Restoration of Standing and Walking through ISMS in Humans

Protocol:

Spinal cord neural circuitry exists in the lumbar enlargement that makes it possible to stand and create synergistic, rhythmic stepping activity in the lower limbs. This circuitry has been described in the literature for nearly 100 years following the seminal works by Sherrington in 1910 and Graham Brown in 1911.[1] In the past 20 years, clinicians have tried to reengage such these circuits for standing and walking in the lower spinal cord of paralyzed humans through novel paradigms of physical therapy[2], pharmacological stimulation of the spinal cord[3,4], or recently – epidural stimulation of the spinal cord[5]. Although standing and stepping with these maneuvers are rudimentary at best, these human studies offer promise to restore controlled, lower extremity movement to the spinal cord injured (SCI) individual. Evidence from animal data suggests that more focal activation of intraspinal circuitry (**IntraSpinal Micro-Stimulation – ISMS)** would produce more fatigue resistant, natural standing and stepping activity in humans. To date, there has been no direct confirmation of such circuitry in the spinal cord of bipedal humans who have been paralyzed. Furthermore, mapping of such circuitry would provide the basis of a novel intraspinal neuroprosthetic that should be able to restore control of standing or walking in a manner that is much more physiologically normal and tolerable than by stimulating each individual muscle group. Proof of the existence of these spinal circuits in man, and the ability to activate and control these circuits by first mapping the spinal cord is the basis of this proposal.

GOAL: Two study volunteers to undergo an acute evaluation of ISMS during an experimental surgical procedure.

The following criteria will be used to initially screen interested volunteers. Screening will be initially carried out to review medical criteria necessary for optimizing the likelihood of successful data capture and avoiding potential for medical complications and drop-out from the study. The potential volunteers will be asked to review and sign a screening consent form prior to initial screening. A follow up screening visit will be carried out by a neuropsychologist to ensure that study participants will be able to comprehend research objectives (expect at least adult reading level and ability to understand the IRB at a 6th grade reading level) which may be difficult in SCI individuals who also have suffered a head injury; and also to avoid enrolling individuals with severe emotional lability associated with a chronic spinal cord injury that would confound accurate data reporting. Once study applicants meet the criteria listed below on initial medical and psychological review, applicants will be reviewed by the research team as to candidacy of enrollment. This would include not only a review by the key study personnel of the research team (Drs. Konrad, Mushahwar, Robinson, and Ms Isom), but a follow up review by the Data Safety and Monitoring Committee (DSMC) prior to patient selection. This is to ensure that the ideal two

patients are selected for this study and that foreseeable issues are identified and risks minimized for the volunteers.

Inclusion criteria for study volunteers:

1. Age 18-50 years old; male or female (no preference)
2. Complete paraplegia (ASIA A classification) as a result of a spinal cord injury between the levels of T2-8
    i. No motor or sensory function below the level of injury as determined by a physician
    ii. No voluntary bladder function – defined as the inability to sense bladder fullness or voluntary contraction of the bladder (meets criteria for no sacral sparing)
    iii. Stable paraplegia.
3. Patients with involuntary spasms are allowed. However, spasticity must be less than Ashworth 4 or spasm rating of 3 or less.
4. History of spinal cord injury greater than 1 year.
5. Intent to undergo spine surgery involving exposure of at least T9-T12 vertebral lamina.
6. MRI studies performed within the past year showing presence of spinal cord between T8-L1 with reasonable normal anatomical shape. No chronic infections.
7. Ability to travel to Vanderbilt Medical Center.

Exclusion criteria for study volunteers:

1. Acute medical conditions that are under active treatment. Examples include active urinary tract infection, respiratory illness, decubital ulcers, fractures, upper extremity injury, back pain.
2. Pregnancy.
3. Presence of a neurostimulator, bladder stimulator, cardiac stimulator or other electrical stimulator device implant.
4. Inability to transfer from wheel chair to chair or bed.
5. Inability to tolerate 1 hour of physical activity such as gait training in a harness.
6. Severe depression requiring active medical treatment or counseling.
7. Cognitive impairment that places the study volunteer under the 6th grade reading level.
8. Inability to provide consent.
9. Intradural or extradural masses compressing or displacing the spinal cord between T8-L1 region.
10. Significant change in motor or sensory function over the previous year.
11. History of spinal cord injury less than 1 year.
12. Previous laminectomy and intradural spinal cord procedure involving the region of T9-T12.

Patients with involuntary spasms with rigidity more than Ashworth 4 or spasm rating of 3 or more

Sequence of study (Overview):

1. *Screening and patient selection.*
    a. Review of applicants who have signed the screening consent form for the study by the study coordinator and PI. *(Web based portal review and follow up phone call interviews)*

b. Neuropsychology screening performed by Dr. Gary Solomon, PhD, to rule out cognitive or emotional factors prohibiting adequate follow-through with the trial, (Phone call / secure web based interview) using the attached documents: Montreal Cognitive Assessment (MOCA), Quality of Life Scale (QOL), Mental Health Screening Form III, MAST (Drug and Alcohol) screening form, Family report: Patient Behavior, Brief Psychiatric Rating Scale (BPRS), and Affective Rating Scale Observer Form.
c. Medical screening for adequate surgical candidacy (PI). – physical interview
d. Review and recommendations by the Research Team – Key Study Personnel.
e. Final review by DSMC committee composed of non-research team members to discuss any concerns about appropriate research potential or possible risks not appreciated by the research team. (Subjects selected)

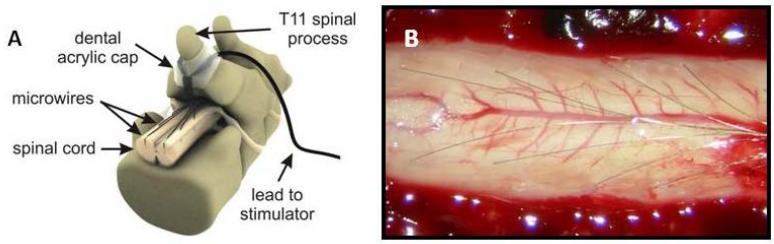

Figure 1. A. Schematic representation of ISMS electrodes. B. Appearance of hair-like micro-wires inserted into the spinal cord of a cat.

2. *Baseline testing.*
(Subject consented)
   a. Assessment of presurgical ASIA score and rating. Level of motor, sensory and autonomic function will be detailed. This assessment will occur by Dr. Konrad (Neurosurgical Clinic - VAV) using the updated ISNCSCI Data sheet.
   b. Baseline Kinesiology measurements will be made by Dr. Robinson (Belmont School of Physical Therapy). This will include videography of the patient in the sitting position and suspended by harness.
   c. Response to FES stimulation will be assessed by Dr. Robinson using videography. Ability to generate lower extremity extension, force generated, degree to which the subject's weight can be supported by FES, will be assessed. Both standing and stepping ability with FES will be assessed, including undesirable response such as pain or spasms.
   d. Quality of life scores and a generalized neuropsychological test will be performed by Vanderbilt Neuropsychologist Dr. Gary Solomon, PhD as part of the screening visit using the attached documents: Montreal Cognitive Assessment (MOCA), Quality of Life Scale (QOL), Mental Health Screening Form III, MAST (Drug and Alcohol) screening form, Family report: Patient Behavior, Brief Psychiatric Rating Scale (BPRS), and Affective Rating Scale Observer Form.
   e. Medical imaging. Spine X-ray, CT and MRI of thoracolumbar spine to assess anatomical structure and continuity of the lower spinal cord.

3. *Surgical Mapping of Lower Spinal Cord.*

Subjects who have volunteered for this study will undergo their intended spinal surgery by the clinical team. The usual indications for undergoing such a surgery is either to correct a deformity involving the lower thoracic region, or stabilizing the lower thoracic region due to chronic instability from degenerative disease. The surgery intended for clinical treatment must involve exposure of the T9-T12 spinal lamina. However, exposure of the spinal cord through a dural opening would not normally be performed in this clinical scenario. The experimental portion of the surgery begins then, with a laminectomy of T9-T12 and exposure of the spinal cord through a durotomy using standard neurosurgical techniques for spinal cord exposure.[2] The anterior horn (grey matter) of the spinal cord will be mapped bilaterally in the region of T9-T12 using FDA approved micro-electrodes for mapping of human neural tissue (Model mTDW microTargeting electrodes™; FHC) The mapping will be guided by pre-surgical MRI measurements focused on identifying the general distribution of motor neuron pools in the lumbosacral region of the cord. Intraoperatively, mapping will involve advancing the micro-electrodes with micron precision into the spinal cord along the anterior-posterior axis and passing a small stimulus (<100 μA) through the electrodes and observing movements in the lower extremities (such as hip and knee extension, ankle flexion, or stepping movements) during surgery. Approximately 4-8 electrodes will be inserted along each side of the spinal cord that correlate with movements created across all three joints (hips, knees, and ankles). A maximum of 16 electrodes (see above) will be inserted into the spinal cord to target locations identified during the mapping (Figure 4). These electrodes will be manufactured out of platinum-iridium (an existing biocompatible metal used in present day, FDA approved human micro-electrodes; Model mTD; FHC Inc) and inserted under sterile conditions.

The micro-electrodes will be connected to a multichannel electrical stimulator (series of Grass isolated stimulators) presently used for other human surgeries involving mapping deep brain nuclei with similar parameters.

a. The dura will be closed in a water-tight manner. Dural sealant may be applied to reduce likelihood of CSF leak.
b. Subjects will be managed in the immediate post-operative period by the surgical team performing the primary intended spinal surgery. This team will be responsible for management of the patients post-operative course. Additional, observation of each subject will occur following release of care by the surgical team.
c. In the first two weeks following surgery, subjects will be transferred from Vanderbilt University Hospital (VUH) to the Vanderbilt Clinical Research Center (CRC) where they can be observed for the following:
    i. Signs of wound infection or CSF leak.
    ii. Document any changes in bowel / bladder habits as a result of the procedure.

iii. Documents any changes in spasticity as a result of the procedure.
iv. Allow to recover strength and independence to return home.

d. Subjects will be discharged home from the CRC center after two weeks with home care instructions. All questions from the subjects will first be handled by Dr. Konrad's clinical trials coordinator, Wuraola Adesinasi, APRN (615-875-5853). Any questions or concerns regarding the surgical follow-up will be forwarded to Dr. Konrad's clinic (615-322-7417; this number is available for clinical concerns 24-7).

4. *Follow up.* All subjects will be expected to return for a follow-up visit with Dr. Konrad at 1, 3 and 6 month follow up visits.
    a. At each visit, documentation of wound healing, spinal complications, subjective patient complaints will be documented.
    b. An MRI will be obtained at 3 months following the procedure to document the impact of the mapping procedure on spinal cord anatomy.
    c. The DSMC will review the data related to complications encountered and final disposition of the patient.
5. **IntraSpinal Micro-Stimulation – ISMS data review: Dr. Mushahwar at the University of Alberta will evaluate the de-identified stimulation data collected during surgery as well as Kinesiology measurement data collected from Dr. Robinson's Gait lab.** **IntraSpinal Micro-Stimulation – ISMS data review: Dr. Mushahwar at the University of Alberta will evaluate the de-identified stimulation data collected during surgery as well as Kinesiology measurement data collected from Dr. Robinson's Gait lab.**

Appendix:

Table 1. American Spinal Injury Association (ASIA) Impairment Scale.[1,3]

Grade	Description
A = Complete	No motor or sensory function is preserved in the sacral segments S4-S5
B = Incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
C = Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3
D = Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more
E = Normal	Motor and sensory function are normal

Table2. Ashworth Score for rigidity due to spasticity.[4]

Grade	Clinical Rating of Tone
1	No increase in tone
2	Slight increase – catch present
3	More increase – but limb still easily flexed
4	Considerable increase – passive movement difficult
5	Limb rigid in flexion and extension

Table 3. Spasm frequency score.[4]

Spasm score	Frequency of Spasms (clonus)
0	No spasms
1	One or less spasms per day
2	Between 1-5 spasms per day
3	Between 5-9 spasms per day
4	Ten or more spasms per day

References

1. *American Spinal Injury Association: Standards for Neurological Classification of Spinal Injury Patients.* 1990.
2. Konrad P, Caputi F, El-Naggar A. Radiofrequency dorsal root entry zone lesions for pain. In: Lozano A, Gildenberg P, Tasker R, eds. *Textbook of Stereotactic and Functional Neurosurgery*. 2nd ed. Heidelberg: Springer-Verlag; 2009:2251-2268.
3. *International Standards for Neurological Classification of Spinal Cord Injury (revised).*

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4. Penn RD, Savoy SM, Corcos D, et al. Intrathecal baclofen for severe spinal spasticity. *N Engl J Med.* Jun 8 1989;320(23):1517-1521.