EFFECT OF TIBIAL NERVE STIMULATION ON GASTROSOLEUS SPASTICITY: A RANDOMIZED CONTROLLED TRIAL

Dissertation submitted to the Tamil Nadu Dr. MGR Medical University, Chennai, in partial fulfilment of requirements for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2015

DECLARATION

I hereby declare that "EFFECT OF TIBIAL NERVE STIMULATION ON GASTROSOLEUS SPASTICITY: A RANDOMIZED CONTROLLED TRIAL" is my bonafide work in partial fulfilment of the requirement of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2015.

Dr. Rahul Jacob Thomas

Candidate Number 201229052

Department of Physical Medicine and Rehabilitation

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Vellore

CERTIFICATE

This is to certify that "EFFECT OF TIBIAL NERVE STIMULATION ON GASTROSOLEUS SPASTICITY: A RANDOMIZED CONTROLLED TRIAL" is a bonafide work of Dr. Rahul Jacob Thomas, Candidate Number 201229052, in partial fulfilment of the requirement of theTamil Nadu Dr. MGR Medical University, Chennai, for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2015, done under my supervision and guidance.

Dr. George Tharion

Professor and Head of the Department

Department of Physical Medicine and Rehabilitation

Christian Medical College

Vellore

CERTIFICATE

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Dr. Alfred Job Daniel

Principal

Christian Medical College

Vellore

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I would like to express my deepest gratitude to Dr. George Tharion whose constant support, patience and guidance has helped me in successfully completing this study. I would also like to thank Dr. Suresh Devasahayam and Dr. Rajdeep Ojha for all the encouragement and guidance with technical aspects related to the electrical stimulator and the EMG machine.

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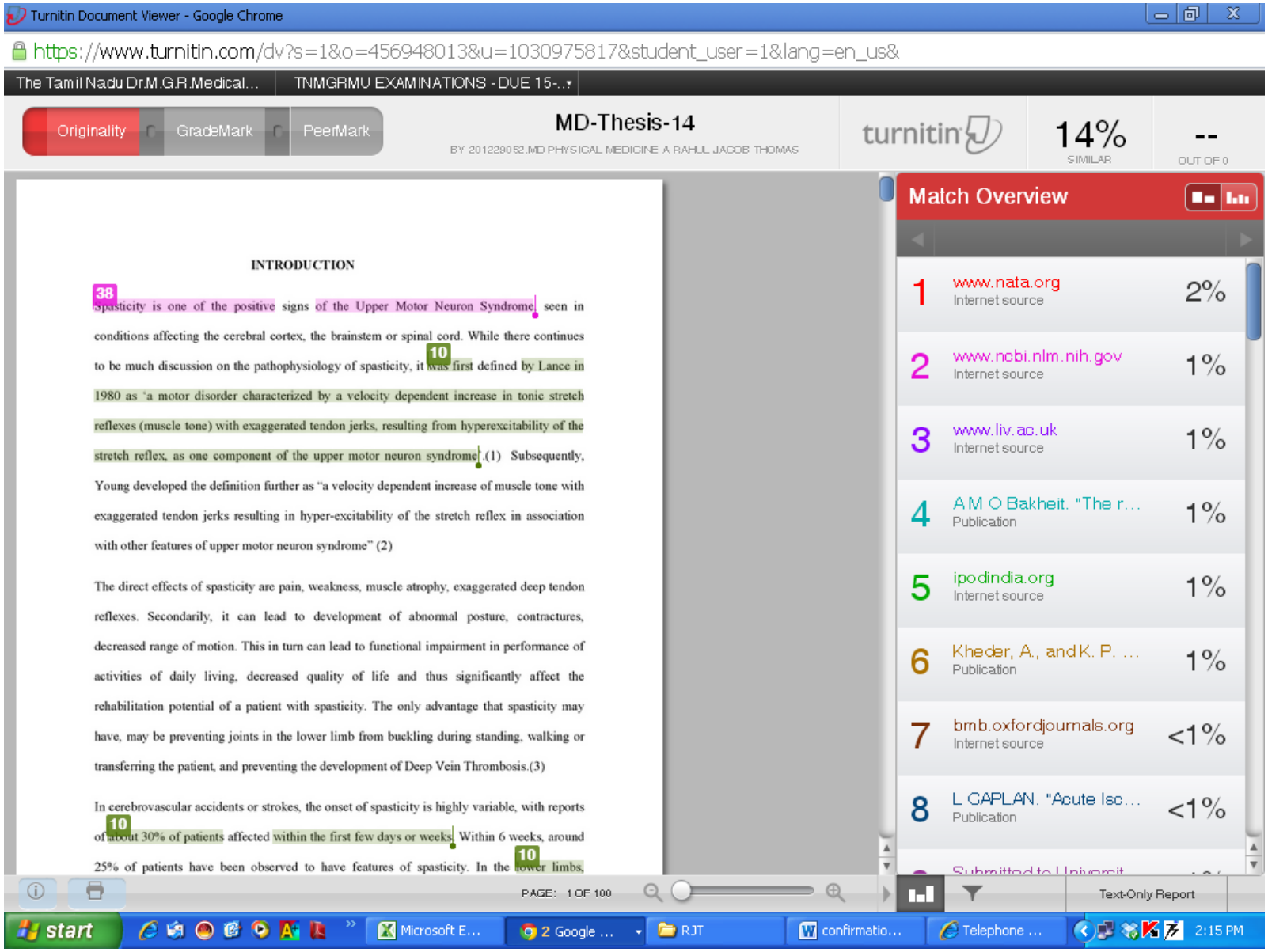
The patients who took part in this study have been extremely co-operative in their efforts to take part in this study and I am deeply grateful for their participation in this study.

I am also grateful to Ms. Gowri Mahasampath, for all her help with the statistical analysis of this study.

Lastly, I am thankful for the encouragement that my family has provided in completing this study.

Rahul Jacob Thomas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INTRODUCTION
Spasticity is one of the positive signs of the Upper Motor Neuron Syndrome, seen in conditions affecting the cerebral cortex, the brainstem or spinal cord. While there continues to be much discussion on the pathophysiology of spasticity, it was first defined by Lance in 1980 as 'a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome'.(1) Subsequently, Young developed the definition further as "a velocity dependent increase of muscle tone with exaggerated tendon jerks resulting in hyper-excitability of the stretch reflex in association with other features of upper motor neuron syndrome" (2)
The direct effects of spasticity are pain, weakness, muscle atrophy, exaggerated deep tendon reflexes. Secondarily, it can lead to development of abnormal posture, contractures, decreased range of motion. This in turn can lead to functional impairment in performance of activities of daily living, decreased quality of life and thus significantly affect the rehabilitation potential of a patient with spasticity. The only advantage that spasticity may have, may be preventing joints in the lower limb from buckling during standing, walking or transferring the patient, and preventing the development of Deep Vein Thrombosis.(3)
In cerebrovascular accidents or strokes, the onset of spasticity is highly variable, with reports of about 30% of patients affected within the first few days or weeks. Within 6 weeks, around 25% of patients have been observed to have features of spasticity. In the lower limbs,
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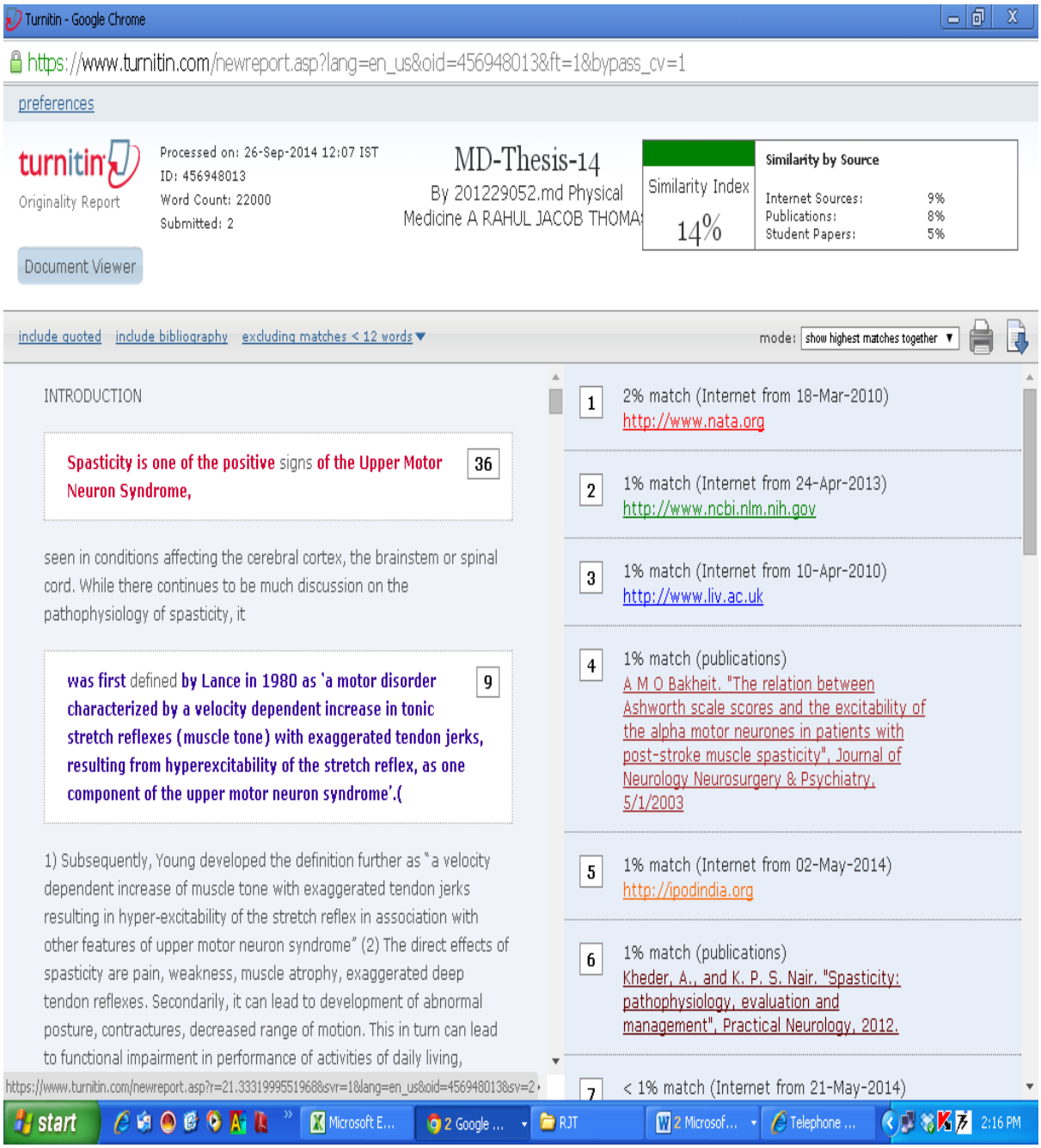
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TITLE OF THE STUDY

EFFECT OF TIBIAL NERVE STIMULATION ON GASTROSOLEUS SPASTICITY: A RANDOMIZED CONTROLLED TRIAL

Place of study

Department of Physical Medicine and Rehabilitation

Christian Medical College, Vellore

ABSTRACT

EFFECT OF TIBIAL NERVE STIMULATION ON GASTROSOLEUS SPASTICITY: A RANDOMIZED CONTROLLED TRIAL

Department of Physical Medicine and Rehabilitation

Rahul Jacob Thomas

MD Physical Medicine and Rehabilitation

Dr. George Tharion (guide)

OBJECTIVES

To compare the effect of repetitive low-threshhold afferent electrical stimulation of the Posterior Tibial Nerve against the standard treatment in the management of gastrosoleus spasticity in patients surviving cerebrovascular accidents.

Objective measurement of the change in gastrosoleus spasticity using an electrodiagnostic technique, namely the H:M Ratio and comparing the same with the Modified Ashworth Scale

METHODOLOGY

Patients attending the weekly stroke clinic were screened and out of the 24 who were enrolled in the study, 4 dropped out, leaving 11 patients in the sham stimulation arm and 9 in the active intervention arm. Baseline values of the levels of spasticity as per the Modified Ashworth Scale (MAS) and H-max/M-max ratio were recorded. A trained physiotherapist administered the electrical stimulation on a daily basis for 2 weeks, with each session lasting 30 minutes. The electrical stimulation was administered over the Posterior Tibial Nerve at the

medial malleolus, on the paretic lower limb. Following 2 weeks of electrical stimulation, levels of spasticity were re-assessed using the MAS and H-max/M-max ratio

RESULTS

The change in the median H/M ratio value from pre-intervention (0.72) to post-intervention (0.56) within the sham arm was not statistically significant (p=0.62). Likewise the change in the median H/M ratio value from pre-intervention (0.52) to post-intervention (0.53) in the active intervention arm was also not statistically significant (p=0.10).

For the sham arm, the median percentage increase after the intervention is 7.46% while in the active intervention group, it is 27.87%, where the difference between the two arms is not statistically significant (p=0.38)

With regard to the Modified Ashworth Scale scores, clonus which was observed prior to starting the intervention was observed even after the two weeks of electrical stimulation.

INTRODUCTION

Spasticity is one of the positive signs of the Upper Motor Neuron Syndrome, seen in conditions affecting the cerebral cortex, the brainstem or spinal cord. While there continues to be much discussion on the pathophysiology of spasticity, it was first defined by Lance in 1980 as 'a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome'.(1) Subsequently, Young developed the definition further as "a velocity dependent increase of muscle tone with exaggerated tendon jerks resulting in hyper-excitability of the stretch reflex in association with other features of upper motor neuron syndrome" (2)

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In cerebrovascular accidents or strokes, the onset of spasticity is highly variable, with reports of about 30% of patients affected within the first few days or weeks. Within 6 weeks, around 25% of patients have been observed to have features of spasticity. In the lower limbs, adduction and extension of the knee with equinovarus foot is the most observed pattern. (4)

Prevalence of spasticity after stroke have been observed to be highly variable, with estimates ranging from 4% to 42.6%, with prevalence of spasticity severe enough to cause disability,

ranging from 2% to 13%. Studies done on spasticity in different phases following a stroke revealed a prevalence of 4% to 27% in the acute phase (1 to 4 weeks post-stroke), 19% to 26.7% in the postacute phase (1to 3 months following stroke) and 17% to 42.6% among those in the chronic stage greater than 3 months following the stroke.(5)

Diagnoses and assessment of outcomes following interventions for spasticity include many scales or tools.As there is no uniform definition in place for Poststroke spasticity (PSS) that can be used across various research settings, associated with difficulties in the validation of assessment tools, the evaluation and appropriate management of spasticity have posed a complex challenge. While some assessment scales are subjective, others are more useful for objective measures of increments in the degree of spasticity. The most common used tool in the clinical assessment of spasticity is the Modified Ashworth's scale. However, due to its subjective nature, more objective measures have been devised, including some using electrophysiology, measures of range of motion and angular acceleration about a joint. The evaluation also includes measures of functional ability such as the Modified Rankin Scale, Barthel Index and Disability Assessment Scales. It is important to know the level of disability or functional limitation a given tool will assess along with its benefits and shortcomings. Quantitative methods including electrophysiologic, imaging methods and biomechanical techniques supplement more traditional measures in assessing the abnormal activity produced by a given spastic muscle. The accurate assessment and evaluation of spasticity is important in setting treatment goals for patients and care-takers alike. This in turn facilitates co-operation, enhances motivation and helps management of their expectations in favourably affecting the patient's rehabilitation. It also plays an important role in scaling of achievable goals, organization, focus and clarification of the aims of the rehabilitative process. (6)

The methods used to evaluate spasticity generally fall into three groups – those that assess resistance to passive muscle stretch, neurophysiological tests and scales of functional

outcome. The Modified Ashworth Scale is one the most widely used test for the evaluation of muscle spasticity. This scale however has some significant limitations. Upper motor neuron lesion hypertonia is a result of a combination of alterations in viscoelastic properties of muscle and spasticity which eventually lead to the formation of fixed muscle contractures.(7)

The Modified Ashworth Scale cannot reliably differentiate these aspects of hypertonia. The intra-rater and inter-rater reliability of this scale in evaluating lower limb spasticity remains questionable. (8)(9)The lack of standardisation of test conditions in which the Modified Ashworth Scale must be conducted is another limitation of this scale. While some clinicians measure muscle tone from a resting state without prior stretch, others recommend extension and flexion before noting the actual measurement. This can lead to measurement errors as stretch reflex excitability in the resting state may vary from that in the activated muscle.(10) The method of scoring severity of spasticity also remains a problem with the Modified Ashworth Scale. This is predominantly because it is dependent on the examiner's subjective impression of the degree of the resistance to passive muscle stretch.(11)

It is in view of the above mentioned limitations of the Modified Ashworth Scale that an additional tool was used in the measurement of change in spasticity following the intervention of Posterior Tibial nerve electrical stimulation.

Muscle spasticity has been attributed to numerous neurophysiological alterations in the segmental spinal circuitry. They include heightened excitability of the α motor neurones, reduction in presynaptic and reciprocal inhibition, and decreased 1A afferent facilitation. (12)

Excitability of the α motor neurones as measured by the Hoffman reflex (H reflex), has been shown to corroborate with the clinically observed elevation in the myotactic stretch reflex activity,(13) and to differentiate spasticity from normal muscle tone.(14) The ratio of the maximum H reflex amplitude to the maximum amplitude of the compound motor action

potential of the soleus muscle have been demonstrated to be reliable measures of α motor neuron excitability.(15) Although this measure of spasticity has not been widely accepted in clinical practice due to time constraints, need for expensive, special equipment and expertise, they are important objective tests that may be used in the validation of other outcome measures on muscle spasticity. With this evidence, the H-max : M-max ratio was considered for assessing the change in spasticity following electrical stimulation.

Treatment options for spasticity involves the removal of noxious stimuli, orthopaedic or surgical interventions, appropriate positioning of the patient, use of casts or splints, pharmacological agents, chemo-denervation, Botulinum Toxin injections, physical modalities and electrical stimulation. In this study, the effect of a non-invasive method of electrical stimulation of the posterior Tibial nerve on spasticity of the Gastrosoleus muscle was evaluated. The effect of low threshold afferent input on the reduction of ongoing activity within interneurons and eventually on the alpha motoneuronsvia spinal segmental, propriospinal or supraspinal pathways has been extensively studied. (16) Subsequent studies have propounded the various mechanisms by which electrical stimulation brings about the neuromodulation required for reduction in levels of spasticity. Electrical stimulation administered with a reasonably priced device could be then sent to the patient's home to continue the stimulation. While being non-invasive, electrical stimulation would have a two-fold advantage over medication in terms of the levels of sedation and cost benefits in long-term management of spasticity.

AIMS & OBJECTIVES

To objectively measure the effect of electrical stimulation of posterior Tibial nerve on gastrosoleus spasticity using an indigenous hand-held machine.

- To compare the effect of repetitive low-threshhold afferent electrical stimulation of the Posterior Tibial Nerve against the standard treatment in the management of gastrosoleus spasticity in patients surviving cerebrovascular accidents.

- Objective measurement of the change in gastrosoleus spasticity using an electrodiagnostic technique, namely the H:M Ratio and comparing the same with the Modified Ashworth Scale

JUSTIFICATION FOR THE STUDY

I. COST & ADVERSE EFFECTS ASSOCIATED WITH ANTI-SPASTICITY DRUGS

The most commonly used oral drugs for the management of spasticity are Baclofen, Diazepam and Tizanidine. A formal cost-anaysis of the average monthly expense on anti-spasticity medication for a stroke patient was beyond the scope of this study. However to provide an alternative therapy or one which can reduce the amount spent on anti-spastic medication, we considered electrical stimulation at a convenient location on the body where the Posterior Tibial nerve could to stimulated. Other commonly used parenteral medication like Botulinum toxin are expensive, while the cheaper Phenol for chemodenervation can lead to side-effects of sensory dysaesthesia.

Electrical stimulation used in a previous study to manage bladder hypertonicity had favourable results without any adverse side-effects. This was the rationale for considering electrical stimulation in alleviating gastrocsoleus spasticity, commonly seen among patients who survived a cerebrovascular accident.

II. THE NEED FOR AN OBJECTIVE MEASURE OF SPASTICITY WHICH CAN BE EFFECTIVELY MONITORED

The most commonly used clinical scale of measuring spasticity is the modified Ashworth scale (MAS). However this scale is subjective with inter and intra-rater variability. A more precise and quantifiable measure was necessary to monitor therapy and progress of the patient. It was with this objective that the Hmax/Mmax ratio was chosen.

REVIEW OF LITERATURE

Spasticity is considered part of a broader "Upper Motor Neuron Syndrome" comprising weakness, decreased motor control with respect to speed, accuracy and dexterity, loss of precise motor control, a positive Babinski sign and increased muscle tone associated with hyperactive stretch reflexes.(17) The Upper Motor Neurons originate in the primary motor cortex (precentral gyrus of cerebrum) and their axons form the corticospinal and corticobulbar tracts.

In 1980, Lance defined spasticity as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome."(18)

There are multiple factors that affect spasticity and it is the loss of balance between the various excitatory and inhibitory inputs into the alpha motor neuron that leads to the clinical presentation of spasticity. The loss of balance stems from changes in the way the spinal alpha motor neuron handles afferent impulses from proprioceptive, exteroceptive, and suprasegmental descending input sources.(19)

In this this study, the effects of spasticity as the result of a cerebrovascular accident have been evaluated.

PATHOPHYSIOLOGY OF CEREBROVASCULAR ACCIDENTS

The two major categories of damage to brain tissue in cerebrovasculare damage are Ischemia and hemorrhage. Ischemia implies a lack of blood flow to the brain, depriving it of nutrition and oxygen. Hemorrhage is the release of blood into the brain and the extravascular regions within the cranium. Hemorrhage destroys brain tissue by severing off connecting pathways

and causing localized or generalized pressure injury to brain tissue. The ensuing spillage of biochemical substances released during and after hemorrhage can adversely afflict vascular and parenchymal tissue in its vicinity.

ISCHEMIA

There are three mechanisms that lead to ischemia, namely thrombosis, embolism and decreased systemic perfusion. Obstruction of blood flow can be either due to localised occlusive processes in the case of a thrombus forming within a vessel supplying the brain, or due to material originating from a proximal site such as the heart. Systemic hypoperfusion is the inadequate supply of blood to the entire body or systemic circulation. Organs such as the brain with a high metabolic demand for the oxygen and nutrients supplied in its blood perfusion can be adversely affected when the systemic supply is compromised.

THROMBOSIS

Thrombosis refers to an occlusive process within the lumen of one or more blood vessels leading to obstruction of blood flow to the brain. The most common type of vascular pathology causing occlusion of the artery is atherosclerosis wherein overgrowth of fibrous and muscular tissues in the subintima, coupled with fatty plaque formation encroach the lumen.

Atherosclerosis commonly affects large extracranialand intracranial arteries. Primary haematological problems such as polycythemia, thrombocytois or a systemic hypercoagulable state can promote the formation of atheromatous plaques, often referred to as microatheromas.

Less common pathologies affecting the vascular system leading to vessel occlusion include (1) fibromuscular dysplasia, a hypertrophy of medial and intimal elements, which in turn

impedes vessel contractility and luminal size ; (2) arteritis, such as Takayasu and giant-cell arteritis are a result of inflammatory diseases targeting blood vessels ; (3) dissection of the vessel wall, with temporary obstruction of the vessel by luminal or extra-luminal thrombi ; (4) hemorrhage into a plaque compromising the lumen and hence the blood flow. Dilatation of blood vessels may also alter the local flow of blood, leading to formation of clots in the dilated segments.

EMBOLISM

Material formed elsewhere in the vascular system may lodge within the lumen of an artery and obstruct blood flow to distal regions. The obstruction may be transient or prolonged for hours or days before flowing distally. This obstruction is not caused by a localized process but originates proximally, most often from the heart, major arteries such as the aorta, the carotid arteries and the vertebral arteries, and from systemic veins. Cardiac causes are mainly due to valvular dysfunction and from clots or tumors within the atrial or ventricular chambers. Clots generated within the systemic veins may enter the circulation to the brain via cardiac defects such as an atrial septal defect or a patent foramen ovale, in a process termed paradoxical embolism. Rarely, air, fat, plaque material, foreign material from injected drugs, bacteria and metastatic tumor tissue can enter the vascular system and occlude cerebral arteries.

DECREASED SYSTEMIC PERFUSION

Diminished systemic perfusion to the brain parenchyma may be caused by low systemic blood pressure. Problems with myocardial contractility, often due of myocardial infarction or an arrhythmia and systemic hypotension due to blood loss or septicaemia are the most common causes of systemic hypoperfusion. This can dramatically affect border zones or so-called water-shed areas at the peripheries of major vascular territories.

DAMAGE CAUSED BY ISCHEMIA

The injury caused in the brain parenchyma may be temporary or permanent, with the latter being termed as an infarction. Capillaries and blood vessels within this infarcted tissue may also be injured leading to a hemorrhagic infarction. Injuries may lead to edema during the hours and days after a stroke. Glial scars form with macrophages gradually ingesting necrotic tissue debris in the chronic phase, resulting in shrinkage of the infarcted parenchyma or development of a cavity.

HEMORRHAGE

Hemorrhage may be further classified as subarachnoid, intracerebral, subdural and epidural. These subtypes each have a different aetiology, a different set of clinical sequelae and a different plan of management.

SUBARACHNOID HEMORRHAGE

In a subarachnoid hemorrhage, blood leaks out of the vasculature, on to the surface of the brain and subsequently disseminates fast via the cerebrospinal fluid pathway to spaces. Aneurysms or arteriovenous malformations, bleeding diatheses and trauma are the most frequent causes of a subarachnoid hemorrhage. The sudden and rapid release of blood into the cranial cavity can elevate the intracranial pressure faster than other causes of bleeding. This blood often carries substances promoting vasoconstriction of basal arteries that are washed in cerebrospinal fluid.

INTRACEREBRAL HEMORRHAGE

Bleeding that occurs directly into the brain substance, often as a result of hypertension damaging small intracerebral arterioles is termed as intracerebral or parenchymal hemorrhage. Bleeding diatheses as a result of iatrogenic anticoagulant prescriptions, trauma, drugs, vascular malformations and vasculopathies such as cerebral amyloid angiopathy may also lead to parenchymal bleeding. The degree of damage depends on the location, velocity, volume and pressure of hemorrhage.

PATHOPHYSIOLOGY OF SPASTICITY

Spasticity can be generally attributed to the loss of suprasegmental control over the spinal cord reflexes. (20) The supraspinal regions can be from altered input as a result of imbalance of inputs from reticulospinal and other descending pathways to the motor and interneuronal circuits of the spinal cord, and the absence of an intact corticospinal system. Lesions involving areas 4 and 6 of the cerebral cortex have shown to cause paresis and increased muscle tone.(21) Interruption of the reticulospinal tracts have also been shown to cause spasticity. (22)There is evidence that the descending tracts directly modulate not only the afferent limb of the peripheral reflex arc, but also the anterior horn cells associated with them.(23)

THE MUSCLE SPINDLE: Enclosed within the bulk of the muscle are stretch receptors known as muscle spindles. They convey information on the level of stretch experienced by the entire muscle, to the central nervous system. Unlike the extrafusal muscle fibres that are attached to the tendons at either end of a muscle these intrafusal muscle fibres are spindle-shaped, not attached to the musculo-tendinous ends of the muscle but enclosed in connective

tissue within the bulk of the muscle. (Fig. 1) They consist of two types of fibres: (i) Nuclear Chain Fibres which have their nuclei arranged in a linear fashion along the long axis of the muscle fiber and sensitive to sustained stretch. (ii)Nuclear Bag Fibres which have their nuclei arranged in a collection at the centre of the muscle fibre and mainly sense the onset of stretch. (Fig. 2) Both sets of fibres however, will respond to rapid stretch. These fibres transmit information to the central nervous system via large myelinated Ia primary sensory or afferent nerve fibres with annulospiral endings. There are secondary sensory afferent neurons with flower spray endings which also transmit information on stretch of the muscle fibres to the central nervous system. Together the primary and secondary sensory nerve fibres enter the dorsal horn of the grey matter within the spinal cord. The rate at which they transmit impulses into the spinal cord is directly proportional to the amount of stretch experienced by the nuclear chain and bag muscle fibres. The sensory neurons to which they transmit information, synapse with Gamma Motor Neurons and Alpha Motor Neurons which send efferent nerve fibres to the intrafusal fibres and the extrafusal fibres respectively. Stimulatory impulses from the Gamma Motor Neurons are responsible for contraction of the intrafusal muscle fibres only and cannot cause contraction of the extrafusal fibres and the entire muscle. Extrafusal muscle fibres contract when stimulated by efferent fibres from the Alpha Motor Neuron in the spinal grey matter. The stretch reflex consists of sensory impulses transmitted by the stretching of the intrafusal muscle fibres, causing efferent fibres from the alpha motor neuron to protectively contract the extrafusal muscle fibres and prevent them from being torn by excessive stretching. The protective contraction of the extrafusal fibres will eventually cause a slack in the stretch of the intrafusal muscle spindle and prevent further transmission of sensory information to the spinal cord. Gamma motor neurons must hence transmit efferent impulses to the intrafusal fibres to maintain their tone. Upper motor neurons at the supra-spinal level control both the Gamma and Alpha Motor neurons by co-stimulation.

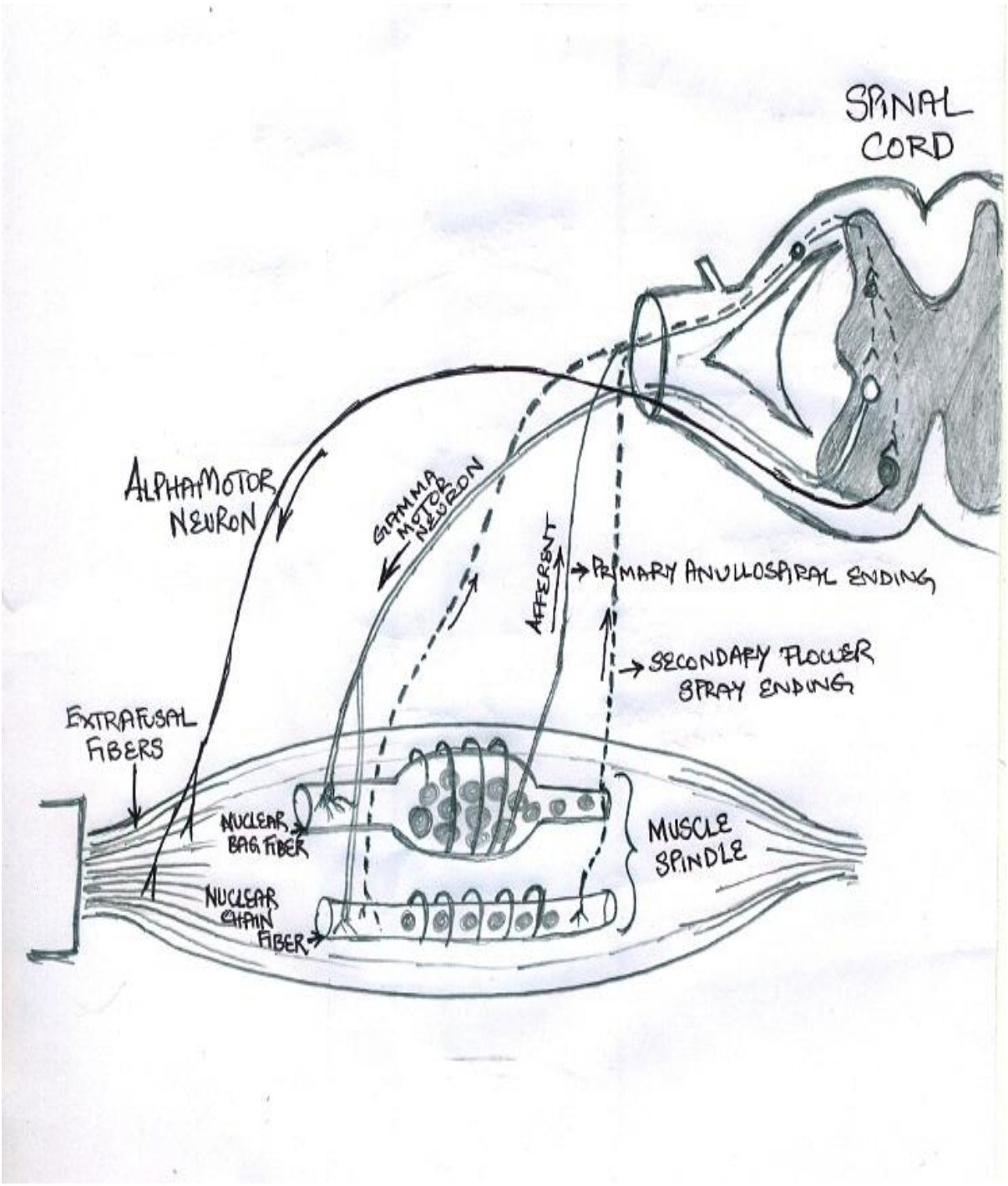


Figure 1 Connections of Extrafusal and Intrafusal Fibres to the Spinal Cord

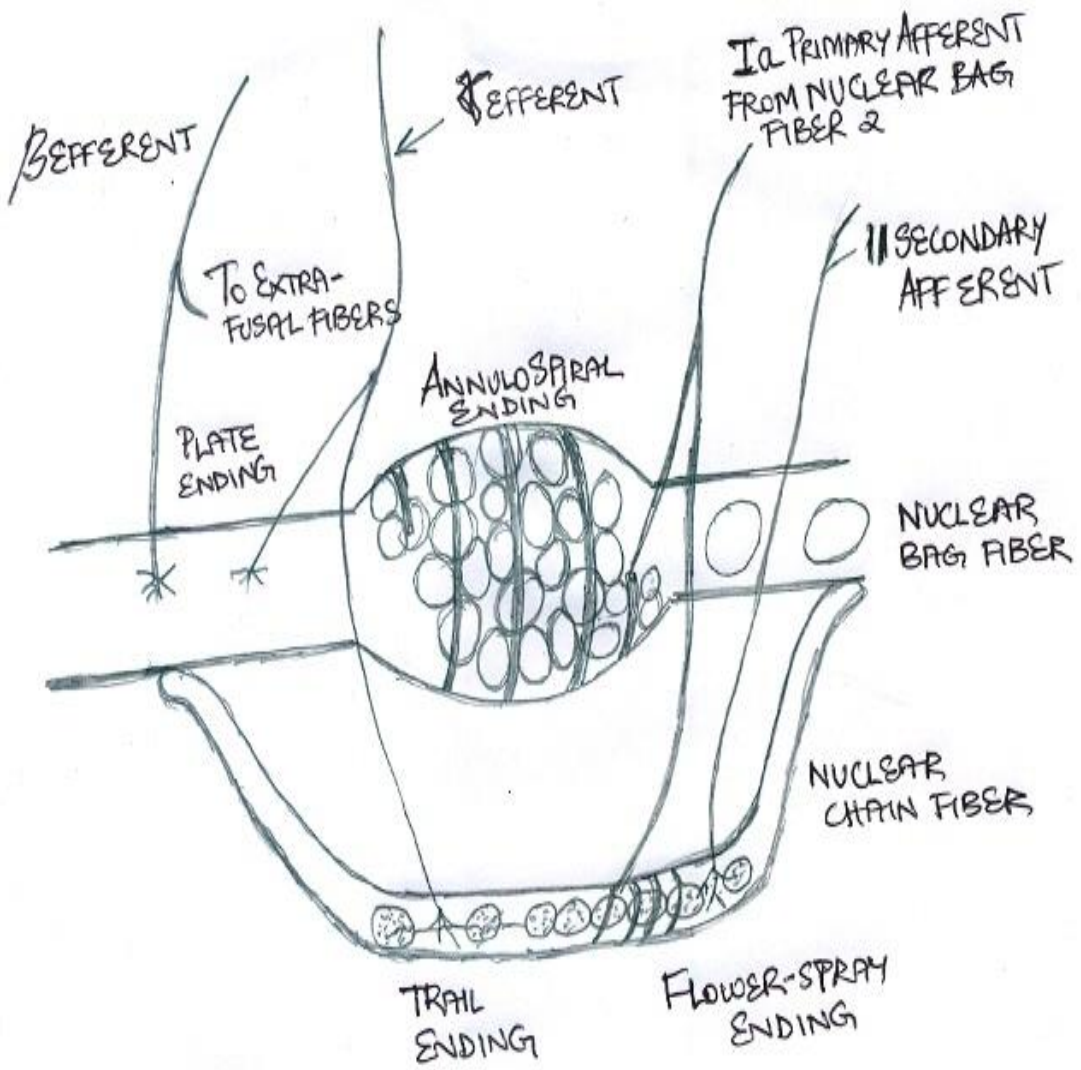


Figure 2 Fibres Emerging From the Muscle Spindle

The activity of Ia and II afferent fibres from the muscle spindle to the alpha and gamma motor neurons, helps control the amount of stretch and contraction of the muscle. This sensory information is modulated by suprasegmental control. Increased reflex excitability could be due to either excessive excitation or to decreased inhibition at the segmental level. The suprasegmental control consists of the following (Fig.3) :

CERBRAL CORTEX – it is essential in sending analytical and command motor signals and executes the same from:

a. Frontal motor area which forms the corticospinal or pyramidal pathway
b. Premotor and supplementary motor cortices which sequence and modulate all voluntary movements
c. Prefrontal cortex which projects to the premotor and supplementary motor areas to help with planning and initiation of willed activity
d. Parietal cortical areas (5,7) which play an important role in guidance of movement.
e. Association areas concerned with conscious (visual, auditory, tactile) or subconscious (proprioceptive) information also guides the motor system.

SUBCORTICAL CENTERS: basal ganglia (pallidum, subthalamic nucleus, striatum, substantianigra) and the cerebellum help in maintenance of tone, posture and co-ordination of movement.

BRAINSTEM is the major relay station which through its nuclei especially in the pons, medullary reticular nuclei, vestibular and red nuclei, influence muscle stretch reflexes, posture, and repetitive movements.

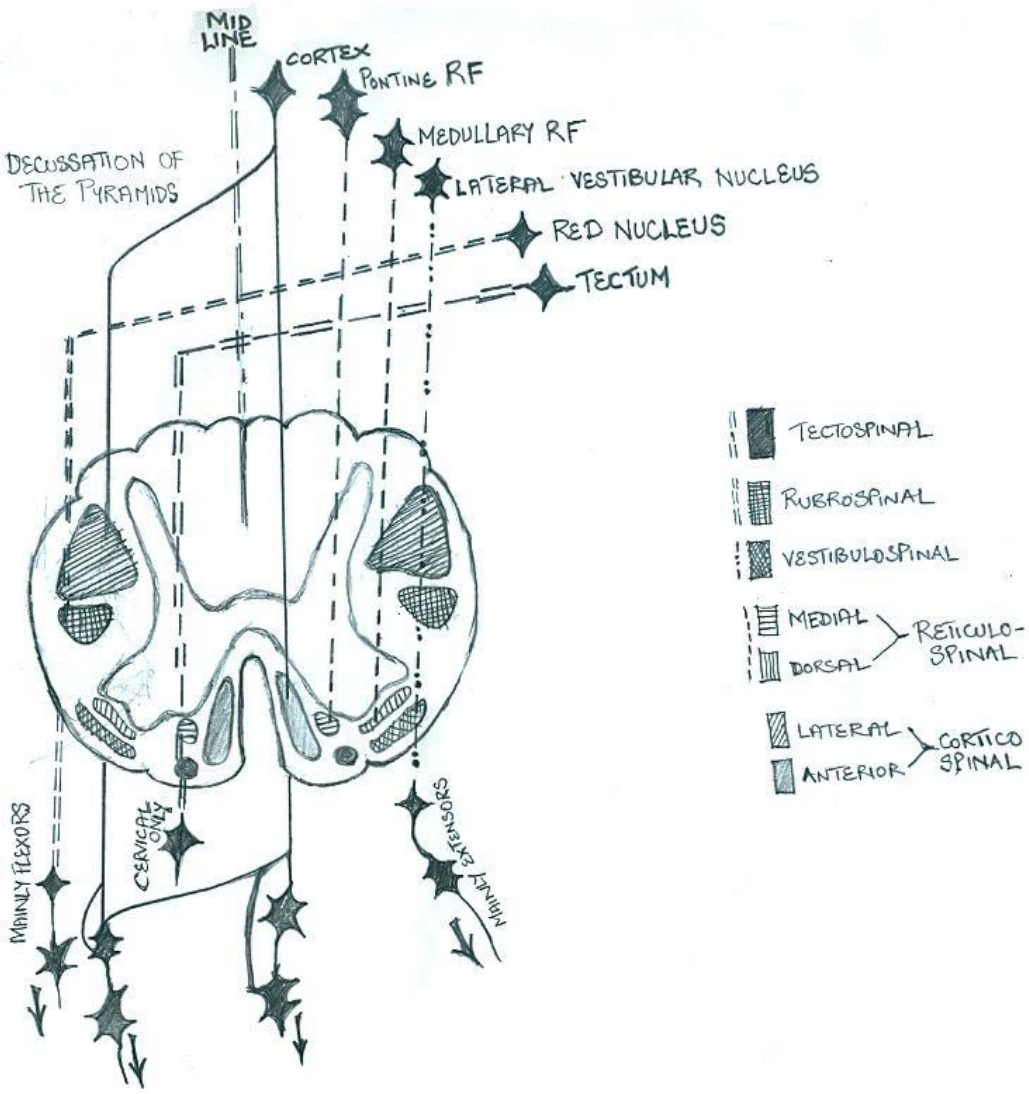


Figure 3 Supraspinal Pathways Involved in Spasticity

GOLGI TENDON ORGANS (GTOs): Golgi Tendon Organs help the muscle spindle fibres as sensory receptors that transmit information regarding muscle stretch, to the central nervous system. They are mechanoreceptors in the myotendinous and myoaponeurotic junctions of the muscle. At one end, they contain Ib afferent fibres intertwined with collagen bundles in continuity with the tendon or aponeurosis. At the opposite end, they are connected with a fascicle of 5-25 muscle fibres from several motor units. When muscle tension exceeds a threshold level, they inhibit further contraction and muscle then relaxes. They send their information to inhibitory interneurons which in turn can decrease the rate of alpha motor neuron firing and the amount of extrafusal muscle contraction. Golgi tendon organs and their Ib afferents are more susceptible to high velocity low amplitude manipulation.. They also inhibit the firing of antagonist spindles by suppression of Ia interneurons, thus protecting the antagonist muscle from firing and injuring the agonist muscle.(19)

SPINAL INTERNEURONS

Spinal Interneurons also play a crucial role in modulation of presynaptic and reciprocal Ia fibres by the release of Gamma Aminobutyric acid (GABA).(24) These inhibitory spinal interneurons are controlled in part by the corticospinal and the spinal cerebellar tract. The loss of Renshaw cell inhibition is another factor affecting the development of spasticity, although the extent of its contribution is not known.(19)The Interneuron systems of the stretch reflex are discussed below (Fig. 4):

1. Renshaw cells are located in the lamina VII of ventral horn medial to the motorneurons. Collaterals from an alpha motoneuron axon excite the Renshaw cell which in turn inhibits the same and other motorneurons innervating synergistic muscles. This motoneuron pathway of inhibition forms a negative feedback circuit

and is also called ‘recurrent inhibition’. (25)Renshaw cells also inhibit gamma motoneurons and 1a inhibitory interneurons. (26)

2. Reciprocal 1a inhibition: while the stretch of a muscle activates 1a afferent fibres to produce monosynaptic excitation of homonymous alpha motoneurons, there also occurs disynaptic inhibition of alpha motoneurons innervating antagonist muscles.
3. Inhibition from Group II Afferents: fibres from secondary spindle can produce flexion reflex by excitation of flexor alpha motoneurons while inhibiting the extensor motoneurons.
4. Non-reciprocal Ib Inhibition: Ib afferent fibres carry impulses from the Golgi tendon organs to inhibitory interneurons which in turn synapse with alpha motoneurons supplying both homonymous and heteronymous muscles. Ib non-reciprocal inhibition is part of a complex system regulating muscle tension controlling posture and movement with diverse segmental and supraspinal inputs.
5. Presynaptic Inhibition: Amplitude of the excitatory post-synaptic potential (EPSP) generated in a motoneuron by Ia afferent stimulation diminishes if specific interneurons depolarize this Ia afferent fibre through an axo-axonic synapse. It is a means of automatic suppression of unimportant afferent information.
6. Flexor Reflex Afferents: Nociceptive or simple pain reflex produces contraction of flexor muscle of a limb (withdrawal) and crossed extensor reflex of opposite limb. Polysynaptic connections between flexor reflex afferents (FRA), interneurons and motoneurons mediate this reflex.

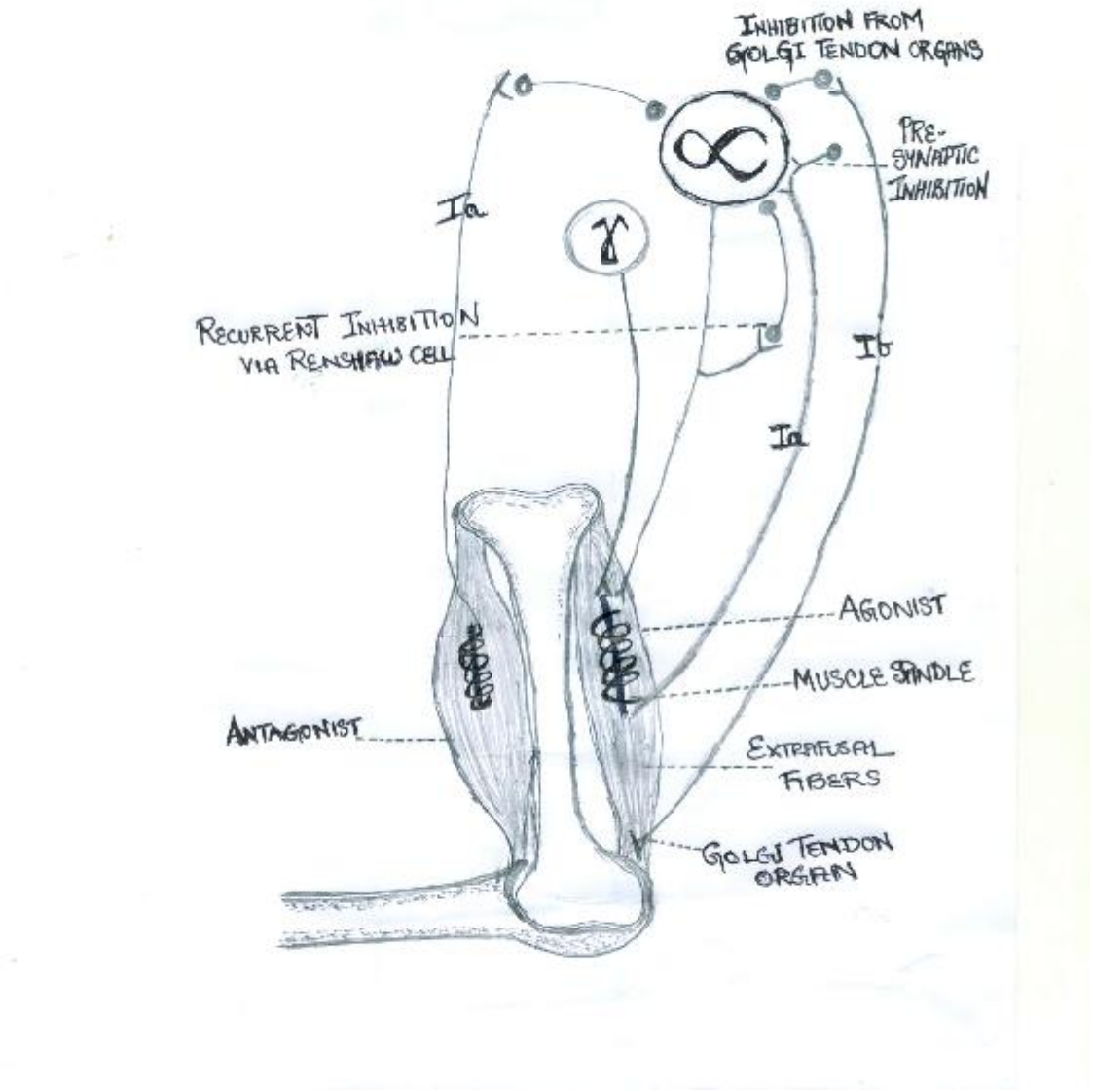


Figure 4 Interneuronal Pathways Ways in the Spinal Cord

EXCITATORY PATHWAYS IN SPINAL CONTROL OF SPASTICITY

1. Increased Fusimotor Drive – erstwhile theory which has now been discredited.

2. Primary Hyperexcitability of alpha motoneurons following upper motor neuron lesions: Voltage dependent, persistent inward Calcium and Sodium currents amplify and prolong the response of motoneuron to synaptic excitation. They produce prolonged depolarizations (plateau potentials) when outward currents are reduced or the calcium channels are facilitated by specific neurotransmitters. Eg. Serotonergic or noradrenergic innervations. The possible contribution of plateau potentials to spasticity in humans is not very evident as it is difficult to demonstrate the existence of such intrinsic membrane properties in the intact organism.(27)

3. Enhanced Cutaneous Reflexes: Flexor or withdrawal cutaneous reflexes have been shown to be enhanced in spasticity. Aside from ascending tracts formed by long axons, the dorsal horn neurons also give rise to short propriospinal axons that innervate motor neurons of the cord. The latter are influenced by descending reticulospinal tract (RST) and in lesions of the spinal cord, the normal gating mechanisms in the dorsal horn are disrupted, causing pain to be experienced by rather innocuous stimuli. These altered segmental inputs, helped by failure of presynaptic inhibition, results in hyperactivity in the alpha motoneurons, experienced as pain associated with spasticity.

At the level of the spinal cord, the mechanisms attributed to development of spasticity can be divided into PreSynaptic and PostSynaptic pathways. Presynaptic pathways can be further elaborated as: (i) presynaptic IA inhibition & (ii) post-activation depression.

Post-Synaptic pathways can be further classified as:

(i) Ib Inhibition

(ii) Recurrent inhibition

(iii) Disynaptic Reciprocal Ia Inhibition.

Increased stretch-evoked synaptic excitation of motor neuron are also attributed as a cause of spasticity and three causes have been propounded for the role of excitatory interneurons in the same: (i) collateral sprouting (ii) denervation hypersensitivity or (iii) diminished presynaptic inhibition.(28)

NEUROTRANSMITTERS IN SPASTICITY: Impulses from the various segmental and supra-segmental centres influence alpha motoneuronvia Excitatory Post Synaptic Potentials (EPSPs) and inhibitory post-synaptic potentials (IPSPs). While the neurotransmitter agents responsible have not yet been clearly defined, aspartate and glutamate are thought to be responsible for EPSPs and glycine and GABA for IPSPs. Inhibition by remote or presynaptic inputs to the motoneuron pool, such as Ia afferent nerve, cutaneous nerve, are mediated by Gamma-Aminobutyric Acid (GABA).(29)

EVALUATION OF SPASTICITY

CLINICAL EVALUATION

The clinical evaluation of spasticity should be based on the following tenets(30):

- Differentiating Spasticity from increased muscle tone resulting from other causes
- Detecting the presence of factors that aggravate spasticity
- Quantifying spasticity
- Assessing its effect on functional ability

VERIFYING SPASTICITY

Spasticity has characteristic features that help differentiate it from rigidity, catatonia, gegenhalten or contractures which also cause increased muscle tone:

Velocity Dependence: The faster the muscle is stretched, greater is the muscle resistance.

'Clasp-knife' phenomenon: After an initial resistance to movement, the spastic limb suddenly gives way, much like that of a folding knife blade. As contractures set in, this phenomenon is replaced by solid non-elastic resistance.

Stroking Effect: a reduction in a given spastic muscle may be brought about by gently stroking its antagonist muscle.

Distribution: anti-gravity muscles are differentially more affected by spasticity

Rigidity: the increased muscle tone is not velocity-dependent and remains throughout the range of its movement.

Gegenhalten ("counter hold"): it is an increase in muscle tone proportional to the force applied to move it passively, and may be falsely mistaken for the patient's own active effort.

Catatonia: this increase in muscle tone results in patients maintaining limbs in positions placed by others for a long time. It is often associated with a wide range of psychiatric, neurological and medical conditions, accompanied by abnormal behavioural, affective and autonomic features.

FACTORS AGGRAVATING SPASTICITY

The history and physical examination should rule out the following factors that may be aggravating the spasticity and interfering with rehabilitative efforts to alleviate the same:

Injuries and untreated fractures

Urinary Tract Infection, Renal or Cystic calculi

Constipation

Pressure Ulcers

In-grown toenails

Deep Vein Thrombosis

Ill-fitting Orthotics or clothing

Improper seating

Post-traumatic syringomyelia

Patients and/or their care-givers must be educated in regularly monitoring for these factors that need immediate attention for reducing spasticity and the complications that arise from it.

MEASURING SPASTICITY

In order to effectively plan interventions for managing spasticity, it must be measured and documented by the right instruments. The degree of spasticity may vary with ambient temperature, fatigue, time of the day, posture and positioning of a limb. While there are several scales by which it may be measured, some are more subjective, others require more technical training to administer and no one scale is clinically acceptable universally. The various tools for measuring spasticity can be broadly classified as follows (30) :

Measures of Increased Tone

- Modified Ashworth Scale
- Tardieu Scale: The Tardieu
- Pendulum Test
- Tone Assessment Scale

Among the scales used to measure tone, clinically the most commonly used ones are the Modified Ashworth Scale (MAS) and the Tardieu Scale, both of which are described in more detail, as follows:

THE ASHWORTH SCALE

Score	Ashworth (Ashworth 1964)
0	No increase in tone
1	Slight increase in tone giving a catch when the limb is moved in flexion/extension
2	More marked increase in tone through most of the ROM, but limb is easily moved
3	Considerable increase in tone – passive movement is difficult, ROM Is decreased
4	Limb rigid in flexion and extension

THE MODIFIED ASHWORTH SCALE

Score	Modified Ashworth (Bohannon & Smith, 1987)
0	No increase in tone
1	Slight increase in tone giving a catch, release and minimal resistance at the end of range of motion (ROM) when the limb is moved in flexion/extension
1+	Slight increase in tone giving a catch, release and minimal resistance throughout the remainder (less than half) of ROM
2	More marked increase in tone through most of the ROM, but limb is easily moved
3	Considerable increase in tone – passive movement is difficult, ROM is decreased
4	Limb rigid in flexion and extension

The Tardieu Scale

Score	Description
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of passive movement, no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by release
3	Fatigable clonus with less than 10 seconds when maintaining the pressure and appearing at the precise angle
4	Unfatigable clonus with more than 10 seconds when maintaining the pressure and appearing at a precise angle
5	Joint is immovable

The Tardieu Scale

Score	Velocity Description
V1	As slow as possible, slower than the natural drop of the limb segment under Gravity
V2	Speed of limb segment falling under gravity
V3	As fast as possible, faster than the rate of the natural drop of the limb segment under gravity

The Tardieu test is performed with patient lying in the supine position, with the head in midline. Measurements are taken at 3 velocities, namely V1, V2, and V3. Responses are recorded at eachvelocity as X/Y, with X indicating the 0 to 5 rating, and Y indicating the degree of angle atwhich the muscle reaction occurs.On moving the limb at different velocities, the response tostretch can be more easily graded since the stretch reflex response to velocity can vary.

Measures of focal spasticity

- Leeds arm spasticity impact scale

Neurophysiological Measures

- H-Reflex
- F-Waves
- H-max/M-max Ratio
- Vibration Inhibition Index (H-Vibration/H-Control)

Patient Reported Scales

- Visual Analogue Scale
- Penn Spasm Frequency Scale (PSFS)
- Patient Reported Impact of Spasticity Measure (PRISM)

Functional Assessment Scales

- Dynamic Gait Index
- 6 Minute Walk Test
- 10 Metre Walk Test
- Timed Get Up And Go (TUG) Test

The Modified Ashworth Scale requires no instruments, can be administered easily and is hence the most frequently used clinical measure. Although it is an ordinal scale, it has the following limitations(31):

*It has poor inter-rater reliability, as the passive force applied by examiners can vary

*The six-level ordinal scale is not sensitive to change

*Soft-tissue contractures cannot be differentiated from spasticity by this scale

It is for this reason that we opted to simultaneously use neurophysiological measures such as the H-Wave, M-wave and a ratio of their amplitudes as a measure of spasticity.

THE H-REFLEX, M-WAVE AND H/M RATIO

Introduction:

The H-reflex was named after Paul Hoffman who originally described it in 1910. It is an electrically induced reflex that is analogous to the spinal stretch reflex, with the difference being the bypassing of the muscle spindle and hence, it is a valuable tool in assessing alpha motoneuron excitability when presynaptic inhibition and intrinsic excitability are constant. The H-Reflex may be used to assess the nervous system's response to various neurologic conditions, musculoskeletal injuries, therapeutic modalities, pain, exercise regimens and in performance assessments.(32)

Eliciting the H-Reflex Pathway & Representation of H-Max:

To elicit the H-Reflex, a percutaneous electric stimulus is applied to a mixed nerve, beginning with a low-intensity stimulus until depolarization of the primary (Ia) afferents from the muscle spindle. The muscle spindle itself is bypassed and activation of Ia fibres arising from it results in action potentials being propagated towards the spinal cord. With sufficient depolarization, neurotransmitters are released from the presynaptic terminal into the Ia-alpha motoneuron synapse, eliciting excitatory postsynaptic potentials (EPSPs). Depending on the alpha motoneuron membrane potential and the size of the EPSPs, action potentials are generated, causing Acetyl Choline release at the NM junction, contraction of muscle and appearance of an H-Reflex tracing on the EMG. At low levels of stimulation, the afferent fibers are preferentially stimulated due to their intrinsic properties and large diameter. More Ia afferent fibers get recruited as the stimulus intensity increases, resulting in activation of more motoneurons and amplitude of the H-reflex.

The length of the H-Reflex pathway depends on the distance of a given muscle from the spinal cord. Action potentials must travel up the afferent fibers to the motoneurons and then down the motor axons to the muscle. The time taken for the H-Reflex to appear on the EMG relative to the introduction of the stimulus and is known as its Latency. While the soleus H-Reflex has a latency of around 30 milliseconds, the vastus medialis appears approximately 15milliseconds after stimulus delivery.

Eliciting the M-Wave Pathway & Representation of M-Max:

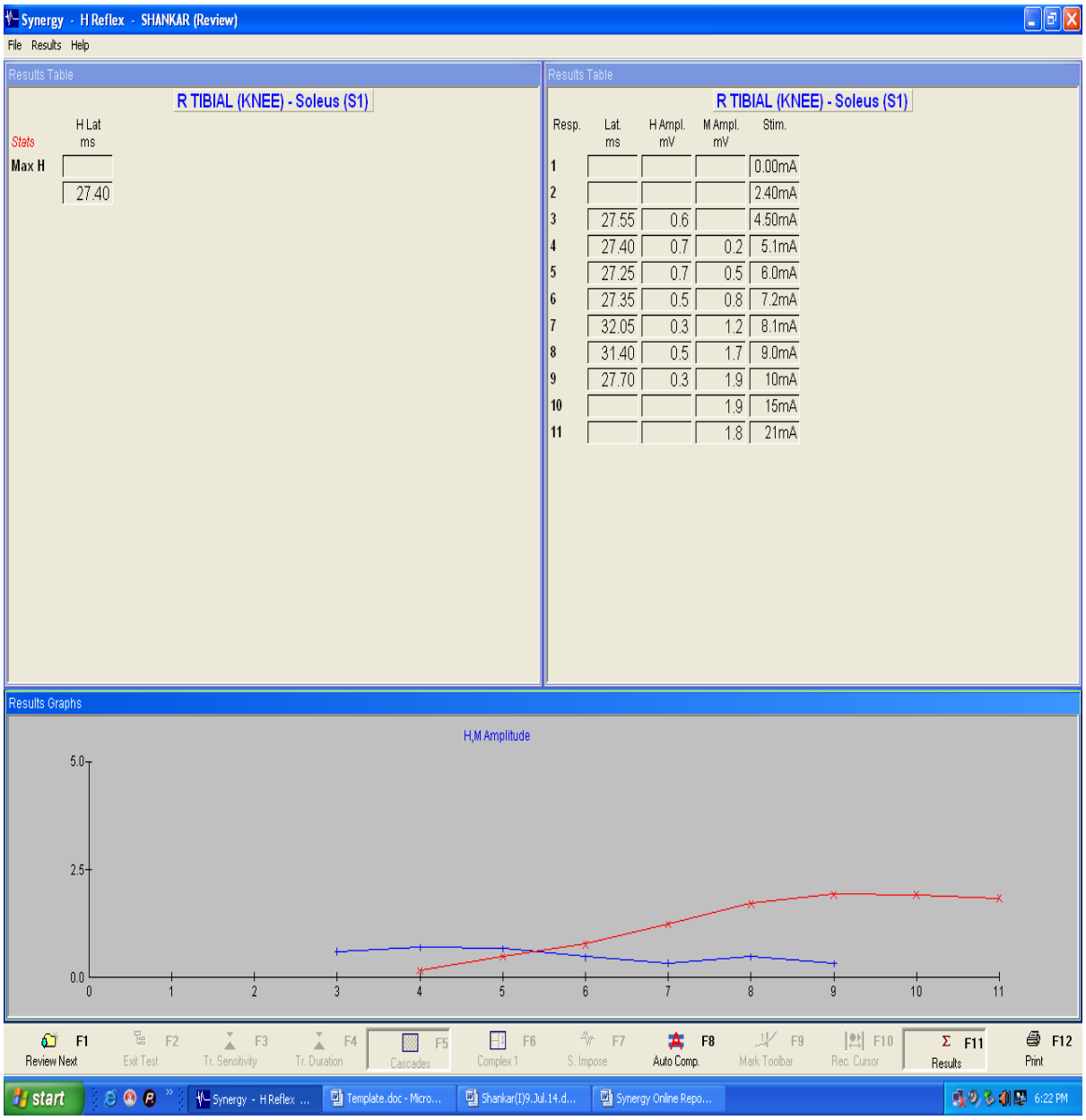
The threshold of a motor axon is higher and hence the stimulus required to activate these fibres is much higher than that required for Ia sensory neurons. The larger the axon, the easier it is to stimulate the neuron, and it is possible to preferentially stimulate the Ia sensory neurons before the motor axons are activated. When the intensity of a stimulus reaches depolarization threshold for the efferent fibers, action potentials are generated towards the neuromuscular junction, causing the muscle to contract. As this impulse did not pass through the spinal cord, it is not referred to as a reflex but termed the M-wave. Relative to the H-reflex, the M-wave has a short path to travel before a muscle response occurs and hence its tracing appear on the EMG at a shorter latency of approximately 6 to 9 milliseconds.

The Recruitment Curve:

The tracings for both Ia afferent and alpha motoneuron fibres present simultaneously once the threshold for each one is reached. The H-reflex tracing begins to appear on the EMG at low levels of stimulation and as the stimulus intensity increases,depolarization threshold for the M-wave is achieved. As the stimulus intensity is increased, the H-reflex reaches its maximum amplitude (H-max). Simultaneously, the M-wave tracing begins to appear on the EMG;

however when stimulus intensity exceeds that required to elicit an H-max, the H-reflex amplitude begins to decrease and the M-wave continues to increase in amplitude. Eventually the H-reflex disappears while the M-wave amplitude reaches its maximum value (M-max) and then continues to plateau, regardless of the strength of the stimulus. (Fig. 1)

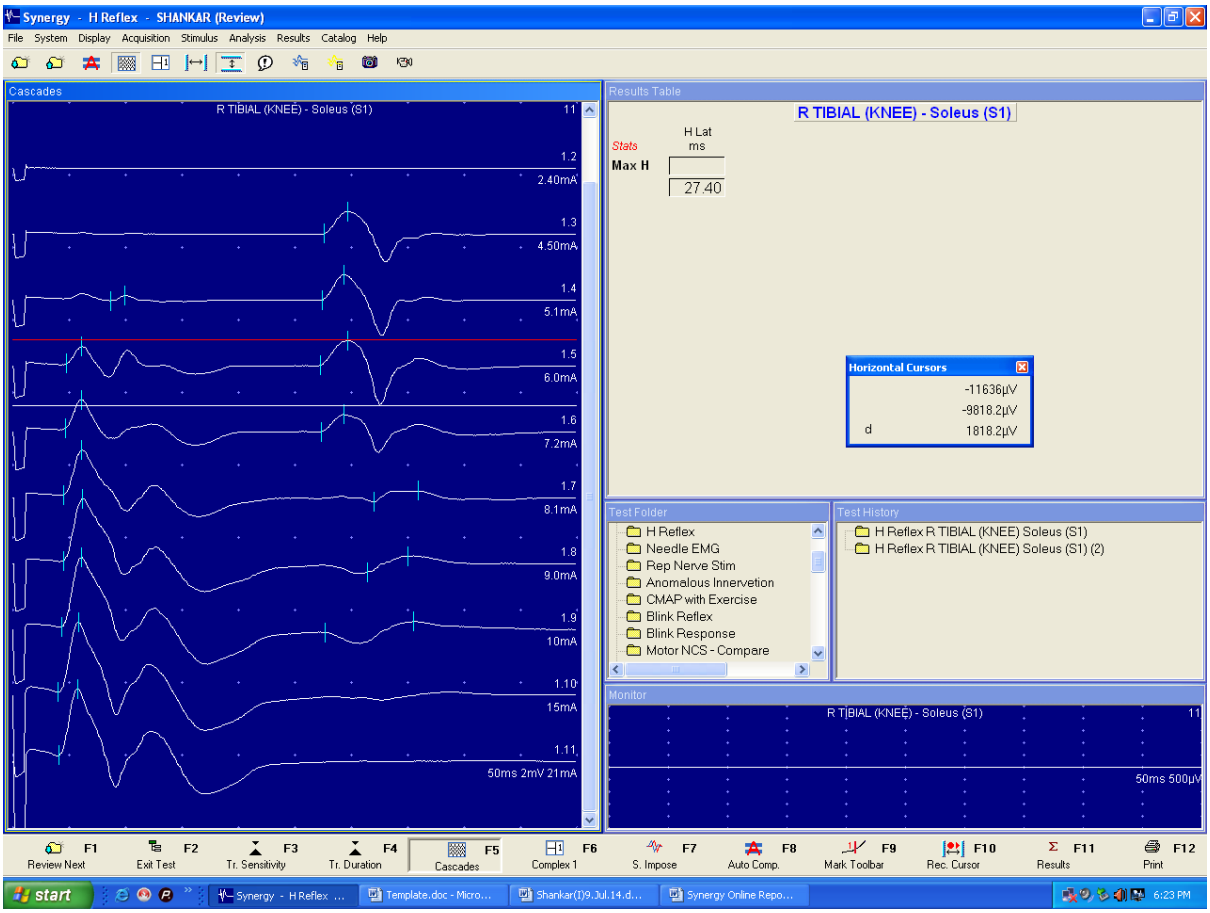
Figure 5. The H reflex and M wave recruitment curve



*The blue line in the graph above represents the H-Reflex amplitudes while the red line represents the amplitudes of the M-wave.

The disappearance of the H-reflex is explained by an effect known as antidromic collision. Antidromic impulses are a volley of electric activity travelling the non-physiological direction in the motor axons. As it travels backward up the motor axon towards the spinal cord, it collides with the reflexive orthodromic (impulse going in the correct direction) volley, which had proceeded up the sensory axon and passed through the spinal cord. When the antidromic volley is smaller than the afferent volley, the afferent volley is reduced but continues to the muscle. This explains the decrease in the H-reflex amplitude after reaching a maximum in the recruitment curve tracing. As the size of the antidromic volley exceeds the afferent volley, no signal proceeds to the muscle and the H-reflex disappears from the tracing.

Figure 6. Tracing of H-reflex and M waves



What H-max and M-max Represent:

H-max is an estimate of the maximum number of motoneurons that are capable of being activated in a given state. M-max represents activation of the entire motoneuron pool and once it is reached, every motoneuron that supplies the muscle of interest is thought to be activated.

The H-max/M-max Ratio:

H-Reflex normalization is commonly done by standardizing the H-max amplitude to the M-max amplitude. H-max is only an indirect estimate of the number of motoneurons being recruited while M-max represents the entire motoneuron pool. The H-max/M-max ratio may be interpreted as the proportion of the entire motoneuron pool capable of being recruited and based on the assumption that the M-wave amplitude is a stable value. As the stimulating or recording electrodes are prone to move, one cannot assume that the same portion of the motoneuron pool is being stimulated. Hence the H-max/M-max ratio is a dependent measure when data are being collected on multiple occasions and it is preferred over the H-reflex as a percentage of the M-wave.

MANAGEMENT OF SPASTICITY

Effective treatment must begin with setting treatment goals which are in agreement with the patient and the therapy team, meaningful and easily understandable for the patient. They may include facilitation of better standing, walking and sitting, performance of activities of daily living, relief of pain & discomfort, reduce the burden on care-givers, prevention of complications such as contractures, heterotopic ossification and pressure ulcers.

Once the triggers for spasticity mentioned earlier have been identified and eliminated, non-pharmacological interventions and medications can be initiated.

Positioning of the patient also plays an important role in preventing the development of abnormal posture while sitting and lying down. Therapeutic positioning of the patient is aimed at the manipulation of primitive reflexes such as labyrinthine and tonic neck reflexes, released from higher motor control.

Physical modalities, electrical stimulation may also be attempted and they have the advantage of not causing the drowsiness induced by many anti-spastic drugs. Intractable cases not responding to the above methods will require surgical intervention.

NON-PHARMACOLOGICAL INTERVENTIONS

PASSIVE STRETCHING

The excitability of motor neurons and the visco-elasticity of muscles and joints can be decreased by passive stretching. (33) Stretching exercises delivered by therapists or carers are time and labour intensive and the duration of stretch may vary along with the intensity of force applied and the repetitions delivered per session.

Stretching is defined as the process of producing elongation. It is used commonly to deal with numerous other impairments including range of motion limitations and functional mobility. Stretching can be administered by manual techniques along with other therapeutic interventions; however, this makes its efficacy difficult to scientifically measure, standardize and objectify. Stretching can also be administered by mechanical devices like the dynamometer (Cybex).

The application of stretch is described by therapists in terms of:

a) Duration: period of time that the stretched structures are elongated within one repetition.
b) Dose: it is the total end range time.
c) Frequency: is used to describe the periodicity ranging from one session to daily sessions over weeks, months or in some instances, years.
d) Repetitions: refer to the times a muscle or joint is stretched in a single session.

Time constraints and cost-effectiveness have fuelled the search to find alternative devices to apply stretch. The use of tilt tables has helped in the management of limitations in joint range of movement; minimize sequelae of spasticity and deficits in the lower limb range of movement, particularly in the gastrocsoleus muscle. Increasing the verticality and making the patient stand more upright causes increased weight-bearing load on the feet and in turn brings about a range of other benefits. If tolerated, the patient then graduates to a standing frame, providing static stretch to the plantar flexors of the ankle and to hip flexors. Dynamometers include Cybex, Kin-Com, and Biodex where intelligent feed-back-controlled devices are being used by clinicians to provide well regulated standardized stretch therapy.

SERIAL CASTING

Serial casting, also known as inhibitory casting has been utilized in the management of spasticity for decades, being first described in the 1960s when it was applied in children with cerebral palsy. Contractures are a leading complication in spasticity due to the prolonged period in which muscles remain shortened in this condition. In most cases, this complication is identified too late and casting is not as productive once contractures have set in completely. Serial casting involves the stepwise circumferential application of fibreglass or plaster of

Paris cast around a joint or multiple joints that are spastic and/or contracted. Repeated application reaps benefits in terms of better range of movement, function and decrease in pain. This repeated procedure may be stopped once maximum range of movement at a given joint is attained or 2 sequential casts do not yield any further improvement in the range of movement. Subsequently, the final cast in bivalved to serve as maintenance orthosis.

Numerous theories have been suggested to explain the benefits of serial casting. A neurophysiological theory suggests the ability to minimize change in muscle length, in turn reducing excitatory input via afferent receptors in the muscle spindles, thus reducing reflexive alpha motor neuron excitability. Raised levels of tension within spastic muscles also result in increased activation of golgi tendon organs which inhibit alpha motoneurons through type Ib afferent fibers. The neutral warmth generated within a cast is an alternative theory stated, wherein motor neuron excitability is inhibited by the warmth and muscle relaxation is prompted. A mechanical explanation has also been suggested, where the cast provides a stretch of load for a long duration, helping to prevent and correct joint contractures. Animal studies have demonstrated the alteration in muscle and tendon properties, showing an increase in sarcomeres in series, as a response to casting.

Casts or splints with or without prior botulinum toxin injections can keep joints stretched for hours or days and even treat contractures. Although a recent study showed no significant benefit with stretching in neurological conditions(34), there has been no evidence to show that it may be harmful.

DYNAMIC SPLINTING

Splints may be dynamic or static in nature. The goal of dynamic splints is to avoid immobilization while still achieving chronic stretch. Static Splints have the advantage over casts in that they can be easily removed, allowing for monitoring of current range of motion, vascular condition and skin changes, and scheduling time windows reserved for passive and active movements.Dynamic splinting consists of devices incorporating active, passive component or active assistance into a device used to maintain stretch of muscle. Commonly used dynamic splints include dynasplint, Saeboflex and other custom fabricated devices often incorporating a system of springs and pulley systems to facilitate the dynamic component of the splint.

SAEBOFLEX

The Saebo splints include the Saeboflex, the Saeboreach and the Saebostretch with each providing specific effects at specific joints. The Saeboflexorthosis allowed for rapid training of grasp and release functions in hemiplegic hands where limited extension is caused due to flexor hypertonicity. While Saeboflex training has also been incorporated as a component of constraint induced movement therapy, currently its applications have been mainly studied in the hands and remain to utilized further in lower limb spasticity management.

DYNASPLINTS

These devices are composed of cushioned adjustable cuffs with struts placed medially and laterally, acting as hinges at the joint axis. This allows for greater amounts of stretch coupled with an increase in duration of time that the splint is worn and in turn progressively improves the range of movement. Wearing time progresses rapidly when the risk of skin breakdown is limited and the patient is not in any form of discomfort. Numerous studies have been

conducted on the efficacy of this modality in improving spasticity, some in combination with other therapeutic interventions such as botulinum toxin injections. Most studies have shown an improvement in the joint range of movement while significant decrease in spasticity was not observed.

LYCRA GARMENTS

These are garments made in segments that are stretched in the desired orientation and accordingly sewn together to facilitate a particular direction of pull. They were designed to worn for several hours each day, producing prolonged stretch of spastic muscles. The elasticity of the material can be harnessed to exert direction to the continuous stretch of targeted segments. Thus far limited evidence is available on whether these garments are capable of improving spasticity significantly. They require custom-fitting and it may not be economical for mass-production. Patients tend to experience heat and discomfort in areas covered by these garments and this has also been an impediment in their role in spasticity management.

ANKLE FOOT ORTHOSES

The ankle foot orthoses (AFO) has been found to be beneficial in reducing plantar flexor tone and for positive support reaction while walking.(41) The most common ankle foot orthosis prescriptions are those for foot drop, plantar spasticity and lumbar spinal cord injury. For plantar spasticity frequently associated with cerebrovascular accidents, either a hinged custom plastic AFO with a single midline posterior stop or a hinged custom plastic AFO with pins incorporated within the posterior channels to ensure plantar stop at 90 degrees. The

former is to be considered in milder cases of spasticity where a significant inversion deformity is not present. The latter is used when a significant inversion deformity is associated with the equinus foot and the common medical measures to address this spasticity have been exhausted. Posterior pins within metal ankle joints would provide better mediolateral support while permitting some dorsiflexion, leaving the anterior channels open. Allowing the foot to dorsiflex can in turn provide a therapeutic stretch with a more normalized gait pattern, stretching the plantar flexors from the midstance to toe-off phases of the gait cycle.

EXERCISES

They consist of manual stretching of muscles shortened by spasticity, with brief high load periods for a few minutes (High-Load Brief Stretch {HLBS}). While mechanical devices can be used to deliver cyclic passive stretching that increases the resting length of muscles(35), self-stretching might be used based on the patient's physical and cognitive abilities, motivation and understanding of instructions received from a therapist. The latter could have potentially have advantages in terms of longer duration of daily stretch per muscle (depending on patient self-discipline), cost-effective in sparing therapist time, and increased limb awareness & decreased disuse.(36) Two therapeutic exercise approaches have been described in dealing with spasticity, namely the Bobath(37) and Brunnstrom(38). The Bobath strategy advocates reduction of primitive postural reflexes followed by facilitation of voluntary activity in paretic muscles through controlled stretching of muscles and attention to trunk posture. The Brunnstrom strategy focuses on the stimulation of the weak agonist muscle groups to bring about Ia mediated reciprocal inhibition of the spastic antagonist muscles. Heat and cold therapy can concurrently provide sensory stimuli, resulting in a short-

duration reduction in spasticity.(39) Contrary to previous belief, exercises do not worsen spasticity and those studied to be beneficial include cycling, strengthening exercises and treadmill-based training.(40) Exercise may be deferred if patient has osteoporosis, coagulation disorders or severe limitation of passive range of movement.

Unloaded cycling was studied to evaluate the effects on spasticity. Research done on this modality has been mainly among patients with multiple sclerosis. It has shown to have a positive effect on spasticity contrary to earlier opinion that it was bringing about a worsening of hypertonia.

Body weight-supported ambulation has been suggested as a means of improving levels of mobility after a stroke. Details of this modality have been discussed further in another section on newer therapeutic modalities in the management of spasticity

Numerous randomised controlled trials have been conducted, examining the benefits of strength training in patients undergoing rehabilitation in poststroke hemiplegia. While no specific improvements in spasticity were observed with high-intensity strength training, progressive resistive training has been shown to have a positive effect on over-all functional ability. In the lower limbs specifically, studies have shown that resistance training produced improvements in gait speed and strength but no increase in spasticity. Further study is required to dispel or support the opinions on whether or not resistance training worsens spasticity.

DRUG TREATMENT OF SPASTICITY

ORAL DRUGS

BENZODIAZEPINES

Benzodiazepines such as Diazepam facilitate pre-synaptic inhibition in the spinal cord by enhancing the post-synaptic effects of Gamma Aminobutyric Acid (GABA) in the spinal cord. They interact with an allosteric protein modulator of GABA-recognition sites and thus increase the receptors' affinity for GABA. This in turn promotes efficient chloride conductance across the nerve membrane – a mediating mechanism for both presynaptic and postsynaptic inhibition. The indirect GABA-mimetic action of Benzodiazepines is exerted only when physiological GABA transmission already occurs – they merely fine tune release of the neurotransmitter at a synapse.(42)

Patients begin treatment with 2mg tablets, twice a day and the dose may be slowly increased by a tablet every 3-4 days until a maximum dose of 10mg thrice daily is achieved. Benzodiazepines are useful to treat spasticity that disturbs sleep – nocturnal spasms respond well to treatment with Clonazepam. Side effects of this category of drugs include marked sedation, cognitive dysfunction (24) and behavioural changes. Diazepam may potentiate the hypotensive action of anti-hypertensive drugs and diuretics. Sudden withdrawal, especially after long-term use or in patients addicted to alcohol can cause seizures or other fatal symptoms.

GABAPENTIN

This drug in an analogue of Gamma amino butyric acid (GABA), however its mechanism of action is still not clear. Although it is not known to mediate its effects through interaction with GABA, that view has now been altered. The current prevailing view is that regardless of

the precise mechanism of action, Gabapentin does increase GABA turnover. It is also used in the adjunctive treatment of seizures and also has been used in the management of neuropathic pain.The most frequently noted side effects of Gabapentin are somnolence, vertigo, nystagmus, headache, tremors, fatigue, ataxia and nausea.

BACLOFEN

This widely used anti-spastic drug is a derivative of GABA and acts specifically as an agonist of GABA-B receptors. It also acts by reducing calcium influx and suppressing the release of excitatory neurotransmitters such as aspartate and glutamate. It is effective in the initial management of spasticity, with a starting dose of 5mg thrice daily, increments of 5-10mg can be made weekly till an optimum effect is achieved. Maximum doses ranging between 100-120mg per day may be well tolerated. Special attention must be paid while adding other classes of medicines such as tricyclic antidepressants and Baclofen must be tapered rather than stopped abruptly in patients with seizures as it reduces the seizure threshold. Sudden withdrawal can also provoke rebound spasticity and hallucinations. Side-effects of this drug include weakness, dizziness and drowsiness.(43)

CLONIDINE

Monoamines are distributed throughout the central nervous system and in spastic hypertonia; they modulate sensory, autonomic and motor functions by facilitating pre-synaptic inhibition of spinal afferent impulses. In this manner, monoamines have an important role in modulating spinal neuron excitability.

Clonidine was one of the initial centrally acting alpha-2 and imidazoline type-I adrenergic receptor agonists to be used in spasticity. It also serves as an alpha-1 central adrenergic agonist. This was realized by its potential as an anti-hypertensive medicine, antagonized by Yohimbine. In spasticity, it modulates pre-synaptic inhibition of sensory afferents via alpha-2 adrenergic receptor effects. It is a highly lipophilic medication with consistent distribution regardless of whether it is delivered via oral, transdermal, intravenous, epidural or rectal routes.

CYPROHEPTADINE

While the mechanisms through which serotonin exerts its effects on spastic hypertonia are not clearly known, serotonin blockers such as cyproheptadine have been studied and utilized in its management. It has also been used to manage symptoms of serotonin syndrome associated with baclofen withdrawal and has been approved for the treatment of headaches, anorexia and hives. Cyproheptadine may alleviate the effects of intrathecal baclofen withdrawal, indicating that GABA-B receptors inhibit the release of serotonin and also supports its role in movement disorders. The most prominent side-effects associated with Cyproheptadine are somnolence and weight gain.

TIZANIDINE

This alpha-2 receptor agonist enhances noradrenergic in the central nervous system while inhibiting excitatory spinal interneurones and tracts from the locus ceruleus. Tizanidine is usually started at a dose of 2mg and increased by the same dose on a weekly basis. The maximum permissible dosage is 36mg, divided into 3-4 doses per day. Liver enzymes must

be monitored periodically during the first 4 months of treatment to detect hepatitis. Hypotension, gastrointestinal disturbance, and a dry mouth are other possible side-effects. The drug must be tapered rather than stopped abruptly to avoid withdrawal symptoms such as tremor, tachycardia, hypertension and anxiety.

DANTROLENE

Dantrolene directly affects muscle contractile mechanisms, specifically on extrafusal fibres and not on the intrafusal fibres involved in reflex pathways. It blocks calcium release from the sarcoplasmic reticulum and interferes with excitation-contraction coupling in the skeletal muscle. As it acts directly on the muscle, it has less central nervous system side-effects like sedation. Beginning with a dose of 25mg daily over the first week, increments of 25mg can be made to a top dose of 100mg, 3-4 times daily. Liver functions must be monitored regularly to detect the presence of hepatotoxicity. Long-term dangers of Dantrolene therapy include pleuropericardial reactions.

CANNABINOIDS

The dorsal spinal cord, basal ganglia, hippocampus and cerebellum contain cannabinoid receptors that can modulate spasticity. While inducing psychotropic effects, Tetrahydrocannabinol, a cannabinoid receptor agonist, also reduces spasticity. An oromucosal spray containing nabiximols, a 1:1 mixture of 9-Δ-Tetrahydrocannabino and cannabidiol was approved in the UK for management of spasticity in multiple sclerosis.(44) However, the side-effect profile including long-term effects on mental health, cognition and behaviour are a deterrent unless the spasticity is non-responsive to combinations of other anti-spastic drugs.

PARENTERAL DRUGS

BOTULINUM TOXIN

This is prepared from the Clostridium botulinium strain of bacteria which produces a potentially fatal neuromuscular paralytic toxin. The toxin contains a heavy chain which is internalised into presynaptic nerve endings where it degrades synaptosomal-associated protein (SNAP) 25, essential for acetylcholine vesicle fusion to the presynaptic membrane. Neuromuscular transmission is then blocked by inhibition of acetylcholine release into the synaptic cleft. The selective weakness induced in a target muscle can be reversed only a few months later with reinnervation and nerve sprouting. Global weakness and sedation are avoided with the selective reduction in spasticity of muscles injected with the toxin. Target muscles may be identified using electromyography, nerve stimulation or ultrasound and post-injection interventions such as physiotherapy, splinting or serial casting must be planned to maximise the effects of botulinum toxin. For maximum benefit, the treating physician must ensure that no significant contractures exist and that all trigger factors affecting spasticity are addressed prior to injecting botulinum toxin.

The duration of effect of Botulinum Toxin is around 3 months, with the causes the loss of effect being attributed to the formation of new neuromuscular junctions and sprouting to new axons proximal to the affected nerve terminal. The preparation of Botulinum toxin A (BT-A) available currently are Dysport and BOTOX with the latter being 3-5 times more potent than the other. While the advantage of using Botulinum toxin lies in the targeting of specific muscles, sparing of sensory fibres and patient tolerability.(45) Outcomes using this intervention are enhanced when used in conjunction with standard physiotherapy and orthoses. The disadvantages of BT are a short duration of action, unwanted weakness in

distant muscles by diffusion of toxin across fascial boundaries or systemic spread, and generalised effects such as flu-like symptoms and fatigue which are self-limiting.

PHENOL NERVE BLOCK

Phenol (Carbolic Acid) can act as a neurolytic agent in concentrations more than 3% and is used to impair the innervation to a spastic muscle. In the lower limb, chemodenervation of the posterior tibial nerve in the popliteal fossa can decrease the equinovarus deformity. Although the duration of its effect may range between a few months to several years, painful dysaesthesia occurring from damage to sensory fibres of mixed nerves is an unwanted side-effect. Electromyography may be used to target the motor point of the target muscle's innervation, thus reducing the risk of sensory disturbance. Damage to blood vessels adjacent to the target nerve has also been observed, leading to vascular occlusion. Fifty percent alcohol may be used as an alternative to phenol, but has lesser efficacy.

INTRA-THECAL BACLOFEN

Intrathecal baclofen infusion through a pump is best applicable in refractory lower limb spasticity affecting patients with spinal cord injury or multiple sclerosis, where multiple muscle groups in both lower limbs are affected. A small study of 3 stroke patients with chronic lower limb spasticity, responded to continuous intrathecal baclofen infusion with reduced tone in the affected side and preservation of muscle power on the non-paretic side. (46)

SURGICAL INTERVENTION

It can be divided broadly into procedures interfering with neuronal pathways and those that correct musculoskeletal deformity. Within the central nervous system, stereotactic neurosurgery and Cerebellar stimulation targeted the brain while Selective Dorsal Rhizotomy (SDR) targeted the spinal cord in attenuating spasticity. Stereotactic neurosurgery and Cerebellar stimulation have not produced satisfactory results. (47)(48) Selective Dorsal Rhizotomy is still being used with variable success in cases of intractable spasticity not responding to other modalities. (49)(50) Neurectomy has been used with some benefits in specific cases. However, neurectomy, particularly of mixed motor and sensory nerves, can have unfortunate consequences leading to permanent painful dysesthetic pain. Hence, the majority of surgical interventions for management of spasticity are performed on peripheral muscles and tendons to bring about significant changes in spasticity.

The goals of surgery for spasticity are not unlike those of non-surgical procedures. While some focus on improving function and active movement, in others, patients have more advanced spasticity demonstrating limited active movement, requiring some form of passive functional improvement. It must be clearly explained to the patients and their care-takers that the goals of surgery are neither the restoration of volitional control to muscles, nor the increased generation of muscle power. Other goals of surgery include pain relief, lesser dependence on systemic medications and their associated side effects, creating a permanent remedy rather than one requiring recurrent interventions, and also to improve cosmetic outcome and in turn the psychological well-being of the patient.

With regard to the timing of surgical intervention, early surgery has the advantage of being able to work with joints which are supple and in turn the duration of disability is shorter. Disadvantages include neurologic conditions which may still be dynamic and unpredictable.

The medical morbidity associated with a recent injury to the central nervous system may also have consequences on an early surgical intervention. Surgical interventions at a later point in the management of spasticity have the advantage of the natural history of the illness taking its course and in turn, better healing of the initial injury. The disadvantages of a late surgical intervention include having to deal with stiffer joints, and the worse outcomes related to an already severe disability.

The most valuable and versatile of techniques used to lengthen muscles in spasticity surgery is the fractional lengthening technique. Most muscles have regions where an overlap between the muscle and tendon exists. It is at this level that fractional lengthening is performed. The region of the myotendinous junction is able to stretch where the tendon was cut, allowing lengthening of the structure in its entirety. The new tendon resulting from healing of this procedure takes about 3 months to develop and fill the ensuing gap. Care must be taken to prevent overstretching of the muscle during this recovery period.

Another surgical technique commonly used is the muscle slide and advancement. In this procedure, the entire origin of the muscle is advanced, thus shortening the work of the muscle and in effect lengthening it relative to its functional movement. Three techniques that lengthen a tendon include V-to-Y lengthening, Z lengthening or lengthening involving multiple hemitenotomies.

Procedures specifically related to the equinus ankle spasticity utilize a lengthening technique and include fractional lengthening of the myotendinous junction and percutaneous hemitenotomies through the tendon. This involves creating a longitudinal incision over either the medial or lateral calf region. Identifying the interval between the gastrocneumius and soleus muscles, the myotendinous junctions of both muscles are demarcated and subsequently lengthened. Alternatively, the Achilles tendon may be approached percutaneously and

lengthened distally using 3 hemitenotomies. The ankle is then passively dorsiflexed, inducing a tear and weakening of the tendon. Hemitenotomies permit longitudinal tear of the Achilles tendon, leaving residual tendon fibres contiguous if appropriate healing takes place. Permitting weight-bearing immediately after the lengthening procedure is debatable and generally the ankle requires 8 to 12 weeks of protection within a cast to prevent rupture of the gastrosoleus muscle. Without adequate bracing and stretching following surgery, in the absence of any active dorsiflexion, the equinus contracture is likely to recur.

Resection of an existing heterotopic ossification may also be required to facilitate better range of movement.

EMERGING TECHNOLOGY IN THE MANAGEMENT OF SPASTICITY IN HEMIPLEGIA

The knowledge gained from research and advancements in neuroimaging have enhanced the understanding of neural plasticity and the role it plays in therapeutic modalities used for the management of spastic hemiplegia With this knowledge, newer emerging modalities of therapy that are as follows:

CONSTRAINT-INDUCED MOVEMENT THERAPY

Constraint-induced movement therapy has emerged as an interesting therapeutic approach for patients with hemiplegia following a cerebrovascular accident. This intensive therapy is administered over the course of 12 to 15 days, restricting the use of the uninvolved limb. The patient is forced to use the limb on the affected side to perform activities of daily living. The theory of learned nonuse states that a limb weakened as a result of the cerebrovascular accident will not improve if it is not actively rehabilitated. Hemiplegic patients are taught not

to use the normal limb in the hope of developing compensatory one-handed strategies with the affected limb. This in turn facilitates cortical reorganisation that promotes use of the plegic limb.(51) Several important factors are required for constraint-induced movement therapy to be successful. They include intensive, repetitive practice using the affected limb for common functional tasks. This must be followed in conjunction with the unimpaired limb physically restricted for up to 90% of the time the patient is awake using a mitt, splint and/or sling. A therapeutic strategy known as shaping is used, which involves training of the plegic limb to perform successive approximation of a desired task. While traditional constrain induced movement therapy is extremely intensive requiring at least six hours of daily therapy for two weeks, the most comprehensive study examining its effectiveness to standard rehabilitative methods was the EXCITE trial. (52) This study included 222 patients with a single stroke that occurred 3to 9 months before the time of enrolment. When compared to the standard therapy group, those who underwent constraint-induced movement therapy had less self-perceptions of limb function difficulty and performed better on several tests of limb function. Challenges faced by the demands of intensity and time spent in constraint-induced movement therapy have prompted several attempts at modifying the ways it is delivered. A regimen providing therapy for 5 hours daily for 5 days followed by 3 hours a day, thrice weekly over approximately 10 additional weeks yielded results comparable to traditional constraint-induced movement therapy. Modifications have also incorporated online computer sessions or combined robotic therapy with constraint induced movement therapy.(53) Factors limiting the effectiveness and application of constraint induced movement therapy include the effort and motivation required on the part of patients receiving this therapy. Compliance with mitt restriction has been reported to be as low as 32%. (54) Other restricting factors include the baseline functions that are required in patients for this therapy to be effective and this in turn translates to only a small percentage of patients benefiting from this therapy.

VIRTUAL REALITY

Computer-based technology has led to the development of virtual reality programs permitting individuals to interact within computer-generated environments simulating real-world settings for clinical and research applications. Technology is used to make virtual environments where the intensity, duration and feedback related to the therapy can be modified with much better control than natural environs. Therapy can be safely conducted in settings that would otherwise be considered too dangerous or complex in actual locations. Specific therapies can be administered using this technology without concerns about the consequences of allowing the patient to perform potentially dangerous exercises or activities on their own. While being extremely flexible, this technology is capable of staying completely consistent over infinite repetitions. Alterations in the type and pattern of sensory feedback and complexity of task can fulfil a range of clinical, research and assessment requirements. Hence virtual reality has been gaining wider applications in rehabilitation settings for both treatment and assessment.

Jaffe et al developed a head-mounted device which could easily be worn like a hat while it displayed virtual objects and scenarios.(55) Patients wearing the device were walking on a treadmill while being attached to a safety-harness. Movements of the lower limb are promoted by negotiating virtual obstructive objects in their path. Inability to avoid a virtual object results in a virtual collision, resulting in appropriate feedback to the patient. With practice, performance was noted to improve on this virtual obstacle course and thus facilitate ambulation training. Fung et al devised a treadmill that could interface with a rear projector providing patients with auditory, visual and sensory feedback, which in turn eventually resulted in better velocities while walking. (56) Deutsch et al devised a seated system

allowing the patient to use their own ankle movement to control a foot pedal and "navigate" a virtual boat while receiving auditory, sensory and visual feedback. Improvements were observed in the endurance and velocity of gait within a month of undergoing 12 hour sessions on a daily basis.(57) Functional MRI has demonstrated that after training, activation in the contralesional hemisphere decreased while ipsilesional sensorimotor activity was predominant and associated with improved motor function. Similar evidence of enhanced activation in the affected hemisphere following the use of various virtual reality related therapies have shown that this modality may be useful to induce cerebral plasticity and improve motor skills after a cerebrovascular accident.(58)

TRANSCRANIAL MAGNETIC STIMULATION

This is a relatively new mode of therapy that is non-invasive capable of both enhancing and inhibiting focal brain activity, with the potential to induce cerebral plasticity and enhance recovery following injury. It consists of short magnetic pulses generated by the passage of a brief electric current through a stimulating coil, usually made of copper encased in plastic, and held to the surface of the scalp. Based on the pattern of pulse provided, either an increase or decrease in cortical excitability ensues. Unlike electrical stimulation where neurons are directly excited, transcranial magnetic stimulation affects neural tissue indirectly by inducing electrical activity via magnetism. The magnetic pulse generated depends on the spatial configuration of the stimulating coil with the position in which it is held.

Transcranial magnetic stimulation can be delivered through single-pulse, paired-pulse and repetitive stimulation. While single-pulse stimulation over the motor cortex delves into information concerning corticospinal tract excitability by measuring motor response in the

muscles corresponding to the area of the brain that is activated, paired-pulse stimulation can provide information on cortical inhibition or excitation.

Repetitive transcranial magnetic stimulation consists of a repeated train of magnetic pulses at either low (1 Hz) or high frequencies (5-20Hz) that can respectively cause depression or enhancement of cortical excitability. (59) The changes induced in excitability may last beyond the application of magnetic pulses implying that repetitive transcranial magnetic stimulation has the capacity to induce long-term potentiation conducive to cerebral plasticity.

The changes in cortical excitability induced by transcranialmagnetic stimulation have been utilized to manage spasticity in several upper motor neuron conditions including stroke. Ia afferent sensory fibres, spinal interneurons, α and γ motoneurons are known to be modulated by corticospinal neurons, which in turn are involved with the generation of spasticity. Increasing the corticospinal tract excitability using repetitive transcranial magnetic stimulation is theorized to inhibit overexcitability of α and γ motoneurons, thereby reducing spasticity. Numerous repetitive transcranial magnetic stimulation theories have been tested with results demonstrating its potential to either reduce spasticity or increase passive range of movement. (60)(61) Functional use of affected limbs can thus be improved using this modality in patients with spastic hemiplegia.

Induction of seizures is one of the primary adverse affect associated with repetitive transcranial magnetic stimulation which can be minimized by abiding by recommendations on stimulation parameters, monitoring guidelines and specifying contraindications. (61) The precise timing of application of transcranial magnetic stimulation to bring about maximum plasticity and alleviate spasticity has not yet been determined; however its effects have been observed at various poststroke stages.

ROBOT THERAPY

Clinicians and engineers have worked in collaboration to develop numerous robotic devices with the intention of improving motor and functional recovery after an insult to the central nervous system, regardless of what the aetiology may be. This technology builds on the existing evidence that intense, repetitive, challenging and functionally relevant therapies are critical factors contributing to motor recovery. (62) Robots designed to highly repetitive and intense therapy are means of improving functional recovery otherwise not practically feasible utilizing traditional rehabilitative measures. Computer programs in robots constrain inaccurate limb movements to promote more functionally appropriate movements during specific tasks. With the intention of substituting the need for trained professionals and compensating for their time and labour constraints, the automated components of robotic therapies enhance patient compliance in interesting ways. They combine games with therapy, providing instant feedback on performance and thus maintain levels of motivation. Therapy can be guided by easily tracking changes in the skill, thus serving as a means of monitoring the efficacy of therapy and modifying it accordingly.

The robotic devices developed thus far have mainly focussed on rehabilitation of hemiparetic upper limbs and a few prominent robotic systems that have emerged include:

- The MIT-MANUS system
- The Mirror Image Motion Enabler
- The Bi-Manu Track
- The GENTLE/s RT system
- The Haptic-MASTER which is a part of the GENTLE/s RT system
- The Activities of Daily Living Exercise Robot
- The Myomo e100

- The Cyberglove and Rutgers Master II-ND glove

  Drawbacks of robotic therapy include the start-up costs and the dearth of validation from clinical trials.

BODY WEIGHT-SUPPORTED TREADMILL TRAINING

This mode of therapy was first described by Finch et al (63) with the objective of assisting neurologically impaired individuals with ambulation and walking. A harness system supports a part of the patient's body weight and helps to unload the lower extremities as the patients train to walk on a treadmill. Gait quality, speed and trunk stability following a stroke have been shown to improve with this therapy. Body weight supported treadmill training may also be effective in encouraging a symmetrical gait pattern, facilitating sensory feed-back and maximizing vital repetition required during the recovery period.

The mechanism of action propounded for body weight-supported treadmill training is the activation of central pattern generators (CPGs) located in the spinal cord. Central pattern generators were first described in invertebrates where it was demonstrated that neuronal networks responded to specific sensory inputs to bring about locomotion.

Studies have been conducted on cats in whom thoracic spinal cord lesions were induced, where body weight-supported treadmill training has brought about improvements in various aspects of gait including, speed and cadence, compared to control animals. Theories of the mammalian spinal cord being capable of producing reciprocal gait patterns without supraspinal inputs, but through the activation of central pattern generators, were thus supported. While there is support for the notion that neural plasticity possible within the spinal cord, supraspinal mechanisms may also be influenced by body weight-supported treadmill training. Mass practice or the need for repetition, and shaping which is the sequential performance of imitations of a task, can be used along with progressive weight-

bearingto facilitate lower limb function. When administered by trained therapists, this system can help control leg movement, patient posture and balance that aids in mimicking the normal rhythmic nature of gait. Along with decrease in the fear of falling, other attributes of this therapy make gait training feasible earlier in a patient who has had an injury to the central nervous system.

Several studies including a metanalysis have failed to demonstrate a definite advantage that body weight-supported treadmill training may have over traditional therapeutic techniques. This can be attributed to the heterogeneity in the nature and severity of stroke, differenced in demographic characteristics of patients, varied intensity and frequency of training, methods used for assistance and the placebo effect. Another important drawback has been the time constraints and physical demand placed on therapists to utilize this therapeutic modality to its maximum potential. Fatigue, not only among patients, but therapists too can limit the duration of a given session.

Barbeau and Visintin (64) in their experience with body weight-supported treadmill training found that the transfer of training from treadmill walking speed to ground walking speed was better in the body weight-supported group compared to the group that trained without this therapy. Improvements in cardiovascular fitness have also been observed in this therapy. This has been attributed to the positive effect of exercise on cerebral blood flow and angiogenesis, facilitating information processing caused by release of dopamine and / or norepinephrine, improved mood and decreased depression, and finally the up-regulation of neurotropins.

While evidence has shown some promising results, the cost of equipment, the labour-intensive requirements, and the uncertain clinical efficacy compared traditional therapy, all support the need for further studies into the viability and true benefits of this therapy.

ELECTRICAL STIMULATION

Electrical stimulation is a non-invasive and simple technique used extensively by physiotherapists, mid-wives and nurses both in the health-care and home setting.(65) It has been used mainly for the management of acute and chronic pain.(66)Various electrical stimulators have been developed for the therapeutic stimulation of tissues. Aside from pain management, electrical stimulation may also be used to contract or relax muscles, and to enhance bone growth. The stimulation is by a portable pulse generator which delivers pulsed currents across the intact skin surface via conducting pads called electrodes. The many different types of electrical stimulation can be classified as:

- Neuromuscular stimulation (NMS)
- Electrical muscle stimulation (EMS)
- Functional electrical stimulation (FES)
- Transcutaneous Electrical Nerve Stimulation (TENS)

The electrical generators commonly used in clinical practice are of the following types:

*Traditional low-voltage current generators, delivering less than 100 volts, below 1 Hz

*High-Voltage direct current generators, with a very short-duration pulse to facilitate penetration in the range of 300 to 500 volts.

*Interferential current generators, delivering between 4000 and 4100 Hz, at a net frequency within the interference zone ranging between 80 to 100 Hz. Its power however lies in the low-voltage range.

*Trancutaneous Electrical Nerve Stimulation units, used specifically for nerve stimulation with frequencies ranging between 1 to 120 Hz, pulse width of 50 to 300μsec, with a medium range amplitude of 10 to 50 mAmps.While an increasing number of devices have been reported in literature, the main types of transcutaneous stimulation described at the

conventional type, acupuncture type and intense type. (67) The conventional type remains the most commonly used for delivery of current in clinical practice. (68)

*Medium-frequency generators, designed to deliver specific frequencies ranging from 2400 to 2500 Hz, useful especially in the management of sports injuries.

*Subliminal generators, delivering stimuli at a non-sensory level to specific targets (acupuncture or trigger points)

*Programmed units, which are tailored towards home use, with variable parameters for delivering stimuli and monitoring facilities

TYPES OF ELECTRODES

- Commercial pads and rubber-coated electrodes, with various mechanism of attachment to the skin surface
- Moistened paper towels, with aluminium foil leads, requiring alligator clips for connection to the leads
- Sponge pads with rubber carriers and electrodes inserted within.
- Carbonized rubber electrodes used in (TENS) which require gel for transmission of stimuli
- Copper-tipped electrodes used for internal administration (intra-vaginal)

ELECTRODE DIMENSIONS:

Treatment technique and current configuration determine electrode sizes which can be varied:

- Equal sizes: they ensure equal distribution of current
- Differential sizes: for shaping of current
- Special instruments for internal administration of current

ELECTRODE TIPS

- Alligator Tip: for connecting aluminium plate electrodes
- Banana Tip: for standard receptors
- Telephone Tip: for pin-shaped receptors
- Snap Tip: for button-type connections

SECURING DEVICES

These devices are required to inhibit movement of electrodes during the administration of electrical stimuli. They have to be composed of an insulating material to prevent conduction of electrical stimuli across their surfaces. They are:

- Soft-rubber sandbags
- Lightweight sandbags
- Adhesive gels
- Velcro bands
- Adhesive tapes

TYPES OF CURRENT:

- Alternating Current: This offers alternating polarity upon recurrent altering between positive and negative numerous times per second. Sine waves are generated when the alternating phases are equal in energy and smooth. It generates a comfortable waveform, usually used for application to neuromuscular components with no reaction of degeneration (RD)

- Direct or Galvanic current which represents a constant flow of electrons from the negative to the positive electrode without any alterations (constant polarity)

- Continuous direct current is one which is used only for iontophoresis.

- Interrupted (pulsed) direct current was used in the past for stimulation of neuromuscular components with RD, as their ability to respond to alternating current has been lost. However it seldom used now in view of its adverse effects on muscle fibers being stimulated.

- Surged direct current which is also rarely used nowadays because of its slow wave rise, leading to tissue accommodation, which in turn causes minimal or no contraction

- Faradic current can safely used with neuromuscular tissues without any RD. Resembling alternating current in most traits, it tends to cause more irritation

- Interferential current is unique in that it results from the combination of two high-frequency waveforms (4000 and 4100 Hz) in a crossed pattern. This net frequency which results from the cancellation or reinforcement phenomena near or at the crossing point roughly equals a 100 Hz. Its penetrating quality is attributed to higher frequencies and a shorter pulse width to reach deeper tissues. Unless high amplitudes are used, this current does not produce visible contractions.

- High Voltage-pulsed Galvanic Current: To be effective in improving muscle strength, electrical stimulation should be capable of producing strong muscular contraction with a low pain response. To produce such an effect, the electric pulse should be have

an altered waveform, duration, frequency and intensity to minimize pain and discomfort. Slow rising pulses minimize pain while high voltage-pulsed galvanic current (HVPC) with its short duration and deep penetration provide effective stimuli to strengthen muscle. High voltage generators produce upto 500 volts, with a short duration (lesser than 100msec), a high peak (up to 2 amperes) with a low average current (less than 150mAmps). The waveform consists of a twin-peaked pulse, spaced 40-80msecs apart.

Three major modes can be used to administer the above mentioned forms of current:

- Continuous Mode: When rate or frequency of stimulus exceeds 50Hz, it is more useful for relaxation of muscle spasm
- Surged Mode: this mode is used to attain maximum current intensity within microseconds to milliseconds. Slow surges (5 to 10 in a minute) stimulate slow muscle fibres better.
- Interrupted or Pulsed Mode: with sharp interruptions, alternating current can reach peak intensity immediately, leading to a brisk muscle response, being suitable for fast muscle fibre stimulation. Pulses exceeding frequencies of 50 Hz cause titanic contraction.

WAVEFORMS

- Sine wave: offer equal energy levels in both the positive and negative phases
- Rectangular Wave: This wave usually describes direct current with a sudden rise, followed by a prolonged duration and a sharp drop-off.
- Spike Wave: this waveform is characterised by a rapid rise rate which is not sudden, then falling rapidly back to zero immediately after attaining maximum amplitude.

- Combined waves: this wave resembles a combination of both the rectangular and spike waveforms.
- Twin-spiked Forms: this waveform achieves greater penetration of the stimulus applying an extremely short pulse width, as in high voltage galvanic stimulation.

PARAMETERS OF ELECTRICAL STIMULATION

- FREQUENCY (Pulse Rate): Frequencies ranging between 80 to 120 Hz are recommended for acute conditions of pain. The resulting tetanising rate produces smooth contraction, which in turn causes relaxation of muscle spasm. Contrarily, low frequencies of 1to 20 Hz are recommended for chronic conditions to stimulate endorphin production and analgesia.

- DURATION (PULSE WIDTH): With most equipment available today, pulse width ranges between 50 and 500 msec. While a medium width of 150 msec is preferred most, increases in pulse width cause an apparent increase in strength of the stimulating current as it is in the "on" phase for a longer period.

- AMPLITUDE (INTENSITY):When subjecting a muscle to electrical stimulation, a visible contraction as tolerated by the patient is recommended as a guide for setting the intensity of stimulation. In interferential current however, the effects are too deep and localized for the therapist to see or feel. Being cautious in patients with impaired sensory function, patient response can be a guide for regulating the intensity of the electrical stimulus.

- MODULATION: current is modulated with the long-term application of TENS for pain management. Modulation of frequency, duration or amplitude can be done with the goal of reducing accommodation or the body's adaptation to the electrical current stimulus.

- BURST PHENOMENON: The burst mode is beneficial for muscle stimulation as it resembles the interrupted mode and may also be used in TENS.

Conventionally, the stimulation is administered using electrical characteristics which selectively activate large diameter (Aβ) 'touch' fibres, avoiding smaller diameter (Aδ and C) nociceptive fibres. This delivers a strong but comfortable paraesthesia at the site of administration, using frequencies ranging between 1-250 pulses per second (p.p.s) and pulse durations between 50-1000 μs. Electrical stimulation has few side-effects or drug interactions and no potential for toxicity or overdose, and patients may themselves titrate the dosage as required. In these ways, it is more cost-effective when compared with long-term drug therapy.

HISTORY OF ELECTRICAL STIMULATION

Evidence of transcutaneous electrical stimulation exists from time of ancient Egyptian civilization which used electrogenic to treat ailments in 2500BC. The Roman physician ScriboniusLargus first documented a report of the use of electrogenic fish in AD46(69)The eighteenth century saw the development of electrostatic generators which were increasingly used by physicians, but declined in popularity due to variable clinical results and other available therapeutic measures. In 1965 Melzack & Wall provided the physiological

rationale for relieving pain with electricity. They proposed that pain-inhibitory pathways descending from the brain and activity in large diameter peripheral afferent nerves can be harnessed to block transmission of noxious information to the brain.

PHYSICAL PRINCIPLES

The standard device delivering transcutaneous electrical stimulation target large diameter nerve fibres such as Aβ and Aα which have low thresholds of activation, when compared to small diameter Aδ and C fibres. The current amplitude required to excite a nerve fibre declines with an increase in pulse duration and frequency. Selective activation of large diameter (Aβ) fibres without activation of small diameter Aδ and C fibres can hence be achieved with low-intensity, high-frequency (10-250Hz) currents with pulse duration between 10 and 1000 μs.(70)

As the impedance of intact skin and underlying tissue is complex and non-homogenous, it is difficult to exactly predict the distribution of current passing through it. With the pulse frequencies used in conventional transcutaneous electrical stimulation, the current is likely to remain superficial, stimulating cutaneous nerve fibres rather than deep-seated visceral and muscle nerve fibres. The pulse waveforms available in devices can be divided into monophasic and biphasic waveforms. (FIG 17.5) The cathode which is usually identified using a black lead excites the axon and in practice, it is placed proximal to the anode to prevent the hyperpolarisation that could block nerve transmission. (Fig 17.6) Devices using biphasic waveforms alternate the cathode and anode between the two electrodes, resulting in zero net current flow. This prevents the build-up or polar concentration of ions that could cause adverse skin reactions.(70)

MECHANISM OF ACTION

Spasticity and motor dysfunction in upper motor neuron lesions result from a combination of lack of descending supraspinal control and a decrease in presynaptic inhibitory mechanisms acting on muscle spindle afferent terminals.(71)Low threshold afferent input has been shown to reduce ongoing activity in alpha motoneurons and or interneurons via segmental, supraspinal or propriospinal pathways.(72)Speculation has also attributed the release of inhibitory neuromodulators for the effects of electrical stimulation on pain management.(73)Previous studies have shown electrical stimulation to produce significant prolongation of H and stretch reflex latencies in calf muscle spasticity, lasting up to 60 minutes following the stimulation.(74)

As spasticity was partly related to enhance stretch reflex excitability(75), Levin & Chan repeated electrical stimulation over a period of weeks (15 days of 60 minute sessions) to observe the effects on hyperactive stretch reflexes, subjective spasticity and maximal voluntary isometric ankle contractions among hemiparetic subjects. They were compared against placebo stimulation applied to a similar group for the same period and found to be beneficial.Repetitive electrical stimulation is speculated to have improved dorsiflexor function by increasing presynaptic inhibition, reducing hyperexcitability of the soleus stretch reflex, and reducing the EMG co-contraction ratio. These changes could have been mediated by plastic mechanisms such as sprouting of intact descending pathways, making new synapses with motoneurons or re-organizing somatosensory-motor cortical connections.(76)

PRINCIPLES FOR APPLICATION OF ELECTRICAL STIMULATION

ELECTRODE POSITION

Electrodes should always be applied to healthy innervated skin. In the case of pain management, they are placed either at the site of pain, proximal to the site of pain over the main nerve trunk innervating that area or over the spinal cord at segments associated with the origin of pain. In cases of spasticity management, electrodes have been placed over the target muscles, nerves supplying the muscles wherever they are sufficiently superficial and accessible, and over the appropriate segments of the spinal cord responsible for innervating of the target muscle.

PREPARATION OF THE PATIENT:

- The skin where electrodes will be placed must be cleaned thoroughly
- Special gels, sprays or water may be applied to the skin as medium to facilitate stimulation
- Electrodes are fixed in position using mending tapes ensuring good contact throughout the period of stimulation. Adhesive electrodes are also available and were used for stimulation by therapists in this study.

ELECTRODE PLACEMENT

Electrode placement is determined by the target nerve, muscle or muscle group.

Placement alternatives recommended are:

- Unilateral: This type of electrode placement is used for stimulation of a limb or one half of a muscle pair.
- Bilateral: This type of stimulation can be used to target both limbs or, both halves of a muscle pair.

- Unipolar: In this technique the motor point is stimulated with the active electrode placed over the target muscle, while the indifferent electrode is placed elsewhere.
- Bipolar: In this technique, two electrodes are used to target the muscle, close to the origin or the insertion.
- Bilateral unipolar: In this technique the electrodes are placed on each of two separate muscles or muscle groups
- Reciprocal: The active electrode is placed on two separate muscles or muscle groups, either agonist or antagonist, or bilaterally, with the indifferent electrode place elsewhere just as in the case of the unipolar technique.
- Interferential: With a minimum of four electrodes, they are placed in crossed pattern over the target area, around 4 to 6 inches apart. The cruciate pattern may also be three-dimensional (lateral/posterior/medial), as in the case of knee or shoulder joints.
- Trans-Arthral: The electrodes are placed on two sides of the target joint. Current is not to pass across the joints, but flows around the joint between the electrodes.

ELECTRICAL CHARACTERISTICS

In conventional electrical stimulation for the management of pain, selective activation of Aβ fibres is targeted such that the impulse causes strong but comfortable paraesthesia, without muscle contraction. A continuous pulse pattern is used with frequency ranging between 10 and 200 p.p.s,and pulse duration ranging between 100 and 200 μsec. Total duration of stimulation lasts for a minimum of 30 minutes. The parameters we used in our study applying electrical tibial nerve stimulation for modifying spasticity were based on previous studies conducted on patients with spastic hemiplegia and have been specified in the section on Materials and Methods.

DECLINING RESPONSE TO ELECTRICAL STIMULATION

Users have claimed that the effectiveness of electrical stimulation can decline over time, although the exact proportion of patients is unknown. With regard to pain relief, studies have shown patients reporting that the magnitude of pain relief from electrical stimulation may decline by around 40% over a period of one year. The decline can be due to multiple causes including weakening batteries, dysfunctional lead electrodes or worsening pain or spasticity. Patients havealso been reported to habituate to the stimulatory current owing to progressive failure of the nervous system to respond to a monotonous stimulus.

CONTRAINDICATIONS

1. Seizures: As it would be difficult to prove side-effects of stimulation as not being the cause of seizures, it is generally advised to avoid doing transcutaneous electrical stimulation among epileptic patients.

2. Pregnant women in the first trimester are not advised to undergo electrical stimulation as there is a risk of inducing labour; administering electrical stimulation over the pregnant uterus is also not permitted in the management of labour pain.

3. Patients with cardiac pace-setter as it could potentially interfere with the implanted electrical devices.

4. Electrical stimulation should not be administered for the management of pain without a physician diagnosing the etiology and prescribing this modality.

5. Other areas of the body over which electrical stimulation should not be administered are as follows:
    a. The carotid sinus
    b. On broken skin
    c. Over dysaesthetic skin
    d. Over mucosal membrane such as within the mouth

MATERIALS & METHODS

INCLUSION CRITERIA

All patients who had past history of a cerebrovascular accident and attending the weekly Stroke Clinic at our outpatient department were screened. Spasticity was graded according to the Modified Ashworth scale, specifically looking for clonus at the ankle joint of the paretic side of the body. Patients between the ages of 18 and 75 years, without any past history of cardiac arrhythmias, not using pacemakers or metal implants in the lower limbs were given informed consent forms. Pregnant women and patients with fixed flexion deformities or contractures involving the knee or ankle joints were also excluding during the screening process; Patients consenting to join the study were then directed to the physiotherapist who would administer the posterior tibial nerve stimulation.

SAMPLE SIZE CALCULATION

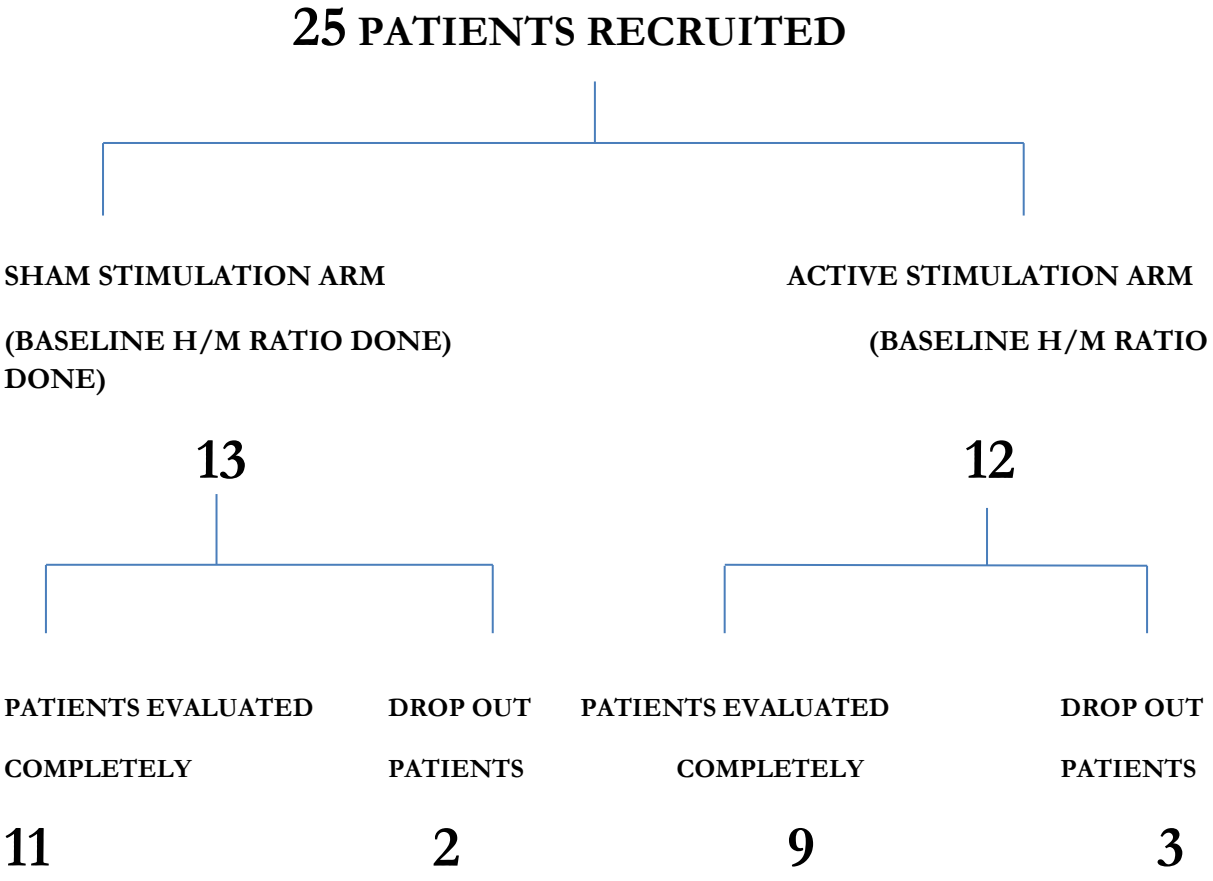
The sample size was calculated based on the results of a study on the relief of spasticity using electrical stimulation in patients who had past history of a cerebrovascular accident. A sample size of 24 with 12 in the sham arm and 12 in the active arm were needed to detect a difference of 30 units in the H/M ratio with a standard deviation of 31.8 and 20.5 in the active and sham arms respectively. The sample size was calculated for an error of 5% and power of 80%.

STUDY DESIGN

This was a randomized controlled study conducted on in-patients as well as patients attending our weekly stroke clinic, with history of a cerebrovascular accident including ischemic and hemorrhagic strokes as well as cortico-venous thrombosis. Patients were recruited over an eighteen month period between April 2013 and August 2014. On an average, around 25 patients would attend each weekly clinic conducted for patients who had survived a cerebrovascular accident. These patients were screened by physicians for ankle clonus and spasticity of the gastrosoleus muscle on the paretic half of their body. After an informed consent was taken, a physician would take a detailed history and record data as per the proforma shown in appendix 1. A baseline recording of H/M ratio was also taken at this stage. Subsequently, patients were assigned by a physiotherapist into one of two groups (A) or (B) based on the randomized allocation, concealed in a sealed envelope given to the patient. The physiotherapist would then administer the electrical stimulation to the posterior Tibial nerve on the paretic lower limb via 2 adhesive patch electrodes attached behind the medial maleolus as shown the figure below. The anode was denoted by the patch attached to a black wire and stuck 2 centimetres proximal to the cathode denoted by the patch attached to a red wire. The electrical stimulus was delivered from a device connected to the patch electrodes by one of two wires marked A or B. Neither the physiotherapist nor the physician performing the H/M Ratio knew whether wire A or wire B was active. The stimulation was administeredover a period of 20 minutes on a daily basis for 2 weeks.

RANDOMIZATION OF PATIENTS

Randomization was done using computer generated random number allocation, placing patients in one of 2 groups (A or B) – the control group receiving the standard protocol of stroke rehabilitation and the intervention group receiving additional PTNS. Standard protocol of stroke rehabilitation in our department consists of 4 hours each of physiotherapy and occupation therapy and when necessary, additional speech therapy. Neither the investigator responsible for randomized allocation of patients, nor the physiotherapist administering the stimulation were aware of which group was receiving active and which group the sham stimulation.


25 PATIENTS RECRUITED
SHAM STIMULATION ARM
(BASELINE H/M RATIO DONE)
DONE)
ACTIVE STIMULATION ARM
(BASELINE H/M RATIO
13
12
PATIENTS EVALUATED
COMPLETELY
DROP OUT
PATIENTS
PATIENTS EVALUATED
COMPLETELY
DROP OUT
PATIENTS
11
2
9
3

INTERVENTION

The electrical stimulator was indigenously made by the Department of Bioengineering in our institution with the parameters of stimulation being **a pulse width of 200 microseconds (µsec), frequency ranging between 32 Hz, and a supra-threshold intensity ranging between 2 and 100mA of current**. This stimulus was applied by an assigned physiotherapist, just posterior to the pulsatile Posterior Tibial artery, located behind the medial malleolus of the spastic lower extremity. The stimulation was administered through a wire connecting the stimulator to adhesive electrodes applied to the afore-mentioned location on the paretic lower limb. One of two wires coded 1/A or 2/B were used to connect the adhesive skin-electrodes to the stimulator. The sham wire was internally disconnected and information of which of the two wires was the sham wire, was only divulged at the end of the data collection, at the time of analysis.

The current from the CMC-DAQ (Data Acquisition System) electrical stimulator were delivered at the posterior tibial nerve using self-adhesive pad electrodes (50x50 mm, made by Sunrise). Polarity of the electrode placement was marked at the beginning of the period of stimulation. (i.e. cathode posterior to the medial malleolus).

Patients in both groups underwent 20 minutes of stimulation per session, once a day for 2 weeks. Simultaneously they continued the standard in-house protocol which constitutes 4 hours each of physiotherapy and occupation therapy. Patients who required speech therapy spent a stipulated amount of time with the speech therapist as well. A history of medications taken prior to and during the time of stimulation were noted although none of them were stopped.

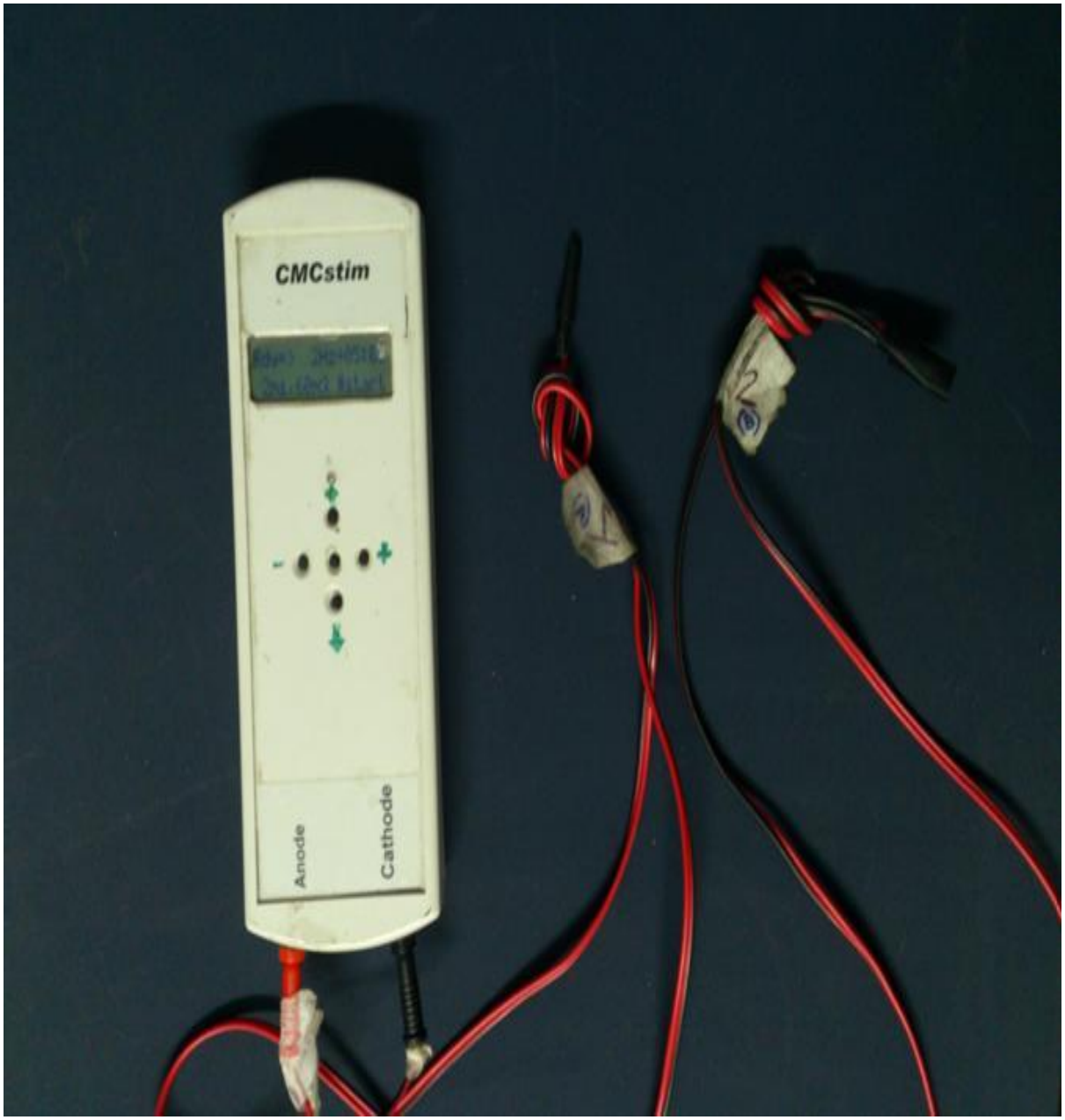


Figure 7 Indigenous Electrical Stimulator

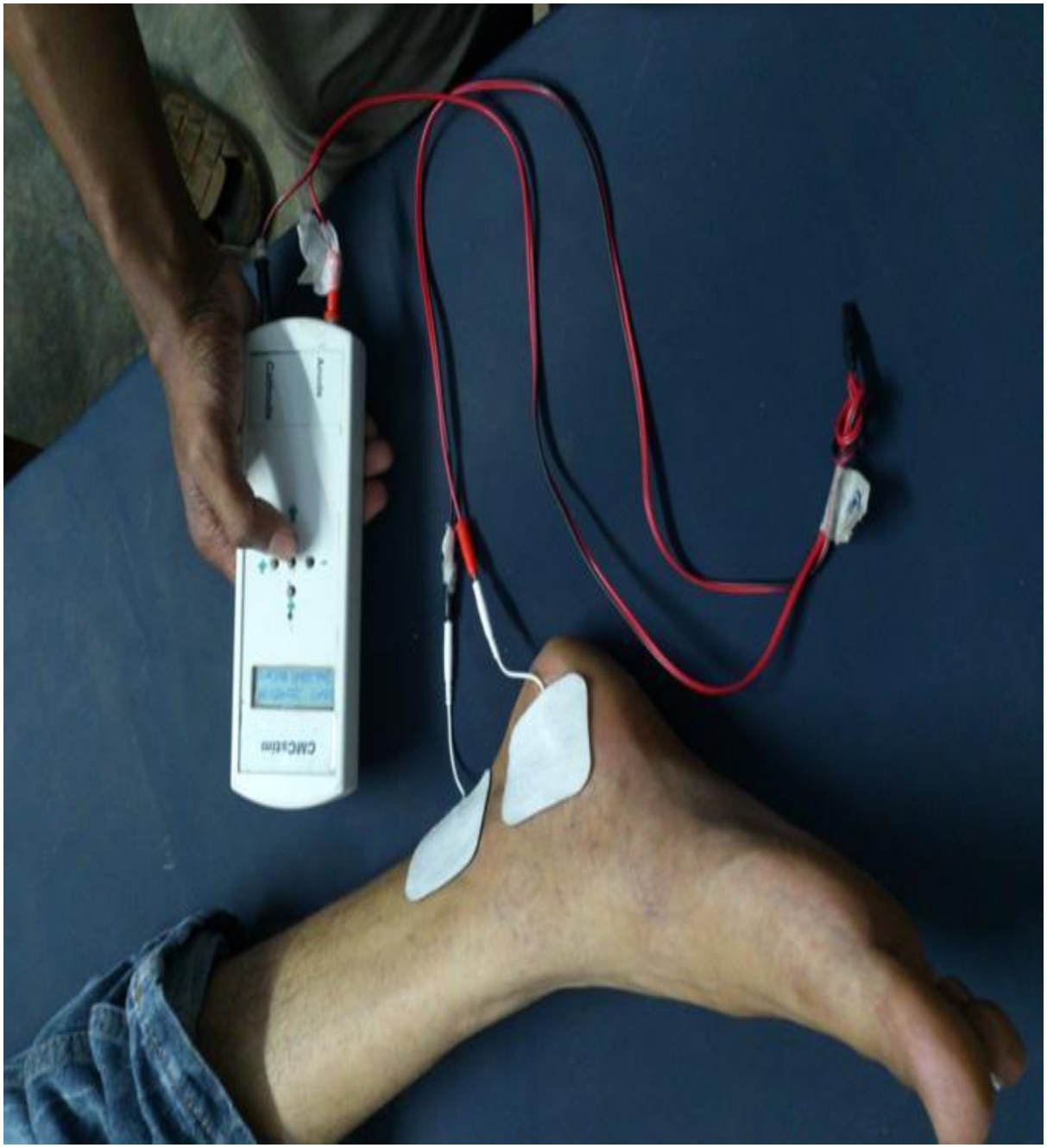


Figure 8 Administering Electrical Stimulation to the Posterior Tibial Nerve

MEASUREMENT OF H/M RATIO:

The machine and software used to obtain the values of H/M Ratio was the Synergy range of multimedia EMG/EP systems designed and manufactured by VIASYS Healthcare UK Ltd, Manor Way, Old Woking Surrey, GU22 9JU United Kingdom. The bandpass filter of the machine was set at 3 Hz to 3 kHz. Amplified signals obtained during the test were digitised and stored in the hard disk of the computer for calculation of the H-max: M-max ratio.

To obtain the H/M Ratio, we placed subjects in a prone position and the feet suspended over the end of the bed and the head resting on a pillow. A surface bar-electrode (Medelec Synergy) with the cathode end facing distallywas placed over the bulk of the Soleus muscle. We prepared the electrode sites by shaving the skin and preparing it with conducting gel. A reference ground electrode was placed 5 centimetres below the Popliteal crease.

The Soleus H-Reflex was elicited by stimulating the tibial nerve in the Popliteal fossa. A hand-held electrode was used to locate the optimum point for nerve stimulation. This motor point of stimulation was determined by its propensity to yield the largest M wave amplitude during low-intensity stimulation. The nerve stimulus was a 1millisecond monophasic square pulse generated by a constant current stimulator. Initially the optimal location for Tibial nerve stimulation in the popliteal fossa was determined by re-positioning the stimulating electrode around till a contraction of the gastrocnemius muscle was clearly visible. The current was subsequently gradually increased till an H reflex was recorded. Rejecting the other values, only the largest amplitude obtained was selected as the H-max. The H reflex was identified by the emergence of a triphasic wave with a small positive deflection followed by a larger negative deflection.

We analyzed the H-Reflex responses by measuring the peak-to-peak amplitude. The stimulus intensity was gradually increased from a level below the H-Reflex or M wave threshold to one capable of eliciting the maximal M wave amplitude. The M wave was analysed by measuring the baseline to peak amplitude. The ratio of the H-max and M-max values was calculated by dividing the maximum amplitude of the H reflex by that of the M wave.

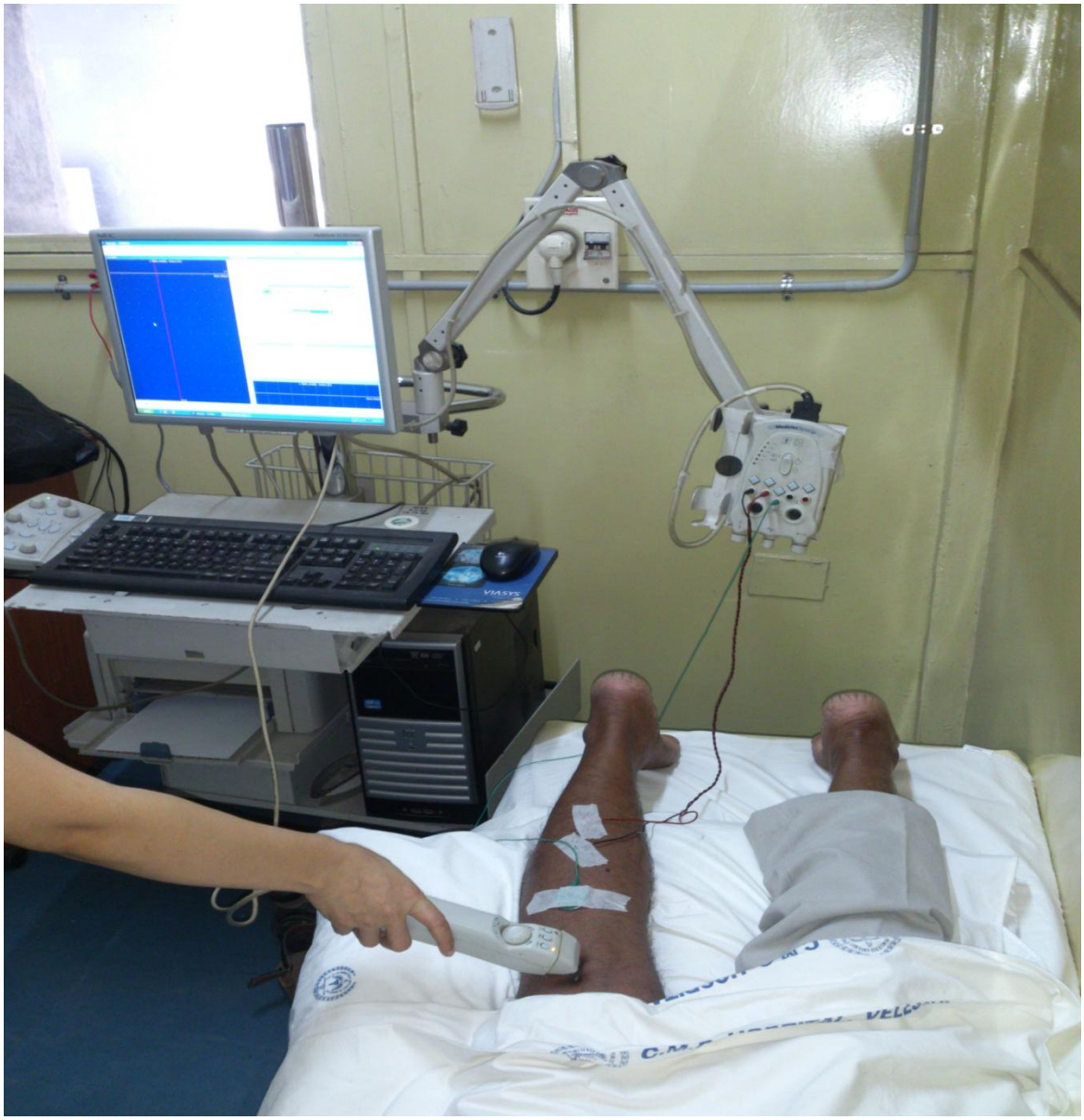


Figure 9 Measurement of H/M Ratio

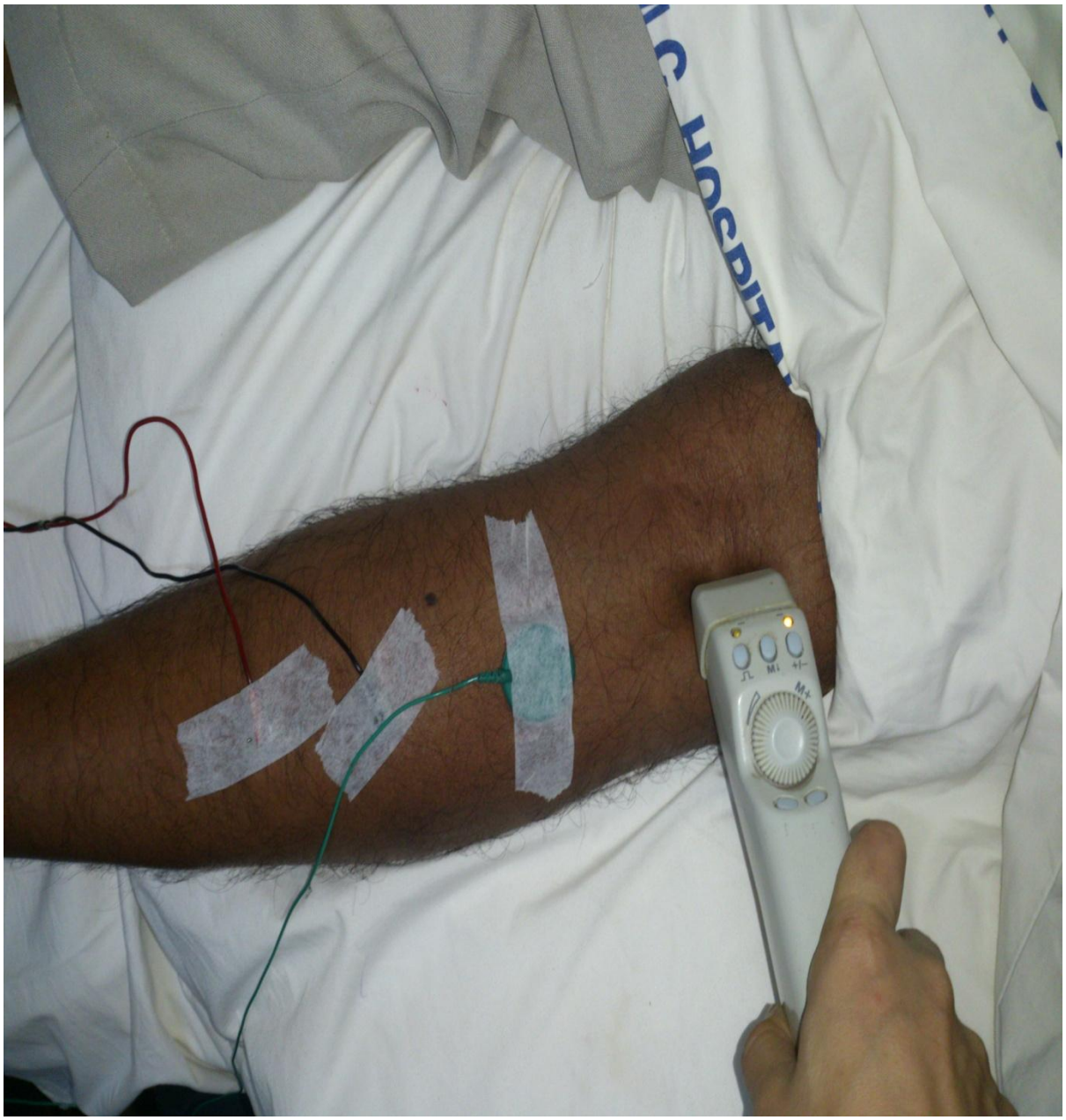


Figure 10 Placement of electrodes and stimulator in measuring H/M Ratio

STATISTICAL ANALYSIS

The data analysis was done using STAT software version 13. The descriptives are provided with the median along with a range for continuous variables, as the data is skewed. The categorical variables were presented with frequency along with percentage.

The pre and post intervention differences in both groups were analyzed using Wilcoxin signed rank test. The percentage change among the two groups was compared using the Mann-Whitney u test.

The baseline characteristics were analysed among the two groups using the Fisher's exact test if the variable was categorical, and if the variable was continuous, the Mann-Whitney u test was used.

RESULTS

The various parameters of subjects recruited were analysed among the two groups in the study. Group 2 received active stimulation to relieve spasticity and group 1 received the sham stimulation.

Factors that are likely to influence the spasticity were compared between the two groups and included demographic characteristics as well as factors that are known to worsen spasticity.

Demographic characteristics compared included the following:

There were 11 patients in the stimulation arm 9 in the control or sham group. Although more males were recruited in the sham group, based on the Fisher's exact test, the gender of subjects in each group was found to be insignificant as per the Fisher's exact test. (p=0.056) (Table 1.)

Table 1. Gender distribution of patients enrolled in the study

GENDER	**ACTIVE INTERVENTION ARM (No. ; %)**	**SHAM GROUP (No. ; %)**	**TOTAL**
MALE	10 ; 90.9	5 ; 55.55	15 ; 75
FEMALE	1; 9.09	4 ; 44.44	5 ; 25
TOTAL	11 ; 100	9 ; 100	20 ; 100
P = 0.056			

The aetiology of cerebrovascular accident among the recruited patients was compared between the active intervention and sham stimulation groups. The percentages of patients with thrombotic strokes were 54.5 and 66.6 percent, while those with hemorrhagic strokes were 27.27 and 11.11 percent respectively among the sham stimulation and active intervention groups. The percentages of patients in each group with cerebral venous thrombosis were comparable at 18.18 and 22.22% and were hence not significantly different.

Table 2. Etiology of cerebrovascular accidents among Patients

DIAGNOSIS	**SHAM STIMULATION ARM (No. ; %)**	**ACTIVE INTERVENTION ARM (No.; %)**	**TOTAL (No. ; %)**
Infarct	6 ; (54.55)	6 (66.67)	12 (60)
Hemorrhage	3 ; (27.27)	1 (11.11)	4 (20)
CVT	2 ; (18.18)	2 (22.22)	4 (20)
TOTAL	11 ; (100)	9 (100)	20 (100)
(P-value: 0.66)			

When comparing the trends of increase and decrease in spasticity as measured by the H/M Ratio, there was no significant change noticed based on the aetiology of the cerebrovascular accident.

Table 3. Comparison of H/M Ratios based on aetiology of cerebrovascular accident

Diagnosis	**ACTIVE INTERVENTION ARM**		**Total**	**SHAM STIMULATION ARM**		**Total**
	Patients with Increase in H/M Ratio No. ; (%)	**Patients with Decrease in H/M Ratio No. ; (%)**		**Patients with Increase in H/M Ratio No. ; (%)**	**Patients with Decrease in H/M Ratio No. ; (%)**	
Infarction	2 (66.67)	4 (66.67)	6 (66.67)	2 (40)	4 (66.67)	6 (54.55)
Hemorrhage	0	1 (16.67)	1 (11.11)	2 (40)	1 (16.67)	3 (27.27)
CVT *	1 (33.33)	1 (16.67)	2 (22.22)	1 (20)	1 (16.67)	2 (18.18)
TOTAL	3 (100)	6 (100)	9 (100)	5 (100)	6 (100)	11 (100)
*__CVT__: Corticovenous Thrombosis						

Only one patient in the intervention group had reached the hospital within the stipulated time to receive thrombolysis. Surgical management of the cerebrovascular accidents among the recruited patients were not significant with 16.67 % and 20% among each of the study arms.

The baseline characteristics of risk factors contributing to the development of cerebrovascular accidents were compared. The most common risk factors contributing to the development of cerebrovascular accidents include smoking, Type II Diabetes Mellitus, hypertension, underlying vasculitis, elevated Homocysteine levels, carotid artery disease, ischemic heart disease andvalvular heart disease.A significant difference in the presence of these risk factors among the patients in each study arm was not detected, as evident in the Table 4.

Table 4. Intrinsic Risk Factor Profile of Study Patients for CVA

Risk Factor	Active Stimulation Arm Number, (%)	Sham Stimulation Arm Number, (%)	P-value
Type II Diabetes	2,(22.22)	3,(27.27)	>0.99
Hypertension	4,(44.44)	5,(45.45)	>0.99
Vasculitis	0	0	-
Homocysteinemia	2,(36.36)	2,(22.22)	0.64
Carotid Disease	3,(33.33)	5(50)	0.65
Ischemic Heart Disease	1(12.5)	0	0.42
Valvular Heart Disease	1(12.5)	0	0.42

Seizures as a complication of cerebrovascular disease could have a bearing on the management of spasticity. Many commonly used anti-epileptic drugs like Benzodiazepines are known to also reduce spasticity.Among the two patients in the active groups and 3 in the sham group had a history of seizures and were on AED. These medications were not changed during the course of the study. Seizures were not observed as an adverse effect following the initiation of electrical stimulation as an intervention in our study.

Table 5. Change in outcome measures based on presence of seizures

Change in H/M Ratio (Level of Spasticity)	**ACTIVE INTERVENTION ARM (No. ; %)**		**TOTAL**	**SHAM STIMULATION ARM (No. ; %)**		**TOTAL**
	SEIZURES ABSENT	SEIZURES PRESENT		SEIZURES ABSENT	SEIZURES PRESENT	
DECREASED	3 (42.86)	0	3 (33.33)	3 (37.50)	2 (66.67)	5 (45.45)
INCREASED	4 (57.14)	2 (100)	6 (66.67)	5 (62.50)	1 (33.33)	6 (54.55)
TOTAL	7 (100)	2 (100)	9 (100)	8 (100)	3 (100)	11 (100)

Factors contributing to the worsening of spasticity were also analysed with regard to the response to electrical stimulation.While there were 2 people in the sham stimulation group who had urinary cultures showing urinary infection after diagnosis of the cerebrovascular accident was made, none of the patients in the active intervention group had previous evidence of a urinary tract infection. While none of the patients in the active intervention group were found to have radiological evidence of heterotopic ossification (HO) or deep vein thrombosis (DVT), in the sham stimulation group, one patient was found to have HO and one had developed DVT. In-grown toe-nails and urinary tract calculi were the other factors that were screened for among the recruited patients, known to develop worsening of spasticity. However these two factors were observed in neither the sham stimulation, nor the active intervention arms of the study.

Table 6. Profile of Risk Factors for Development of Spasticity among study patients

Risk Factor	Active Stimulation Arm Number, (%)	Sham Stimulation Arm Number, (%)	P-value
Urinary Tract Infection (UTI)	0	3,(72.73)	0.21
Urinary Tract Calculi	0	0	-
Heterotopic Ossification		1,(9)	>0.99
Deep Vein Thrombosis	0	1,(10)	>0.99
In-grown toe nails	0	0	-

As urinary tract infections and heterotopic ossification were the only major risk factors for spasticity that were observed among patients in the two arms of the study, they were analysed for any effect they might have had on the levels of spasticity after 2 weeks of electrical stimulation. The results of the analyses are as shown in the tables below, showing that neither heterotopic ossification nor urinary tract infections had any significant effect on the change in spasticity (as manifested by H/M Ratio) after the two weeks of intervention.

Table 7. Effect of Heterotopic Ossification on spasticity, following the 2 week intervention

Change in H/M Ratio (Level of Spasticity)	**ACTIVE INTERVENTION ARM (No. ; %)**		**TOTAL**	**SHAM STIMULATION ARM (No. ; %)**		**TOTAL**
	H.O* ABSENT	H.O* PRESENT		H.O* ABSENT	H.O* PRESENT	
DECREASED	3 (33.33)	0	3 (33.33)	4 (40)	1 (100)	5 (45.45)
INCREASED	6 (66.67)	0	6 (66.67)	6 (60)	0	6 (54.55)
TOTAL	9 (100)	0	9 (100)	10 (100)	1 (100)	11 (100)
*H.O: Heterotopic Ossification						

Table 8. Effect of Urinary Tract Infection on spasticity, following the 2 week intervention

Change in H/M Ratio (Level of Spasticity)	**ACTIVE INTERVENTION ARM (No. ; %)**		**TOTAL**	**SHAM STIMULATION ARM (No. ; %)**		**TOTAL**
	UTI* ABSENT	UTI* PRESENT		UTI* ABSENT	UTI* PRESENT	
DECREASED	3 (33.33)	0	3 (33.33)	3 (37.50)	2 (66.67)	5 (45.45)
INCREASED	6 (66.67)	0	6 (66.67)	5 (62.50)	1 (33.33)	6 (54.55)
TOTAL	9 (100)	0	9 (100)	8 (100)	3 (100)	11 (100)

*UTI: Urinary Tract Infection

Medications commonly prescribed to manage spasticity were also screened among the recruited patients. Three people in the sham group and two in the active intervention group were using Baclofen; one person in the active intervention group was using Tizanidine while one person each in the active intervention and sham groups were using Benzodipine. The dosages of these medications were not changed during the course of the study. The number of patients using anti-spastic medication in each arm did not render any statistically significant difference between them.

Table 9. Profile of medications used for control of Spasticity among study patients

Medication	**Active Stimulation Arm Number, (%)**	**Sham Stimulation Arm Number, (%)**	**P-value**
Benzodiazepine	**1(11.11)**	**1,(10)**	**>0.99**
Baclofen	**1,(11.11)**	**3(30)**	**0.58**
Tizanidine	**0**	**0**	**-**

As Diazepam and Baclofen were the only major two drugs used to alleviate spasticity among patients in the two arms of this study, they were analysed for any effect they might have had on the levels of spasticity after 2 weeks of electrical stimulation. The results of the analyses are as shown in the tables below showing that neither Baclofen nor Diazepam had any significant effect on the change in spasticity (as manifested by H/M Ratio) after the two weeks of intervention.

Table 10. Effect ofBaclofen on spasticity, following the 2 week intervention

Change in H/M Ratio (Level of Spasticity)	**BACLOFEN IN THE ACTIVE INTERVENTION ARM (No. ; %)**		**TOTAL**	**BACLOFEN IN THE SHAM STIMULATION ARM (No. ; %)**		**TOTAL**
	ABSENT	PRESENT		ABSENT	PRESENT	
DECREASED	3 (37.50)	0	3 (33.33)	2 (28.57)	2 (66.67)	4 (40)
INCREASED	5 (62.50)	1 (100)	6 (66.67)	5 (71.43)	1 (33.33)	6 (60)
TOTAL	8 (100)	1 (100)	9 (100)	7 (100)	3 (100)	10 (100)

Table 11. Effect of Diazepam on spasticity, following the 2 week intervention

CHANGE IN THE H/M RATIO (Level of Spasticity)	**DIAZEPAM IN THE ACTIVE INTERVENTION ARM (No. ; %)**		**TOTAL**	**DIAZEPAM IN THE SHAM STIMULATION ARM (No. ; %)**		**TOTAL**
	ABSENT	PRESENT		ABSENT	PRESENT	
DECREASED	3 (37.50)	0	3 (33.33)	4 (44.44)	0	4 (40)
INCREASED	5 (62.50)	1 (100)	6 (66.67)	5 (55.56)	1 (100)	6 (60)
TOTAL	8 (100)	1 (100)	9 (100)	9 (100)	1 (100)	10 (100)

Ankle foot orthoses with wedges which maintain the toes in dorsiflexion have been known to decrease spasticity. While fifty percent of the patients in the sham stimulation used ankle foot orthoses, only twenty percent in the active stimulation group used the same. Among the patients in whom there was a decrease in spasticity manifested by a decrease in H/M ratio, 40% wore an AFO on the paretic limb in the sham stimulation arm while only 33% of the patients in the active stimulation arm were using an AFO.

The various etiological factors in the development of a cerebrovascular event and factors which are responsible for worsening spasticity among patients with stroke were screened for among the active stimulation and the intervention group. However, the number of patients in which these factors were present has not caused any statistically significant difference in the baseline characteristics of the two groups.

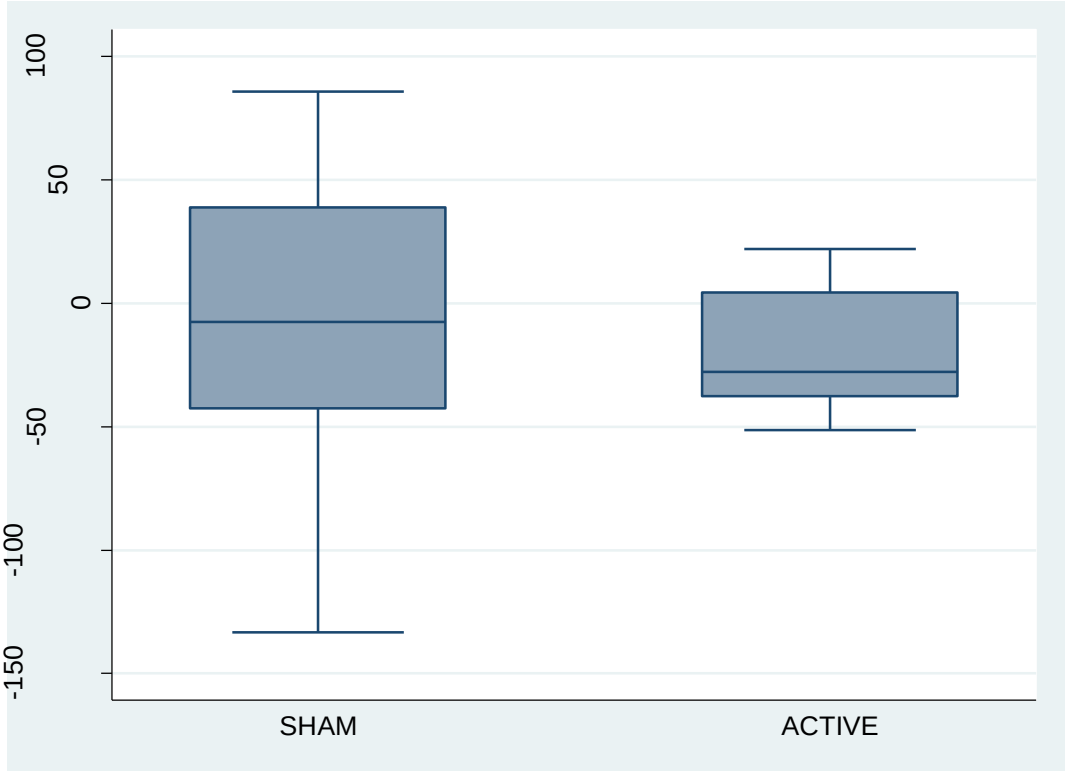


Figure 11 Percentage Change of H/M Ratio in Sham and Active Stimulation Arms

The descriptive in the graph above were presented as frequency percentages and analysed using Fisher's exact test. The percent change in the sham arm has a wider range compared to the active intervention arm. For the sham arm, the median percentage increase after the intervention is 7.46% while in the active intervention group, it is 27.87%, where the difference between the two arms is not statistically significant (p=0.38)

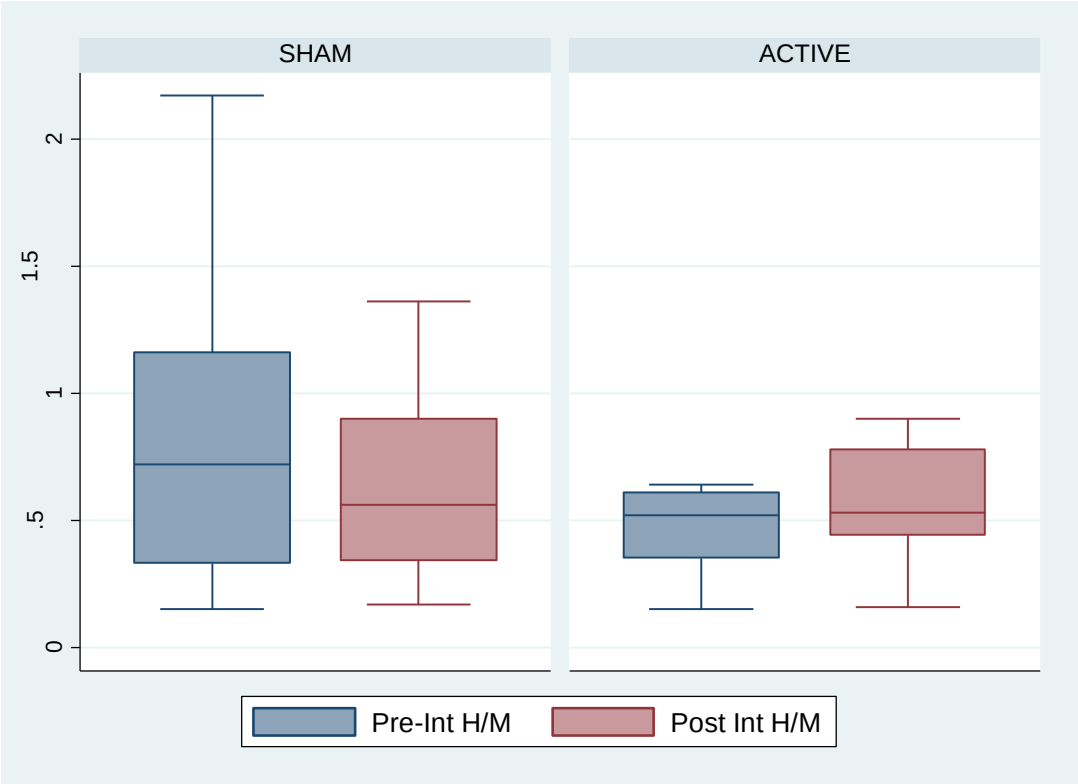


Figure 12 Comparison of Pre and Post-Intervention H/M Ratios in the Sham & Active Stimulation Groups

Comparison of the change in spasticity was done using measurement of H/M ratios at the time of recruitment and also after two weeks of intervention. The values of the change in H/M ratios were highly skewed, and since the number of patients in each arm was small, a two-sample Wilcoxon sign rank-sum test was used to compare the two arms. As demonstrated in the graph above, change in the median H/M ratio value from pre-intervention (0.72) to post-intervention (0.56) within the sham arm was not statistically significant (p=0.62). Likewise the change in the median H/M ratio value from pre-intervention (0.52) to post-intervention (0.53) in the active intervention arm was also not statistically significant (p=0.10).

With regard to the Modified Ashworth Scale scores, clonus which was observed prior to starting the intervention was observed even after the two weeks of electrical stimulation.

DISCUSSION

This study was undertaken to observe the effect of a non-pharmacological, non-invasive method to decrease spasticity following a cerebrovascular accident. Earlier studies have shown the beneficial effects of electrical stimulation. In this study, a portable device delivering a stimulus with a pulse width of 200usec, frequency of 40Hz and the intensity ranging between 0-100 mA, based on the patient's pain tolerance. These parameters can be set into a hand-held device designed by the Department of Bioengineering, Christian Medical College, Vellore. The adjustments to settings can be easily taught to patients, enabling them to administer this form of therapy themselves. The point of stimulation, namely the course of the Posterior Tibial Nerve just behind the medial malleolus where it is most superficial, can also be easily located by patients or their care-takers for administering the stimulation.

The idea of using electrical stimulation of peripheral nerves as a means of modulating spinal excitability has been propounded in earlier studies. Levin and Hui-Chan had performed studies comparing the effects of active electrical stimulation versus placebo stimulation on the common peroneal nerve of spastic hemiparetic patients. Numerous studies have been done on electrical stimulation of a peripheral nerve to reduce spasticity in the detrusor muscle of the bladder, including one within our own institution (77) . The study by Levin et al demonstrated significant benefits with repeated application of electrical stimulation. Although patients in this study also underwent 15 days of electrical stimulation, the duration of the therapy session itself was longer, with each lasting 60 minutes compared to 30 minutes used in our study protocol.

Spasticity was evaluated in this study by both a clinical scale and an electrophysiological test. While it is the most widely used clinical assessment of spasticity, the Modified Ashworth Scale (MAS) has been shown to have much inter-rater variability and hence the need arose

for a more objective test. The H-reflex is known to be a reflexion of spinal anterior horn cell excitability and was hence the H/M ratio has been utilized to objectively measure spasticity which is determined by the level of spinal excitability. Clinically, patients in both arms were found to have spasticity in the form of ankle clonus, even after the two weeks of electrical stimulation. While the H/M ratio was not found to decrease in all the patients studied, there was no statistically significant improvement in the H/M ratios.

Electrical stimulation was offered as an additional mode of therapy supplementing the standard therapy. Patients were also expected to continue anti-spastic medication that they were taking prior to being enrolled in the study. There was no significant difference between the groups in terms of the number of patients on anti-spastics, namely Benzodiazepine ($p>0.99$) and Baclofen ($p=0.58$) at the beginning of the study. While Tizanidine is another commonly used anti-spastic, none of the patients enrolled in our study used this drug. All of the three above mentioned drugs act via pathways in the central nervous system and the decision to not stop the drugs was to ensure that the prior use of an anti-spastic would not become a confounding factor in the outcomes measured at the end of two weeks of electrical stimulation.

The various factors known to aggravate spasticity were evaluated at the time of enrolment to ensure that there was homogeneity between the two groups. There was no statistically significant difference between the groups in terms of factors likely to worsen spasticity. These factors hence had no bearing on the effect of the electrical stimulation as observed in the decrease in H/M ratios

Spasticity is also known to worsen with increasing duration from the onset of hemiplegia. This is further aggravated when other complications set in, such as heterotopic ossification, urinary tract infection and deep vein thrombosis, which in turn affect spasticity. However, in

our study, there was no difference between the active intervention and the sham arms of the study with regard to the mean duration of hemiplegia from the onset of the cerebrovascular accident to the time of initiating electrical stimulation.

Other baseline characteristics evaluated were gender, prior history of seizures and interventions for management of the cerebrovascular accident that may have had a bearing on the level of spasticity and the response to treatment. While the sham arm of the study did not have any women, the active intervention group had an equal distribution of both genders. However while analysing the decrease in spasticity as measured by a decrease in the H/M Ratio, no significant difference was found between male and female patients. Prior history of seizures was also considered in the evaluation of those patients who had a drop in the H/M Ratio following the two weeks of electrical stimulation. Seizures have not been found to increase the level of spasticity; however, patients may be subsequently started on medications such as benzodiazepines for seizure prophylaxis.Medicines such as benzodiazepines which are used for management of seizures may also act on centrally acting neurotransmitters such as Gamma Amino Butyric Acid (GABA) which may affect the level of spasticity in patients. On taking a history of drugs used for seizure-prophylaxis among the three patients in the sham arm and two patients in the active intervention arm, all of them were on oral Phenytoin and in some cases, Leviteracetam was also being used. These drugs were also not stopped during the two-week course of the study. However, these drugs are not known to affect spasticity and this in turn corroborates with the lack of significant difference in the levels of spasticity and reduction of the same with the posterior tibial nerve stimulation. Other interventions immediately following the cerebrovascular accident include thrombolysis and surgery. The early detection of infarcts and thrombolysis within the permissible time frame of four hours would definitely have an impact on the overall outcome of the patient. We evaluated the effect of electrical stimulation on those patients who had undergone

thrombolysis and whether there was any supplementary benefit on the levels of spasticity. There was neither a significant difference in the numbers of patients in each of the study arms who had undergone thrombolysis, nor was there any significant difference in the improvement of levels of spasticity among those who underwent both thrombolysis as well as electrical stimulation. Only two patients in each of the study arms had undergone surgery following onset of the cerebrovascular accident. Surgery in the event of raised intra-cranial tension following the cerebrovascular accident, would also improve the over-all survival outcome. The raised intracranial tension, for which surgery was indicated, also did not show any effect on the baseline levels of spasticity among the patients who required surgical intervention. There was no significant decrease in the level of spasticity among those who underwent surgery among patients in either arm of the study.

Underlying diseases among the patients such as diabetes were also considered in their effect on the outcome following spasticity as measured by the H/M ratio. Although no formal assessment of nerve conduction was conducted on the Posterior Tibial Nerve on the paretic side of the study patients, the effect of peripheral neuropathy on conduction may have a bearing on the efficacy of electrical stimulation. Only three out of eleven (22.2%) patients in the sham arm and two out of nine (27.2%) patients in the active intervention were known to have diabetes mellitus as an underlying risk factor for a cerebrovascular accident. These numbers did not contribute significantly to any change in the baseline characteristics of the two arms that might have had a confounding effect on the efficacy of the electrical stimulation.

Limitations of the study and Scope for Further Studies

This study was conducted with the primary objective of evaluating if electrical stimulation with a reasonably priced device which was affordable and easily portable for patients could have an added benefit in the management of spasticity. If patients could be further segregated based on prior use of anti-spastic medication, a cost-effectiveness study could also have been done to assess any monetary advantage that the device delivering electrical stimulation might have over the anti-spastic drugs.

The other benefit that electrical stimulation was speculated to have over anti-spastic medicines was that of avoiding the sedative effects of the latter. The sedative adverse effects of anti-spastic medication have been known to decrease compliance with scheduled physiotherapy and in carrying out activities of daily living. This in turn can have a bearing on the overall quality of life of a patient. No formal assessment of levels of sedation, participation in activities of daily living or compliance with scheduled physiotherapy was compared in this study between patients receiving electrical therapy versus those receiving anti-spastic medication alone. Studying the above-mentioned benefits of electrical stimulation over anti-spastic medication was beyond the scope of this study as ethical clearance was not obtained for the withdrawal of anti-spastic medication in patients with spastic hemiplegia.

The objective measure of spasticity we chose in this study was the H/M ratio. Levin and Hui-Chan in their study on the effect of electrical stimulation on spasticity in hemiplegic patients also did not see a significant effect on the H/M ratio, despite a decreasing trend in the same after 2 weeks of this therapy. However a variation on the H/M ratio, namely the vibration inhibition index (Hvib/Hctl ratio) did detect a significant trend after two weeks of electrical stimulation of the peripheral nerve. As a significant change in H/M ratio was not detected in our study, we speculate whether the conducting the vibration inhibition index on the patients

in our study may have detected a significant change in levels of spasticity. The vibration inhibition index which requires the measurement of the H-reflex while a vibratory stimulus is applied over the tendon of the spastic muscle (in this case, the Achilles tendon), was not conducted in our study due to technical constraints.

Duration of electrical stimulation both in terms of the number of days of stimulation as well as that per session might not have been sufficient in this study. The studies conducted by Levin and Hui-Chan scheduled 45 minutes and 60 minutes each over a period of 15 days. In our study, we wanted to evaluate the effect of half an hour of stimulation which might increase compliance among patients and their care-takers who have limited time in a session of physiotherapy. Shorter sessions of stimulation if equally efficacious would be more beneficial in a tertiary hospital set-up where therapists have large numbers of patients to fit into their daily schedules. Further studies may be required to determine the minimum effective duration per session of electrical stimulation to bring about significant decrease in spasticity levels.

CONCLUSION

This study was conducted with the intention of evaluating the neuromodulatory effect of electrical stimulation on the hyper-excitable state observed in patients with spastic hemiplegia following a cerebrovascular accident. The results of the electrophysiological test, namely the Hmax:Mmax ratio used to measure the levels of spasticity have not shown any significant difference following the 2 weeks of electrical stimulation. Based on these results and those of studies conducted earlier on electrical stimulation as a means of alleviating spasticity in the hemiplegia, we conclude that the parameters of stimulation followed were inadequate. The duration of stimulation will need to be increased while further studies will be required to determine if changes in parameters such as pulse width, pulse frequency and type of stimulation are also necessary to bring about a significant decrease in spasticity.

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ANNEXURE

1. Institutional Review Board Acceptance Letter
2. Patient Information Sheet and Consent Form
3. Database with the main results

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No : ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

Dr. George Thomas, D Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (EDI
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

August 12, 2013

Dr. Rahul Jacob Thomas
PG Registrar
Department of PMR
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project NEW PROPOSAL:**
A randomised control trial to observe the efficacy of proposed Transcutaneous Tibial Nerve Stimulation against standard treatment on gastrosoleus spasticity in patients with traumatic brain injury or cerebrovascular accidents.
Dr. Rahul Jacob Thomas, PG Registrar, PMR, Dr George Tharion, PMR, Mr. Rajdeep Ojha, Dr Suresh Devasahayam, Bioengineering

Ref: IRB Min. No. 8363 [INTERVEN] dated 26.06.2013

Dear Dr Rahul Jacob Thomas,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr George Tharion, Professor, Department of PMR, CMC

PATIENT INFORMATION SHEET

Title of the study**:**

A randomised control trial to observe the efficacy of proposed Transcutaneous Tibial Nerve Stimulation against standard treatment on gastrosoleus spasticity in patients with traumatic brain injury or cerebrovascular accidents.

Principal Investigator: Dr. Rahul Jacob Thomas

Department: Physical Medicine & Rehabilitation (PMR), CMC, Vellore

Spasticity is a condition where there is damage to the central nervous system, namely the brain and the spinal cord, which results in increased tone of muscles and tightness of joint movements. The increased tone in the feet cause the affected foot or both feet to point downwards and this in turn can affect the ability to stand or walk with stability. While there are medicines that can be used to decrease spasticity, they also tend to have side-effects such as excessive drowsiness, which in turn can affect the progress in physiotherapy. While medicines tend to affect all muscles of the body, by electrical stimulation, only the key muscles selected will be acted upon. Electrical stimulation by the device made in our department could be a cost-effective alternative to those requiring expensive drugs to decrease the level of spasticity

There are many ways to reduce the tightness in the muscles of the leg. We are trying to bring about that effect by providing electrical stimulation to a nerve that supplies the calf muscle, as it passes by the ankle joint. As the nerve can be easily stimulated in this region, we hope that it will send signals to the higher control centres in the body to reduce the tightness in the legs.

There are many ways of measuring the amount of spasticity present in a given part of the body. One of the most common ways is a grading scale known as the Modified Ashworth Scale. However, this does not give a precise quantifiable measure of the spasticity. Electromyography is a method understanding properties of muscles based on their reaction to external stimulation of the nerves supplying them. Spasticity of the calf muscle can be studied by stimulating the Tibial Nerve as it passes through the diamond shaped area at the back of the knee. The reaction of the muscle is recorded by sensors connected to a computer, when it is stimulated by passing an electrical stimulus over the Tibial nerve. You may experience some discomfort while the external stimulation of the Tibial Nerve is being conducted.

The PMR Department of CMC is conducting a study using electromyography to measure the amount of spasticity present in patients using electrical stimulation This will be conducted among patients with head injuries, who might have spasticity in muscles of both the lower

limbs and among patients who have had a stroke and have spasticity only on one half of the body.

If you are willing to be part of the study, you will be required to:

- Undergo a clinical examination to assess any additional factors contributing to spasticity in your legs.

- Undergo a clinical assessment of level of spasticity, followed by the electromyography test explained above to get a quantifiable assessment of the spasticity in your legs.

- Have an electrical stimulator attached to your ankle for 30 minutes, once a day, over a period of 14 days.

- Undergo a second clinical and electromyography assessment of the spasticity in your legs.

Participation in this study is not likely to cause harm to your health in any foreseeable manner. Electromyography is a standard test of studying muscle properties. You could be part of one of two groups – one in which the electrical stimulator will be active and in the other, a sham electrical stimulator which does not deliver any electrical stimulus will be used.

If you do not want to participate in this study, you are free to say so. You can choose to withdraw from the study at any time without being obliged to provide an explanation. This will not affect the treatment you receive in this hospital in any way.

If you need additional information, you are welcome to contact us and the contact information is provided below. Additional information on electrical stimulation and the electromyography test will be provided on request.

Dr. Rahul Jacob Thomas

Department of PMR

CMC Hospital

Vellore, Tamil Nadu-632004

Phone: +91-8870003550

E-Mail: rjthomas@cmcvellore.ac.in

INFORMED CONSENT

Title of the study: A randomised control trial to observe the efficacy of proposed Transcutaneous Tibial Nerve Stimulation against standard treatment on gastrosoleus spasticity in patients with traumatic brain injury or cerebrovascular accidents.

Principal Investigator: Dr. Rahul Jacob Thomas

Department: Physical Medicine and Rehabilitation (PMR), CMC, Vellore

I, _____ have understood the details of the proposed study. The following aspects of the study have been explained to me in a comprehensible manner:

1. If I give consent to participate in this study, I will be willing to undergo electrical stimulation of the posterior tibial nerve and the tests to assess the level of spasticity in my lower limbs

2. It has been explained to me that I may be in one of two groups, one of which will receive stimulation, and the other in which a sham stimulator will be used.

3. Usage of stimulator is not likely to adversely affect my health in any foreseeable manner.

4. I can choose not to give consent to be part of this study. I can also choose to withdraw myself from the study at any time without being obliged to provide an explanation. In any case, my decision will not affect the treatment given to me in this hospital.

I am willing to give consent to be part of this study voluntarily and without any coercion from the investigators of this project.

Signature of patient Signature of investigator

Signature of witness

Date:

DATABASE WITH THE MAIL RESULTS

DOI	Date of Stroke	No. of Past (Y/N)Strokes	Time Since Last Stroke (Months)	Current Diagnosis
Side of Lesion(R/L/B)	Duration (days)	Admit Dt.	Tardeiu I (X,Y)	MAS Gr. I
H-Amp (I) (uV)	M-Amp (I) (uV)	H/M (I) (%)	Hvib/Hctl(I) (%)	ES Start Dt
ES End Dt	Tardeiu II (X,Y)	MAS Gr.II	H-Amp (II) (uV)	M-Amp (II) (uV)
H/M (II) (%)	Hvib/Hctl(II) (%)	Diabetes(Y/N)	Hypertension(Y/N)	Vasculitis(Y/N)
Smoking (Y/N)	UTI(Y/N)	H.O(Y/N)	DVT(Y/N)	In-Grown Toe-Nails(Y/N)
Diazepam(Y/N)	Tizanidine(Y/N)	Baclofen(Y/N)		

		Pre			Post		
ID NUMBER	STUDY ARM	Hmax(p-p)	M-max	H/M	Hmax (p-p)	M-max	H/M
651329D	1	1.5	2.23	0.672646	1.32	1.81	0.729282
902057F	2	1.06	2.98	0.355705	1.09	2.05	0.531707
207804F	1	1.45	6.02	0.240864	1.42	2.5	0.568
904212F	2	0.57	3.7	0.154054	0.8	4.93	0.162272
878348F	1	0.67	4.28	0.156542	1.16	3.4	0.341176
882335F	2	1.09	1.76	0.619318	1.25	1.48	0.844595
880495F	1	2.07	6.75	0.306667			#DIV/0!
892134F	1	2	1.71	1.169591	2.83	2.07	1.36715
895709F	2	1.07	1.29	0.829457			#DIV/0!
898255F	1	1.94	3.05	0.636066	1.81	2.01	0.900498
346483B	2	1.26	2.41	0.522822	2.11	3.11	0.678457
530174D	1	1.27	6.36	0.199686	1.09	6.36	0.171384
354470F	2	1.55	2.51	0.61753	2.44	3.11	0.784566
001652F	1	1.37	1.35	1.014815	1.1	1.58	0.696203
681695F	1	0.73	0.88	0.829545	2.3	2.5	0.92
700453B	2	1.6	2.5	0.64	1.31	2.59	0.505792
759186F	2	0.53	1.73	0.306358	1.44	5.32	0.270677
899932C	2	0.78	1.66	0.46988	0.74	1.66	0.445783
857065F	1	1.9	5.7	0.333333	1.5	5.71	0.262697
843008F	2	2.88	4.61	0.624729	2.48	2.75	0.901818
854107F	1	1.35	0.62	2.177419	1.18	2.48	0.475806

		Pre Trace			Post Trace		
ID NUMBER	STUDY ARM	Date(I)	Hmax(p-p)	M-max	Date(II)	Hmax (p-p)	M-max
651329D	1	6.MAY.14	4	11	23.MAY.14	7	15
902057F	2	21.MAY.14	5	12	17.JUN.14	7	12
207804F	1	30.MAY.14	12	18	12.JUN.14	13	18
904212F	2	30.MAY.14	6	10	10.JUN.14	6	11
878348F	1	24.JUN.14	11	18	12.JUL.14	6	11
882335F	2	25.JUN.14	9	15	12.JUL.14	7	13
880495F	1	1.JUL.14	7	17			
892134F	1	2.JUL.14	8	15	14.JUL.14	11	18
895709F	2	9.JUL.14	9	18			
898255F	1	9.JUL.14	12	21	24.JUL.14	5	10
346483B	2	23.JUL.14	13	19	7.AUG.14	13	19
530174D	1	26.JUL.14	11	15	9.AUG.14	10	16
354470F	2	24.MAR.14	25	28	11.APR.14	24	25
001652F	1	24.MAR.14	9	18	15.APR.14	14	22
681695F	1	28.MAR.14	9	15	13.APR.14	11	20
700453B	2	10.APR.14	15	24	02.MAY.14	6	14
759186F	2	10.APR.14	15	24	02.MAY.14	12	19
899932C	2	7.MAY.14	11	18	30.MAY.14	8	17
857065F	1	7.MAY.14	15	21	29.MAY.14	13	18
843008F	2	7.MAY.14	5	15	31.MAY.14	7	13
854107F	1	8.MAY.14	22	27	06.JUN.14	13	21