Study on feasibility of Targeted epidural spinal stimulation to Improve MObility recovery in patients with sub-acute spinal cord injury

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The objectives of STIMO-2 are to demonstrate the safety and feasibility and to obtain preliminary evidence on the effectiveness of mobility rehabilitation facilitated by TESS to improve neurological recovery when this intervention is delivered in...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON49181

Source
ToetsingOnline

Brief title
STIMO-2

Condition

- Spinal cord and nerve root disorders
- Nervous system, skull and spine therapeutic procedures

Synonym
Spinal Cord injury; rehabilitation for controlling the legs

Research involving
Human

Sponsors and support

Primary sponsor: École Polytechnique Fédérale de Lausanne
Source(s) of monetary or material Support: École Polytechnique Fédérale de Lausanne

Intervention

Keyword: Mobility recovery, Spinal Cord Injury, Targeted epidural spinal stimulation

Outcome measures

Primary outcome

The primary safety and feasibility outcome of this feasibility study is

composed of 2 measures:

* The safety measure will report on the number of patients with a Serious

Adverse Event that is deemed related or possibly related to study procedure or

to study investigational system, from implant surgery until the end of study.

The safety population will account for all enrolled patients eligible for

implant surgery. Patients enrolled in the study but withdrawn before implant

will not account for the safety population.

* The feasibility measure will quantify the integration of TESS in standard

clinical mobility rehabilitation procedures, as measured by the absolute and

relative usage of TESS (in minutes) during mobility rehabilitation sessions.

Secondary outcome

Secondary outcome:

A predictive model, based on the EMSCI** database will be used to calculate the

expected outcomes for the patient at 12 months when using standard

rehabilitation practices, based on the patient*s clinical evaluations at 1

month (ISNCSCI score).

The secondary endpoint will compare each patient*s clinical evaluation results at 12 months post Date Of Injury (DOI) to the expected results based on the predictive model. The clinical evaluation will assess the functional recovery of leg motor function using the 6 mnWT distance and SCIM III-mobility score for mobility assessment.

**European multicenter study about Spinal Cord Injury (www.emsci.org); ClinicalTrials.gov Identifier: NCT01571531

Other outcomes of interest include:

* Effective length of TESS supported mobility rehabilitation period to achieve initial predicted 12 months outcome (post-hoc analysis data collected for secondary objective)

* Immediate and long-term effect of TESS-supported mobility rehabilitation on voluntary leg movements, standing and locomotion, muscle strength, gait quality (* clinical evaluations, kinematic analysis, EMG recordings, force measurements, video recordings)

Abbreviations: ISNSCI = International Standards for Neurological Classification of Spinal Cord Injury; 6mnWT = 6 minutes walk test, SCIM III = Spinal Cord Independence Measure version III. EMSCI=European Multicenter study about Spinal Cord Injury; MVC: maximum voluntary contraction with isokinetic dynamometer, EMG: electromyogram.

Study description

Background summary

The World Health Organization estimates that up to 400,000 people worldwide experience a Spinal Cord Injury (SCI) every year. More than 6 million individuals are currently wheelchair-dependent due to paralysis, which dramatically affects their quality of life. Up to now, no treatment other than rehabilitation has shown efficacy to improve functional recovery after a SCI. Epidural Spinal Stimulation (ESS) applied to the lumbar region enables walking in rodent and primate models of leg paralysis. As demonstrated by the Courtine laboratory, targeted ESS (termed TESS), stimulating at the correct place at the correct time, enables and/or augments the ability of the descending commands to produce the intended movements. Recently, the STIMO pilot study (ClinicalTrials.gov Identifier: NCT02936453), using existing neurostimulator technologies (off-label), provided the first evidence that TESS has the potential to effectively facilitate voluntary leg movements and locomotion immediately in humans with chronic (>12 months) SCI, and to improve long-lasting neurological recovery due to neuroplasticity resulting from rehabilitative training facilitated by TESS.

Study objective

The objectives of STIMO-2 are to demonstrate the safety and feasibility and to obtain preliminary evidence on the effectiveness of mobility rehabilitation facilitated by TESS to improve neurological recovery when this intervention is delivered in the sub-acute phase (<6 months) after SCI.
Primary objective: Assess the safety and feasibility of targeted ESS at supporting mobility rehabilitation in patients with sub-acute spinal cord injury (less than 6 months after injury)
Secondary objective: Evaluate the preliminary effectiveness of mobility rehabilitation facilitated by TESS to improve the recovery of leg motor functions and mobility after 12 months post-injury.

Study design

Single arm, non-blinded, international multi-center interventional feasibility study with up to 12 months follow-up after spinal cord injury

Intervention

The study intervention consists of 4 phases preceded by pre-screening: baseline, surgery, intensive rehabilitation facilitated by TESS, out-patient rehabilitation supported by TESS.
0. Pre-screening

- Patients hospitalized after a spinal cord injury are screened for eligibility in the study.
- Patients fulfilling eligibility criteria and willing to provide signed informed consent are enrolled.

Clinical evaluations are performed from enrollment until 12 months after date of injury, according to EMSCI study timeline.

1. Baseline
- After enrollment in the study, an MRI, a CT scan and, if appropriate, a pregnancy test will be done to confirm eligibility criteria regarding implant.
- Baseline data are collected (imaging, EMSCI URP cohort at 1 month, pregnancy, anesthesiologist, psychological interview)
- Patients not passing baseline tests terminate the study
- Clinical evaluations are performed from enrollment until 12 months follow-up, according to EMSCI study timeline

2. Surgery (implantation of neurostimulator at surgical department or dedicated surgical site)
- As needed, patient is transferred to hospital where neurosurgery is performed
- Standard pre-surgical procedures are performed
- The investigational device is implanted
- Post-operative CT is performed
- When deemed appropriate, the patient is transferred (back) to rehabilitation center

3. Intensive rehabilitation facilitated by TESS (rehabilitation site)
- TESS stimulation is configured following surgery, and prior to the beginning of TESS-supported rehabilitation. This procedure aims at optimizing the spatial and temporal parameters of TESS in order to facilitate recruitment of specific muscle groups for strength training and/or motor task. This activity will be repeated over time for optimization purpose.
- In-patient setting
- Duration: target 100 (+/- 10) sessions of rehabilitation training supported with TESS, spread over a period of 4 to 6 months
- TESS is embedded into the standard clinical rehabilitation program supervised by physiotherapists, for example, but not limited to, for lower extremity strength and locomotion training sessions.

4. Out-patient rehabilitation (rehabilitation site, at home)
- Out-patient setting (at least 2 sessions per week in a rehabilitation centre)
- Duration: from end of Intensive phase until 12 months after injury
- The patient will receive continued supervised training by a physiotherapist on functional use of TESS during activities of daily life. Unsupervised use is allowed in parallel to out-patient rehabilitation after patient training by physiotherapist.

During TESS supported rehabilitation sessions (3. and 4. above), technical tests as well as stimulation evaluations will be regularly performed. Stimulation evaluations include optimization of stimulation parameters by a team of Experts.

5. End of study at 12 months
- After final clinical evaluation at 12 months post injury, the patient may

choose between inactivation of the stimulator or explant of the investigational system, unless further use is deemed beneficial for the patient.The implanted device has an expected lifetime of 5 years. The study ends after final study procedures.

Study burden and risks

The risk associated with study participation is twofold: 1) Risks associated to the surgery procedure, and 2) risks associated with TESS combined with rehabilitation. Based on literature review on use of similar systems in patients with chronic SCI and on the risk assessment of the vestigational system, the main risks associated with participating in the study include:
* Risks associated to surgery procedures:
* The risks associated with the implant of the IPG and paddle electrode array are similar to risks associated with implants for chronic pain with epidural stimulation (see IFU of devices) and include. swelling at implant sites, hematoma or bleeding, infection, neuropathic pain, cerebrospinal fluid leak and wound complications.
* The risks associated with general anaesthesia include pneumonia, stroke, anoxia and post-operative confusion.
* A new paddle electrode array (Go-2 Lead) will be used in the study. The Lead was designed to recruit individual posterior roots from the lumbosacral spinal cord unilaterally * preventing crosstalk between roots associated with the left leg versus right leg. The lead is slightly wider and longer than existing leads used for chronic pain, which could bring additional (unknown) risks during implantation, such as pressure to the spinal cord. The Go-2 Lead is also used in another clinical study setting (STIMO study). Extensive pre-clinical validation testing was performed to minimize the risk, i.e. computer simulations, and surgical implant in cadavers by experienced neurosurgeons. Moreover, personalized computational models of the spinal cord elaborated from pre-operative MRI scans mitigate risks and increase confidence in the feasibility of Lead insertion. Only patient with confirmed eligibility after baseline evaluations will undergo the implant procedure. Risks associated to the paddle
electrode arrays include lead migration and electrode damage, which, in worst case scenario, may necessitate a replacement surgery (*redo*, see associated risk below).
* During the implant procedure, a few low dose fluoroscopy images are needed in lateral and antero-posterior positions. Additionally, if needed, a CT scan is performed at the initial placement of the paddle electrode array to confirm appropriate position in the spinal canal. The total study dose of radiation from imaging procedures is 18,3 mSv.
* The paddle electrode array is inserted by partial laminectomy at level T12-L2 of the spinal cord (for details see 6. Procedures). In case the initial Go-2 Lead cannot be permanently implanted and the Specify 5-6-5 lead will be used instead * as allowed per protocol, the same opening will be used.
o Previous studies including STIMO have shown that insertion of the lead

through a partial laminectomy between the T12 and L2 vertebra is appropriate to access the L1 posterior roots. However, S1 and S2 posterior roots can be located more caudally, preventing an optimal access to these roots. In this scenario, the laminectomy needs to be enlarged, or, in rare situations, a second opening needs to be performed between the L1 and L2 vertebra. These adjustments could increase the surgical time by approximately 30 minutes. Additional risks are very limited. Since the lateral window of the laminectomies remains limited, the stability of the spine is unlikely to be further compromised. The enlargement of the laminectomy might slightly increase the haemorrhagic risk or the risk of cerebrospinal fluid leak. Extra care is taken in this case by the eurosurgeon. Both risks are transient and without need for further intervention.
o When permanently implanting the Specify 5-6-5 Lead after the larger Go-2 Lead was inserted, a concern could be raised related to the positional stability of the lead. The stability of the paddle electrode array is mainly guaranteed by the quality of lead anchoring to the spine, rather than by the epidural space per se. Therefore, no problem is anticipated for the stability of the lead in this case.
o As stated in 5.4.2 Concomitant treatments, an unforeseen medical need for an MRI should be handled with special caution and the sponsor should be contacted.
* Risks associated with using TESS during rehabilitation:
During the STIMO study, only one device or procedure related serious adverse event is recorded to date (a replacement surgery of the Lead). In addition, some of the following risks may exists:
o The patient may feel tingling
o The patient may feel overstimulation
o During device technical verification and optimization of stimulation parameters, the patient may feel transient electrical discharges due to impedance and frequency testing as well as following change of trunk positioning
o Rehabilitation sessions will follow standard of care, but introduction of TESS supported sessions may result in a higher training intensity, which can result in fatigue and, in worst case scenario
* bruise and oedema on the calf and the ankle
* decrease of lower limbs motor strength
* fluctuation of mood and motivation levels
* increase frequency of clinical risks known for people with SCI (e.g. urinary tract infection)
* joint pain
* neuropathic pain
* pain in the lower limb joints or feet
* pain during movement of the lower limb
* psychological distress
* signs of autonomic dysreflexia
* skin erosion
* spasticity
* stress

* tendinitis
o When training in an upright position, the patient may encounter the risk of falling. As a preventive measure, patients will train using assistive device(s) deemed appropriate by the therapist, depending on the abilities of the patient, for example using body weight support, walker, and/or crutches during overground walking. However, in the long term, the patient is anticipated to gain balance, stability and become independent, hence the risk will reduce over time. Patients with SCI at cervical level may develop a scoliosis due to their inability to properly contract abdominal muscles.
o In case of device deficiency during the course of rehabilitation, low dose fluoroscopy images may be needed to evaluate the deficiency. A redo procedure may take place.The risks of the procedure are similar to the initial implantation, the complication rate is expected to be slightly higher.
At study end, the patient may opt for removal of the implanted device. The risks of the explant procedure are similar to the ones of the implant procedure.
o A patient may be a non-responder to the TESS supported therapy. In that case, the patient will obtain no benefit (equal or worse outcome) from TESS supported therapy in comparison to regular clinical rehabilitation program.

Risks related to the patient condition and unrelated to the study
The study is recruiting patients who have recently sustained a SCI and are therefore in a physical and psychological medical situation that can be unstable. The study starts when the patient is hospitalized. The local investigational site is in charge of standard of care, including physiological and psychological support.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient enrolled in the EMSCI study
2. Patient eligible following stratification based on URP model* (see Figure 3)
3. Age 18 to 70 years old included
4. Focal spinal cord injury due to trauma
5. Patient with history of SCI within the past 6 months (sub-acute SCI)
6. Level of lesion (confirmed by MRI):
o vertebral lesion T11 or above, and the distance between the tip of the conus medullaris and the location of spinal cord damage must be at least 70 mm, allowing for electrode placement
o and neurological lesion T11 or above, with conus function preserved
7. Psychological condition compatible with study participation
8. Able and willing to fulfil all study procedures

Exclusion criteria

1. Spinal cord lesion due to neurodegenerative disease, spondylitis, tumor, or presence of a spinal stenosis
2. Severe or chronic medical disorder pre-existing SCI affecting rehabilitation
3. Active implanted device such as a pacemaker, implantable cardiac defibrillator or indication that might lead to implantation of such device.
4. Inability to follow study procedures, e.g. due to language problems, psychological disorders, dementia
5. Hematological disorders with an increased risk of hemorrhagic event during surgical interventions
6. Permanent artificial ventilation
7. Congenital or acquired lower limb abnormalities (affection of joints and bone)

8. Known or suspected drug or alcohol abuse
9. Life expectancy of less than 12 months
10. Pregnant or breast feeding
11. Participation in other interventional study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	Stimo-2 Investigational system
Registration:	No

Ethics review

Approved WMO Date:	21-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT04196114
CCMO	NL72342.091.19