES mechanisms of action have been studied extensively and include: regeneration-associated gene expression, neurotrophic factors and androgen-related cell signaling pathways. Low-frequency continuous ES at 20Hz, 100 microsecond pulses during 1 hour following surgically nerve repaired reduces the regeneration time for motor axons from 56-70 days to 21 day. In sensory nerves, up to 87% of individuals treated with post op ES achieved normal s2PD compared to 14% to 37% of patients receiving standard surgical treatment alone. Propagation of action potentials to the cell body is necessary for ES to be efficacious. Infiltration of local anaesthetics with sodium-channel blockade would render ES ineffective, therefore patients need to have general anaesthesia.

There is sufficient high quality evidence to support that ES is a safe and cost-effective adjuvant therapy to enhance nerve regeneration after surgical repair of peripheral motor and sensory nerves. Our primary hypothesis states that ES accelerates axon growth across the repair site, and enhanced specificity of reinnervation in motor and sensory axons of median nerve in humans.

Current results have shown success in hastening nerve regeneration and functional recovery regardless of the type of neuron involved (motoneuron vs. sensory neuron). These studies have shown significant success in animal studies where mixed nerves were transected and repaired within a short period of time (often immediately post transection). Gordon et al. (2009) has performed an study to establish the effects of ES in patients with severe carpal tunnel syndrome. Despite its focus on the effects of ES on a mixed motor and sensory nerve such as the median nerve, the mechanism of chronic nerve compression in carpal tunnel release is not comparable to acute nerve transaction of neurotmesis. Outcome assessment following complete sensory nerve transaction has only been tested through Wong et al. (2015) in the clinical environment.

**PROTOCOL**

A randomized, double-blind, parallel-group, placebo controlled clinical trial.

The project has been submitted for approval by the Ethics Board of Monash Health.

The study is registered with the Australian New Zeland Clinical Trial Registry (ANZCTR)

**-Participants**

Patients will be recruited from the Hand Trauma Centre at the Dandenong Hospital, part of the Monash Health Network.

**-Preoperative assessment**

Clinical history, examination and investigation of the upper limb following the currently accepted standards of care for upper extremity soft tissue trauma.

**-Inclusion criteria:**

1. Age 18 to 70 years with a suspected injury of the medial and ulnar nerve.

2. Receiving surgery within 72 hours of injury.

3. Standard primary end-to-end nerve repair

4. Consenting to general anesthesia and standard surgical repair of peripheral nerve injury

5. Consenting to participate in the Electric Stimulation trial

**-Exclusion criteria**

1. Concomitant bone injury of the affected digit,

2. De-vascularization

3. Diabetic and other polyneuropathies.

4. Cognitive impairment.

**-Informed consent Process**

Informed consent must be obtained from all patients for standard surgical repair of injuries of the upper limb following the *National Health and Medical Research Council Act 1992* and *RACS* guidelines for Informed Consent (see attached documents).

In addition, patients willing to participate in the Electric Stimulation trial as adjuvant therapy to enhance the outcomes of peripheral nerve injury, must provide procedure-specific informed AND voluntary consent (see attached documents).

**-Randomization and Controls**

Given the subjective nature of sensory nerve response and assessment, randomization and appropriate control are essential.

Patients meeting the inclusion criteria will be randomised and assigned to the electric stimulation or control group. A suitable control group is been implemented in order to reinforce the validation of the outcomes assessment process and strengthen the statistical significance of the results obtained.

A retrospective audit on upper limb peripheral nerve injury in Monash Health from January 2015 to December 2015 established that 30 patients with complete transection of the ulnar and/or median nerve were managed at Monash Health in a year.

We have received preliminary TCPC approval to treat 30 patients per year in a period of 2 years. An electronic program has randomised a set of 30 unique numbers, which correspond to the study group in order of presentation. The remaining numbers will be allocated to the control group (www.randomizer.org 1 Set of 30 Unique Numbers Range: From 0 to 60— Sorted from Least to Greatest. 7/Dec/16)(see attached document).

**-Intraoperative**

Repair of upper limb injuries that involve nerve are performed under general anesthesia as standard of care.

The subjects with suspected median nerve injury will undergo surgical exploration under general anesthesia in the standard fashion.

The subjects with a complete median or/and ulnar nerve transection will undergo standard tension-free epineurial repair of the nerve under the microscope.

The subjects included in the study, and have provided consent to participate, will receive either placebo or electric stimulation depending on the randomization process.

**-Electric Stimulation Procedure**

*NOTE*

1. *Electric stimulation is an Adjuvant Therapy only. Electric stimulation aims to reduce the nerve regeneration time along the repair site and enhance the functional outcomes after peripheral nerve injury.*
2. *To date, there are not other readily available alternatives to standard surgical repair of peripheral nerves. Outcomes of peripheral nerve injury are very poor and have not changes despite the advances in medicine and surgery.*
3. *Electric stimulation is not an experimental procedure. ES has been used previously in humans to improve outcomes of peripheral nerve injury. Multiple randomized controlled studies have proven that electric stimulation is a safe procedure. There is no extra cost for the patient or the health system (see attached documentation and TCPC approval).*
4. *The randomization process does not compromise patient care. Patients included in the control group or opting out the electric stimulation therapy, will receive the highest standard of care available for their injury.*

After standard microsurgical repair of median or/and ulnar nerve injury is performed, two sterilized, stainless steel wires are placed proximal and distal to the coaptation site. These are secured to the skin with surgical suture material. The proximal wire is connected to the cathode and the distal wire to the anode port of the source of current calibrated to 20Hz balanced biphasic pulses, voltage: 3 volts, 1mA to 5mA current, duty cycle of 0.2%, continuous.

Patients included in the trial will receive Low frequency continuous electric stimulation of the nerve for 1 hour as per protocol.

In the mean time, surgical repair of other injury structures is performed. It is well documented that isolated traumatic nerve injury is frequently associated to vascular and musculoskeletal injuries.

Standard closure of skin is performed . Electric stimulation wires are removed and standard dressings and immobilization applied.

In the placebo group, subjects received 5 seconds of similar intensity ES but the stimulator was turned off for the remainder of the hour.

**-Post Operative**

Subjects will return to clinic following the standards of care for patients with soft tissue injury of the upper limb:

Wound review 1 week after surgery.

Hand therapy review 1 week after surgery

Hand therapy follow-up every 2-4 weeks for 12 months.

Plastic surgery outpatient clinic follow up every 2 months for at least 1 year.

**-Outcomes Assessment**

Specific nerve recovery assessment at 3 months , 6 months, 12 months and 2 years, following standards of care of patients with peripheral nerve injury , without changes in respect to patients undergoing microsurgical repair alone.

* Sensory function
* Motor function
* Pain and discomfort
* Neurophysiology
* Patient Reported Outcomes (PRO)

**Data Collection**

Data from the Scheduled Outcomes assessments will collected by Hand Therapist

* 3 months
* 6 months
* 12 months
* 24 months

*NOTE*

*Patients and hand therapy team will remain blind in regards the use of electric stimulation. The assessment of sensory function and pain modules are subjective and operator-dependant and represent an identifiable source of bias.*

**TCPC Reporting Schedule**

Progress Report and Outcomes Spreadsheet (six-months intervals)

* 18 Aug 2017
* 16 Feb 2018
* 17 Aug 2018
* 16 Feb 2019

**Quality Improvement (QI) Activities**

* QI Activity Application in Dec 2016 (Prior to start).
* Presentation of cases in the weekly Plastic Surgery Audit.
* Yearly presentation in the Combined Monash Health & Peninsula Health Journal Club
* Presentation in National and International meetings in the filed.