Bioelectric Stimulation for the Treatment of Spinal Cord Injury:
A Randomized Controlled Study
Neuro Muscular Connection and Cal-X-Stars
Costa Mesa, Califonia

Introduction

Spinal cord injury (SCI), including quadriplegia and paraplegia, is prevalent worldwide for both men and women of all ages. SCI significantly impacts functional motor movement (i.e., fine and gross motor movement that requires the ability to sense what a muscle is doing and control its' actions for both small and large muscle groups). In the past few decades, scientists and medical professionals have illustrated the effectiveness of bioelectric stimulation (BES) of the spinal cord as a therapy for the central and peripheral nervous system functional restoration (Ho et al., 2014). Most people move without thinking about it. The brain is continually sending messages to and from the body via afferent and efferent nerve pathways, densely compacted in the spinal column. The transmission of messages is interrupted for people with SCI, resulting in a lack of control of gross and fine motor movements (Torregrosa & Koppes, 2016).

The spinal column has 33 individual bones divided into four regions, the neck, thoracic, lumbar, and sacral. The spinal cord branches into 31 pairs of nerve roots, and exit on each side of the spinal column, through the neural foramen, and nerves further branch travel through the rest of the body. The cervical spine nerves (C1-C7) control the arms and upper chest, the thoracic spine nerves (T1-T12) control the chest and abdomen, and the lumbar spine nerves (L1-L5) control all movement below the trunk, including bowel, bladder, and legs. SCI patients experience comorbid symptoms, this study is focused on increased improvement for voluntary movement.

Epidural spinal cord stimulation (ES) was initially investigated in a pilot study by a research team from UCLA, The University of Louisville, and the Pavlov Institute of Physiology. Four young men who were paralyzed for years were able to regain movement in their legs after receiving ES of the spinal cord. The four participants that had been paralyzed for two years prior were able to flex their toes, ankles, and knees during stimulation. Over time, the long-term movement for all four patients also improved for patients that simultaneously kept active in their regular rehabilitation regime (Angeli, Edgerton, Gerasimenko, et al., 2014). Two out of the four patients had complete motor and sensory paralysis, meaning the pathway that allows them to feel the sensation and move the legs were blocked (Angeli, Edgerton, Gerasimenko, et al., 2014). Researchers were surprised that both motor and sensory pathway communications improved.

Although ES has shown to enable motor function for animals and humans with paralysis, the procedure is invasive (Gad, Kreydin, Zhong, et al., 2018). Noninvasive BES has also shown to activate neural circuits and enables movement of upper and lower extremities and trunk (Gad et al., 2018; Inanici et al., 2018). The current study examines the effects of non-invasive BES with the Cal-X-Stars patented precise signaling for the upregulation in the tissue of several pro-

regenerative proteins. Proteins that are produced through the precise signaling are known as some of the most pro-regenerative proteins in the body, including SDF1 for stem cell homing, PDGF, VEGF for enhanced blood supply, Sonic Hedgehog for nerve regeneration, IGF1 for cellular repair, and klotho for muscle regeneration and reduced inflammation. Electrical stimulation is delivered through via gel adhesive electrodes applied to the skin near the spine in the area of SCI.. Due to small sample size (n=8), this study will be treated as a pilot proof of concept open label single arm study with quantitative analysis of the end points of change in motor and/or sensory function in areas of current paralysis, A In addition, There will be two areas of stimulation including a pair of electrodes placed over the quadriceps muscle to up regulate Klotho expression, as well was a pair on opposite sides of the spine in the area of SCI.wo adhesive patch electrodes will be applied to the thighs and two adhesive patch electrodes will be applied to the kidneys to increase circulating systemic klotho.

All subjects will continue to receive their current 1 hour exercise regimen that includes locomotor training as well as passive, passive-active, or active range of motion exercises at 3 sets of 3 repetitions for 3-4 affected myotomes at or below the spinal cord injury location. During the rest phase of exercise, class IV laser therapy is administered to maximize recovery, using 30 watts, a total of 10, 000 joules of laser is administered to the spinal cord region over the course of the hour. Changes in locomotor movement and muscle strength will be evaluated before, mid-way through, and after the study. Assessment and questionnaires will be given to demonstrate users perspectives of the different therapies and changes that may or may not occur from treatment.

The hypotheses of this study is that noninvasive BES will be a novel and effective therapy to improve locomotor movement for SCI by regenerating neuro muscular connections through up upregulation of expression for severalpro-regenerative proteins. pro

Study Name: Bioelectric Stimulation for treatment of Spinal Cord Injury

Study Sponsor: ()

Principle Investigator: Steven E. Shaffer, DC

Number of Study Sites: 1

Study Locations: Neuro Muscular Connection, Costa Mesa, California

Study Design: Multiple Case Stud with quantitative analysis Prospective, observational, single arm, open label feasibility study

Treatment Group:

Experimental Gp.-1 hour exercise regimen with locomotor training and class IV laser therapy, spinal column BES, and klotho thigh stimulation

Number of Subjects: 8

Duration of Each Treatment: 30 minutes
Frequency of Treatments: 2 x's/week for 12 weeks
Number of Treatments: 36
Stimulator to be Used: FDA 510K approved Mettler model 240

Objectives
The current study's objective is to assess whether task-specific locomotor training and spinal cord BES for nerve and muscular regeneration induces the neural reorganization of the human spinal cord to improve standing and stepping in individuals. The investigators propose that locomotor training will result in more effective efferent coordination of standing and stepping by restoring phase-dependent modulation of reflexes and reciprocal inhibition, reducing spasms, and mediating interlimb coordination. The investigators propose that BES will optimize the physiological state of the spinal cord interneuronal circuitry compromised by compensating for the loss of supraspinal input for the retraining of these tasks.

Co-Primary End Point 1:
Change in locomotor movements from baseline to end of study measured with internationally accepted (what assesments are we using?, change in locomotor, standing, walking?) ASIA Impairment Scale

Co-Primary End Point 2:
I think that you should use only objective measurement of movement initially and unbiased observers are the best judge or actual movement changes.
I

Secondary End Points:
Adverse effects, including pain or inflammation at the sites of patch electrodes or pain radiating from back and spine. Any device-related or BES related adverse events including local pain, skin irritation.

Treatment Group: (n=8 subjects)
Locomotor training, spinal column BES using patch electrodes at 4 locations (Sacum region-L5, L1-T11, T7-T5, C7-C3), and thigh BES for klotho using patch electrodes at 4 locations (two on thigh and two on kidney).

Inclusion criteria:
1. Men and women, 30 – 70 years
2. History of Thoracic or Cervical Spinal Column Injury (SCI), and patients currently being treated at NMC 2-3 times per week.

3. Willing and able to sign the Informed Consent
4. Able to attend all clinic visits defined in the protocol

Exclusion criteria:
1. (what is our criteria?) We have one subject with preexisting thyroid cancer that does not receive laser therapy. We would still like to include him in study. Thoughts?

StudyEligibility:
All patients that meet all the inclusion and none of the exclusion criteria and sign the Consent Form will be enrolled in the study.

Pre-Treatment Screening:
(need to decide on this)
ASIA Impairment Assessment carried out by Dr. Shaffer. Exam is video recorded.

sEMG Assessment using Thought Technology Bio Infinity Biofeedback software. This would be conducted bilaterally for the 2 most affected myotomes at or below the level of spinal cord injury. Test protocol is 15 sec of baseline at rest, 5 rounds of 5 seconds of work and 5 seconds rest, 20 sec endurance hold, and 15 sec post baseline at rest.

Pre blood work: TBD

Pre-Treatment Questionaires:
(Need to decide which questionaries?)

Protocol:
BES Treatment:
Each subject will receive protocol treatment for 30 minutes two times per week for 12 weeks to occur in the Neuro Muscular Clinic following their standard therapy as part of treatment at NMC.

Each subject will have 1hour of locomotor training, exercise, and laser therapy and after will receive spinal column BES using patch electrodes at four locations (Sacum region-L5, L1-T11, T7-T5, C7-C3). Patch electrodes are attached to the skin and connected by wires to receive electrical currents from the Mettler stimulator.

Data Analysis:
The data will be analyzed by a statistician not involved in the study.
All objective measures of changes in motor and sensory function as well as the questions completed at baseline and at end of therapy will be collated

and expressed as grouped and individual data using both mean and standard deviation as well as median and range for all end points