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EFFECT OF TRANSCUTANEOUS SPINAL CORD STIMULATION ON EXCITABILITY AND SPASTICITY IN SPINAL CORD INJURIES: A RESEARCH PROJECT PROPOSAL.

MASTER'S THESIS

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ABBREVIATURES

Abbreviated Injury Scale
AIS, 11
alpha Motor Neurons
αMN, 3
Baseline assessment
A0, 20
Central Nervous System
CNS, 2
Central Pattern Generator
CPG, 3
Control Group
G2, 20
Dynamic Component of Spasticity
DCS, 23
electromyography
EMG, 7
Final assessment
A3, 20
Follow-up assessment
A4, 20
gamma Motor Neurons
γMN, 3
Initial assessment
A1, 20
Intermediate assessment
A2, 20
Interneurons
IN, 5
Intervention Group
G1, 20
Lower Moto Neurons
LMN, 5
Modified Ashworth Scale
MAS, 18
Modified Tardieu Scale
MTS, 23
Penn Spasms Frecuency Scale
PSFS, 23
Posterior Root Muscle reflexes
PRM, 15
Propriospinal System
PSS, 15
Reticular Formation
RF, 3
Spasticity Index
SI, 24
Spinal Cord Injuries - Spasticity Evaluation Tool
SCI - SET, 23
Spinal Cord Injury
SCI, 2
Transcutaneous Spinal Cord Stimulation
tSCS, 13
Upper Motor Neurons
UMN, 5
Visula Analogue Scale
VAS, 23
Wartenberg Pendulum Test
WPT, 23

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ABSTRACT

BACKGROUND

Transcutaneous electrical stimulation in the spinal cord can cause spinal excitability and affect the muscles of the lower limbs. However, the efficacy of non-invasive spinal stimulation for lower extremity muscle spasticity reduction remains unclear. This proposal aims to analyze the feasibility and efficacy of non-invasive transcutaneous spinal cord stimulation on spasticity in people with spinal cord injury.

METHODOLOGY

A randomized clinical trial with a control group was proposed in 36 patients during an intervention period of 2 weeks, with a baseline week at the beginning and a subsequent follow-up. A prospective and longitudinal data collection was described. For data analysis, an intention-to-treat analysis was proposed and intra- and inter-group comparisons were described.

RESULTS

Previous studies have shown a reduction in spasticity after the application of non-invasive spinal cord stimulation. Similar results to these previous studies are expected, and also superior results from the intervention group to those expected in the control group. The strengths and limitations of the proposal to be taken into account were described.

CONCLUSIONS

The process of carrying out this master's thesis was especially interesting and motivated me to have more interest on this topic every day and to overcome the obstacles involved in trying to create an innovative, creative and viable proposal for a potential technique that is still in a very early stage in terms of scientific evidence.

1. NEUROPHYSIOLOGY OF THE MOTOR CONTROL: UNDERSTANDING THE MUSCLE TONE

This first chapter aims to understand the control of the muscle tone, which is crucial for explaining spasticity after a Spinal Cord Injury (SCI). The muscle tone it is tightly related with the voluntary movement, the postural control and the circuits of spinal reflexes. (1,2)

The structures that comprise the networks for the control of a variety of human functions, like movement, posture or muscle tone, are found at different levels of the Central Nervous System (CNS) and are hierarchically organized **(Figure 1)**. They cooperate with each other and perform information processing loops between cortex and subcortical structures, regulating the activity of the spinal motor neurons that innervate the skeletal muscles. (3)

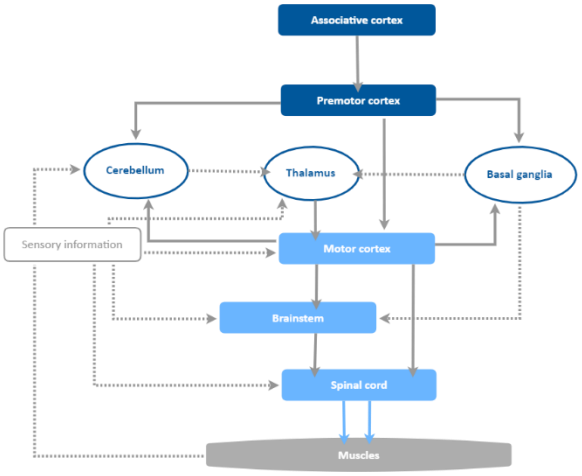


Figure 1. Motor control organization within neural structures. Image from: Juan-García FJ. Evaluación Clínica y Tratamiento de la Espasticidad. Alcocer A, editor. Madrid: EDITORIAL MÉDICA PANAMERICANA, S.A; 2009.

Automatic, effortless, and quality regulations of motor functions always require a constant flow of somatosensory information that is combined with additional information previously stored in a process called integration. This is the reason why the sensory influence on motor circuits it is important for the constant feedback in the control and accuracy of motor regulation. (4,5)

1.1. Motor control higher centers in human motion

As it is logic, higher level centers in the hierarchy are related to increasingly more complex aspects of the motor task. Reflexes, for example, are lead up by local circuits in the spinal cord and they are way more simple, while voluntary movements are governed by motor programs in the brain. (4,6)

1.1.1. The Motor Cerebral Cortex

The regulation orders and the complex actions of human motion will occur in at the motor cortex in the first place. Its main function is to control motor programs, give specific orders for voluntary movement and facilitate or inhibit spinal reflexes. (3,6)

The main areas involved in motor control are the following: the Primary Motor Area, the Primary Somatosensory Area, the Premotor Area and the Supplementary Motor Area. (3,7)

1.1.2. Cerebellum and Basal Ganglia

The cerebellum and the basal ganglia also participate in the motor control. The former is more related to the anticipation and harmonization of the motion's sequence. It receives

sensory input via the ventral spinocerebellar tracts, the corticospinal tracts, the rubrospinal tracts, and the spinal Central Pattern Generator (CPG). (6)

The medial and lateral parts of the anterior lobe of the cerebellum activate the Reticular Formation (RF) of the brainstem, from which the reticulospinal tracts arise. These are important pathways in the regulation of muscle tone. By influencing these tracts, the cerebellum inhibits muscle tone indirectly through motor neurons called gamma Motor Neurons (γMN). On the other hand, the vestibulocerebellum is connected to the vestibular nucleus of the brainstem, from which the vestibulospinal tracts arise. This part stimulates the other type of motor neurons, alpha Motor Neurons (αMN). Hence, the cerebellum is an important regulatory center of the alpha-gamma system. (2)

The basal ganglia project primarily to the different areas of the cortex, and to the brainstem, regulating their arousal through direct (excitatory) and indirect (inhibitory) pathways that have previously projected to the thalamus. Its function is mainly to help the cortex with carrying out complex already learnt motor patterns. (6,7)

1.1.3. The Brainstem

The brainstem could be defined as an extension of the spinal cord towards the brain, connecting these two structures. At a functional level, the brainstem is involved in performing rhythmic movements (such as breathing, locomotion, swallowing, etc.), in to the postural control, balance, muscle tone and others. (1,8)

The brainstem constitutes the pyramidal pathways and other indirect pathways that descend through the spinal cord tightly connected to the previous ones. These are the extrapyramidal tracts, which are characterized by the realization of synaptic scales in different nuclei of the brainstem. The nuclei that constitute the most important extrapyramidal pathways in the control of muscle tone are the red nucleus, the vestibular nuclei, and the RF. (3,6,8)

1.2. The Spinal Cord

It is the structure of the CNS that maintains the tracts of the ascending (sensitive) and descending (motor) pathways, connecting with the higher centers in the form of “roads” that transport information between them and to the different parts of the body. As well as transmitting the orders or informing higher centers, it also constitutes functions by itself in a reflexive way and independently from the brain. However, the brain will always exert regulation on the spinal mechanisms, by excitatory/inhibitory descending pathways. (5,8)

1.2.1. Protection structures and external anatomy of the spinal cord

The spinal cord is an almost cylindrical structure, which shows an anteroposterior flattening. In adult humans it measures 40 centimeters approximately and its diameter is about 2 centimeters wide in the central thoracic region, with some widening in the cervical region from the fourth cervical to the first thoracic vertebrae, coinciding with the roots that form the spinal nerves of the upper limbs. The same happens in the lumbar region from the ninth to the twelfth thoracic vertebrae, coinciding with the spinal roots of the lower limbs **(Figure 2)**. (5,8)

The spinal cord extends from the medulla oblongata to the upper border of the second lumbar vertebra. Below the twelfth thoracic segment, the spinal cord begins to narrow, forming the conus medullaris, which continues to narrow up to the upper base of the second lumbar vertebra, where it divides to form the cauda equina and the filum terminale, which attaches the spinal cord to the coccyx. The aforementioned spinal nerves are the pathways through which the spinal cord communicates with the different parts of the body. Altogether there are 31 pairs and they carry both motor and sensory fibers. (5,8)

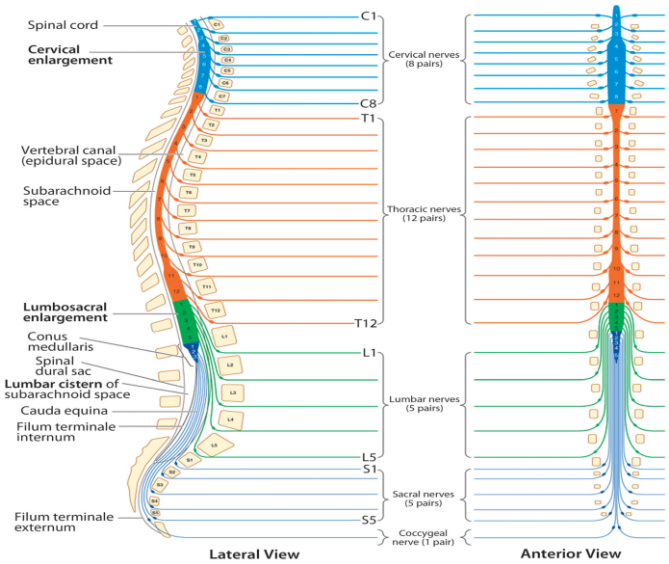


Figure 2. External anatomy of the spinal cord. Modified image from: Moore KL, Dailey AF, Agur AM. Clinically Oriented Anatomy. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2013.

The spinal cord's main protective structures are the spinal column and the meninges. The spinal column is formed by overlapping vertebrae connected through intervertebral discs. This structure forms the spinal canal where the spinal cord is lodged. The second line of protection is formed by the three meninges layers. (5,8)

1.2.2. Internal anatomy of the spinal cord

Its interior is formed by the H-shaped gray matter in the center, surrounded by the white matter. Regarding the gray matter, it is divided into two dorsal horns and two ventral horns. The dorsal horns are the entrance of the afferent sensory information. However, the body of sensory neurons is found in the dorsal root ganglia and these send their axons to the posterior dorsal horn to make synapses. (5,8)

The motor neuron bodies are located in the ventral horns of the gray matter, organized in different somatic motor nuclei. Linking the two sides of the gray matter there is the gray commissure. In addition, depending on the region of gray matter in which they are located, the cells may present different cytoarchitectonic structures, with the consequent functional differences. Specifically, they can be classified into 10 different zones called the Rexed lamina. (5,8)

The white matter is organized in columns that carry similar information through myelinated nerve axons, hence its white color. These columns are the tracts of sensory and motor information, the closer they travel, the more interconnected the information of the pathways is. As a reminder, the tracts mentioned to explain the control of muscle tone are the pyramidal pathway or corticospinal tracts and the extrapyramidal pathways, more particularly three of these pathways: the rubrospinal tract, the lateral vestibulospinal tract, and the anterior and lateral reticulospinal tracts. (5,8)

Starting from the higher centers downwards are the Upper Motor Neurons (UMN), which descend to the spinal cord to facilitate the initiation of movement, although they do not execute it directly. Actually, they synapse with the Lower Moto Neurons (LMN), the ones in charge of going to the target organs, i.e., the skeletal muscles. Given the importance of sensory feedback in motor control, the Local Circuit Neurons or Interneurons (IN), which are responsible for integrating the sensory information to process a motor response, are located within the spinal gray matter. (1,5)

An external stimulus evokes a graded potential in the sensory receptors, which will transmit the information to the IN and higher centers through nerve action potentials. Subsequently, this information can trigger a reflex arc or the motor centers can give an order for voluntary movement through another graded potential towards the UMN and then to the LMN. The LMN communicates the contraction order to the muscle through a muscle action potential. (1,5)

1.2.3. The Supraspinal system: Upper Motor Neurons

The UMN send fibers, both excitatory and inhibitory, down the spinal cord to control spinal motor neurons activity, projecting the orders of the brain. The topographical arrangement of such neurons gives an insight of their function. Cell bodies lay either in different centers of the brainstem and cerebral cortex, performing different pathways along the spinal cord that synapse to IN or, more rarely, directly with LMN. (1,3,5,7)

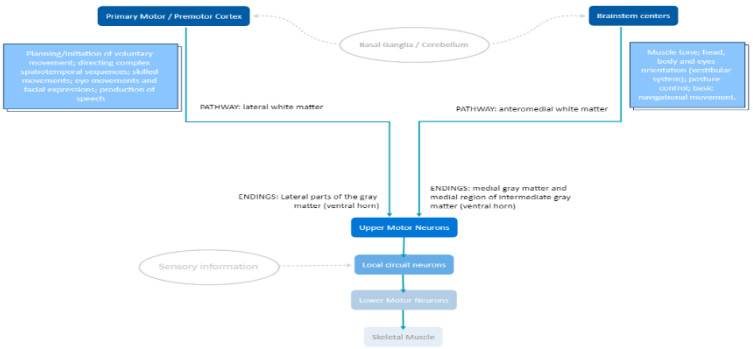


Figure 3. Overview of the descending motor trajectory. (1,5)

The spinal ending sections of the tracts coming from the cortex and brainstem gives a clue to the functional distinctions on the control of axial muscles and distal muscle groups. UMN coming from the indirect or extrapyramidal pathways (brainstem) pass antero-medially through the white matter and project to the medial parts of the ventral horn and medial region of the intermediate part of the gray matter. Meanwhile, the direct or pyramidal pathways course along the lateral side of the white matter, penetrating more lateral parts of the anterior horn **(Figure 3)**. (1,5)

This distribution suggests that brainstem neurons are primarily concerned with axial and proximal musculature, which involves postural control, balance, orientation, and regulation of stereotyped and rhythmic behavior. Contrarily, the distribution of neurons coming from the cortex suggests more control of accurate and skilled movements in distal parts. (1,5)

The tracts through which the UMN course have their own features. In order to understand the muscle tone, the most important tracts are those of the direct or corticospinal

tracts and some of the extrapyramidal tracts belonging to the corticobulbar tracts **(Figure 4)**. (1,3,5)

After they leave the cortical layer 5, UMN run through the internal capsule of the brain and the cerebral peduncle of the midbrain. When they reach the medulla oblongata, they form the medullary pyramids and are scattered in two different tracts, i.e. the lateral and the anterior corticospinal tracts. (1,3,5)

The lateral corticospinal tract represents 90% of the axons, that decussate (cross the midline) at this same level and synapse with the motor neurons of the limbs. The remaining 10% of the axons form the anterior corticospinal tract that course ipsilaterally and will later decussate at the cervical or thoracic levels. This tract commands the axial musculature. The main functions of the corticospinal tracts is directing orders towards the spinal motor neurons in order to facilitate or inhibit spinal reflexes, voluntary movement and maintain muscle tone. (1,3,5)

Regarding the extrapyramidal tracts, they perform synaptic scales in the different nuclei of the brainstem mentioned above. They also have an important function of modulating the motor control, by means of neurotransmitters such as dopamine, serotonin, acetylcholine and gamma-aminobutyric acid. The descending fibers of these tracts terminate at the spinal level by synapsing with IN of Rexed lamina VI-VIII. (1,3,5)

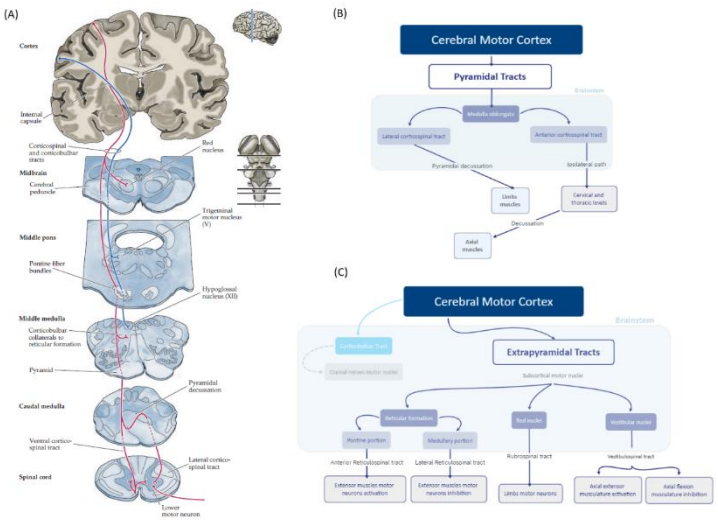


Figure 4. The pyramidal and extrapyramidal tracts involved in the muscle tone. (A) The corticospinal and corticobulbar tracts. Image from: Purves D, Augustine G, Fitzpatrick D, Hall W, Lamantina A-S, McNamara J, et al. Neurosciences. 3rd ed. Sunderland

1.2.4. The Local Circuit Neurons

Interneurons are located throughout the spinal gray matter and constitute the major synaptic input of the LMN. They possess a high excitability and act as integrating centers for supraspinal orders, afferent stimuli and propriospinal signals (that is, among spinal cord segments) to modulate the excitation, mainly inhibitory, of the LMN. This inhibition is essential for the proper maintenance of muscle tone, as well as the coordination and organization of movement. (1,3,6)

1.3. The muscle tone

The definition of muscle tone would be the degree of tension presented by the muscles at rest. This is caused by weak and involuntary contractions sustained over time. To keep muscle tone, small motor units are constantly active and inactive in an alternate way,

which is the reason why the tone is basically the outcome of motor control, through which its power the tone is intrinsically balanced. The function of muscle tone is to keep the muscles firm but without producing enough force to generate movement. (1,2,5)

But this tone will not only serve as a support, but also provides the muscle with the optimal conditions to generate voluntary or reflex movement. For example, when going from sitting to standing, the muscle tone of the extensor muscles will prevent the common sway that occurs when increasing length. In addition, this background level of contraction will act as a reservoir of mechanical energy that enhances the elastic qualities of the muscle. (1,2,5)

The main feedback loop by which it is possible to maintain adequate muscle tone is the same as the one provided by the stretch reflex. It basically depends on the discharge of the αMN and the activity of the muscle spindles. The muscle spindles are the major contributors to this tonic level of firing. (1,2,5)

In addition to the contractile component resulting from motor unit activation, muscle tone also has a passive or viscoelastic component, which is independent from neural activity and cannot be detected by electromyography (EMG). This viscoelastic component depends on multiple factors, such as actin-myosin sarcomeric cross-bridges, the viscosity, elasticity and extensibility of the contractile filaments, the filamentous connection of other non-contractile sarcomeric proteins, osmotic pressure of the cells, and also of the surrounding connective tissues. (2,9,10)

1.4. Peripheral sensory influence and proprioceptive organs

External sensory influences are the framework in which the motor systems plan, coordinate and execute the motor programs responsible for purposeful movement. Hence, sensory information and motor action are intimately bound. In contrast to motor systems, which produce movement throughout descendent pathways by translating neural signs into contractile force in muscles, sensory system transforms physical energy into neural signs. (3,4)

Actually, the hierarchy of motor representations depends on a parallel hierarchy of sensory input. More complex sensory information is extracted at each level and, successively, higher levels of the motor hierarchy increasingly specify more complex aspects of a motor task. (4,5)

For this process to start, we need to consciously or subconsciously feel a change in the internal or external environment at first. We can have sensations of different types, an example of this would be the proprioceptive sensations given by the muscle spindles and Golgi receptors that will be paramount for the right regulation of the movement and muscle tone. (5,6)

The muscle spindles are sensory receptors embedded between the muscles and organized in intrafusal fibers aligned in a parallel way to extrafusal fibers, those of the skeletal muscles. (1,3)

According to their structure and function, two types of these intrafusal fibers can be found: nuclear bag fibers and nuclear chain fibers. Their main differences are the organization

of their myofibrils, the arrangement of their nucleus and their dynamic sensitivity to stretching. (1,3,7)

Muscle spindles concern two different sensitive fibers. The Ia afferent fibers wrap around the nuclear bag chains of each intrafusal fiber of the muscle spindle, while the II afferent fibers adhere to the nuclear chain fibers. These Ia and II fibers constitute the longest axons in peripheral nerves, and because action potential conduction velocity is a direct function of axon diameter, they mediate very rapid reflex adjustments when the muscle is stretched. (1,3,7)

The other proprioceptive organ mentioned is the Golgi tendon organ, encapsulated sensory receptors located in the muscle tendons. Its function is to detect tension in the muscle and transmit it, as well as the rhythm of change of such tension. The main difference between muscle spindles and Golgi receptors, apart from their location, is that the muscle spindles detect changes in muscle length, while the Golgi tendon organs identify the degree of muscle tension. (3,6)

All the peripheral sensory information that influence over human motion is integrated as a whole in the CNS giving the right motion answers, which will go from the simplest answers, given by the motor reflexes in the spinal cord (local circuits), to more complex systems extended towards the brain (large circuits). (4,6)

1.5. Local circuits: the spinal reflexes

Spinal reflexes are activated by an external sensory stimulus. These circuits are coordinated by the spinal cord but also participate in voluntary movements governed in a more complex way by higher centers. The area of integration of these reflexes is the spinal cord gray matter. They enter through the dorsal roots and then split. One of the branches will travel to higher centers while the other will synapse with IN, eliciting the spinal reflexes. (4–6)

1.5.1. Stretch Reflex Pathways

The simplest reflex, also called “myotatic reflex” or “deep tendon” reflex **(Figure 5)**, is a monosynaptic reflex whose function is to maintain an adequate muscle length. The phasic component of this reflex can be tested on the base of the knee, ankle, jaw, biceps, and triceps during a physical examination. The feedback concerning the excessive stretching of the muscle fibers is given by the muscle spindles. (1,3)

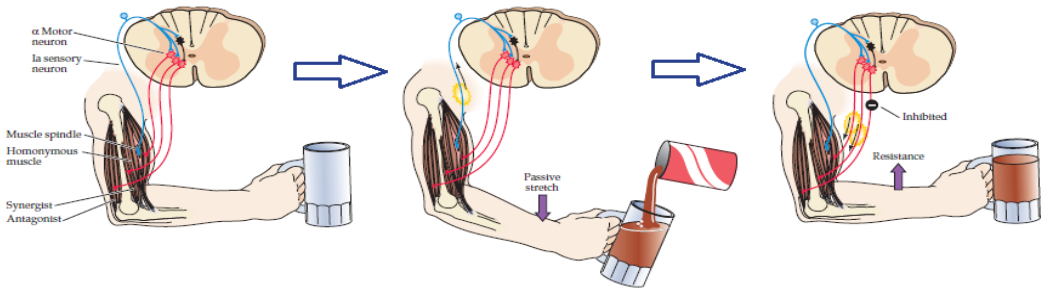


Figure 5. Stretch reflex circuitry. Image from: Purves D, Augustine G, Fitzpatrick D, Hall W, Lamantina A-S, McNamara J, et al. Neurosciences. 3rd ed. Sunderland: Sinauer Associates, Inc.; 2004.

The stretch of the extrafusal fibers impose a stretch of the intrafusal or muscle spindle fibers that is detected by Ia and II afferent fibers. The Ia fibers detect faster elongations and sudden changes in length, they are more sensitive to speed and detect dynamic changes (phasic stretch reflex). II fibers detect static stretch (tonic stretch reflex), that is, the level of sustained fiber stretch over time. (1,3)

The branches of Ia and II fibers connect in a monosynaptic and excitatory way to αMN in the ventral horn of the spinal cord, exciting the homonymous muscle, which is being stretched. Additionally, these afferent fibers will also synapse with αMN by IN called reciprocal-Ia-inhibitory interneurons (GABAergic interneurons), in order to inhibit the heteronymous muscle and allow contraction of the antagonist. This phenomenon is an example of reciprocal innervation. (1,3)

The musculature is always subjected to a certain static stretching. Therefore, this circuit is responsible for the level of tension in the muscles, that is, the muscle tone, which will vary if this circuit is affected by some pathology. Within the context of motor control, as a consequence, appropriate muscle length and muscle tone is regulated by the UMN influencing the lower ones. (1,3)

It is important to mention that within the muscle spindles there are the γMN, which constitute a servo-aid system for muscle contraction. This gamma circuit is not only essential for the stretch reflex, but also for maintaining muscle tone. Following supraspinal orders, γMN contract the poles of the intrafusal fibers, creating a cleft force in the center of the fibers, that is, in the nuclear bag chains. Hence, the result of this distention will be a greater activation of the fibers, responsible for detecting this distention to report the length of the muscle and, consequently, more activity of the αMN on the extrafusal fibers. Accordingly, this "gamma loop" constitutes a servo aid system. In addition, during voluntary contraction, excitatory signals are sent in parallel to αMN and γMN, for this reason intra and extrafusal fibers are activated at the same time, this is called the alpha-gamma coactivation. (1,3,7)

1.5.2. Tendon Reflex Pathways

The Tendon reflex or T-reflex controls the tension of the muscles during movement so that there are no sudden variations on the myotendinous insertion point. This tension is captured by the Golgi tendon organs. Like in the case of the muscle spindles, these tendon receptors also have a double response: dynamic and static. Impulses are conducted by Ib afferent fibers (large fast-conducting nerve fibers) to Ib IN. In this case, αMN of the homonymous muscle will be inhibited, while αMN of the heteronymous muscle are excited to contract, producing the corresponding muscle tension reduction. (3,6)

Therefore, this reflex has an inhibitory character. If the tension applied to the muscle were very intense, the inhibitory effect produced could become so great that it would lead to a sudden spinal reaction capable of producing an instantaneous relaxation of the entire muscle. This effect is called the lengthening reaction and is believed to be a protective mechanism to prevent tearing of the muscle or ripping the tendon from its insertions. (3,6)

In addition, this reflex has another very important function in regulating the force of contraction between muscle fibers, by exerting a selective inhibition of the fibers that contract

excessively and by promoting that less activated fibers are more excitable due to the lack of reflex inhibition. It is a phenomenon of muscular load dispersion. (3,6)

1.5.3. Flexion Reflex Pathways

Although it can be activated by a large number of external stimuli, it is activated mainly by painful stimulus such as a pinprick or the heat of a flame. This reflex will modulate the withdrawal of the limb in pain **(Figure 6)**. (1,3,5)

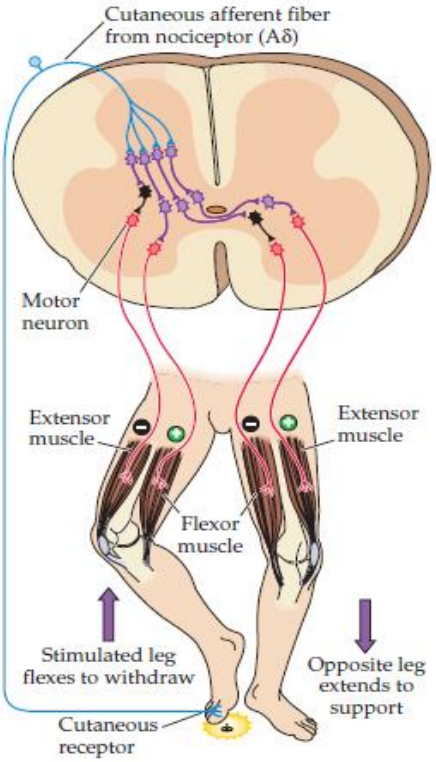


Figure 6. Spinal cord circuitry for the flexion-crossed extension reflex. Image from: Purves D, Augustine G, Fitzpatrick D, Hall W, Lamantina A-S, McNamara J, et al. Neurosciences. 3rd ed. Sunderland: Sinauer Associates, Inc.; 2004.

These nociceptive afferent fibers (III and IV) conduct to interneurons in the posterior horn of the spinal cord, located in Rexed lamina II and III. Through these interneurons, they will connect with motor neurons in the ventral horn, which will trigger the contraction of ipsilateral flexor muscles and a reciprocal inhibition of ipsilateral extensor muscles. (1,3)

In turn, these nociceptive fibers are capable of activating contralateral motor neurons that will activate the crossed extension reflex. In the opposite limb, the motor neurons that innervate flexor muscles will be inhibited, while the motor neurons of the extensor muscles will be excited, that is, reciprocal inhibition also occurs. The reason for this to take place is to provide postural stability after withdrawal of the opposite limb. Unlike the flexor reflex, which is ipsilateral, the cross-extension reflex is a contralateral reflex arc. (1,3,5)

2. A NEUROLOGICAL DISORDER: SPASTICITY IN SPINAL CORD INJURIES

Spinal cord injury is the consequence resulting from the interruption of the nerve pathways that connect the brain with the rest of the body. This interruption causes a cessation of the motor, sensitive and vegetative functions in the part of the organism that is below the injury. It can also cause lack of sphincter control, sexuality and fertility disorders, alterations of the central vegetative system and risk of other complications such as decubitus ulcer, spasticity, kidney processes, etc. The damage in the spinal cord leads to a neurological deficit that will persist throughout life and that will have a great impact in different areas such as social life, emotional aspects, quality of life and daily life activities. (15,16)

Injury mechanisms of the spinal cord can be non-traumatic etiology (infectious, degenerative, neoplasic, ischemic spinal cord infarction, etc.) or traumatic, when it refers to a direct impact on the spinal cord that is intense enough to produce the injury or a fast-moving object hitting the spine. Indirect traumatic injuries are forces caused by movements of the spine, which are beyond the physiological range. These injuries are usually related to compression, flexion, extension, or rotation movements. (17,18)

2.1. Spinal Cord Injury classification and main diagnose strategies

Patients with a SCI must undergo a neurological evaluation in order to establish the severity of the injury and its characteristics by classifying it on the Abbreviated Injury Scale (AIS). It is an anatomical-based coding system created by the Association for the Advancement of Automotive Medicine to classify and describe the severity of injuries **(see ANNEX 1)**. (22,27)

This scale classifies SCI scored on a 5 point ordinal scale from A, which is a sensory and motor complete SCI, to E, a normal sensory and motor function **(Table 1)**. (28)

Table 1. SCI classification according to the AIS statements (15,22)

A	**COMPLETE INJURY.** There is no preservation of motor or sensory function in the sacral segments S4-S5.
B	**INCOMPLETE SENSITIVE INJURY.** There is preservation of sensory but not motor function in the more distal sacral segments S4-5 (fine touch or pinprick at S4-S5 or deep anal pressure), and there is no preservation of motor function more than three levels below the motor level on one or the other side of the body.
C	**INCOMPLETE MOTOR INJURY.** Motor function is preserved in the most caudal sacral segments during voluntary anal contraction or the patient meets the criteria for incomplete sensory injury (sensory function preserved in sacral segments S4-S5), with motor function present in more than three segments below the ipsilateral motor level on either side of the body.
D	**INCOMPLETE MOTOR INJURY.** Incomplete motor status as defined above, with at least half (half or more) of key muscle function below the neurologic level of injury with a muscle classification greater than or equal to 3.
E	**NORMAL.** If the sensation and motor function being examined are classified as normal in all segments but the patient had had deficits.

A SCI can also be classified by its location on the spinal cord and affected body areas. That defines the concepts of tetraplegia and paraplegia. Tetraplegia occurs when the damage happens on the cervical sections causing weakness, paralysis and loss of sensation in the hands, arms, shoulders legs and breath muscles to a greater or lesser extent depending on the severity of the injury and its location (upper or lower cervical spine). The other term used to

classify SCI is paraplegia, i.e., when the injury is on the thoracic or lumbar regions. Meaning that only legs and muscles of the trunk will be affected. (21)

2.2. The epidemiology of Spinal Cord Injuries

In Spain it is estimated that there are between 25,000 and 30,000 people who live with a SCI. The incidence is between 800 and 1,000 new cases per year, being thoracic injuries the most common ones **(Figure 7/8)**. With these data, SCI can be classified as a minority injury. However, the high incidence in young people and the complications that involves, make it a devastating injury for both the health system and the socioeconomic system. (3–5)

One of the most common complications that occur in SCI is spasticity, which develops during the first year of injury in approximately 65% and 78% of the cases. Spasticity could be defined as a sensorimotor disorder resulting from the injury of the upper motor neurons that produces an involuntary activation (intermittent or sustained) of the muscles. It is usually characterized by being velocity-dependent due to reflex hyperexcitability. (6–9)

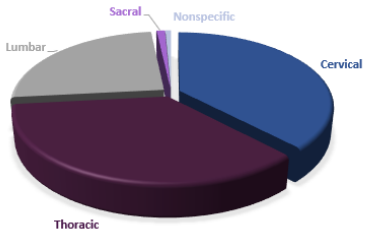


Figure 7. Men annual rate of hospital discharges due to traumatic SCI per 1,000,000 inhabitants, according to affected anatomical region. Spain 2000-2008. Font: *Conjunto Mínimo Básico de Datos de Altas Hospitalarias (CMBDAH), Instituto Nacional de Estadística (INE)*

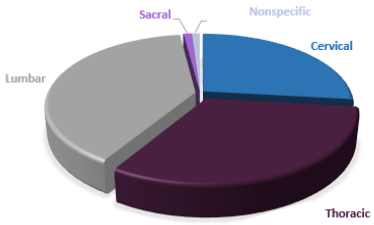


Figure 8. Women annual rate of hospital discharges due to traumatic SCI per 1,000,000 inhabitants, according to affected anatomical region. Spain 2000-2008. Font: *Conjunto Mínimo Básico de Datos de Altas Hospitalarias (CMBDAH), Instituto Nacional de Estadística (INE)*

2.3. Spasticity in Spinal Cord Injuries

The main features of spasticity are as follows: increased muscle tone and hyperactive spinal stretch reflexes. These alterations are due to the loss of descending control over the spinal structures, as a consequence, the reflexes try to adapt to supply this lack of modulation. (4)

The affected UMN used to be responsible for sending both excitatory and inhibitory signals in order to regulate the movements and muscle tone that are now lost or altered. After injury the spinal tracts are "cut off" and adaptations begin to occur in an attempt to control all of the spinal circuitry and maintain motor control. (3)

Although the cortical tracts supposedly involved in the production of spasticity have been previously explained, pathophysiological studies have observed that some of these pathways are more involved than others. For example, the corticospinal or pyramidal tracts only produce pure pyramidal syndromes with mild motor deficits, without much involvement in the production of hypertonia and spasticity. In fact, spasticity and other upper motor neuron

signs are more associated with extrapyramidal pathways with little involvement of corticospinal pathways. (37,38)

Under normal conditions, the main extrapyramidal tract that inhibits spinal reflexes is the lateral reticulospinal tract. Therefore, this will have a great impact on the production of hyperreflexia. Other tracts, such as the vestibulospinal tract, have been found to be less decisive in the production of spasticity. (3,39)

Spasticity has been and continues to be a major question mark when it comes to making an objective assessment out of it and also when treating it. There are also many questions regarding its pathophysiology which, studies show it seems to be multifactorial **(Figure 9)**. There is evidence that after a SCI there is a gain in motor unit recruitment so that motoneurons begin to adopt a firing pattern typical of low-threshold motoneurons, which makes a minimal signal trigger exaggerated responses. (6)

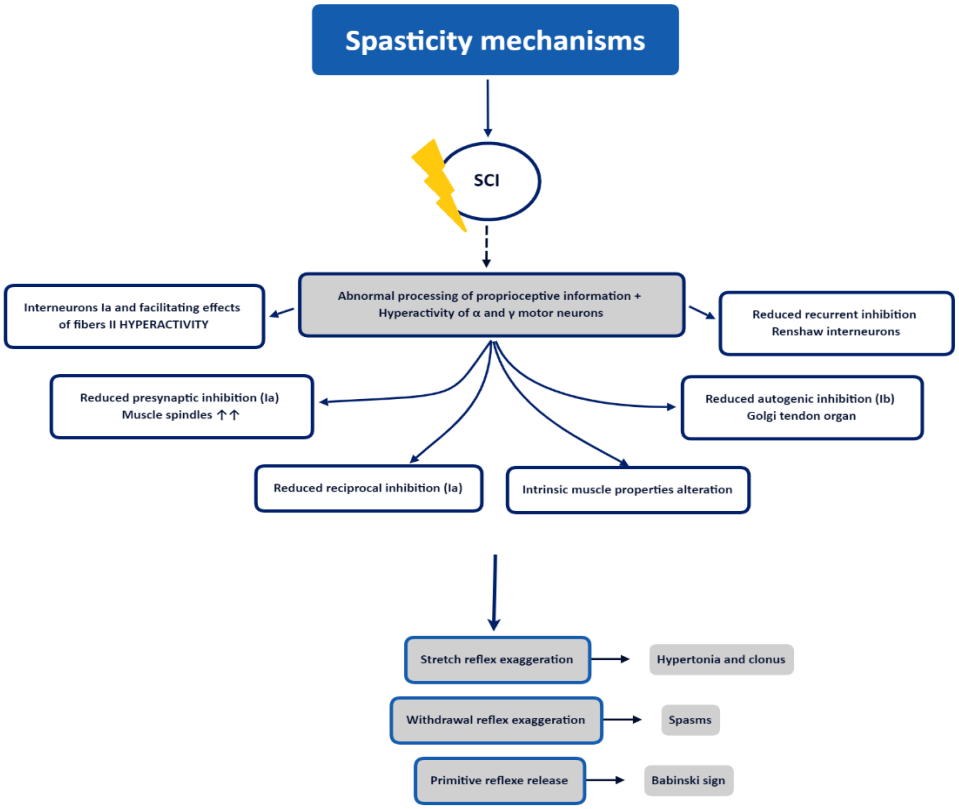


Figure 9. The mechanisms of spasticity after a SCI. (10–15)

Not infrequently spasticity represents a complication that comes to put physical, psychological and participation impediments and barriers for people who suffer from it. In order to provide therapeutic strategies for this problem, the purpose of this proposal is to present an intervention using transcutaneous Spinal Cord Stimulation (tSCS) in order to analyze its potential as a possible technique to take into account when treating spasticity in patients with SCI. (6–9,16–18)

The tSCS is a spinal electrostimulation technique that has sought to improve function in people with different neurological pathologies (including SCI) by modulating spinal excitability non-invasively. This represents a therapeutic window for the treatment of different dysfunctions that a SCIs encompass, in this case, spasticity. (19)

2.4. Current evidence of the transcutaneous spinal cord stimulation

The tSCS stems from invasive epidural stimulation, which was first implemented in an attempt to treat neuropathic pain and later to activate the CPG in the lumbar spine and promote locomotion function in people with SCI **(Figure 10)**. This technique consists of a device implanted in the thoracolumbar epidural space or along various spinal segments that supplies electrical current to the spinal cord. This device has allowed improvements on the motor control in people with SCI. (20,21)

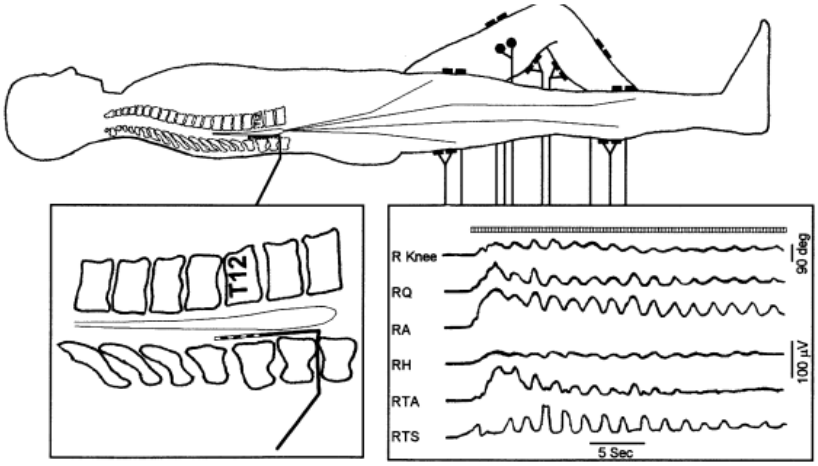


Figure 10. Diagrammatic sketch of the human lumbar CPG level. Image from: Dimitrijevic MR, et al. Evidence for a spinal central pattern generator in humans. In: Annals of the New York Academy of Sciences [Internet]. John Wiley & Sons, Ltd; 1998 [cited 2

The positive results that were obtained over the years of research encouraged the appearance of a technique that was capable of stimulating non-invasively and that produced similar benefits, thus avoiding the inconveniences of surgical intervention. Hence the birth of tSCS, the first studies of which focused on demonstrating stimulation of the posterior lumbar spinal columns in healthy subjects. (22–24)

Since then, having obtained positive results in spinal excitability, the tSCS has been mainly studied in locomotion function in SCI, through the stimulation of lumbar CPG. However, this technique has also shown potential to be considered a neuromodulation strategy capable of helping to promote the recovery of other functions. For this reason, its effects on other dysfunctions have begun to be studied, such as the recovery of respiratory function, bowel function, bladder function and muscle tone or spasticity. (25–28)

The electrodes placed superficially on the spinal column induce electrical current to the spinal cord producing rhythmic, alternating and coordinated patterns and other muscular responses with similar neurophysiological characteristics. (63,64)

Thus, this spinal cord stimulation applied at specific points, most commonly called “trigger points”, has the ability to activate the CPG by exciting the Posterior Root Muscle reflexes (PRM). Different studies have already shown the possibility of neuromodulating functions such as gait, muscle tone, postural control, etc. using tSCS. (64–66)

It is also theorized that tSCS may modulate interneuronal spinal excitability, which may explain the observed motor recovery when used in people with SCI. By activating networks such as the CPG and the Propriospinal System (PSS), spinal excitability can be increased and the threshold for motor impulse propagation can be lowered. The PSS has been described as an interface between spinal segments that contributes to rhythmic movement and coordination, as well as providing a background of subthreshold arousal. (12)

So far, some studies have published cases of improved lower extremity, trunk, and upper extremity function in chronic SCI. Despite these promising initial results, a recent review evaluating the therapeutic effects of tSCS on motor recovery in people with SCI reported that due to small and heterogeneous sample sizes, diverse range of outcome measures, and low quality methodological analysis of the studies reviewed, no conclusions can be drawn about their effectiveness. (66–72)

This modality is under the relatively early stages of investigation and so, there is still much to learn about its implementation and clinical potential. Despite the findings already described after transcutaneous stimulation, all studies related to spasticity have been conducted in case series studies without a control group, so it is unknown whether the effect is greater than the placebo effect or other interventions. (19,29)

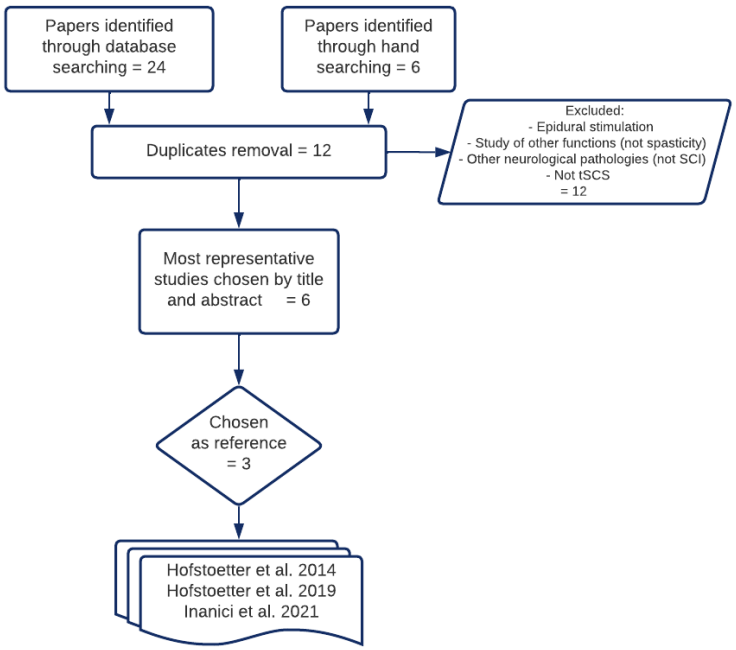


Figure 11. Flowchart of the literature search on tSCS in spasticity on people with SCI.

For this reason, and taking into account the biopsychosocial consequences and the high costs of SCIs, it is extremely important to develop methodologically powerful studies that allow the evaluation of the effects of tSCS on the complications in SCI. In order to tSCS to be considered as a future strategy treatment that

helps improve the quality of life of this population and avoid dire consequences derived from the mentioned complications. (3)

In order to give an overview of the current state of research on tSCS in spasticity with people with SCI, a bibliographic review was accomplished in the following databases: PubMed, Physiotherapy Evidence Database and ResearchGate. In addition, an inverse manual search of some references of doctoral theses and papers related to this topic was carried out. The search was performed using combinations of the following keywords: "spinal cord injuries", "muscle spasticity", "spinal cord stimulation" [MeSH Terms], "hypertonia", "transcutaneous spinal cord stimulation" **(Figure 11)**.

From the studies selected for containing data on motor control improvements, only 3 included data form spasticity and 2 of them were specifically carried out to measure changes in parameters related to spasticity.

Study I

Hofstoetter US, McKay WB, Tansey KE, Mayr W, Kern H, Minassian K. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. J Spinal Cord Med. 2014;37(2):202–11.

Study II

Hofstoetter US, Freundl B, Danner SM, Krenn MJ, Mayr W, Binder H, et al. Transcutaneous Spinal Cord Stimulation Induces Temporary Attenation of Spasticity in Individuals with Spinal Cord Injury. J Neurotrauma. 2020;37(3):481–93.

Study III

Inanici F, Brighton LN, Samejima S, Hofstetter CP, Moritz CT. Transcutaneous Spinal Cord Stimulation Restores Hand and Arm Function after Spinal Cord Injury. IEEE Trans Neural Syst Rehabil Eng. 2021;29:310–9.

3. STUDY AIMS AND HYPOTHESIS

3.1. Hypothesis

The general hypothesis of this intervention is that the tSCS produces changes in the spinal cord excitability that will have a neuromodulatory effect on spasticity. This neuromodulatory effect of the tSCS on the lower limbs is expected to be greater than the one given by a sham tSCS and, therefore, constitutes an effective treatment for lower limbs' spasticity in cervical or thoracic spinal cord injured patients, AIS A – C. It is also expected that changes on spasticity will last for a certain time after the cessation of the treatment, in the intervention group. The real tSCS treatment on spasticity will have a positive impact on the improvement of these patients' perception of spasticity and quality of life during the time of intervention and during the maintenance period of the changes compared to the same patients receiving placebo treatment.

3.2. Aims of the study

The main objective of this proposal is to assess the spasticity-modulating effect of transcutaneous electrical stimulation on lower extremities in cervical or thoracic spinal cord injuries, AIS A – C.

3.2.1. Specific objectives

- To study the changes in the excitability of the spinal cord through reflex pathways in cervical/thoracic SCI (AIS A – C).
- To evaluate tSCS lasting effects on spasticity of the lower limbs in cervical/thoracic SCI (AIS A – C).
- To analyze subjective changes in perception of spasticity and impact in daily life in cervical/thoracic SCI (AIS A – C).

4. METHODOLOGY

4.1. Study design

A double-blinded, randomized, controlled clinical trial was designed. All participants (n = 36) will receive 10 sessions of tSCS (18 = real-tSCS / 18 = sham-tSCS). All participants and the assessor will be blinded, only the intervenor who applies the stimulation won't be. The order for each recruited participant to receive either the sham or active tSCS intervention will be randomized, with the patient's number from 1 to 36 concealed in individual sealed envelopes. Randomization will be performed using the web software www.randomizer.org, in order to know the assignment group of each participant number. Both interventions and assessments will take place in the morning always at the same time.

In order to check the reliability of the sham treatment a final questionnaire **(see ANNEX 2)** will be facilitated at the end of the study, asking the patients which treatment they think they have received. The same questionnaire will also ask about the sensation during the intervention.

The assessments will take place one-week before the first intervention, before the first intervention, in the middle of the two weeks of intervention and at the end of the last intervention. Also, a follow-up measurement will be recorded, one week after the last intervention to determine the duration of the neuromodulatory effect of the tSCS.

4.2. Sample size calculation

The "Sample Size and Power Calculator GRANMO" (https://www.imim.cat/offertadeserveis/software-public/granmo/) tool was used to make the sample size calculation, set at means → repeated measurements. Based on the improvement of the variable of spasticity in the study of Inanici et al. measured by the Modified Ashworth Scale (MAS), it is estimated that accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 18 subjects are necessary in first group and 18 in the second to recognize as statistically significant a difference greater than or equal to 2.6 units. The common standard deviation is assumed to be 3 and the correlation coefficient between the initial and final measurement as 0.65. It has been anticipated a drop-out rate of 15%.

The characteristics of the sample will be represented by the following table **(Table 2)**, according to the International Standards for Neurological Classification of Spinal Cord Injury. Any change in the characteristics described during the study must be specified. (30)

Table 2. Participants data and neurological status according to the International Standards for Neurological Classification of Spinal Cord Injury

No.	Sex	Age	Time post-I (m)	SCI level	AIS	WISCI II	LEMS / UEMS	PP C4-T2/L1-S2	LT C4-T2/L1-S2	AS.Med.

No.: Participant Number, AIS: American Spinal Injury Association Impairment Scale, WISCI II: Walking Index for Spinal Cord Injury II score, LEMS / UEMS: Lower Extremities Motor Score / Upper Extremities Motor Score (max.50), PP: Pin Prick sensory score (max.28), LT: Light Touch sensory score (max.28), AS.Med.: Anti-Spasticity medication (daily dosage)

4.3. Recruitment and selection criteria

The sample consists of patients in the first year of the SCI recruited by consecutive admission to the neurorehabilitation service of the Guttmann Institute. All patients should read and sign the established informed consent of this institution. These patients will be submitted to an initial assessment to determine compliance of the following criteria **(Table 3/4)**:

Table 3. Inclusion criteria

- Age between 18 – 60
- Traumatic and non-traumatic SCI etiology
- Cervical or thoracic SCI
- AIS rated A, B, C or D
- Stage of evolution: < 1-year post-injury
- Spasticity rating >2 MAS in minimum 2 movements of the lower limbs
- Spasticity treatment have been stable for the last 2 weeks
- Signature of the informed consent

Table 4. Exclusion criteria

- Ischemic spinal cord infarction
- Dependency on ventilation support
- Concomitant neurological disease (central or peripheral), such as multiple sclerosis, traumatic brain injury, peripheral neuropathies, stroke or others.
- Unstable medical conditions or other significant medical illnesses, such as uncontrolled systemic hypertension with values above 170/100 mmHg, heart or lung disease, contagious chronic diseases, uncorrected coagulation abnormalities or need for therapeutic anticoagulation, unhealed fracture, contracture, pressure sore, urinary tract infection, or other diseases that may interfere with the intervention.
- Having received injections of botulinic toxin during the previous 6 months
- Tendon or nerve transfer surgeries
- Any implanted stimulator in the body, such as, cardiac pacemaker, intrathecal baclofen pump, vagus nerve stimulator, etc.
- Implants or metal osteosynthesis in the area to be stimulated.
- Cognitive impairment based on the Mini-Mental State Examination (MMSE) (score <27)
- Pregnancy
- Active cancer
- Alcohol and/or drug abuse
- Inability to read or understand the informed consent

However, treatment may be suspended in any of the following cases **(Table 5)**:

Table 5. Withdrawal criteria

- Dysreflexia that makes it impossible to carry out the treatment - Appearance of medical complications, such as pressure sore, infections, etc. - Missing more than 20% of the stimulation sessions or the rehabilitation treatment. - Worsening or appearance of adverse effects - Abandonment due to personal reasons

The assessments in both the selection and in the different stages of assessment will always be carried out by the same assessor and following the same criteria and protocols.

4.4. Procedure and intervention

Data will be taken prospectively and longitudinally over a 4-week period. The study will consist of an intervention group, who will take the real or active tSCS (G1 = Group 1) and the control group, who will take the placebo or sham tSCS (G2 = Group 2).

As mentioned before, the double blind will apply to the patient and the controller who performs the assessments and analyzes data. Whereas, only the person applying the tSCS will know if it is the placebo group or the real tSCS group. So, two controllers will be required.

The times will be divided into a first baseline week, with assessments at the beginning (A0) and at the end, just before starting the first intervention (A1). After the first assessment before the intervention, the next assessment will take place at the end of the first week (A2) and then, at the end of the last intervention (A3). After the two weeks of treatment, a week will be left and a follow-up (A4) will be done a week after the end of the treatment **(Figure 12)**.

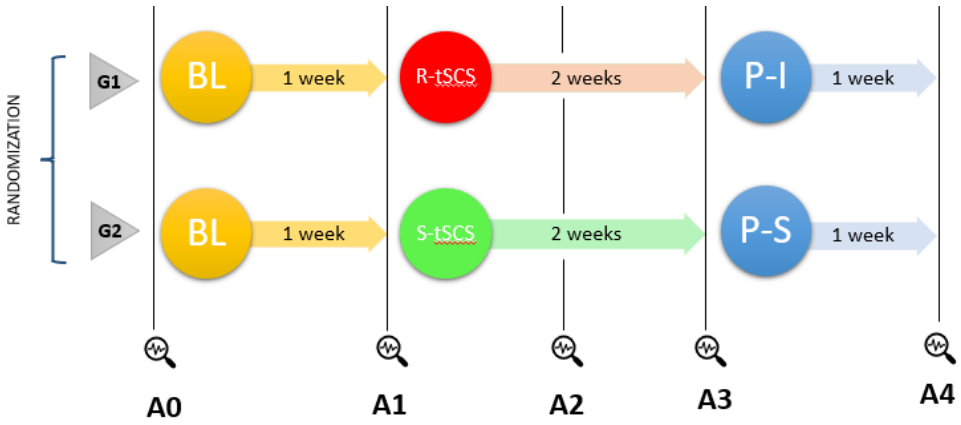


Figure 12. Outline of the study procedure. G1 = intervention group; G2 = control group; BL = baseline; R-tSCS = real-tSCS; S-tSCS = sham-tSCS; P-I = post-intervention; P-S = post-sham; A0 = assessment 0; A1 = assessment 1; A2 = assessment 2; A3 = assessment 3; A4 = assessment 4.

In total, 5 weeks will be needed amongst recruitment, controls, intervention and follow-up, assuming that there is no abandonment. Each of the subjects will go through the following procedure **(Figure 13)**:

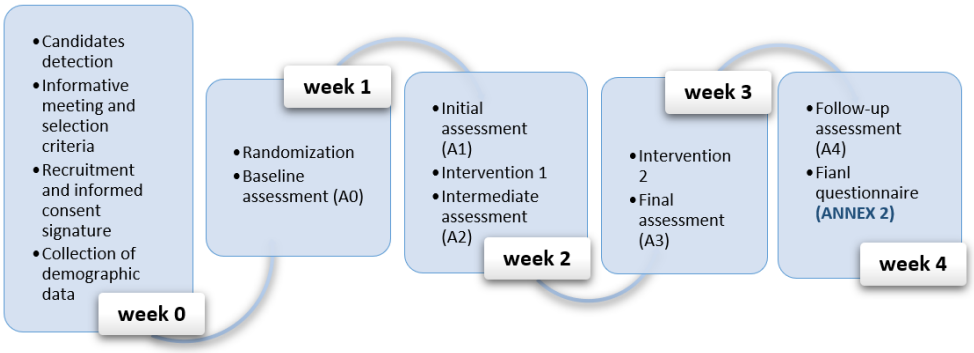


Figure 13. Study process flowchart

The interventions (both, real and sham) will be carried out from Monday to Friday in 30-minute sessions. Therefore, a total of 10 sessions (5h) will be held. Both the interventions and the data collection will take place in the morning before the rehabilitation session, always at the same time.

The rehabilitation that the two groups will carry out in Guttmann Institute will consist of physiotherapy, occupational therapy, psychology and physical training. Physiotherapy rehabilitation will consist of: hydrotherapy, manual therapy, therapeutic exercise, standing, walking and transfers. Other electrotherapy, vibration or shock wave treatments should be avoided. If it is strictly necessary to apply any of these treatments, it must be reported in the results of the study.

4.4.1 Transcutaneous Spinal Cord Stimulation regulation parameters

The configuration parameters for the tSCS on spasticity were extracted from the previous studies that were taken as a reference. **(Table 6)**.

Table 6. Therapeutic parameters to set tSCS in spasticity

Study	*Localization*	*Polarity*	*Waveform*	*Frequency (Hz)*	*Pulse width (ms)*	*Intensity*	*Duration (min)*
Inanici et al. 2021 (31)	Cervical (Above+Below injury)	Cathode	B/M	30	1	0-120 mA	120
Hofstoetter et al. 2014 (32)	T11-T12	-	SBR	50	2	20V (± 2)	30
Hofstoetter et al. 2020 (33)	T11-T12	Cathode	SBR	50	1	15-90 mA	30

SBR = Symmetric, Biphasic Rectangular; B = Biphasic; M = Monophasic

The main difference between the real treatment and the placebo is that in the case of the placebo the intensity will be established in the same way as in the real treatment and will remain at the patient's tolerance threshold for 30 seconds, but then it will gradually decrease to zero. This method has been previously validated as an appropriate sham stimulus for controlled studies. (34,35)

Therefore, the parameters that are established will be the following:

REAL-tSCS	SHAM-tSCS
Session time: 30 minutes **Subject position:** lying supine **Wave:** rectangular biphasic waveform **Frequency:** 50 Hz **Pulse width:** 1 ms x phase **Intensity:** Between 40-90 mA. Increments of 5 mA to a subthreshold level.	**Session time:** 30 minutes **Subject position:** lying supine **Wave:** rectangular biphasic waveform **Frequency:** 50 Hz **Pulse width:** 1 ms x phase **Intensity:** Between 40-90 mA. Increments of 5 mA to a subthreshold level. Sensory threshold for 30 sec. → decrease to 0.

Two self-adhesive hydrogel surface electrodes will be required. The cathode (5 cm in diameter) will be placed between levels T11-T12 and the anode (8x13 cm) will be placed over the right anterior iliac crest of the pelvis **(Figure 14)**.

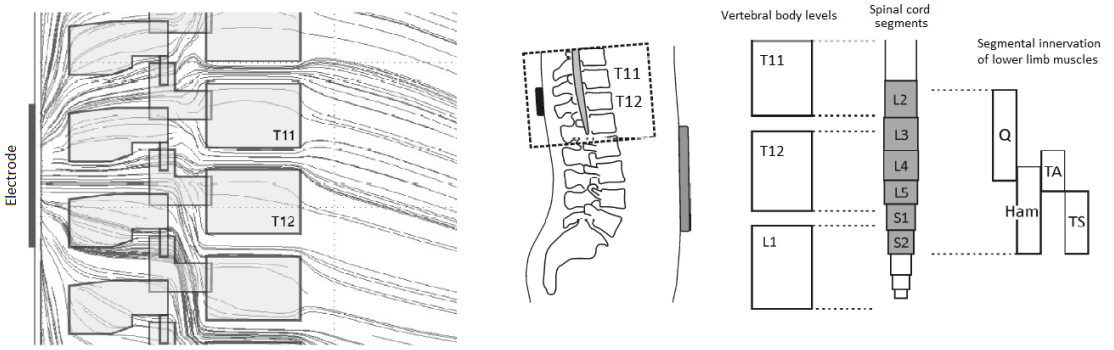


Figure 14. Electrode placement and corresponding muscle innervation levels in the spinal cord. Q = Quadriceps; Ham = Hamstrings; TA = Tibialis Anterior; TS = Triceps Surae. Modified image from: Száva Z, M. Danner S, Minassian K. Transcutaneous electrical spinal.

4.5. Study variables and clinical assessment tools

To make a good assessment of spasticity, variables related to both objective criteria and observer dependent criteria and also other subjective criteria related to the patient's perception and the impact of spasticity on their daily life will be taken into account **(Table 7)**. The variable assessment proposal was established in accordance with the spasticity assessment criteria of the international initiative proposed by The Ability Network 2019. (8)

Table 7. Study variables description and assessment tools

Dependent variables	Variable nature	Variable values	Measure tools	ANNEX
Dynamic Component of Spasticity (DCS)	Quantitative	Continuous	MTS	3
Tonic spasticity	Quantitative	Discrete	MAS	4
	Quantitative	Continuous	WPT	5
Clonus	Categorical	Ordinal	MTS	3
	Quantitative	Continuous	Oscillation's number	
Spasms	Quantitative	Discrete	PSFS	6
Spasticity perception	Quantitative	Discrete	VAS	7
Daily life impact	Quantitative	Discrete	SCI-SET	8
Spinal cord excitability	Quantitative	Continuous	H-Reflex H/M Ratio T-wave	-

MTS = Modified Tardieu Scale; MAS = Modified Ashworth Scale; WPT = Wartenberg Pendulum Test; PSFS = Penn Spasm Frequency Scale; VAS = Visual Analogue Scale; SCI-SET = Spinal Cord Injury – Spasticity Evaluation Tool;

4.5.1. Modified Tardieu Scale

This measurement tool allows spasticity to be assessed using three different speeds to discriminate the influence of speed on resistance to stretching. Furthermore, unlike the MAS, the MTS scale has a higher specificity for spasticity. (36,37)

In the first place, a slow speed or Velocity 1 (V1) will be applied. This speed allows to measure the range of joint passive movement (R2). Later, velocities 2 and 3 (V2/V3) will be used to measure the effect of spasticity. The V2 is established as the speed in which the limb would fall under the effect of gravity, and the V3 determines the effects that occur when the movement is performed as quickly as possible. In V3, the range of joint movement will be measured again at the point where a catch or clonus appear (R1) to obtain the range difference between V1 and V3 and establish the DCS. (36,37)

$$DCS = R2 - R1$$

A large difference between R1 and R2 values in the outer to middle range of normal muscle length indicates a large dynamic component. A small difference in the R1 and R2 measurement in the middle to inner range indicates predominantly fixed contracture. (36,37)

The assessment of the quality of the movement will be carried out using the numerical scale that goes from 0 to 5, where 0 corresponds to normal resistance and 5 the impossibility of movement or immobility of the joint. The quality of movement in the hip flexion, knee extension and ankle dorsiflexion will be assessed (bilaterally). The DCS will be measured in knee extension and dorsiflexion. (36,37)

The clonus assessment will be made by causing a rapid dorsiflexion and it will be graded depending on the corresponding MTS values (3 = clonus that lasts less than 10 seconds; 4 = clonus that lasts more than 10 seconds). In case the clonus is qualified with a 3, the seconds

and the number of oscillations should be noted. In case of being qualified with a 4, the number of oscillations in the first 10 seconds will be recorded.

4.5.2. Modified Ashworth Scale

This tool tests resistance (applied by the explorer) to passive movement about a joint. Scores range from 0 (which corresponds to no alterations in muscle tone) to 5 where the affected part is stiff in flexion or extension. The scale incorporates the +1 score that corresponds to a slight increase in muscle tone characterized by a slight stop, followed by a minimal resistance through the range of motion (less than half of the joint range). (38)

The test will be applied bilaterally (with the patient in a supine position) on the following muscles **(Figure 15)**:

PASSIVE MOVEMENT	MUSCLES EXPLORED
Hip extension	*Psoas-Iliacus, Rectus Femoris, Sartorius*
Hip flexion	*Gluteus Maximus, Hamstrings*
Hip abduction	*Adductors (major, long, short), Pectineus, Gracile*
Hip internal rotation	*Internus/Externus Obturators, Inferior/Superior Gemellus, Quadratus Femoris, Piriformis*
Hip external rotation	*Gracile*
Knee extension	*Hamstrings*
Knee flexion	*Quadriceps*
Ankle dorsiflexion	*Triceps Surae*
Ankle plantar flexion	*Tibialis anterior*

Figure 15. Lower limbs assessed muscles with the MAS.

4.5.3. Wartenberg Pendulum Test

The purpose of this test is to evaluate spasticity in both Quadriceps muscle. To perform this test, the patient must be seated with a backrest at an angle of 45º. The examiner will extend the knee until the leg is fully extended and then drop the leg to produce oscillating movements. Data will be taken from the knee joint range during the swing by an electrogoniometer, in order to get the Spasticity Index (SI). (39)

The SI is calculated based on the knee angle of the initial horizontal leg position of the WPT, the angle at which the leg reversed for the first time from flexion to extension, and the final knee resting angle. Values ≥ 1 denote non-spastic conditions, and 0 extreme spasticity. (33)

$$\mathrm{SI} = \frac{(peak\ knee\ flexion\ angle\ of\ first\ swing) - (starting\ knee\ angle)}{1.6\ [(final\ resting\ knee\ angle) - (starting\ knee\ angle)]}$$

4.5.4. Penn Spasm Frequency Scale

It will be used to assess the frequency of spasms of the lower extremities of the participants. It consists of two questionnaires. First, the frequency of spasms is evaluated, the score can range

from 0, which corresponds to no spasms, to 4, which indicates more than 10 spasms per hour. Secondly, the severity of the spasms is asked, which is described as 1 (mild), 2 (moderate) or 3 (severe). (40)

4.5.5. Visual Analogue Scale assessment for Spasticity

The aim of this scale applied in spasticity is to measure the subjective perception of the patient regarding his/her spasticity. The scale will be supplied with the corresponding colors and numbers from 0 to 10 and the following question will be asked: Taking into account your sensation of spasticity today, which number would you rate it from 0 to 10, with 0 being no spasticity and 10 being the maximum amount of spasticity you have ever had so far? (41)

4.5.6. Spinal Cord Injury – Spasticity Evaluation Tool

It is a self-report questionnaire that is based on the measurement of both the useful and problematic effects that spasticity has had on daily life activities during the last 7 days. It will be carried out at the end of each week of intervention (baseline, intervention and follow-up). (42)

4.5.7. Electromyography assessment tools

The verification of the changes in spinal cord excitability will be carried out according to the study by Murillo et al. (43)

Records of the H-reflex, H_{max}/M_{max} Ratio and T-wave will be carried out (3 of each). The patient will be placed in a sitting position with the knee and ankle joints flexed at 90º.

The H-reflex will be recorded in the soleus muscle. Surface Ag-AgCl bipolar recording electrodes (0.8 cm Æ and 2 cm distance between electrodes) will be placed on top of the soleus. The stimulation electrodes (rectangular pulse 1 ms) will be placed overlying the surface of the popliteal fossa over the posterior tibial nerve. The maximum amplitude of the reflex will be determined using as many stimuli as needed (at stimulation steps of 0.2 mA) until reaching intensities close to the one that causes the greatest amplitude of the reflex H (H_{max}).

The maximum amplitude of the M-wave (M_{max}) will be determined as the size of the response to a stimulus of supramaximal intensity. The EMG signal will be amplified (1 mV/D) and band-pass filtered (2–10,000 Hz).

Then, the relationship or ratio between these two will be established. An increased ratio indicates spasticity, although this does not reveal the severity of spasticity. Changes in the pre/post-intervention will indicate changes in the spinal cord excitability.

T-wave will be taken while percussing the Achilles tendon with an electric hammer.

4.6. Data analysis

4.6.1. Data treatment

For the analysis of MAS, a single score (the total MAS score) will be obtained per each assessment by summing the individual scores of the different movements tested per leg, resulting in a value ranging from 0 – 90. In the same way, the analysis of the quality of the movement in the MTS will be carried out, resulting in a value ranging from 0 – 90.

To assess the DCS, the mean DCS of the movements of a leg will be assessed and then, the mean between the two legs and the mean between all movements, resulting in a global value of DCS. For the evaluation of the clonus, the oscillations per second of each leg will be calculated and a mean of the two legs will be made. The analysis of the WPT will be carried out according to the Spasticity Index described, a mean of the results of the two legs will give a single value regarding the quadriceps muscles. The peak-to-peak amplitude of Hmax, Mmax and T-wave will be measured, and the Hmax/Mmax ratio will be calculated.

In order to preserve the advantages of randomization, an intention-to-treat analysis will be performed.

4.6.2. Statistical methods

A descriptive analysis of the demographic characteristics of the subjects will be performed to quantify the degree of homogeneity between the two groups **(Table 2)**. The description of the data will be done through the mean and standard deviation (SD) for the quantitative variables and through the frequencies and percentages for the nominal variables.

The normality of the data distribution will be determined through the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Base homogeneity will be compared through the Chi-square test for categorical variables.

To compare changes in percentages between various groups, the Krusskall-Wallis test will be used, followed by the Mann-Whitney U test for comparison between two groups, in the event that there is no normal distribution variable. For the parametric values, the One-way ANOVA test will be used. In the other hand, Wilcoxon's nonparametric t-test will be used to compare the results before and after the treatment if the variable does not have a normal distribution. The level of statistical significance for all comparisons is set at $p \leq 0.05$.

4.7. Consideration of ethical aspects

All participants will be informed about the advantages, disadvantages and objectives of the project at the initial meeting to be recruited, where any doubts that may arise will be resolved.

After acceptance of participation, they will be given the informed consent, which must be returned with the signature, in order to participate in the study. An attached document will also be provided containing the description of the project, the objectives and the necessary information.

The protocol must be approved by the Ethics Committee of the institution. During the clinical trial, the subject will have the rights present in the Declaration of Helsinki for research on human beings. The personnel involved must respect the privacy of the person.

The clinical history of the patients will be confidential and will not be provided to unauthorized persons. The participant will have the rights specified in Organic Law 3/2018, of the 5th of December on Protection of Personal Data and guarantee of digital rights.

Participation in the clinical trial will be completely voluntary and participants will have the right to withdraw at any time.

5. EXPECTED RESULTS AND STUDY LINE NEEDS

Through non-invasive spinal cord stimulation, a decrease in spasticity of the lower limbs in patients with cervical/thoracic spinal cord injury AIS A – C is expected, both clinically and neurophysiologically. Changeability between the participants due to differences in AIS, the level of injury, severity, time post-injury and anatomical and pathophysiological characteristics of each patient are likely to be found. However, significant results are expected regardless of the aspects mentioned, as shown by previous pilot studies from Hofstoetter et al. 2014 (32), Hofstoetter et al. 2020 (33) y Inaici et al. 2021 (31).

These studies highlight the decrease in pathophysiology (spasticity) and the improvement of normal physiology (voluntary control), in single sessions of tSCS and the effects last between 2h – 6h, a period described by patients as a period of greater lightness of the limbs and improvements in their motor control when performing certain activities.

Analyzing the expected results and the results of the aforementioned pilot studies, non-invasive spinal stimulation for spasticity could constitute a therapeutic approach used in parallel to the administration of antispastic drugs and applied together with the neuro physical therapy treatment (at the beginning of the session). If the expected results are proven to be effective, the application of the tSCS before the sessions could decrease co-contractions and dyssynergias, giving the possibility of training voluntary control more effectively. (32)

Nonetheless, more studies examining the potential of this technique are required, in order to correctly define its applicability. For this reason, the application of more specific, personalized and individualized intervention protocols would be recommended. Although, carrying out a first clinical trial in this line of study would represent a great step forward. It would also be necessary to carry out methodologically stronger studies to validate the application parameters of the tSCS suitable for each type of patient, times, conductance and penetration of the current in the tissues, etc.

Another important aspect regarding the expected results would be that, given the difficulty that spasticity represents in the context of quality of life and daily activities, the improvement of spasticity with lasting-effects will have an indirect impact on the improvement of these two aspects, granting an increased functional independence of patients.

The possible results of this study would complement the scientific evidence that already exist in pilot studies, since it is a recent technique that still requires interventions that provide significant data for practical application. So far, the current evidence presents small samples, focuses on patients with incomplete lesions and evaluates only the effects of a single stimulation session mainly.

5.1. Study strengths and limitations

Although the expected results are promising and represent strengths and advances for this line of research, this proposal is not exempt of limitations.

The strengths of the proposal lie in the possibility of taking several pilot studies with significant results to a clinical trial that will allow analyzing aspects not observed so far. The advantages of this study would fall on:

- The comparison between a placebo and real non-invasive spinal cord stimulation treatment.
- The longer duration of treatment (application of 10 sessions).
- The level of significance of the treatment in a larger and more representative sample of spinal cord injury.

Nevertheless, the proposed study has the following limitations:

- Recruitment problems as SCI is a rare injury, i.e. to not reaching the planned sample size.
- Too much dispersion in the time post-injury, which means that patients with less stabilized injuries may havethe typical changes of the natural evolution of the pathology.
- The annoying/painful effect of tSCS that can hind reaching an adequate intensity threshold, remaining below the really necessary threshold. Fact that would entail insufficient doses.
- Non-blinding of the person applying the real/sham treatment.
- Possible appearance of adverse effects.
- Co-interventions that may influence the final results (medication changes, physical therapy, etc.).
- Abandonment of participants.

6. CRITICAL EVALUATION AND CONCLUSIONS OF THE LEARNING PROCESS

Carrying out this Master's thesis has been especially enriching in terms of knowledge of the scientific method and it has been especially interesting to start learning about the world of research that had always caught my attention.

Although this work is a theoretical work based rather on previous studies, my logic, creativity, and knowledge of the scientific method, I have also had the opportunity to experience a little the practical difficulties involved in carrying out an assessment plan for taking data of subjects involved in research. This was especially useful when it came to realizing the difficulties of putting a proposal into practice and the importance of both making a good approach to a study, controlling all aspects as much as possible, and the ability to adapt to each situation.

It has been quite a challenge for me to make this proposal on a line of study for which there is still little scientific evidence, but at the same time it has been encouraging for me to overcome the obstacles that I encountered along the way. Spasticity, spinal cord stimulation and spinal cord injuries have aroused a special interest of knowledge on me and have firmly contributed to my professional growth as a physical therapist and my desire to carry out research and keep learning about this topic.

BIBLIOGRAPHY

1. Tortora G, Derrickson B. Principios de Anatomía y Fisiología. 13th ed. Madrid: EDITORIAL MÉDICA PANAMERICANA, S.A DE C.V.; 2013. 1222 p.

2. Crossman A, Neary D. Neuroanatomía. 3rd ed. Barcelona: Elsevier Doyma; 2007. 185 p.

3. Strassburguer K, Hernández Y, Barquín E. Lesión Medular: Guía para el manejo integral del paciente con LM crónica. Madrid; 2013. p. 161.

4. Pérez C, Novoa A, Ferrando J, Santamariña-Rubio E, García-Altés A, Seguí-Gómez M, et al. Lesiones Medulares Traumáticas y Traumatismos Craneoencefálicos en España, 2000-2008. 2011;188. Available from: http://www.msssi.gob.es/profesionales/saludPublica/prevPromocion/Lesiones/JornadaDecenioAccionSeguridadVial/docs/Lesiones_Medulares_WEB.pdf

5. WHO. THE INJURY CHART BOOK. A graphical overview of the global burden of injuries. Int Classif. 2002;

6. García FJ. Evaluación Clínica y Tratamiento de la Espasticidad. Alcocer A, editor. Madrid: EDITORIAL MÉDICA PANAMERICANA, S.A; 2009. 187 p.

7. Burns AS, Lanig I, Grabljevec K, New PW, Bensmail D, Ertzgaard P, et al. Optimizing the Management of Disabling Spasticity Following Spinal Cord Damage: The Ability Network—An International Initiative. Arch Phys Med Rehabil [Internet]. 2016;97(12):2222–8. Available from: http://dx.doi.org/10.1016/j.apmr.2016.04.025

8. Ertzgaard P, Nene A, Kiekens C, Burns AS. A review and evaluation of patient-reported outcome measures for spasticity in persons with spinal cord damage: Recommendations from the Ability Network–an international initiative. J Spinal Cord Med [Internet]. 2020;43(6):813–23. Available from: https://doi.org/10.1080/10790268.2019.1575533

9. Sainz-Pelayo MP, Albu S, Murillo N, Benito-Penalva J. Spasticity in neurological pathologies. An update on the pathophysiological mechanisms, advances in diagnosis and treatment. Vol. 70, Revista de Neurologia. Revista de Neurologia; 2020. p. 453–60.

10. Sheean G. The pathophysiology of spasticity [Internet]. Vol. 9, European Journal of Neurology, Supplement. Eur J Neurol; 2002 [cited 2022 Mar 30]. p. 3–9. Available from: https://pubmed.ncbi.nlm.nih.gov/11918643/

11. Nielsen JB, Petersen NT, Crone C, Sinkjaer T. Stretch reflex regulation in healthy subjects and patients with spasticity. Neuromodulation [Internet]. 2005 Jan [cited 2022 Mar 30];8(1):49–57. Available from: https://pubmed.ncbi.nlm.nih.gov/22151383/

12. Nielsen JB, Crone C, Hultborn H. The spinal pathophysiology of spasticity - From a basic science point of view. In: Acta Physiologica [Internet]. Acta Physiol (Oxf); 2007 [cited 2022 Mar 30]. p. 171–80. Available from: https://pubmed.ncbi.nlm.nih.gov/17250567/

13. Nielsen J, Petersen N, Crone C. Changes in transmission across synapses of Ia afferents in spastic patients. Brain [Internet]. 1995 Aug 1 [cited 2022 Mar 30];118(4):995–1004. Available from: https://academic.oup.com/brain/article/118/4/995/279977

14. Morita H, Crone C, Christenhuis D, Petersen NT, Nielsen JB. Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. Brain [Internet]. 2001 Apr 1 [cited 2022 Mar 30];124(4):826–37. Available from: https://academic.oup.com/brain/article/124/4/826/354726

15. Marque P, Brassat D. Pathophysiology of spasticity. Rev Neurol (Paris) [Internet]. 2012 [cited 2022 Mar 30];168(SUPPL.3). Available from: https://www.semanticscholar.org/paper/%5BPathophysiology-of-spasticity%5D.-Decq/bb16a8d2b2120940b7cd7aff3ff0e86735c33fe7

16. Cabahug P, Pickard C, Edmiston T, Lieberman JA. A Primary Care Provider's Guide to Spasticity Management in Spinal Cord Injury Episodic Care Key Points. Top Spinal Cord Inj Rehabil [Internet]. 2020 [cited 2022 Mar 14];26(3):157–65. Available from: www.asia-spinalinjury.org

17. Little JW, Micklesen P, Umlauf R, Britell C. Lower extremity manifestations of spasticity in chronic spinal cord injury. Am J Phys Med Rehabil [Internet]. 1989 [cited 2022 Mar 14];68(1):32–6. Available from: https://pubmed.ncbi.nlm.nih.gov/2917056/

18. Sangari S, Lundell H, Kirshblum S, Perez MA. Residual descending motor pathways influence spasticity after spinal cord injury. Ann Neurol [Internet]. 2019 Jul 1 [cited 2022 Mar 14];86(1):28–41. Available from: /pmc/articles/PMC6786768/

19. Megía García-Carpintero Á. Efecto de la estimulación eléctrica transcutánea de la médula espinal sobre la excitabilidad del sistema motor. Tesis Doctoral. Universidad de Castilla-la Mancha; 2022.

20. Rowald A, Komi S, Demesmaeker R, Baaklini E, Hernandez-Charpak SD, Paoles E, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Med [Internet]. 2022 Feb 1 [cited 2022 May 18];28(2):260–71. Available from: https://pubmed.ncbi.nlm.nih.gov/35132264/

21. Kumru H, Flores Á, Rodríguez-Canõn M, Soriano I, Garciá L, Vidal-Samsó J. Non-invasive brain and spinal cord stimulation for motor and functional recovery after a spinal cord injury. Rev Neurol. 2020;70(12):461–77.

22. Minassian K, Persy I, Rattay F, Pinter MM, Kern H, Dimitrijevic MR. Human lumbar cord circuitries can be activated by extrinsic tonic input to generate locomotor-like activity. Hum Mov Sci. 2007 Apr;26(2):275–95.

23. Hofstoetter US, Minassian K, Hofer C, Mayr W, Rattay F, Dimitrijevic MR. Modification of reflex responses to lumbar posterior root stimulation by motor tasks in healthy subjects. In: Artificial Organs [Internet]. John Wiley & Sons, Ltd; 2008 [cited 2022 May 18]. p. 644–8. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1525-1594.2008.00616.x

24. Danner SM, Hofstoetter US, Ladenbauer J, Rattay F, Minassian K. Can the Human Lumbar Posterior Columns Be Stimulated by Transcutaneous Spinal Cord Stimulation? A Modeling Study. Artif Organs [Internet]. 2011 Mar 1 [cited 2022 May 18];35(3):257–62. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1525-1594.2011.01213.x

25. Hofstoetter US, Hofer C, Kern H, Danner SM, Mayr W, Dimitrijevic MR, et al. Effects of transcutaneous spinal cord stimulation on voluntary locomotor activity in an incomplete spinal cord injured individual. Biomed Tech [Internet]. 2013 Aug 20 [cited 2022 May 18];58(SUPPL. 1 TRACK-A). Available from: https://pubmed.ncbi.nlm.nih.gov/24042607/

26. Hofstoetter US, Krenn M, Danner SM, Hofer C, Kern H, Mckay WB, et al. Augmentation of Voluntary Locomotor Activity by Transcutaneous Spinal Cord Stimulation in Motor-Incomplete Spinal Cord-Injured Individuals. Artif Organs [Internet]. 2015 Oct 1 [cited

2022 May 18];39(10):E176–86. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/aor.12615

27. Minassian K, Hofstoetter US, Danner SM, Mayr W, Bruce JA, McKay WB, et al. Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. Neurorehabil Neural Repair [Internet]. 2016 Mar 1 [cited 2022 May 15];30(3):233–43. Available from: https://journals.sagepub.com/doi/10.1177/1545968315591706

28. Gad P, Gerasimenko Y, Zdunowski S, Turner A, Sayenko D, Lu DC, et al. Weight bearing over-ground stepping in an exoskeleton with non-invasive spinal cord neuromodulation after motor complete paraplegia. Front Neurosci. 2017 Jun 8;11(JUN):333.

29. Alashram AR, Padua E, Raju M, Romagnoli C, Annino G. Transcutaneous spinal cord stimulation effects on spasticity in patients with spinal cord injury: A systematic review. J Spinal Cord Med. 2021;1–8.

30. Rupp R, Biering-Sørensen F, Burns SP, Graves DE, Guest J, Jones L, et al. International standards for neurological classification of spinal cord injury [Internet]. Vol. 27, Topics in Spinal Cord Injury Rehabilitation. Top Spinal Cord Inj Rehabil; 2021 [cited 2022 May 17]. Available from: https://pubmed.ncbi.nlm.nih.gov/34108832/

31. Inanici F, Brighton LN, Samejima S, Hofstetter CP, Moritz CT. Transcutaneous Spinal Cord Stimulation Restores Hand and Arm Function after Spinal Cord Injury. IEEE Trans Neural Syst Rehabil Eng. 2021;29:310–9.

32. Hofstoetter US, McKay WB, Tansey KE, Mayr W, Kern H, Minassian K. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. J Spinal Cord Med. 2014;37(2):202–11.

33. Hofstoetter US, Freundl B, Danner SM, Krenn MJ, Mayr W, Binder H, et al. Transcutaneous Spinal Cord Stimulation Induces Temporary Attenuation of Spasticity in Individuals with Spinal Cord Injury. https://home.liebertpub.com/neu [Internet]. 2020 Jan 9 [cited 2021 Nov 27];37(3):481–93. Available from: https://www.liebertpub.com/doi/abs/10.1089/neu.2019.6588

34. Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. Am J Phys Med Rehabil [Internet]. 1990 [cited 2022 May 21];69(1):6–10. Available from: https://pubmed.ncbi.nlm.nih.gov/2137345/

35. Petrie B, Hazleman J. Credibility of placebo transcutaneous nerve stimulation and acupuncture. Clin Exp Rheumatol. 1985;3(2):151–3.

36. Ansari NN, Naghdi S, Hasson S, Azarsa MH, Azarnia S. The Modified Tardieu Scale for the measurement of elbow flexor spasticity in adult patients with hemiplegia. Brain Inj [Internet]. 2008 [cited 2022 May 20];22(13–14):1007–12. Available from: https://pubmed.ncbi.nlm.nih.gov/19117179/

37. Boyd RN, Graham HK. Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. In: European Journal of Neurology. Blackwell Publishing Ltd.; 1999. p. s23–35.

38. Meseguer-Henarejos AB, SăNCHEZ-MECA J, López-Pina JA, CARLES-HERNăNDEZ R. Inter- and intra-rater reliability of the Modified Ashworth Scale: A systematic review and meta-analysis [Internet]. Vol. 54, European Journal of Physical and Rehabilitation

Medicine. Eur J Phys Rehabil Med; 2018 [cited 2022 May 19]. p. 576–90. Available from: https://pubmed.ncbi.nlm.nih.gov/28901119/

39. Nordmark E, Andersson G. Wartenberg pendulum test: Objective quantification of muscle tone in children with spastic diplegia undergoing selective dorsal rhizotomy. Dev Med Child Neurol [Internet]. 2002 [cited 2022 May 20];44(1):26–33. Available from: https://pubmed.ncbi.nlm.nih.gov/11811646/

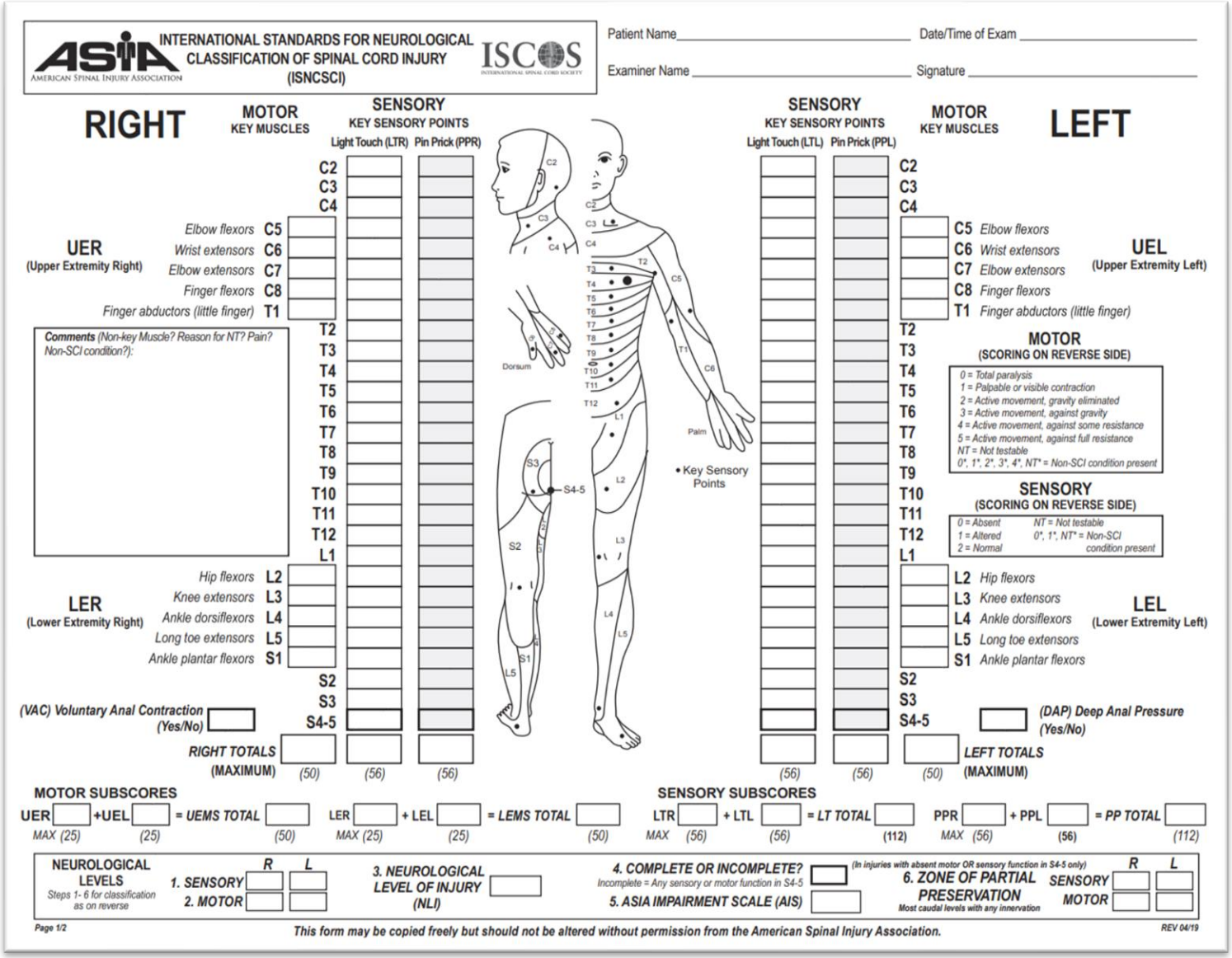
40. Mills PB, Vakil AP, Phillips C, Kei L, Kwon BK. Intra-rater and inter-rater reliability of the Penn Spasm Frequency Scale in People with chronic traumatic spinal cord injury. Spinal Cord. 2018 Jun 1;56(6):569–74.

41. Vles GF, de Louw AJA, Speth LA, van Rhijn LW, Janssen-Potten YJM, Hendriksen JG, et al. Visual Analogue Scale to score the effects of Botulinum Toxin A treatment in children with cerebral palsy in daily clinical practice. Eur J Paediatr Neurol [Internet]. 2008 May [cited 2022 May 20];12(3):231–8. Available from: https://pubmed.ncbi.nlm.nih.gov/17933567/

42. Ansari NN, Kashi M, Naghdi S. The Spinal Cord Injury Spasticity Evaluation Tool: A Persian adaptation and validation study. J Spinal Cord Med [Internet]. 2017 Aug 31 [cited 2022 May 20];40(4):380–8. Available from: https://europepmc.org/articles/PMC5537954

43. Murillo N, Kumru H, Vidal-Samso J, Benito J, Medina J, Navarro X, et al. Decrease of spasticity with muscle vibration in patients with spinal cord injury. Clin Neurophysiol [Internet]. 2011 [cited 2022 May 20];122(6):1183–9. Available from: https://pubmed.ncbi.nlm.nih.gov/21172739/

ANNEX



INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI)

ASIA American Spinal Injury Association — ISCOS International Spinal Cord Society

Patient Name _____ Date/Time of Exam _____

Examiner Name _____ Signature _____

RIGHT

	MOTOR KEY MUSCLES		SENSORY KEY SENSORY POINTS Light Touch (LTR)	Pin Prick (PPR)
		C2		
		C3		
		C4		
UER (Upper Extremity Right)	Elbow flexors	C5		
	Wrist extensors	C6		
	Elbow extensors	C7		
	Finger flexors	C8		
	Finger abductors (little finger)	T1		
		T2		
		T3		
		T4		
		T5		
		T6		
		T7		
		T8		
		T9		
		T10		
		T11		
		T12		
		L1		
LER (Lower Extremity Right)	Hip flexors	L2		
	Knee extensors	L3		
	Ankle dorsiflexors	L4		
	Long toe extensors	L5		
	Ankle plantar flexors	S1		
		S2		
		S3		
		S4-5		
	RIGHT TOTALS (MAXIMUM)		(50)	(56) (56)

Comments (Non-key Muscle? Reason for NT? Pain? Non-SCI condition?):

(VAC) Voluntary Anal Contraction (Yes/No) ☐

LEFT

	SENSORY KEY SENSORY POINTS Light Touch (LTL)	Pin Prick (PPL)	MOTOR KEY MUSCLES	
			C2	
			C3	
			C4	
			C5	Elbow flexors
			C6	Wrist extensors
			C7	Elbow extensors
			C8	Finger flexors
			T1	Finger abductors (little finger)
			T2	
			T3	
			T4	
			T5	
			T6	
			T7	
			T8	
			T9	
			T10	
			T11	
			T12	
			L1	
			L2	Hip flexors
			L3	Knee extensors
			L4	Ankle dorsiflexors
			L5	Long toe extensors
			S1	Ankle plantar flexors
			S2	
			S3	
			S4-5	
	(56)	(56)	(50)	LEFT TOTALS (MAXIMUM)

UEL (Upper Extremity Left)

LEL (Lower Extremity Left)

MOTOR (SCORING ON REVERSE SIDE)

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, gravity eliminated
3 = Active movement, against gravity
4 = Active movement, against some resistance
5 = Active movement, against full resistance
NT = Not testable
0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present

SENSORY (SCORING ON REVERSE SIDE)

0 = Absent
1 = Altered
2 = Normal
NT = Not testable
0*, 1*, NT* = Non-SCI condition present

(DAP) Deep Anal Pressure (Yes/No) ☐

MOTOR SUBSCORES

UER ☐ +UEL ☐ = UEMS TOTAL ☐ (MAX (25) (25) (50))

LER ☐ + LEL ☐ = LEMS TOTAL ☐ (MAX (25) (25) (50))

SENSORY SUBSCORES

LTR ☐ + LTL ☐ = LT TOTAL ☐ (MAX (56) (56) (112))

PPR ☐ + PPL ☐ = PP TOTAL ☐ (MAX (56) (56) (112))

NEUROLOGICAL LEVELS (Steps 1- 6 for classification as on reverse)

	R	L
1. SENSORY	☐	☐
2. MOTOR	☐	☐

3. NEUROLOGICAL LEVEL OF INJURY (NLI) ☐

4. COMPLETE OR INCOMPLETE? ☐ (In injuries with absent motor OR sensory function in S4-5 only) Incomplete = Any sensory or motor function in S4-5

5. ASIA IMPAIRMENT SCALE (AIS) ☐

6. ZONE OF PARTIAL PRESERVATION (Most caudal levels with any innervation)

	R	L
SENSORY	☐	☐
MOTOR	☐	☐

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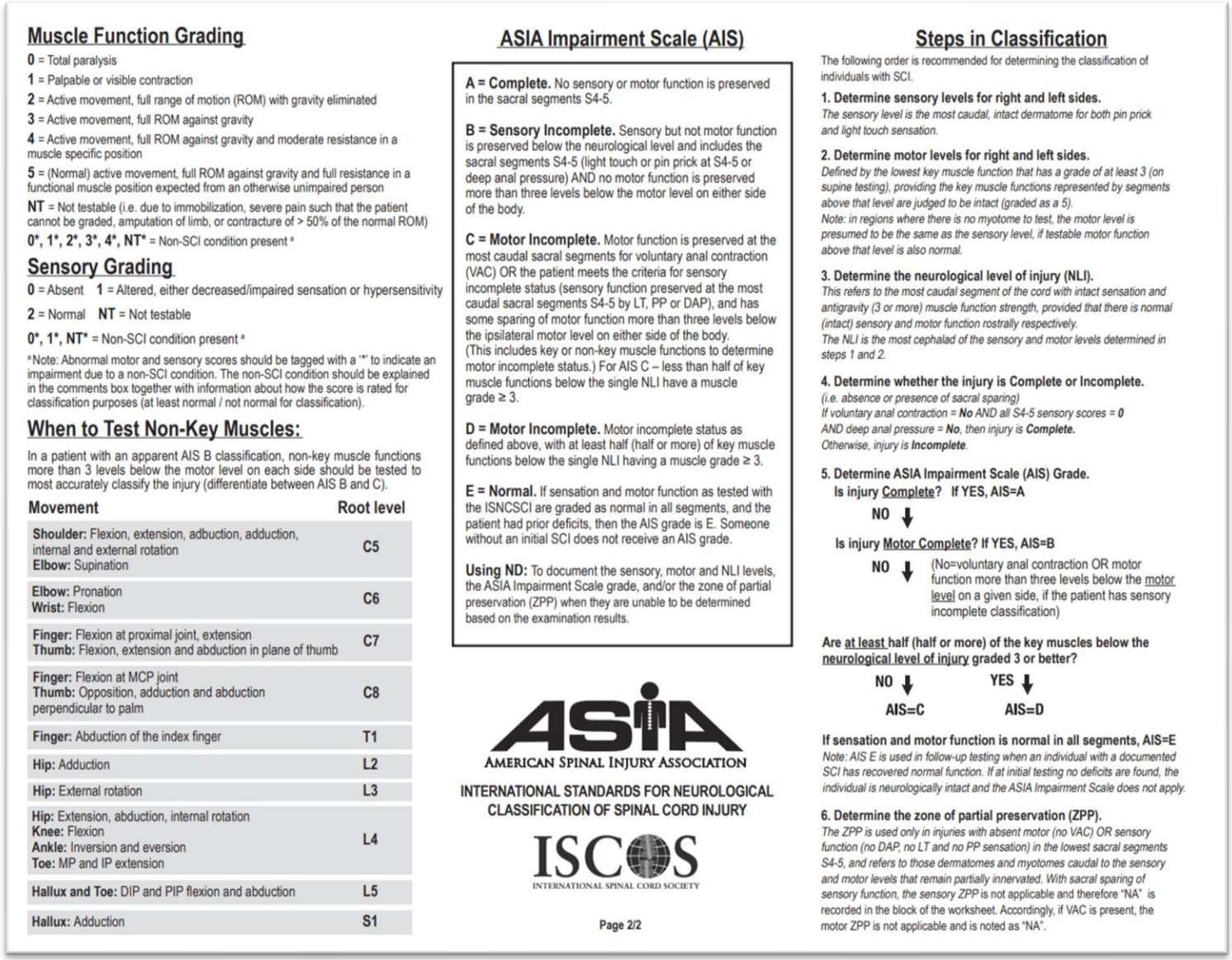
REV 04/19

Betz R, Biering-Sørensen F, Burns SP, Donovan W, Graves DE, Guest J, et al. The 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)—What's new? [Internet]. Vol. 57, Spinal Cord. Spinal Cord; 2019 [cited 2022 May 29]. p. 815–7. Available from: https://pubmed.ncbi.nlm.nih.gov/31530900/

Instructions for use: American Spinal Injury Association Impairment Scale (AIS): International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) - Spinal Cord Injury Research Evidence (scireproject.com)



Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a '*' to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

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Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete.***
*Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A
NO ↓
Is injury Motor Complete? If YES, AIS=B
NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO ↓ AIS=C **YES ↓ AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Betz R, Biering-Sørensen F, Burns SP, Donovan W, Graves DE, Guest J, et al. The 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)—What's new? [Internet]. Vol. 57, Spinal Cord. Spinal Cord; 2019 [cited 2022 May 29]. p. 815–7. Available from: https://pubmed.ncbi.nlm.nih.gov/31530900/

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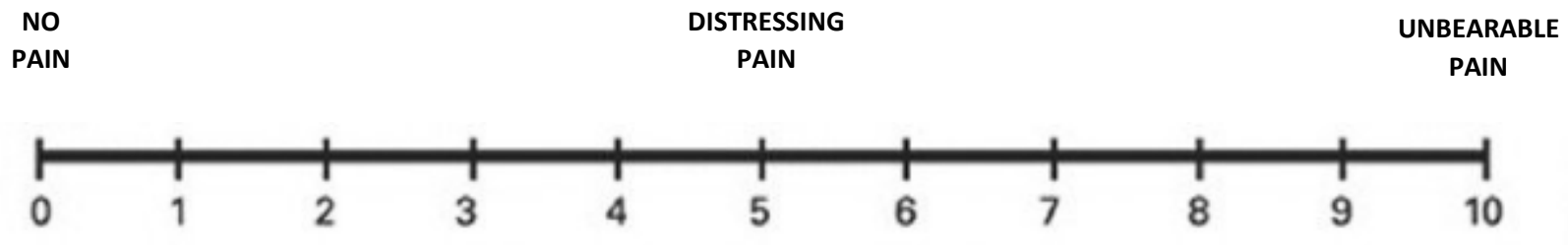
1. Do you think you received the real treatment or a placebo treatment?

2. What makes you think that?

3. Select which of the following best represents the sensation you felt during the intervention:

I did not feel anything	Tickling	Annoyance	Pain

4. In case you have selected pain: on the following scale from 0 to 10 (with 0 being NO PAIN, and 10 the MAXIMUM PAIN you could endure) with what number would you rate the painful sensation of the intervention?



ANNEX 3: MODIFIED TARDIEU SCALE

EQUIPMENT REQUIRED

- Mat table
- Chronometer
- Manual goniometer

INSTRUCTIONS

- Place the patient in a supine position.
- If testing flexion movements, place the joint in a maximally extended position and move to a position of maximal flexion at the indicated speed.
- If testing extension movements, place the joint in a maximally flexed position and move to a position of maximal extension at the indicated speed.
- Score based on the classification below.
- Patient should be instructed to relax.

QUALITY OF MOVEMENT SCORING	
0	No resistance throughout the course of the passive movement.
1	Slight resistance throughout the course the course of the passive movement, followed by a release.
2	Clear catch at precise angle, interrupting the passive movement, followed by release.
3	Fatigable clonus (<10 seconds when maintaining pressure) occurring at precise angle.
4	Infatigable clonus (>10 seconds when maintaining pressure) occurring at precise angle.
5	Joint is immobile.

	RIGHT HIP FLEXION		LEFT HIP FLEXION	
V1		**R2**		**R2**
V2				
V3		**R1**		**R1**
SUM OF SCORING	/15		/15	
TOTAL SCORING	/30			
DCS				
DCS MEAN				

	RIGHT KNEE EXTENSION		LEFT KNEE EXTENSION	
V1		**R2**		**R2**
V2				
V3		**R1**		**R1**
SUM OF SCORING	/15		/15	
TOTAL SCORING	/30			
DCS				
DCS MEAN				

	RIGHT ANKLE DORSIFLEXION		LEFT ANKLE DORSIFLEXION	
V1		**R2**		**R2**
V2				
V3		**R1**		**R1**
		CLONUS TIME		**CLONUS TIME**
		OSILATIONS Nº		**OSILATIONS Nº**
SUM OF SCORING	/15		/15	
TOTAL SCORING	/30			
DCS				
DCS MEAN				

TOTAL HIP/KNEE/ANKLE DCS MEAN:

TOTAL HIP/KNEE/ANKLE SCORE: /90

Haugh A, Pandyan A, Johnson G. A systematic review of the Tardieu Scale for the measurement of spasticity [Internet]. Vol. 28, Disability and Rehabilitation. Disabil Rehabil; 2006 [cited 2022 May 29]. p. 899–907. Available from: https://pubmed.ncbi.nlm.nih.gov/16861197/

EQUIPMENT REQUIRED

- Mat table

INSTRUCTIONS

- Place the patient in a supine position.
- If testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position of maximal extension over one second (count “one thousand one”).
- If testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count “one thousand one”).
- Score based on the classification below.
- Patient should be instructed to relax.

SCORING	
0	No increase on muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion.
2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
3	More marked increase in muscle tone through most of the range of motion, but the affected part can be easily moved
4	Considerable increase in muscle tone, movement is difficult
5	Affected parts completely rigid in flexion or extension

SCORING SHEET

	RIGHT LIMB	LEFT LIMB
HIP		
Flexion *(knee extended)*		
Extension		
Abduction		
Internal Rotation *(hip/knee 90º)*		
External Rotation *(hip/knee 90º)*		
KNEE		
Flexion		
Extension		
ANKLE		
Dorsiflexion *(hip/knee 90º)*		
Plantar Flexion *(hip/knee 90º)*		
TOTAL LIMB SCORE	___ / 45	___ / 45

TOTAL SCORE: ___ / 90

Reference for test instructions: Bohannon R, and Smith M (1987). Interrater reliability of a Modified Ashworth Scale of muscle spasticity. Physical Therapy 67(2): 206.

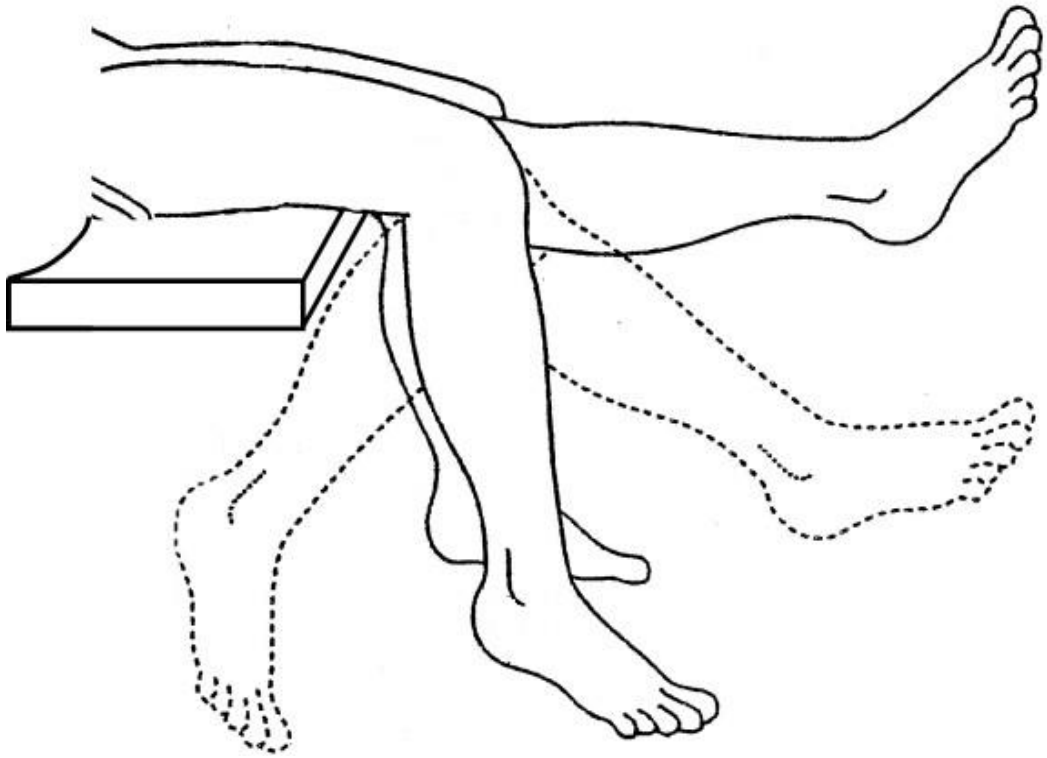
EQUIPMENT REQUIRED

- Mat table
- Electrogoniometer

INSTRUCTIONS

1. Raise the relaxed leg into knee extension to a horizontal position.
2. Drop it by gravity to cause passive oscillations.

$$SI = \frac{(1st\ swing\ flex) - (starting\ angle)}{1{,}6 * (fianl\ resting\ angle) - (starting\ angle)}$$



RIGHT LEG	
Starting angle	
1st swing flex	
Final resting angle	

RIGHT LEG	
Starting angle	
1st swing flex	
Final resting angle	

	RIGHT KNEE	LEFT KNEE
SI		
SI MEAN		

Bajd T, Vodovnik L. Pendulum testing of spasticity. J Biomed Eng [Internet]. 1984 [cited 2022 May 29];6(1):9–16. Available from: https://pubmed.ncbi.nlm.nih.gov/6694374/
Instructions for use: Microsoft Word - Clinician Summary v.5.0_Pendulum Test.docx (scireproject.com)

ITEM 1: Spasms frequency

0	No spasms
1	Mild spasms induced by stimulation
2	Infrequent full spasms occurring less than once per hour
3	Spasms occurring more than once per hour
4	Spasms occurring more than 10 times per hour

RATE =	

ITEM 2: Spasms severity

1	Mild
2	Moderate
3	Severe

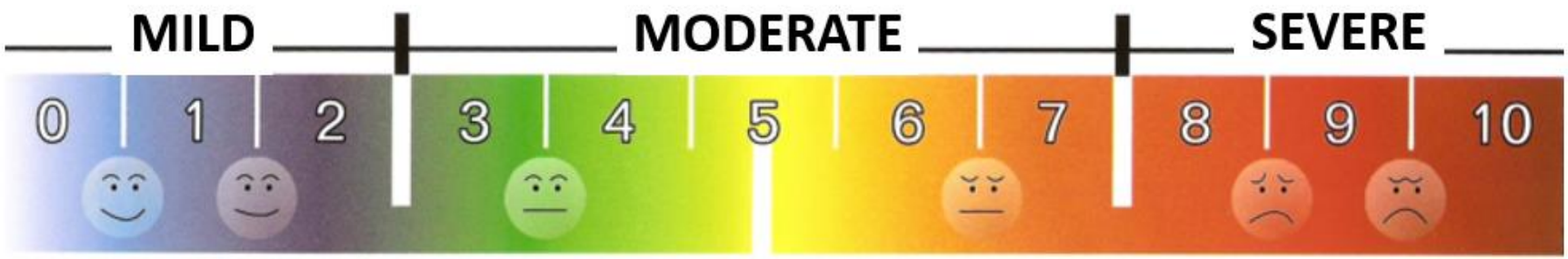
RATE =	

If the patient indicates NO spasms in Item 1, then they do not proceed to Item 2.

Mills PB, Vakil AP, Phillips C, Kei L, Kwon BK. Intra-rater and inter-rater reliability of the Penn Spasm Frequency Scale in People with chronic traumatic spinal cord injury. Spinal Cord. 2018 Jun 1;56(6):569–74.
Instructions for use: Microsoft Word - Clinician Summary_PSFS v.7.0.docx (scireproject.com)

On the following scale from 0 to 10 (with 0 being NO SPASTICITY, and 10 the MAXIMUM OF SPASTICITY you have ever had) with what number would you rate the spasticity you have right now?

RATE =	



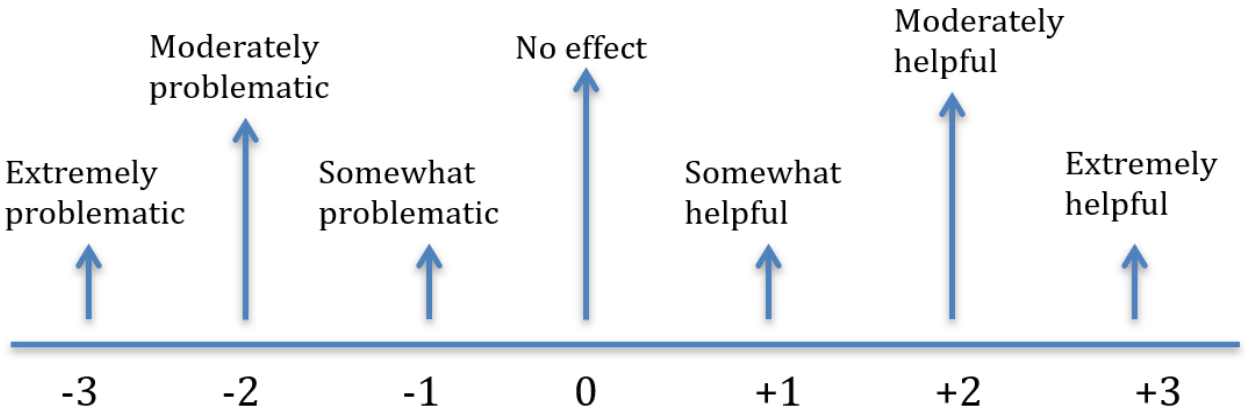
INSTRUCTIONS TO THE PATIENT

"For each of the following, please choose the answer that best describes how your spasticity symptoms have affected that area of your life ***during the past 7 days.*** *When I talk about "spasticity symptoms", I mean:*

a) uncontrolled, involuntary muscle contraction or movement (slow or rapid, short or prolonged)
b) involuntary, repetitive, quick muscle movements (up and down, side to side)
c) muscle tightness
d) what you might describe as "spasms"

Please let me know when a question is not applicable to you."

RATING SCALE:



SCORING

The SCI-SET is scored by summing all the responses from the applicable items then dividing the sum by the number of applicable items, generating a total score between -3 and +3.

Adams MM, Ginis KAM, Hicks AL. The Spinal Cord Injury Spasticity Evaluation Tool: Development and Evaluation. Arch Phys Med Rehabil [Internet]. 2007 Sep [cited 2022 May 29];88(9):1185–92. Available from: https://pubmed.ncbi.nlm.nih.gov/17826466/

During the last 7 days, how have your spasticity symptoms affected:	**Score**
1. your showering?	
2. your dressing / undressing?	
3. your transfers (to and from bed, chair, vehicle, etc.)?	
4. your sitting positioning (in your chair, etc.)?	
5. the preparation of meals?	
6. eating?	
7. drinking?	
8. your small hand movements (writing, use of computer, etc.)?	
9. your ability to perform household chores?	
10. your hobbies / recreational activities?	
11. your enjoyment of social outings?	
12. your ability to stand / weight-bear?	
13. your walking ability?	
14. your stability / balance?	
15. your muscle fatigue?	
16. the flexibility of your joints?	
17. your therapy / exercise routine?	
18. your manual wheelchair use?	
19. your power wheelchair use?	
20. your lying positioning (in bed, etc.)?	
21. your ability to change positions in bed?	
22. your ability to get to sleep?	
23. the quality of your sleep?	
24. your sex life?	
25. the feeling of being annoyed?	
26. the feeling of being embarrassed?	
27. your feeling of comfort socially?	
28. your feeling of comfort physically?	
29. your pain?	
30. your concern with falling?	
31. your concern with getting injured?	
32. your concern with accidentally injuring someone else?	
33. your ability to concentrate?	
34. your feelings of control over your body?	
35. your need to ask for help?	

Sum: _____

Total score (sum/35): _____

Adams MM, Ginis KAM, Hicks AL. The Spinal Cord Injury Spasticity Evaluation Tool: Development and Evaluation. Arch Phys Med Rehabil [Internet]. 2007 Sep [cited 2022 May 29];88(9):1185–92. Available from: https://pubmed.ncbi.nlm.nih.gov/17826466/