EFFICACY OF THETA BURST STIMULATION AND FUNCTIONAL ELECTRICAL STIMULATION AS COMPARED TO PHYSIOTHERAPY IN STROKE REHABILITATION: A RANDOMIZED CONTROLLED TRIAL

A THESIS PRESENTED BY

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CERTIFICATE

, Fayaz.R.K, hereby certify that I had personally carried out the work depicted in the thesis entitled, "**Efficacy of theta burst stimulation and functional electrical stimulation as compared to physiotherapy in stroke rehabilitation: a randomized controlled trial**", No part of the thesis has been submitted for the award of any other degree or diploma prior to this date.

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1. Introduction

Introduction

This chapter provides background information, introduce terms used throughout the thesis, set objectives of the thesis, define open problems, and formulate research questions that are to be answered by the thesis. Overall goal of this research was to find the efficacy of Theta Burst Stimulation, Functional Electrical Stimulation and Physiotherapy in the rehabilitation of stroke patients.

1.1 Extent of the problem

Stroke one of the major causes of death and a leading cause of adult long term disability worldwide (Strong *et al* 2007; Murray and Lopez 1997) is caused by an interruption of blood supply to the brain either due to blood vessel blockage (ischaemic stroke, approx. 82%) or blood vessel rupture (haemorrhagic stroke, approx. 14%)(Feigin *et al* 2009) both which leads to a sudden break down in oxygen and nutrition supply and may cause permanent brain tissue damage. The World Health Organization (WHO) has used a standard criterion to define stroke as: "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Anon 1988). In a population based study conducted by (Sridharan *et al* 2009) it was found that the adjusted annual incidence rates per 100,000 were 135 for total, for urban population it was 135 and for rural population it was 138. Among the survivors, at three weeks of stroke onset, 39% had mild disability (Rankin score, I & II), 44% had moderate disability (Rankin score, III & IV), and 17 % were bedridden (Rankin score V), nearly two thirds of the survivors

were moderately or severely disabled at three weeks, highlighting the social burden. Stroke survivors frequently exhibit persistent functional disability that impairs the quality of life (Olsen 1990), although most patients regain their walking ability, impairment of upper extremity functions is a major disability. While the lower extremity functions improve in 89%, upper extremity functions improve in only 50% of the post stroke patients. The recovery process of upper extremity functions is also slower than that of lower extremity functions. The motor weakness, by compromising the performance of activities of daily living (ADL) leads to disability and permanent dependency on community (Olsen 1990; Lawrence *et al* 2001)

Hemiplegia after stroke is one of the most prevalent diagnoses treated by the neurologists and the rehabilitation team (occurring in more than 80% of patients), followed by sensory deficits (approximately 45%) and speech deficits (approximately 24%) (Rathore *et al* 2002). Treatment of hemiplegia after stroke continues to be a challenging, and often frustrating experience for clinicians. The ability to live independently after stroke largely depends on reconstitution of motor control (Rathore *et al* 2002). Although stroke damage can be devastating, many patients survive the initial event and undergo some spontaneous recovery, which can be further augmented by rehabilitative therapy (Murphy and Corbett 2009).

Post stroke motor rehabilitation aims to enable patients to regain hand, arm and leg function, as well as other vital functions, and to return to independent life-style in the easiest, simplest, and fastest way. Efficacy of rehabilitation depends on the degree of initial severity of stroke and the initial treatment, as well as on the time interval from stroke to initiation of voluntary movement. Rehabilitation encompasses various techniques which are used to manipulate elements of the central and peripheral

nervous system and includes traditional conventional motor therapy, constraint induced movement therapy, mirror therapy, and electrical stimulation (Ward 2005b; Ward and Cohen 2004; Hömberg 2005; Krakauer 2006)

Functional Upper Limb (UL) recovery after stroke is typically poor, with 30 to 66% of individuals failing to achieve functional recovery after six months and only 5-20% (Wade *et al* 1983; Sunderland *et al* 1989) of individuals with stroke make full UL recovery depending on initial severity (Nakayama *et al* 1994). Studies have shown that individuals demonstrate difficulties with functional activities and dexterity that persist into the chronic post-stroke phase (Heller *et al* 1987). Currently, physical and occupational therapy and at times neurostimulation techniques are used for treatment of stroke-induced hand motor deficits. However, additional therapeutic strategies are needed since stroke is the most common cause for permanent disability in adults and one of the most expensive diseases in world (Kolominsky-Rabas *et al* 2006).

1.2. Rationale of the study

Clearly, post stroke motor rehabilitation strategies to maximize contralateral UL functioning as soon after stroke onset as possible are of paramount importance, present management strategies involving conventional physiotherapy have limited efficacy in facilitating the motor recovery following stroke (Murray and Lopez 1997). Finding an effective and functionally based intervention to improve motor control in individuals with hemiplegia is very important for improving the functional outcome and enabling the independent living by improving the functional capacity of the individuals and thus, making them independent can have enormous implications for

the family and the health care resources, which are often limited in developing countries (Murray and Lopez 1997; Lawrence *et al* 2001; Bhalla *et al* 2002).

Treatment approaches which can facilitate this reorganization process by enhancing the cortical plasticity might have a very important role on improving the functional outcome following neuronal injury. Previous studies have established that following an acute stroke, the excitability of the affected cortex is decreased as demonstrated by an increased Resting Motor Threshold (RMT) and a decrease in the amplitude of the Motor Evoked Potential (MEP) (Liepert *et al* 2000b; Di Lazzaro *et al* 2008a). Experimental studies suggest that brain hyper-excitability may influence the recovery by facilitating neuronal plasticity (Di Lazzaro *et al* 2008a; Maeda *et al* 2000b; Talelli *et al* 2007). Excitability of the human cortex can be modulated non-invasively by using transcranial methods of cortical stimulation. Two types of approaches which can be used are: (1) increasing the excitability of cortex in the affected hemisphere – ipsilesional hemisphere; and (2) suppression of the non-stroke hemisphere – contralesional hemisphere to reduce its interference with the functions of the opposite hemisphere (Liepert *et al* 2000b; Di Lazzaro *et al* 2008a; Maeda *et al* 2000b; Talelli *et al* 2007).

Transcranial Magnetic Stimulation (TMS), a non-invasive means of electrically stimulating neurons in the human cerebral cortex, is able to modify neuronal activity locally and at distant sites when delivered in series or trains of pulses. Data from stimulation of the motor cortex suggests that the type of effect on the excitability of the cortical network depends on the frequency of stimulation (Wassermann and Lisanby 2001). While the high frequency repetitive TMS (rTMS) is excitatory to the cortex, the low frequency rTMS has inhibitory effects. Focal high frequency rTMS to

the motor cortex of the affected hemisphere in conjunction with motor practice intervention paradigm can enhance the corticomotor excitability, which would improve the motor performance in stroke patients. Repetitive TMS is able to modulate the corticospinal excitability and these effects appear to last beyond the duration of the rTMS itself (Maeda *et al* 2000b). In preliminary studies, high frequency rTMS have been shown to produce a increase in corticospinal excitability leading to enhanced motor skill acquisition (Kim *et al* 2006; Talelli *et al* 2007; Nowak *et al* 2009), these studies suggest that TMS might be a suitable method to combine with physiotherapy for improving the recovery of UL functions in stroke patients (Pomeroy *et al* 2007).

Although rTMS has been proven to be very safe in human subjects, it has a theoretical risk of inducing seizures in susceptible individuals especially with higher field strengths. Theta Burst Stimulation (TBS) is a novel method of delivering rTMS at lower intensities without the risk of any major adverse effects and has been found to be safe in chronic and acute stroke patients (P Talelli, R J Greenwood and J C Rothwell 2007). In preliminary studies, intermittent (facilitatory) TBS (iTBS) to the ipsilesional hemisphere and continuous (inhibitory) TBS (cTBS) to the contralesional hemisphere have been shown to transiently improve the motor behavior and corticospinal output in the paretic hands (Di Lazzaro *et al* 2008a; Talelli *et al* 2007).

Similarly, surface Neuromuscular electrical stimulation applied to wrist and fingers have been shown to improve the range of joint movements and volitional muscle contraction in patients with acute/subacute stroke (Alon *et al* 2007; Cauraugh and Kim 2003a) which is also believed to work by enhancing the cortical plasticity. More recent investigations have focused on regaining upper extremity function rather than

simply minimizing impairments, in particular the recovery of the ability to grasp, hold, and release objects (Alon *et al* 2007) Cauraugh and Kim 2003a; Popovic *et al* 2003).

Upper extremity task-oriented training that begins soon after stroke that incorporates neuromuscular electrical stimulation with the addition of volitional, task-specific functional training (Functional Electrical Stimulation, FES) may improve upper extremity functional use in patients with mild/moderate paresis more than task-oriented training without FES (G Alon, A F Levitt and P A McCarthy 2007; Kimberley *et al* 2004; Duncan *et al* 2003).

Thus both the rTMS and FES has a potential of improving the motor functions and the functional outcome following ischemic stroke. However, these strategies have not been used in clinical setting and their usefulness in promoting motor recovery over and above that of conventional physiotherapy needs to be proven before these can be used on a wider scale in the community. If proven to be useful, these techniques would have a potential of improving the otherwise dismal outcome and by reducing the levels of dependency on community care, which will have far reaching consequences for the individual and the society. The purpose of this study is to determine the additional benefits by combining the rTMS or FES to the conventional physiotherapy programme for the stroke rehabilitation.

1.3 Significance of the study

In spite of very high incidence of the stroke and subsequent disability, there are no definite guidelines and treatment protocols for the rehabilitation of the stroke patients. Majority of patients are cared at primary and secondary care health centers without

any uniform guidelines, which can contribute to persisting disability. There is usually a nihilistic view among the physicians regarding the rehabilitative treatment of stroke patients. However, as the current researches have shown that, brain has significant plasticity and reorganization capacity even in the old age. By enhancing this plasticity by using noninvasive stimulation, there is a potential for improving the functional outcome of stroke patients. Previous studies utilizing the noninvasive stimulation have not been able to establish their clinical utility in improving the long-term motor outcome in stroke subjects.

Efficacy of rTMS or FES, if proven by this study can help in developing the evidence-based guidelines for rehabilitation of stroke patients particularly related to patient population in india. Any intervention to improve the functional ability of these patients can have long-lasting effects on the society in general and on healthcare in particular.

In view of this fact, the study objectives are to create evidence-based data for incorporating into uniform rehabilitation protocol providing comprehensive benefit to a larger group of patients and to initiate a cross referral practices to encourage integrative treatment approach. By this study the researcher will be able to formulate a rehabilitation protocol for the stroke patients integrating different approaches. Once finalized, this protocol will be widely circulated for use to all the stroke care centers through publications and various communications. This is likely to benefit a large number of patients who are left with permanent disability and dependency in their Activities of Daily Living (ADL).

1.4 Statement of the problem

As the goal of this research was to find the efficacy of different approaches like Theta burst stimulation, Functional electrical stimulation and Physiotherapy in the rehabilitation of stroke patients, the problem can be stated as "Efficacy of Theta Burst Stimulation and Functional Electrical Stimulation as Compared to Physiotherapy in Stroke Rehabilitation: A Randomized Controlled Trial".

1.5 Operational Definitions

Efficacy – By efficacy the researcher means the capacity for therapeutic effect of a given intervention (TBS/FES/Physiotherapy).

Theta Burst Stimulation (TBS) - TBS is a novel method of delivering rTMS at lower intensities; by TMS here researcher means it is a technique for noninvasive stimulation of the human brain applied with magstim rapid^2.

Functional Electrical Stimulation (FES) – Application of small electrical pulses to paralyzed muscles to restore or improve their function applied with mega XP, Cybermedic Corporation.

Physiotherapy (PT) – By physiotherapy here, researcher means conventional physiotherapy for the stroke patients.

Stroke Rehabilitation – By stroke rehabilitation here, researcher means rehabilitation of upper limb functions of post stroke patients measured by primary outcome measure, the fugl meyer assessment of motor performance.

1.6 Objectives

1. To find the efficacy of Theta Burst Stimulation along with Physiotherapy in rehabilitation of stroke patients as assessed by fugl meyer assessment scale, modified rankin scale, barthel index, NIHSS, resting motor threshold and cortical silent period.

2. To find the efficacy of Functional Electrical Stimulation along with Physiotherapy in rehabilitation of stroke patients as assessed by fugl meyer assessment scale, modified rankin scale, barthel index, NIHSS, resting motor threshold and cortical silent period

3. To find the efficacy of Physiotherapy alone in rehabilitation of stroke patients as assessed by fugl meyer assessment scale, modified rankin scale, barthel index, NIHSS, resting motor threshold and cortical silent period

4. To compare the efficacy of Theta Burst Stimulation along with Physiotherapy and Functional Electrical Stimulation along with Physiotherapy as compared to Physiotherapy alone in rehabilitation of stroke patients as assessed by fugl meyer assessment scale, modified rankin scale, barthel index, NIHSS, resting motor threshold and cortical silent period

1.7 Hypothesis

Null Hypothesis 1: There will be no significant improvement in rehabilitation of stroke patients receiving Theta Burst Stimulation along with Physiotherapy.

Null Hypothesis 2: There will be no significant improvement in rehabilitation of stroke patients receiving Functional Electrical Stimulation along with Physiotherapy.

Null Hypothesis 3: There will be no significant improvement in rehabilitation of stroke patients receiving Physiotherapy alone.

Null Hypothesis 4: There will be no significant difference between the rehabilitation stroke patients receiving Theta Burst Stimulation along with Physiotherapy, Functional Electrical Stimulation along with Physiotherapy and Physiotherapy alone.

1.8 Methodology in Brief

This single blind randomized controlled trial included 60 patients, block randomized into three groups of 20 each to receive the designated interventions: TBS combined with PT, FES combined with PT and PT alone. All the patients presenting within one month after a diagnosis of acute stroke was screened for the eligibility, outcome were assessed at baseline visit, after intervention at one month, and follow-up assessments at three months, six months and at one year.

1.9 Chapter Scheme

This study is divided into six chapters including the present introductory chapter. The following chapter (chapter 2) provides a comprehensive review of literature on stroke epidemiology and consequences available from different parts of the world. For ease of exposition, this chapter is divided into eight broad sections. The first section focuses on the introduction to stroke and consequences, followed by plasticity, motor control, reorganization of brain, different approaches used in this study and the outcome measures used.

Chapter 3 provides a detailed description on the methodology used in the study. The study involves three interventions namely TBS, FES and PT and their effectiveness on stroke rehabilitation.

In chapter 4, the results of the study are described in 9 parts (4.1 to 4.9). Each part describes the results of each outcome measures used to find the efficacy of the treatment interventions. The first part (4.1) is on the outcome of fugl meyer assessment scale on upper limb motor performance. The second part (4.2) gives the overall picture of the disability by modified rankin scale. In the third part of the part (4.3), the results of assessment done by barthel index to find out the independence in activities of daily. The next section (4.4) is on the global stroke outcome assessed by the National Institute for Health Stroke Scale (NIHSS) and the corresponding sections on the neurophysiological assessment by the TMS measures and the last section on the correlation of Fugl Meyer Assessment (FMA) scale with other outcomes used.

Chapter 5 discusses the study results in the light of the existing literature and had made a conclusion of the study findings.

Chapter 6 is summary and conclusion followed by bibliography.

2. Review of Literature

2.1. Stroke

The World Health Organization (WHO) has used a standard criterion to define stroke as: "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Anon 2002). Stroke is caused by an interruption of blood supply to the brain either due to blood vessel blockage (ischaemic stroke, approx. 82%) or blood vessel rupture (haemorrhagic stroke, approx. 14%) (Feigin *et al* 2009a) both which leads to a sudden breakdown in oxygen and nutrition supply and may cause permanent brain tissue damage

In a population based study conducted in our institute by (Sridharan *et al* 2009) it was found that the adjusted annual incidence rates per 100,000 were 135 for total, for urban population it was 135 and for rural population it was 138. Among the survivors, at three weeks of stroke onset, 39% had mild disability (Rankin score, I & II), 44% had moderate disability (Rankin score, III & IV), and 17 % were bedridden (Rankin score V), nearly two thirds of the survivors were moderately or severely disabled at three weeks, highlighting the social burden. Stroke survivors frequently exhibit persistent functional disability that impairs the quality of life (Olsen 1990). Although most patients regain their walking ability, impairment of upper extremity functions is a major disability, while the lower extremity functions improve in 89%, upper extremity functions improve in only 50% of the patients.

Stroke is a major cause of impairment and functional disability in millions of people worldwide (Rossini *et al* 2003; Young and Forster 2007) it not only impairs the motor system but also the emotional and cognitive functions seriously (de Vries and Mulder

2007). Stroke leads to massive distortion of brains capacity to formulate neural information, which may be due to heterogeneous consequences.

Sequelae of impairments after stroke include upper and lower limb motor and sensory loss, language, communication and cognitive difficulties, perceptual difficulties, bowel and bladder dysfunction and dysphagia (Wolfe 2000). Stroke also leads to limitations in activities like walking, feeding, dressing grooming and toileting (Wolfe 2000). Activities of daily living are adversely affected which impairs their quality of life (Kauhanen *et al* 2000). In about 23% to 27% of stroke sufferers depression is a major concern (Herrmann *et al* 1998).

Hemiparesis is the most common impairment seen in stroke patients (80% of patients), followed by reduced sensation (approximately 45%) and aphasia (approximately 24%) (Rathore *et al* 2002). Upper Limb (UL) hemiparesis is most common (76%), in Lower Limbs (LL) its (69%) and in the face its (55%) (Rathore *et al* 2002).

It has been reported that hemiparesis can reduce the muscle mass available for contraction during physical activity which can lead to weakness in both UL and LL. Weakness of UL compromises the hand functions and leads to dependency in activities of daily living, whereby the weakness of LL often affects mobility (Jørgensen *et al* 1995a; Jørgensen *et al* 1995c; Jørgensen *et al* 1995b; Wandel *et al* 2000). Few studies have reported a reduction in muscle strength of non-paretic limb too at early stages following stroke (Harris *et al* 2001; Carin-Levy *et al* 2006), which negatively affects mobility and balance thereby increases the risk of falling (Anon 2002; Ramnemark *et al* 1998).

2.1.1. Consequences and recovery after stroke

About 20% patients who had hemiparesis after stroke regains at least part of their lost motor functions in the subsequent months; thus the rest 50 – 60% patients are left with a chronic motor disorders. These disorders may lead to problems with balance, co-ordination, further loss of strength or may lead to increased tone in affected side (Hendricks *et al* 2002).

Contralateral UL dysfunction is common after stroke, impairments include paresis (Kwakkel *et al* 2003) loss of muscle power (Canning *et al* 2004), reduced activity and co-ordination on task performance (Canning et al. 2004) reduced sensation (Broeks *et al* 1999), proprioceptive loss (Rand *et al* 1999) and spasticity (Pandyan *et al* 2005). These impairments may lead to considerable limitations in daily function and negatively impacts quality of life (Nichols-Larsen *et al* 2005) and also secondary problems such as pain (Dromerick *et al* 2008), loss of range of movement and muscle contracture which in turn cause functional limitations.

Out of 70% of stroke survivors who had an UL paresis, 32% of them were severely parlysed, which was defined as the inability to move the arm against gravity or to bend the fingertips to the palm (Nakayama *et al* 1994). At 3 months, 17% had severe paralysis in the UL, 7% moderate, 50% mild, and 26% no detectable weakness (Parker *et al* 1986). About one third of stroke patients in a rehabilitation trial regained some dexterity at 6 months.

The overall percentage of patients who were independent before onset but dependent in primary ADL at 3 months post stroke was 20.7%. This further resulted in increased expense for caregivers, and increased incidents of depression, in stroke survivors (Parker *et al* 1986).

2.2. Plasticity

The term plasticity refers to the ability of the nervous system to change in structure or function in response to a variety of internal and external pressures (Boroojerdi *et al* 2001; Sanes and Donoghue 2000). It was assumed that central nervous system has limited capacity to regenerate, but recent studies reveals that adult brain undergoes dynamic change throughout life (Ljubisavljevic 2006). These occur at synaptic, cellular network and systems level (Nudo *et al* 2001; Ward 2005a).

Cortical development is divided into two stages, an initial phase where connections are formed, and a secondary phase where existing connections are refined. Both intrinsic and extrinsic factors impact on these two phases and consequently on the structure and function of cortex.

Plasticity mechanisms include neurochemical, neuroreceptor and neuronal structural changes. The neuronal connections between the central and periphery, and also the intracortical connections are physiologically silent because of inhibitory influences (Wall 1977). The role of gamma-amino butyric acid (GABA) which is an inhibitory neurotransmitter (Jones 1993) is crucial in mediating short term plasticity (Chen *et al* 2002). Other mechanisms which make changes over longer time are axonal regeneration and sprouting (Carr and Shepherd 2010; Chen *et al* 2002; Murphy and Corbett 2009).

Functional recovery is attributed to reorganization process in the damaged brain; self organization may be possible, when damage to functional system is partial. When the functional system is completely damaged it occurs by substitution (i.e.) neighboring areas take over the functions of damaged areas (de Vries and Mulder 2007).

Repetitive stimulation or activation leads to increased excitability and neuro-facilitation and leads to increased synaptic activity, which in turn leads to impaired performance (Nudo *et al* 1996). In human beings prolonged immobilization (Liepert *et al* 1995) has shown to decrease cortical representation, on contrary repeated exercise or use of body part have shown to increase or shift in cortical representation (Liepert *et al* 1995; Pascual-Leone *et al* 1995; Liepert *et al* 2000a).

Availability of noninvasive neuroimaging and electrophysiological techniques allows us to study the reorganization of the human brain. The Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) are used for studying the reorganization of functional representations, while TMS gives additional information on the human cortico-spinal motor output. More recently paired pulse TMS has provided the opportunity in knowing the intracortical facilitation and inhibition (Bütefisch *et al* 2000), The significance of all these techniques have been reported in various studies which include increase in motor output areas (Traversa *et al* 1997), decrease in motor threshold demonstrated by TMS (Di Lazzaro *et al* 2008a) and changes in regional blood flow demonstrated by PET (Nelles *et al* 1999) and fMRI (Cramer *et al* 1997) when patients underwent training programs of neurorehabilitation.

2.2.1. Neuroplasticity in Stroke

In post stroke patient's, neuroplasticity occur through reorganization of spared neuronal tissue (Matthews *et al* 2004), it may occur spontaneously or in response to activity. However their relationships remain unclear (Rossini and Dal Forno 2004). Initially blood flow around the lesion site is restored (Turton and Pomeroy 2002)

followed by reduction in inhibitory transmitters such as GABA which enhances synaptic transmission, thus increases transient excitation.

The exact role and interactions between these mechanisms and motor recovery remains debatable (Rossini *et al* 2003). These literatures provides the evidence that training induced plasticity is possible, even after many months or years post stroke. So the researchers developing and testing rehabilitation interventions must determine optimal practice characteristics to stimulate and refine post stroke cortical reorganization to drive motor and functional recovery.

2.3. Recovery of brain functions following stroke

2.3.1. Cerebral hemispheres

Throughout the manuscript, the term ipsilesional will be used to refer to the side of the stroke lesion and the term contralesional will be used to refer to the side opposite to the stroke lesion. Hence, the ipsilesional hemisphere is ipsilateral to the stroke lesion and the contralesional hemisphere is contralateral to the stroke lesion. (Grefkes *et al* 2008a) (Figure 2.1).

The terms ipsilesional hemisphere and contralesional hemisphere should not be confused with the terms ipsilateral hemisphere and contralateral hemisphere which are used to refer to the hemisphere which is ipsilateral or contralateral to an event such as hand movements or an intervention. During movements of the affected hand (sometimes referred to as the paretic hand) the ipsilateral hemisphere refers to the contralesional hemisphere and the contralateral hemisphere refers to the ipsilesional hemisphere (Grefkes *et al* 2008a) (Figure 2.1).

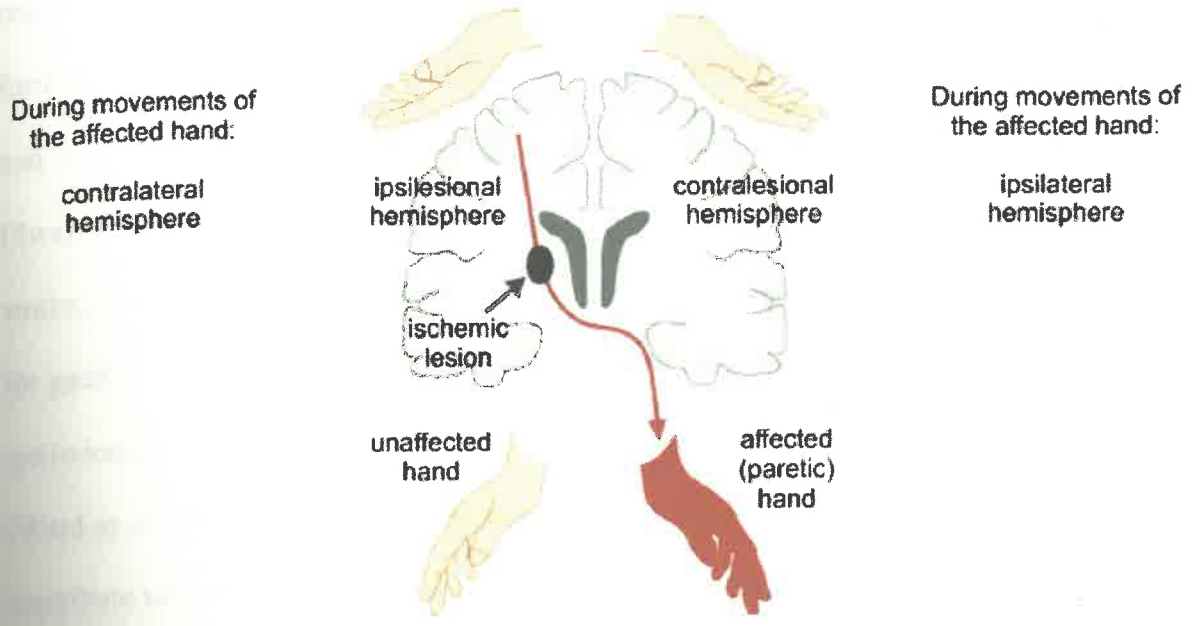


Figure 2.1: Designation of cerebral hemispheres. The ipsilesional hemisphere is on the same side as the stroke lesion, whereas the contralesional hemisphere is the hemisphere opposite to the stroke lesion. During movements of the paretic (i.e. affected) hand, the contralateral hemisphere corresponds to the ipsilesional hemisphere and the ipsilateral hemisphere corresponds to the contralesional hemisphere.

2.3.2. Reorganization of ipsilesional hemisphere.

Transcranial magnetic stimulation studies have revealed that in a post stroke brain there is an decrease in excitability in ipsilesional cortico-motor pathway and absence of MEPs even at maximum stimulator output (100% MSO) (Traversa *et al* 1997) or sometimes typically abnormal. A neurophysiological presentation of increased threshold, prolonged latencies and decreased MEP amplitude are seen in the ipsilesional TMS output compared to contralesional hemisphere (Delvaux *et al* 2003; Traversa *et al* 2000).

This MEP response property normalizes with time in patients who showed good recovery. In patients who showed improvement in symmetry of corticomotor excitability between Motor (M1) areas of both hemispheres showed some motor

recovery. In patients whose ipsilesional M1 excitability was not increased showed a further increase in contralesional M1 excitability, which leads to further imbalance and a moreover little improvement in motor functions. In a study conducted by (Swayne *et al* 2008) there was an increase in ipsilesional M1 in first 6 months post stroke. These results suggest that the return of ipsilesional M1 MEP is an instrumental for good recovery and this was correlated with fMRI findings, showing that return of ipsilesional control of paretic hand movement is associated with better UL recovery (Ward *et al* 2003). Areas that have anatomical connections to the paretic limb may contribute to recovery, like M1 pre motor cortex has pyramidal cells (from layer V) with fibers that project via the posterior limb of the internal capsule, to the spinal cord and synapse onto alpha neurons (Zarei *et al* 2007). These connections may enable pre motor cortex to take on some of the roles of ipsilesional M1.

2.3.3. Reorganization of the contralesional hemisphere

Transcranial magnetic stimulation studies have shown that there is an opposite trend in the neurophysiological parameters in the contralesional M1, such as increase in MEP amplitudes compared with normal healthy subjects (Traversa *et al* 2000). The balance in corticomotor excitability tends to improve over time in patients who showed good recovery (Swayne *et al* 2008). A reduction in contralesional M1 excitability and normalization of intracortical inhibition may promote a return of ipsilesional M1 control of the paretic hand. Functional MRI studies also provided evidence for continued abnormal activation in contralesional motor areas, mostly in severe stroke patients (Grefkes *et al* 2008b).

The recruitment of contralesional motor regions could provide a compensatory mechanism for achieving some paretic UL movement, which leads to activation of UL musculature via ipsilesional projections to the alpha motor neurons. The uncrossed pathways from contralesional M1 (iMEP) may contribute to the control of paretic UL, mostly the proximal musculature, indeed there is only a sparse projection to the hand (Rothwell 1987). In post stroke patients iMEPs are most frequent in proximal muscles and are seen in patients with poorer recovery (Misawa *et al* 2008; Caramia *et al* 2000). Evidences from the recent studies show that there is a role of propriospinal motor neurons which receive inputs from reticulospinal tract in the coordinated movement of UL in healthy adults (Bradnam *et al* 2010). The role of dorsal pre-motor cortex is also important in the recovery of UL; this is supported by the studies done by (Johansen-Berg *et al* 2002; Nirkko *et al* 2001).

2.3.4. Interhemispheric inhibition

Studies on TMS reveals that in normal subjects before the movement there is a reduced Inter-Hemispheric Inhibition (IHI) from ipsilateral M1 to the contralateral M1 and an increase in IHI from the contralateral to the ipsilateral M1(Grefkes *et al* 2008a). In post stroke patients there is an imbalance in the corticomotor excitability presenting with an reduction of IHI to contralesional M1 (Bütefisch *et al* 2008).

The rebalance of IHI leads to improved ipsilesional M1 activity (Murase *et al* 2004). The IHI from contralesional M1 to ipsilesional M1 is excessive in chronic stroke patients, on the contrary those patients with better clinical recovery had reduced IHI acting onto ipsilesional M1 when compared to patients who have poor recovery

(Duque *et al* 2005). As to brief out, a rebalancing of IHI contributes to better motor outcomes whereas a persistent imbalance can lead to impairment of UL functions (Di Lazzaro *et al* 2010a).

2.4. Motor control.

Neurorehabilitation is based on different theories of motor control (Bobath 1978; brunnstrom 1970a; Carr and Shepherd 2010). The reflex theory, hierarchal theory and motor programming theory are most commonly discussed (Shumway-Cook and Woollacott 2000). These theories have different view points on how brain controls and programs the movements, inspite of their serious limitations (Shumway-Cook and Woollacott 2000). Systems theory is formulated from older theories and explains the motor control in relation to cognitive, perceptual and sensori-motor processes and also into complex relations. Systems theory is most commonly discussed compared to other theories in practical neurorehabilitation aspects, as it is also an successor of older conventional theories (Shumway-Cook and Woollacott 2000).

Motor learning is the study of acquisition or modification of movement in normal subjects (Shumway-Cook and Woollacott 2000). Normal human beings are born with a child's preprogrammed development of motor functions and activities. When the child grows into an adult he can acquire new skills throughout their lives, like computer proficiency, reading, bicycling, driving etc. When an adult is insulted with a brain injury affecting the motor performance, the process of rehabilitation is purely motor relearning, which in turn is aimed at reacquisition of optimal movements (Carr and Shepherd 2010; Shumway-Cook and Woollacott 2000). Motor relearning aims to optimize relearned activities to daily activities, well in the treatment of neurological

conditions it's a relearning process where problem solving, programming and strategy development are important, which can be achieved by training in the real time environment and the interaction of individual, task and environment is necessary (Carr and Shepherd 2010; Davies 2004).

Let us consider with an example of hand function, for the proper functioning of the hand certain basic components should be considered (Shumway-Cook and Woollacott 2000). The basic components are (i) Locating a target, including eye, head and trunk coordination (ii) Reaching in which the arm unit is in action towards the object including the postural support (iii) Grasping and releasing (iv) In hand manipulation skills (Shumway-Cook and Woollacott 2000). There should be a serious interaction between the musculoskeletal and neural systems with planning and initiation for the arm and hand to function as a single unit in co-ordination (Carr and Shepherd 2010). Thus the hand function includes a co-ordinated activity of different muscles which are used for various skilled actions. The key muscles of hand function are the wrist muscles, since they stabilize the wrist in optimal positions to keep the finger muscles at a favorable length. So the grip strength is dependent on the position of the wrist (Carr and Shepherd 2010; Hunter *et al* 1995). Post stroke patients not only produce delayed and irregular grip force compared to controls, but also excessive grip force prior to commencing a lift, fluctuating irregular forces and reduced adaptation. They also show slow disorganized sequencing of the gripping and lifting forces and difficulty in maintaining a stable grip (Blennerhassett *et al* 2006). So the rehabilitation strategies should be focused on patient involvement and individually designed goals (Carr and Shepherd 2010; Timmermans *et al* 2009).

Rehabilitation of patients is fundamentally a process of relearning on how to move, to carry out needs successfully (Gilmore and Spaulding 2007). There are four factors that contribute to motor learning: (i) Stages of learning (ii) Types of tasks (ii) Practice and (iv) Feedback. All four factors must be considered by clinicians when designing treatment programs for patients who have experienced with stroke of that practice and feedback are considered to be the two most important factors in skill acquisition (Krakauer 2006).

2.5. Physiotherapy

The aim of physiotherapy post stroke is to increase function through recovery of affected side (Shumway-Cook and Woollacott 2000) and if recovery of the affected side is not achieved then it may be done through the use of compensation strategies, during both processes brain plasticity is active (Levin *et al* 2009).

Orthopedic approach emphasizes on strength training, joint mobility, bracing and training with orthotics; it has a less role in normalizing the tone which were the major neurophysiological deficits of brain disorders. New approaches were developed which had an importance in normalizing tone, so the ideas were grounded over the reflex-hierarchical model of motor control (Sherrington 1910). These approaches may be summarized as Bobath treatment (Bobath 1978), Brunstrom model (Brunnstrom 1970) and Proprioceptive Neuromuscular Facilitation (PNF) (Voss *et al* 1985).

According to (Bobath 1978) strength training of the paretic muscles was prohibited in view that strength training would enhance the spastic resistance from antagonist muscles and further impairs functions. They were of the view that muscle atrophy was not a contributing factor to post stroke weakness. According to (Kabat and Knott

1953; Voss *et al* 1985) who developed PNF, repetitive manual resistance to strengthen weak spastic muscles should be emphasized. Hence weak limbs should overcome the manual resistance applied in specific movement patterns.

Brunstromm's (Brunnstrom 1970) approach was developed over synergy patterns and hypothesized that the synergies should be encouraged to hasten recovery of voluntary control. Scientific evidence for these approaches were few and inadequate. Later on Bobath approach was developed into a treatment concept (Davies 2004) that dominated the physiotherapy practice for stroke patients (Davidson and Waters 2000; Lennon *et al* 2001; Lennon 2003).

Later on in the early 1990's Carr and shepherd questioned the concepts of Bobath approach in the concern that motor deficits post stroke cannot be only attributed to hyper tonicity and they formulated a new approach gathering knowledge from neurophysiology, muscle physiology, motor learning, biomechanics and motor control. Their emphasis was moreover for relearning process whereby the patients through cognition and practice regains an improved motor control (Carr and Shepherd 2010).

Nowadays PT treatment post stroke has been based on clinical knowledge and mostly addressing the ability to regain motor control and mobility. In a study conducted by (De Wit *et al* 2006), the results suggest that PT aims mainly on training of selective movements and exercises for balance, sitting, standing and ambulation (De Wit *et al* 2006). A study done by (Pollock *et al* 2007b) comparing the effect of different treatment approaches concluded that none of the approaches are superior to the other. Other recently updated reviews (20 trials, 1087 patients) concluded that the only significant result was found in the use of a mix of components from different

approaches compared with no treatment (Pollock *et al* 2007a). Some other reviews also found no difference in outcome between different physiotherapy approaches (Ernst 1990; Moseley *et al* 2003).

Recently evidence based practice among physiotherapist has improved. In several reviews the importance of good methodological quality of trials has been emphasized (Maher *et al* 2003; Morris *et al* 2004; Patten *et al* 2004; Taylor *et al* 2005).In a study conducted in our institute on the knowledge and practice of physiotherapists in the state of kerala, india we found that majority of the physiotherapists (76.1%) preferred to use conventional approach. This study also revealed that evidence based practice among the physiotherapists in our state was less compared to international standards (Khan *et al* 2012).

Intense and repetitive practice has been proposed as advantageous for people after stroke, based on learning principle with in movement science (Langhorne *et al* 2009). This stresses the use of various training strategies that increase the repetitions. An extensive systematic review of repetitive functional task practice (31 trials, 1078 patients) did not give a positive result for upper limb interventions (French *et al* 2008).

Another review done by (van der Lee *et al* 2001) revealed that more intensive exercise therapy may be beneficial but was not supported by evidence. On contrary (Kwakkel *et al* 2004) showed a positive association between added therapy time and outcome on activities of daily living (ADL).

There are different techniques used for UL rehabilitation for post stroke patients, namely bilateral arm training, mirror therapy and bio-feedback therapy. In fact all these techniques showed a limited support for effectiveness (Van Peppen *et al* 2004).

The only significant effect was found with respect to constrained induced movement therapy.

Hence these reports might have enlightened the physiotherapists on their perspectives in administering intensive training approaches. This makes it difficult and moreover confusing for the physiotherapists in making a decision on effective management of UL functions.

2.6. Functional Electrical Stimulation.

The Key words used for search were FES, CVA, Stroke, Upper limb; 52 studies were found from a period of 1990 to 2012 and screened to 16. Functional Electrical Stimulation (FES) is used in post stroke patients to improve their motor and voluntary control of activities (Blickenstorfer *et al* 2009). When neuromuscular electrical stimulation (NMES) is combined with voluntary activity it is called FES, it facilitates recovery in post stroke patients in an additive and interactive way compared to conventional electrical stimulators (Popovic *et al* 2003; Popovic *et al* 2004). Recent studies have stated a positive trend in FES when applied to acute and chronic hemiplegia when compared to conventional treatment (Popovic *et al* 2004).

The electrical stimulation works on a mechanism of sensorimotor coupling (Cauraugh *et al* 2000). So an increase in proprioceptive signals from evoked movements due to stimulation of target muscles will bombard the somatosensory cortex (Rosenkranz and Rothwell 2006) and this increases the corticoneuronal excitability (Ridding and Taylor 2001; Sawaki *et al* 2006) this in turn facilitates the voluntary activation and leads to improved function (Wu *et al* 2005). There by applying FES increases more of

neural information to the brain and further leads to increased neural plasticity (Popovic *et al* 2003)

Although positive studies are apparent about the effects of FES, the specific mechanism is not yet described. A few studies have shown that motor training causes cortical reorganization and somatosensory inputs lead to changes in cortical excitability (Kaelin-Lang *et al* 2005).A good understanding of how FES interacts with central nervous system is important to improve the treatment. Noninvasive techniques like fMRI and TMS can be used to find the relationship between cortical reorganization and recovery of motor function (Rossini *et al* 2003). Whether FES acts via cumulative effects of cortical excitability or voluntary activation is still a matter of debate.

In one of the earliest studies done by (Merletti *et al* 1975) on 8 stroke subjects with FES to the elbow and finger/wrist extensors, the results were positive towards FES. They observed a recovery of hand and elbow movements in 5 stroke subjects and in remaining 3 the improvement was confined to the elbow joint alone. In another study conducted by (Chae *et al* 1998) the treatment group received surface neuromuscular stimulation to produce wrist and finger extension exercises and the controls received placebo stimulation over the paretic forearm 1 hour per day for 15 sessions. The outcome measured by FMA assessment scale revealed a positive effect for the experimental group after 4 and 12 weeks of treatment.

In the recent literatures, a study done by (Chan *et al* 2009) on 20 chronic stroke patients which combined FES with bilateral arm training revealed gains in FMA scores for the experimental group after 15 sessions of treatment.

In another study conducted by (Alon *et al* 2007) in 15 acute stroke patients they compared FES protocol with a control intervention of task specific training for 12 weeks which revealed a positive effect towards the FES group when assessed with box and block test and jebson taylor light object lift test at 4 weeks, 8 weeks and 12 weeks. Similarly, (Thrasher *et al* 2008) has used FES on 21 acute stroke patients; the patients were randomly assigned to receive either FES treatment or conventional therapy for 5 days a week for 12 to 16 weeks. The outcome as measured by FMA scale showed gains towards the FES group at the end of the treatment.

Recent literatures on FES and voluntary movement to find out the cortico-motor excitability showed an increase in Motor Evoked Potential (MEP) magnitude throughout the stimulation range suggesting an increase in cortical excitability. In contrast neither FES nor voluntary movement alone had such an effect (Barsi *et al* 2008).

These results suggest that the combination of voluntary effort and FES has a greater potential to induce plasticity in the motor cortex. Literature reveals that the effects of FES was not merely limited to the peripheral muscles but the cortical activity as well is altered as shown by transient changes in MEP with TMS (Barsi *et al* 2008), PET (Ledberg *et al* 1995), magnetoencephalography (Lin and Forss 2002) and fMRI (Smith *et al* 2003).

2.7. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) was introduced in 1985 by Barker et al. and has since then gained recognition as a safe technique to stimulate the human cerebral cortex non-invasively and pain free (Barker *et al* 1985; Hallett 2007). It

works with the Faraday's principle of electromagnetic induction (Sadiku 2000). TMS is most frequently used as a research tool to study brain physiology, but it has some clinical utility and is also being developed as a therapeutic tool (Hallett 2007).

During the application of TMS, a copper stimulation coil is held tangentially to the scalp. The electric current in the stimulation coil produces a strong magnetic pulse of short duration (2 tesla and typically lasts for about 100μs). This current passes through the skull and produces an electric field (EF) in the underlying brain tissue (Figure.2.2). This EF can cause depolarization of the pyramidal cells most likely trans-synaptically via intracortical interneuron connections (Rothwell *et al* 1991). This is produced when the stimulator coil is held tangentially against the scalp over motor area (M1) at approximately 45^0 to the sagittal plane. Hence, TMS pulses may finally result in MEP's in contralateral peripheral muscles which can be recorded by means of electromyography (EMG) (Hallett 2007). The site of stimulation over the scalp that produces the largest MEP amplitude in the target muscle is referred to as the 'hot-spot'. The descending waves from M1 are rapidly transmitted (60-70 ms) synchronized action potentials in fast conducting axons of pyramidal cells, which innervate motor neurons in the spinal cord (Amassian *et al* 1987). The D waves or the direct waves, which are first of these is thought to be produced by direct excitation of axons in white matter due to its short latency (Amassian *et al* 1987). The D wave is followed by I wave or indirect wave, which has a duration of about 1.5 ms and correlate with excitatory post synaptic potentials (Amassian *et al* 1987)

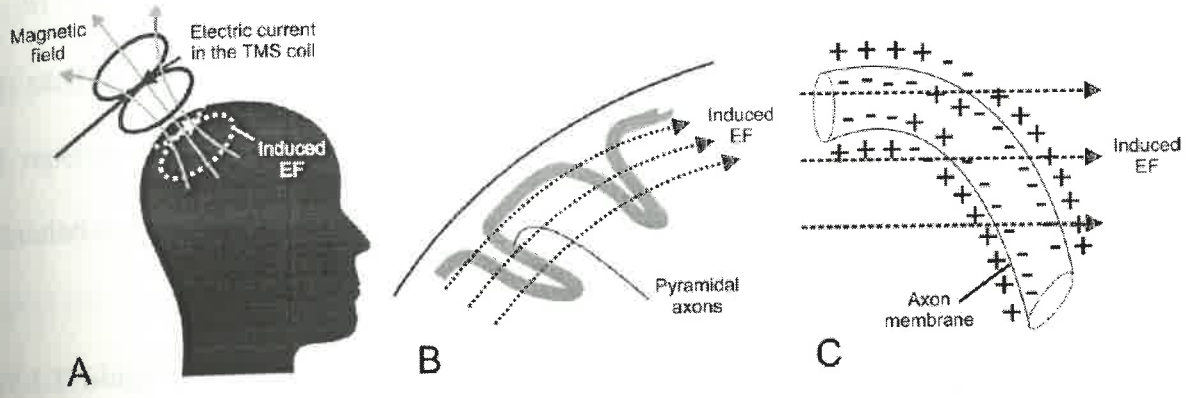


Figure 2.2: Principles of Transcranial magnetic stimulation (TMS). A: The electric current in the TMS coil (solid black line; flowing in posterior-anterior direction) generates a transient magnetic field (solid grey line), which induces an electric field (EF) in the brain (dashed white line; in posterior-anterior direction). B: Motor cortex stimulation and trajectory of pyramidal axons. The induced EF runs in posterior-anterior direction and approximately parallel to the gyral surface. C: Direct axonal excitation at the microscopic level. The induced EF causes local depolarisation of the axon membrane at the position where the pyramidal axon bends downwards.
(Modified from http//www.biomag.hus.fi/tms/thesis/fig.1.jpg)

Excitation of motor neurons has been demonstrated to be maximal if the induced EF is approximately perpendicular to the central sulcus and in posterior-anterior (PA) direction (Mills *et al* 1992).

The circular coils induce strong electric fields whereas figure of eight TMS coils offer advantage of increased focality since maximal current is induced in a relatively small area at the intersection of the two round components (Lontis *et al* 2006).

2.7.1. Two major approaches of TMS:

(i) Investigation of physiological properties of neural tissues by means of several pulses applied at low frequencies (< 1 Hz)

Two different subtypes are:

a) Single pulse TMS (to assess e.g. corticospinal excitability)

b) Paired pulse TMS (to assess intra-cortical or inter-cortical pathways)

(ii) Modulating corticospinal excitability beyond the period of stimulation by means of repetitive TMS (rTMS) i.e., many pulses (usually > 500) applied at higher stimulation frequencies (≥1 Hz) (Ljubisavljevic 2006; Pascual-Leone *et al* 1999).

2.7.1.1. Single pulse TMS

Single pulse TMS provides information regarding the integrity and conduction of the entire corticomotor pathway from cortex through to the target muscle.

2.7.1.1.1. Motor evoked potential (MEP) and Motor Threshold (MT)

Corticomotor excitability can be assessed with measures of MT and MEP recorded from the target muscle. Mostly two small hand muscles serve as target muscles (i) the first dorsal interosseous muscle (FDI) (ii) abductor pollicis brevis (APB); particularly FDI muscle has the advantage of having relatively large representation area in M1 and are well suitable for EMG recordings due to their superficial anatomical position. Motor threshold probably reflects properties of the neuronal membrane (i.e., resting threshold). When threshold membrane is hyperpolarized MT increases. In contrast, when threshold membrane is depolarized MT decreases. MT is the minimum TMS intensity (in % maximum stimulator output) required to elicit an MEP in the target muscle which can be recorded with the muscle at rest (Resting Motor Threshold-RMT) and during active contraction (Active Motor Threshold-AMT). RMT is defined as the maximum stimulus intensity that produces a peak to peak amplitude of 50μv in 50% of trials (Rossini *et al* 1994). AMT is obtained in a similar manner, however recordings are taken when the subject is performing an isotonic contraction at the

target muscle at around 10-20% of maximal voluntary contraction (Day *et al* 1987). MT is frequently used to set TMS intensity in experimental paradigms. The RMT depends on at least 3 different independent factors: (i) excitability of cortico-spinal axons (ii) excitability of intra-cortical synapses and (iii) excitability of synapses in the spinal cord. The AMT is usually lower than the RMT of the same subject, since tonic muscle contraction pre-activates synapses in the spinal cord to generate an MEP if a TMS pulse is simultaneously applied (Rösler *et al* 2008). Since synapses in the spinal cord are pre-activated, AMT is assumed to depend mostly on the excitability of cortical axons and intra-cortical synapses. Hence, AMT is thought to be a measure of cortical rather than cortico-spinal excitability (Talelli *et al* 2006).

2.7.1.1.2. MEP and MT early after stroke

In some post stroke patients TMS to the ipsilesional hemisphere fails to elicit any MEPs in acute phase (Foltys *et al* 2003), which states to be a predictor of poor motor recovery (Hendricks *et al* 1997). However if MEPs can be elicited from the ipsilesional hemisphere of post stroke patients, the RMT is occasionally increased (i.e., cortico-spinal excitability is decreased) when compared to contralesional hemisphere and to healthy subjects both in acute (Manganotti *et al* 2002) and sub-acute phase (Cicinelli *et al* 1997).This excitability gradually increases over time (i.e., MEPs increase and MTs decrease) (Manganotti *et al* 2002).

2.7.1.1.3. Silent Period

When an MEP is evoked by a single suprathreshold TMS pulse during voluntary contraction a period of EMG inhibition follows, termed as silent period (SP). The

duration of EMG silence is typically 50-300 ms and it begins at 30 ms after the stimulus. Longer SPs indicate increased inhibition whereas shorter SPs indicate reduced inhibition (Chen *et al* 2008).

2.7.1.2. Repetitive Transcranial Magnetic Stimulation (rTMS)

The Key words used for search were rTMS, CVA, Stroke; 1922 studies were found from a period of 1990 to 2012 and screened to 44. Repetitive transcranial magnetic stimulation can be used to modulate cortico-spinal excitability beyond the stimulation period, different techniques used are:

2.7.1.2.1. Conventional rTMS

Conventional, so called simple rTMS protocols are characterized by many (usually > 500) stimuli applied at one intra stimulus intervals (ISI). Their effects are bidirectional depending on the frequency applied: low frequency rTMS (1 Hz) produces inhibition whereas high frequency rTMS (5-25 Hz) produces facilitation of cortical excitability (Pascual-Leone *et al* 1994; Rossi *et al* 2009). High frequency rTMS at sub-threshold stimulation intensities induces modulation of MEP amplitude (Bagnato *et al* 2005), if large number of stimuli ($\geq$ 1200 stimuli) are delivered (Fitzgerald *et al* 2007; Maeda *et al* 2000a), for example 5 Hz TMS (90% RMT) with 150 stimuli did not alter corticomotor excitability whereas protocols with 900 and 1800 stimuli increased M1 excitability for 20 and for > 40 minutes respectively (Peinemann *et al* 2004).

The mechanism of rTMS action are assumed to be intra-cortical and involve Long term potentiation (LTP) and Long term depression (LTD) like changes in synaptic

efficacy (Di Lazzaro *et al* 2010b). rTMS at 1 Hz (110% RMT) suppressed late I waves which was correlated with MEP reduction (Di Lazzaro *et al* 2008b). However both D wave and I wave components of the MEP are facilitated by 5 Hz rTMS (120% RMT) (Di Lazzaro *et al* 2002). Together these results indicate that rTMS modulates intra-cortical circuitry. Pharmacological studies have shown that at least some rTMS protocols are influenced by drugs that act on the NMDA receptors suggesting that the effects may be due to altered efficacy of synaptic connections (Huang *et al* 2007; Teo *et al* 2007).

2.7.1.2.2. Theta Burst Stimulation (TBS)

The Key words used for search were TBS, CVA, Stroke; 17 studies were found from a period of 1990 to 2012 and screened to 7. Theta burst stimulation is a method of applying rTMS in a patterned protocol (i.e., 5 Hz=theta rhythm) (Huang *et al* 2005) were the first who used rTMS with a TBS stimulation pattern to modulate motor cortex excitability non-invasively in humans. The basic element of TBS patterns are bursts (3 pulses given at 50 Hz) which are applied at 5 Hz (Huang *et al* 2005). A 40 seconds of continuous TBS (cTBS) significantly suppressed motor cortex excitability for nearly 60 minutes, whereas intermittent TBS (iTBS) in which a 2 seconds train of stimulation (10 bursts) is followed by 8 seconds pause, significantly increased motor cortex excitability for about 15 minutes (Figure.2.3)

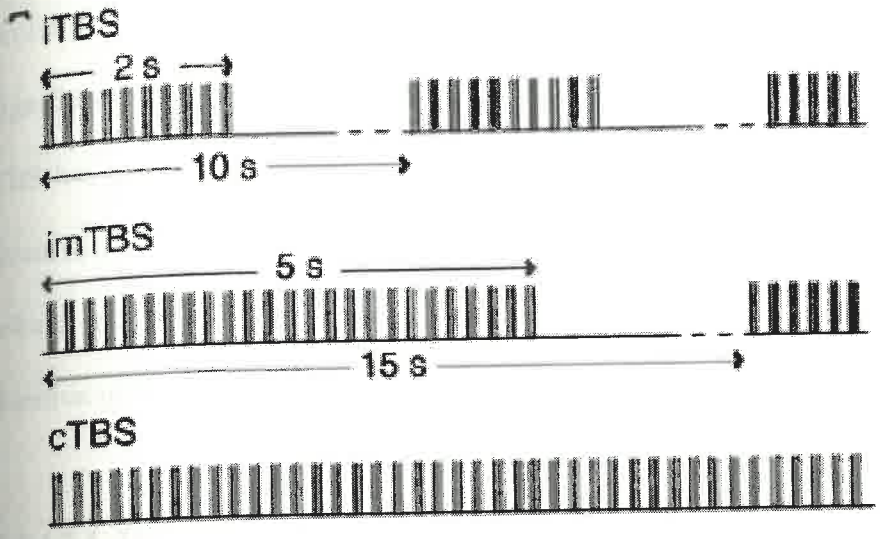


Figure 2.3: The basic elements of TBS patterns (3 pulses of stimulation are given at 50 Hz, repeated every 200 ms) , iTBS- intermittent TBS (a 2 s train of TBS is repeated every 10 s for a total of 190 s (600 pulses), imTBS intermediate TBS a 5 s train of TBS is repeated every 15 s for a total of 110 s (600 pulses), cTBS- continuous TBS (40 s train of uninterrupted TBS is given (600 pulses).
(Modified Hoogendam et al 2010)

Even though both iTBS and cTBS contain equal number of pulses (600 pulses), they show inhibitory and facilitatory effects on cortical excitability. (Huang *et al* 2005) have given a theoretical model based on certain assumptions: (i) TBS induces both facilitatory and inhibitory effects simultaneously in the human brain (ii) inhibitory effects build up slower than facilitatory effects (iii) inhibitory effects dominate over facilitatory effects when both have reached saturation. According to this model, short trains of stimulation (as during iTBS) would favour facilitatory effects which build up faster than inhibitory effects. However during longer stimulation periods (as during cTBS) inhibitory effects build up and dominate over facilitatory effects in the long run since facilitatory effects saturate at lower levels. An alternative would be that iTBS and cTBS act on different neuronal circuits. This hypothesis is supported by findings from patients with electrodes implanted in the epidural space of the spinal cord (Di Lazzaro *et al* 2010b). The reaction times of the contralateral hand were

prolonged 10 minutes after cTBS whereas reaction times of the ipsilateral hand were significantly shorter 30 minutes after cTBS.

TBS has several advantages over conventional rTMS protocols i.e., low stimulation intensities reduce the risk of seizures (Bezard *et al* 1999) and also shown to have robust and long lasting effects (Hoogendam *et al* 2010) with shorter stimulation duration of only 1-3 minutes.

2.7.1.2.3. The neurophysiological basis of rTMS effects

The mechanism underlying changes in cortico-motor excitability are poorly understood. But there are several lines of evidence supporting the hypothesis that TMS acts on small neurons in the outer layers of the cortex (intracortical neurons) subsequently activating the pyramidal cells contributing to the cortico-spinal tract (Hallett 2007). It is also explained that high frequency rTMS which is facilitatory induces a process like LTP and low frequency rTMS which is inhibitory/suppressive induces a process similar to LTD (Ridding and Rothwell 2007). There are various characteristics of rTMS induced effects which follow key features of synaptic plasticity (i) effects outlast the period of stimulation (ii) direction and duration of effects depend on temporal patterns of stimuli (iii) induced changes depend on physiological activity and the history of activation (iv) effect interact with skill learning (Hoogendam *et al* 2010).

There is also some evidence that NMDA receptors which play a key role in synaptic plasticity (Cooke and Bliss 2006) is involved in rTMS mediated effects, since NMDA receptor antagonist memantine blocks both the facilitatory effect of iTBS and inhibitory effect of cTBS in humans (Huang *et al* 2007).

2.7.1.2.4.. *Interhemispheric Competition.*

When the brain is at rest there is a balanced reciprocal interhemispheric inhibition (IHI) between both primary motor cortices via trans callosal fibre tracts. In healthy subjects during unilateral hand movements the active primary motor cortex (M1) contra-lateral to hand movements exerts increased IHI on to the M1 ipsilateral to hand movements. Whereas in post stroke patients during movements of the paretic hand the contralesional hemisphere exerts increased IHI on to the ipsilesional M1.

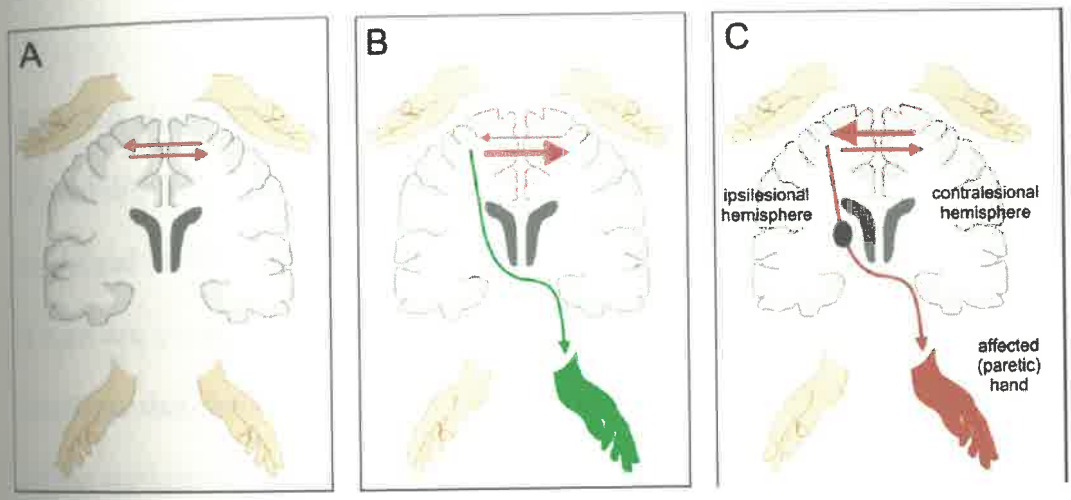


Figure 2.4: The model of hemispheric competition. A: There is balanced reciprocal interhemispheric inhibition (IHI) between both primary motor cortices via transcallosal fibre tracts in the healthy human brain at rest. B: In healthy subjects, reciprocal IHI is modulated by the state of activation. During unilateral hand movements, the "active" primary motor cortex (M1) contralateral to hand movements exerts increased IHI onto the M1 ipsilateral to hand movements. C: Modulation of IHI is abnormal in stroke patients. During movements of the paretic hand, the contralesional hemisphere (ipsilateral to paretic hand movements) exerts pathologically increased IHI onto the "active" ipsilesional M1 (contralateral to paretic hand movements).

Hence by applying the two rTMS/TBS strategies, this imbalance can be modulated: (i) increasing the cortical excitability of the ipsilesional hemisphere by means of simple rTMS protocols (Kim *et al* 2006) or applying iTBS to the ipsilesional hemisphere (P Talelli, R J Greenwood and J C Rothwell 2007) (ii) decreasing the cortical excitability of the contra-lesional hemisphere by means of low frequency

simple rTMS protocols (Fregni *et al* 2006) or cTBS to the contralesional hemisphere (P Talelli, R J Greenwood and J C Rothwell 2007) (Figure 2.4).

2.7.1.2.5. Therapeutic potential of rTMS

Since rTMS induces long lasting changes in cortical excitability or activity, it has therapeutic potential for treatment of various neurological diseases in which the pathomechanism is related to either decreased or increased cortical excitability.

2.7.1.2.6. Applying rTMS to the primary motor cortex of the ipsilesional hemisphere

Feasibility and safe use of high frequency rTMS (3-20 Hz) and iTBS has been explained in many studies (Ameli *et al* 2009; Khedr *et al* 2005; Kim *et al* 2006). There are promising results from experimental studies with stroke patients which confirms that facilitatory rTMS/iTBS over ipsilesional M1 increases the excitability of the corticomotor pathway to the paretic hand (Kim *et al* 2006; Talelli *et al* 2007). A review done by Nowak et al. showed a 25% to 125% improvement in paretic hand after facilitatory rTMS to the ipsilesional M1 (Nowak *et al* 2009). Studies also have proven that a single session of rTMS/iTBS to the ipsilesional M1 has enhanced the strength, dexterity and range of motion of the paretic hand in mild to moderately impaired patients (Kim *et al* 2006; Talelli *et al* 2007). Studies also have suggested that greater the increase in excitability, the greater will be the improvement in hand function, so it suggests that amount of improvement in motor behavior was correlated to the increase in ipsilesional M1 excitability (Kim *et al* 2006). However changes in overall UL function after rTMS of ipsilesional M1 are largely unexplored. A study by (Khedr *et al* 2005) has reported that patients who received high frequency rTMS to

the ipsilesional M1 prior to their normal therapy sessions had a greater reduction in disability. In an another study done by (Di Lazzaro *et al* 2008a) to explore the efficacy of iTBS to the ipsilesional M1 on 12 acute stroke patients showed increased excitability of the lesioned M1 after the iTBS sessions.

2.7.1.2.7. Applying rTMS to the primary motor cortex of the contraleional hemisphere

Typically 1 Hz rTMS or cTBS to the contra-lesional M1 decreases the cortico-motor excitability to the nonparetic hand. This might be due to the reduction in the inhibition passed from contralesional to ipsilesional M1 (Takeuchi *et al* 2005).

The application of cTBS to the contra-lesional M1 has also been investigated by (P Talelli, R J Greenwood and J C Rothwell 2007) on 6 stroke patients, which showed a transient improvement in motor behavior and cortico-spinal output in paretic hand. In another study it was found that after the application of cTBS to the contralesional M1, excitability of the lesioned cortico-motor pathway has been shown to increase. (Di Lazzaro *et al* 2008a) or remain unchanged (P Talelli, R J Greenwood and J C Rothwell 2007).

In a study done by Nowak et al where low frequency rTMS to the contra-lesional M1 reduced the neural activity of the overactive contra-lesional hemisphere and increased the neural activity in the lesioned hemisphere thereby rebalancing the cortical excitability of both hemispheres, and this was supported by the fMRI (Nowak *et al* 2008). Thus the mechanisms of different rTMS protocols applied to contralesional M1 require more investigation. Studies to date have shown modest improvements (10% to

60%) in motor performance after inhibitory rTMS applied to the contralesional M1 (Nowak *et al* 2008; Nowak *et al* 2009)

2.7.1.2.8. Priming therapy with rTMS

Research investigating rTMS primed therapy for stroke patients is in its infancy. Two single session sham controlled studies have shown that the effect of motor training was enhanced by priming M1 with rTMS (Kim *et al* 2006; Takeuchi *et al* 2008). Though they reported short term improvements, it is unclear whether these results can be generalized.

In a study done by (Khedr *et al* 2005) on acute stroke patients who received 3 Hz rTMS prior to 10 consecutive therapy sessions had an immediate and sustained (follow up at 20 days) improvement in barthel index and NIHSS. In a study by (Ackerley *et al* 2010) on 10 chronic stroke patients where iTBS was combined with motor training showed improvement in performance of paretic hand on contrary cTBS to the contralesional hemisphere resulted in deterioration of UL functions when assessed with action research arm test, MEP amplitude and grip lift kinetics. On contrary in a recent study done by (Talelli *et al* 2012) on 41 chronic stroke patients where TBS was combined with UL physical therapy for 10 days and compared with sham stimulation showed no significant difference between the two study groups. Suppressive rTMS of contralesional M1 has also been used to reduce the excitability of the contralesional hemisphere, but may not be an important contributor to recovery in some patients to at least partial recovery of the UL when corticospinal tract integrity is significantly affected (Ward *et al* 2006). Which states that more research is

needed to find out the potential benefit of rTMS primed therapy for UL rehabilitation for post stroke patients.

2.8. Outcome Measures

2.8.1. Fugl Meyer Assessment

The Fugl-Meyer Assessment (FMA) is a stroke-specific, performance-based impairment index. It is designed to assess motor functioning, balance, sensation and joint functioning in patients with post-stroke hemiplegia (Fugl-Meyer *et al* 1975; Gladstone *et al* 2002). It is applied clinically and in research to determine disease severity, describe motor recovery, and to plan and assess treatment. The FMA has been used as the gold standard against which the validity of other measures has been assessed. In this study we have used only the upper extremity component of fugl meyer assessment scale

*2.8.1.1. **Reliability:*** (Lin *et al* 2004) examined the internal consistency of the FMA in 176 patients with stroke from 14 to 180 days after stroke. Cronbach's alphas for the FMA at four time points post-stroke were excellent, ranging from alpha = 0.94 to 0.98. The inter-rater reliability of the total score of the FMA was also excellent, with an intra-class correlation coefficient (ICC) of 0.93. (Duncan *et al* 1983) examined the test-retest reliability of the FMA in 18 patients with chronic stroke was found to be excellent.

*2.8.1.2. **Validity:*** Construct validity of the FMA upper extremity items (including items from the Motor function, Sensation and passive joint motion/joint pain sub scores), the Action Research Arm Test (ARAT), and the Box and Block Test using the Spearman correlation coefficient, in patients with upper limb paresis either from

stroke (n=37) was assessed by (Platz *et al* 2005). Excellent correlations were found between the FMA and the ARAT (r = 0.93), the Box and Block Test (r = 0.92), and the Motricity Index (r = 0.86).

Convergent validity of the FMA upper extremity item (motor domain), ARAT, the NIH Stroke Scale , the Functional Independence Measure (FIM) total score, and FIM activities of daily living subscore was assessed by (Rabadi and Rabadi 2006) in 104 in patients with acute stroke at a rehabilitation unit using the Spearman rank correlation coefficient, the ARAT and the Motor domain upper extremity subscore of the FMA correlated excellently with one another, both at admission (r = 0.77) and at discharge (r = 0.87). The Motor domain upper extremity subscore of the FMA and the FIM activities of daily living subscore at the time of admission were adequately correlated (r = 0.54).

Content validity was assessed by (Woodbury *et al* 2008) for the upper extremity items of the FMA in 377 clients with stroke with a mean age of 60 years (SD 11.2). Rasch Analysis, showed an acceptable fit statistics, except for the item hook grasp. This result suggests that all items reflect the same construct, except for the item hook grasp.

Concurrent validity assessed by (Wood-Dauphinee *et al* 1990) compared the FMA to the Barthel Index in 167 patients with stroke at two time points: the acute stage (3 to 5 days post-stroke), and 5 weeks post-stroke. Using Pearson correlation coefficients, the correlation between the FMA Motor domain upper extremity subscore and the Barthel Index total score was excellent at both the acute stage (r = 0.75) and at 5 weeks (r = 0.82).

2.8.2. Modified Rankin Scale (MRS)

The MRS is a single item, global outcomes rating scale for patients post-stroke. It is used to categorize level of functional independence with reference to pre-stroke activities rather than on observed performance of a specific task.

*2.8.2.1. **Reliability:*** (Wilson *et al* 2005) examined the test-retest reliability of the MRS in patients at least 6 months post-stroke, using two raters who performed repeat assessments with a mean test-retest interval of 7 days. Agreement was measured using the kappa statistic. Comparison of Rankin grades showed that there was excellent agreement between the first and second assessments.

Intra-rater reliability was examined by (Wolfe *et al* 1991) in a sample of 14 patients who were assessed twice by the same observer within a 2-week period at least 3 months post-stroke. Exact agreement was reported in 86% of observations (kappa w = 0.95). The intra-rater reliability of the MRS as reported to be excellent.

Inter-rater reliability was examined by (Wilson *et al* 2002) in 63 patients with stroke. The MRS was administered by two raters. Inter-rater reliability was measured with the kappa statistic and was found to be excellent (kappa w = 0.78). However, overall agreement between the 2 raters was only 57%, and one rater assigned significantly lower grades than the other (p = 0.048).

*2.8.2.2. **Validity:*** Concurrent validity of the MRS, Barthel Index (BI), and the motor component of the Functional Independence Measure (M-FIM) using Spearman correlation coefficients was examined by (Kwon *et al* 2004). Excellent correlations

were observed between the MRS and the BI (r = -0.89) and between the M-FIM and the MRS (r = -0.89).

Construct validity was examined by (Wolfe *et al* 1991) for the MRS and the Barthel Index to 50 patients post-stroke showed an excellent correlation (kappa = 0.72; weighted kappa = 0.91) between the two scales, which lends support to the assertion that the MRS is closer to a disability scale than a handicap scale.

2.8.3. National Institute for Health Stroke Scale (NIHSS)

The NIHSS is a 15-item impairment scale, intended to evaluate neurologic outcome and degree of recovery for patients with stroke. The scale assesses level of consciousness, extra ocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect) (Lyden *et al* 1999; Lyden *et al* 2001). The NIHSS was designed to assess differences in interventions in clinical trials, although its use is increasing in patient care as an initial assessment tool and in planning postacute care disposition (Schlegel *et al* 2003; Schlegel *et al* 2004).

*2.8.3.1. **Reliability:*** Test-retest reliability was adequate to excellent (mean kappa = 0.66 to 0.77). The correlation between the first examination scores and the second examination scores (within 24 hours) was excellent (r = 0.98). (Meyer *et al* 2002) examined the inter-rater reliability of the NIHSS and the mNIHSS in 45 patients with a history of stroke. Two neurologists tested each patient, ten items were found to have excellent inter-rater reliability. Kappa scores ranged from 0.289 to 0.975. The kappa value for the total NIHSS score was excellent (kappa = 0.969).

2.8.3.2. Validity: Concurrent validity was examined by (Schiemanck *et al* 2005) of infarct volumes in 94 patients with stroke as assessed by magnetic resonance imaging (MRI) with stroke severity as measured by the NIHSS at 2 weeks post-stroke. A strong correlation between lesion volume and NIHSS score was found (r = 0.61), suggesting that the NIHSS has excellent concurrent validity with infarct volumes using MRI.

Content validity examined by (Lyden *et al* 1999) used data from the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator Trial to determine whether the NIHSS was valid in patients treated with tissue plasminogen activator. The results showed that NIHSS has a good content validity

2.8.4. Barthel-Index (BI)

This index measures the extent to which somebody can function independently and has mobility in their activities of daily living (ADL) i.e. feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing. The index also indicates the need for assistance in care.

2.8.4.1. Reliability: (Hobart and Thompson 2001) compared the psychometrics of the modified BI, the FIM and the 30-item FIM + Functional Assessment Measure (FIM+FAM) in 149 patients with various neurological disorders. All measures were found to be psychometrically similar measures of physical disability. The internal consistency of the BI was excellent, with a Cronbach's alpha of 0.94 (Cronbach's alpha of the Functional Independence Measure ranged from 0.89-0.96).

2.8.4.2. Validity: Concurrent validity for BI was examined by (Wade and Hewer 1987) where they showed excellent concurrent validity of the modified BI (r = 0.73 - 0.77) with a measure of motor ability. Predictive validity examined for Modified BI scores have been shown to predict hospital length of stay (Chang *et al* 2002).

2.8.5. Modified Ashworth Scale (MAS)

The MAS is considered the primary clinical measure of muscle spasticity in patients with neurological conditions. However, some publications question its ability to measure spasticity and advocate the MAS as a rating scale to measure abnormality in tone or the resistance to passive movements, since there is no clinically direct method for measuring spasticity (Gregson *et al* 1999).

2.8.5.1. Reliability: Intra-rater reliability was examined by (Gregson *et al* 1999) on 32 clients with acute stroke and a median age of 74 years by measuring muscle tone at the elbow. Participants were assessed by the same rater within a 1-day interval at the same time of the day. Intra-rater reliability, as calculated using weighted kappa was excellent (weighted kappa = 0.83).

Inter-rater reliability was examined by (Gregson *et al* 1999) on 32 clients with acute stroke and a median age of 74 years by measuring muscle tone at the elbow. Participants were assessed by two different raters at approximately the same time of the day. Inter-rater reliability as calculated using weighted kappa was excellent (weighted kappa = 0.84).

2.8.5.2. Validity: (Lin and Sabbahi 1999) measured the convergent validity of the MAS by comparing it to hyperactive stretch reflex measures such as electromyography, torque response and velocity sensitivity of the stretch reflexes as well as to motor performance measures such as the FMA (Fugl-Meyer *et al* 1975). Correlations were calculated at two points in time using Spearman's rho. Correlations between the MAS and motor performance measures for both day 1 and 2 were all excellent: FMA (rho1 = -0.83; rho2 = -0.76).

3. Methodology

3.1. Introduction

This chapter details the methods of the randomized controlled trial and the statistical analysis to be conducted to answer the aims and research questions listed at the end of Chapter 1. Section 3.2 details the study methodology including the study design, measures, participants and recruitment methods, randomization and blinding followed by details of sample size calculations. The intervention is described next with a rationale for each component and then a brief description of the statistical analyses to be done.

3.2. Study Design

This trial was to determine the efficacy of theta burst stimulation and functional electrical stimulation as compared to physiotherapy in stroke Rehabilitation. The aim of the present study was to find out an effective integrated rehabilitation program for stroke patients incorporating the TBS, FES and PT. The study design was a randomized controlled trial with concealed allocation, blinded assessment using six measures repeated at baseline (T1), post-intervention assessment at 1 month (T2) and follow-up assessments at 3 months (T3), 6 months (T4) and at 1 year (T5). The present study included 60 patients randomly divided into 3 groups of 20 each by block randomization method to receive the designated intervention. Participants were recruited from the outpatient and inpatient clinics of neurology department of sree chitra tirunal institute for medical sciences and technology. Patients with a diagnosis of acute stroke in last 01 month were screened for the eligibility

3.2.1. Inclusion criteria

1. First episode of ischemic stroke in the internal carotid artery territory defined on CT scan or MRI brain.
2. Presentation within 10 days to 1 month of stroke onset.
3. Age group between 15-70 years
4. FMA score less than 20.

3.2.2. Exclusion criteria

1. Brain stem stroke
2. Bilateral stroke
3. Hemorrhagic stroke
4. Significant joint deformity preventing effective physiotherapy
5. Severe internal carotid artery stenosis requiring intervention
6. Unstable cardiopulmonary status and other diseases which are likely to hamper the 1 year follow up
7. Intracranial metallic implants
8. History of seizure
9. Cardiac implants or pacemakers
10. Pregnancy or likely to become pregnant during study period
11. History of past neurological disease likely to interfere with assessment of response
12. Taking regular medications likely to interfere with TMS assessment like benzodiazepines.

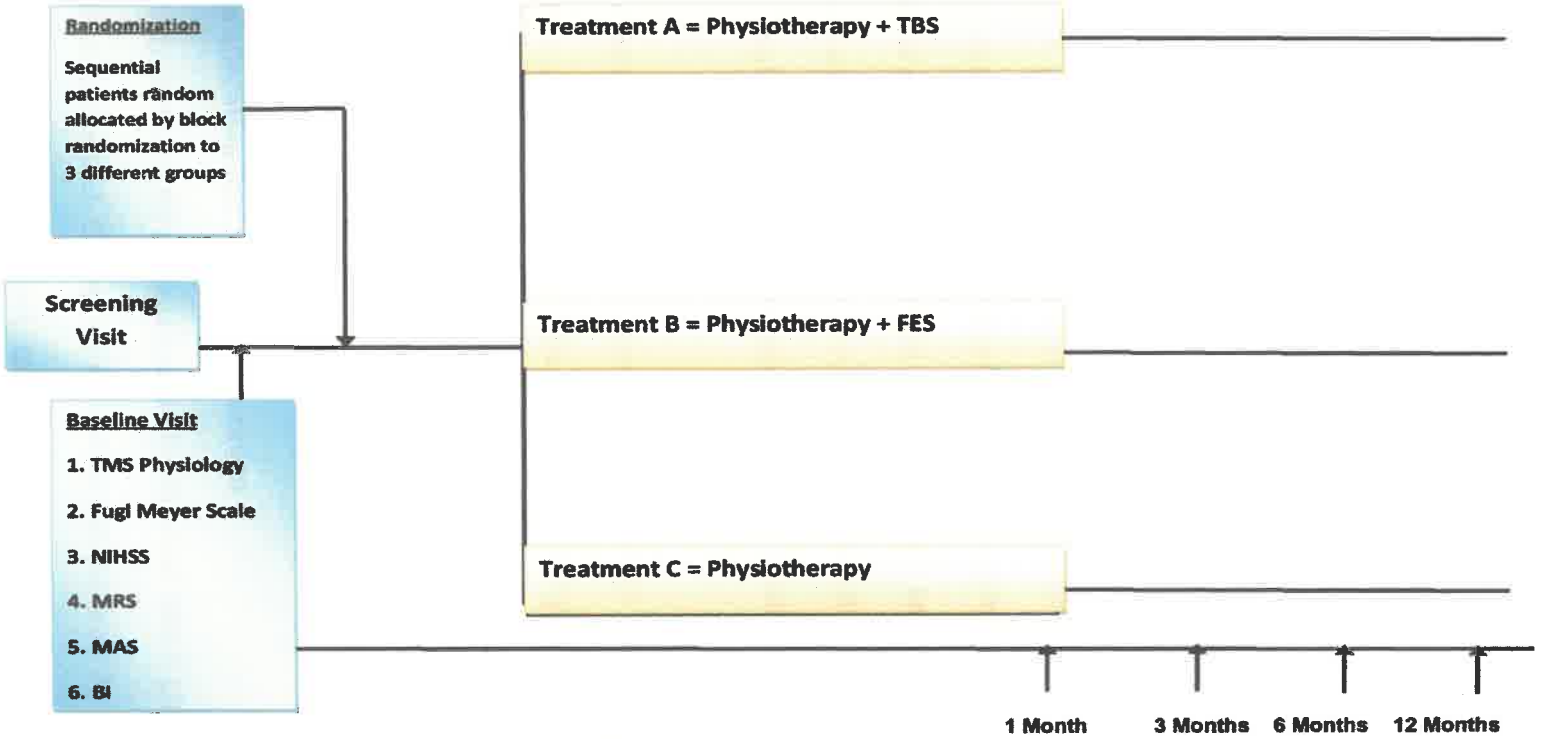


Figure: 3.1 Flow Diagram of the Randomization Procedure.

Abbreviations: TBS, Theta burst stimulation; FES, Functional electrical stimulation; MRS, Modified rankin scale; MAS, Modified ashworth scale; BI, Barthel index.

3.2.3. Sample size calculation

Primary outcome measure for this study is the Fugl Meyer Assessment of physical performance at 01 year. This is a 66 point scale to evaluate hand functions, a standard tool used for this purpose. Previous studies have shown that in control patients this score increases by 16.5 ± 9.4 at one year (Hemmen and Seelen 2007), for a clinically meaningful outcome the intervention should produce an increase of 10 points. Thus to detect a significant difference of 10 points between control and active groups, a sample size of 14 in each arm is required for achieving 80% power with alpha fixed at 5%. A few studies which used same outcome measures in stroke rehabilitation had even lesser sample size.

In a study conducted at our institute, the post stroke mortality was 27.2 % at one year, of these 72.1% died within 10 days after the stroke. We have planned to include patients between 10 to 30 days of stoke onset. Hence to account for the mortality rate of 7.6% after 10 days, required sample size will be 16 in each group. We have kept the sample size at 20 in each arm for rounding and to account for the drop outs, if any.

3.2.4. Random allocation and sequence generation

The present study included 60 patients randomly allocated into 3 groups of 20 each by block randomization method. Concealed allocation was be done by Neurologist I who was blindly allocating the subjects to different groups according to the block randomization table to receive the designated intervention. All the patients presenting to

our institute with a diagnosis of acute stroke in last 01 month was screened for the eligibility.

3.2.5. Blinding

After providing the informed consent, a subject fulfilling the inclusion and exclusion criteria was initially assessed by Neurologist II for all the outcome measures and neurophysiological parameters. Patients who were eligible for the study was allocated to different intervention groups by Neurologist I. Intervention were done by research physiotherapist for all the subjects. Follow-up assessments were done by the Neurologist II who was blinded to the allocation to intervention groups.

3.2.6. Ethical considerations

Patients were given verbal and written information about the study and their written consent was obtained prior to inclusion. All participants provided voluntary, informed consent before inclusion. The ethical committee of the sree chitra tirunal institute for medical sciences and technology approved the study protocol (Institutional Ethics Committee – SCT/IEC/223).

3.2.7. Dropout rate in each group

Two subjects from TBS group (due to Permanent pacemaker implantation and the other due intracranial stenting) and one subject from Physiotherapy group (due to intra cranial

space occupying lesion) did not complete the intervention. However these 3 subjects were substituted in the corresponding groups.

3.3. Clinical assessment

During the first visit, between 10-30 days after the stroke, patients underwent a detailed neurological examination, patients was assessed for global outcome rating by modified rankin scale, stroke severity by National Institute of Health Stroke Scale (NIHSS), UL motor functions with Fugl Meyer Assessment for motor performance scale (FMA), activities of daily living by Barthel Index (BI) and measure of spasticity by modified ashworth scale (MAS). The follow up assessment was done after intervention at 1 month, 3 months, 6 months and at 1year with the same rating scales.

All patients recruited for the study underwent baseline TMS neurophysiological assessment with protocol described below.

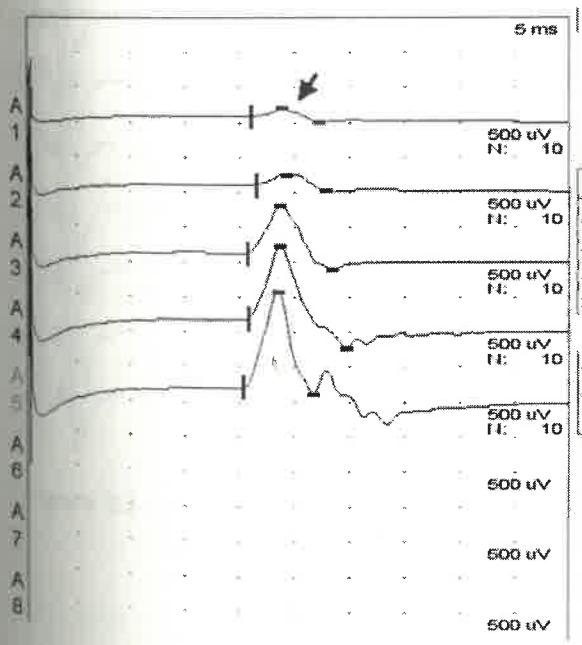
3.3.1. TMS Protocol

Patient underwent primary TMS neurophysiological assessment after assessing the patient for possible contraindication. The researcher performed single pulse TMS measurements as well as TBS with Magstim Rapid^2 (Whitland, Wales, UK) stimulator using figure-of-eight coil, with external loop diameter of 9 cm.

After making the patient seated comfortably in an armchair, the coil was held in a posterior-anterior plane over the M1 at the optimum scalp position to elicit MEP in the

contralateral first dorsal interosseous (FDI) muscle. The parameters were checked in both the hemispheres, first ipsilesional hemisphere and then the contralesional hemisphere. Surface electromyograms (EMGs) were recorded from the FDI muscles bilaterally using Ag-AgCl electrodes with a gain of 1-2 mv. Signals were filtered (10Hz-10 KHz), and then stored for off-line analysis. To assist subjects in maintaining complete relaxation, they were given audio–visual feedback of the EMG signal at high gain and we discarded the trials contaminated by EMG activity.

3.3.1.1. ***Resting Motor Threshold (RMT):*** This is the minimum intensity of stimulator output in percent required to elicit a MEP at least in five out of 10 stimuli given. The output is usually started at 40% stimulator intensity and gradually increased by 5% after every ten stimulus to get the appropriate response (Figure 3.2).

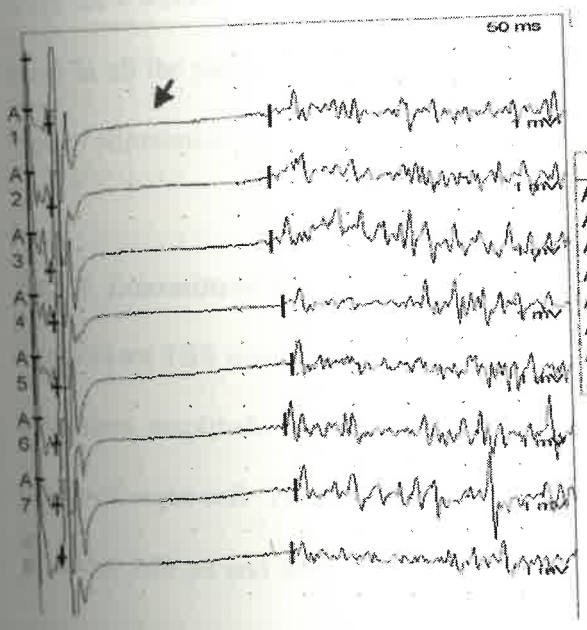


Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms
A1: 80	21.0		0.211	
A2: 85	21.5		0.233	
A3: 90	20.7		0.935	
A4: 95	20.8		1.462	
A5:100	20.3		1.451	
A6:				
A7:				
A8:				

Figure 3.2: Recruitment curve; Arrow indicates the **Resting Motor Threshold** at a magnetic stimulus intensity of 80.

3.3.1.2. Cortical Silent Period (CSP): This is time interval from the stimulus artifact to the return of voluntary electromyographic activity while subjects maintained 30% contraction of the contralateral first dorsal interossei (FDI) muscle with the help of audio-visual feedback (Figure 3.3).

Patients were assessed with these basic neurophysiological parameters before and immediately after TBS study, to note the immediate change brought by TBS. Patients were reassessed with clinical and TMS neuro-physiological parameters at one month, and subsequently at 3 months, 6 months and at the end of 1year



Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms
A1:	23.0	208.0	2.141	Ofl
A2:	22.8	205.7	3.135	Ofl
A3:	19.8	208.7	3.242	Ofl
A4:	21.8	216.2	2.897	Ofl
A5:	23.0	222.0	2.962	Ofl
A6:	20.0	217.0	2.845	Ofl
A7:	19.4	225.1	2.856	Ofl
A8:	21.8	218.2	2.469	Ofl

Figure 3.3: Arrow indicates the **Cortical Silent Period**

3.4. Intervention

Patients underwent one of the interventions as per the randomization group: Physiotherapy combined with TBS as group A; Physiotherapy combined with FES as group B and Physiotherapy alone as group C.

3.4.1. Theta Burst Stimulation

TBS will include two components: intermittent TBS (iTBS), also known as facilitatory TBS given to the affected hemisphere; and continuous TBS (cTBS), also known as inhibitory TBS given to unaffected hemisphere. TBS will be delivered for 3 times in a week for 4 weeks. The order of the experiments (facilitatory and inhibitory TBS) will be same in all the patients. Investigator responsible for analyzing MEPs was blinded to the type of stimulation (iTBS or cTBS).

3.4.1.1. Intermittent TBS

Intermittent TBS was delivered over the affected motor cortex ''hot spot'' (site where the maximum amplitude of MEP was generated) using a Magstim Rapid^2 connected to a figure-of-eight coil. The magnetic stimulus had a biphasic waveform with a pulse width of about 280 μs and maximum magnetic field strength of 2 Tesla. The stimulation was given with an intensity of 60% of RMT. The iTBS protocol of 10 bursts of high-frequency stimulation (3 pulses at 50 Hz) was applied at 5 Hz every 10 s for a total of 600 pulses.

When no MEP was elicited from the ipsilesional M1(<0.05mV), 100% stimulator intensity was applied at the mirror location of the contralesional M1.

3.4.1.2. Continuous TBS

Continuous TBS (inhibitory) was delivered to the unaffected hemisphere at the "hot-spot" with an intensity of 60% of RMT, 3 pulses at 50 Hz, repeated every 200 ms for a total of 600 pluses.

3.4.2. Functional Electrical Stimulation.

Patients in the FES group received electrical stimulation by means of Mega XP (Cybermedic Corporation). The system is composed of 8 channels, 2 electrodes for each channel. The patient received the electrical stimulation in sitting position with affected arm positioned over the pillow, electrodes were positioned according to pattern 3 [Grasp/Flexion/Extension, PATT (pattern movement)] of the FES (F) mode of the instrument.

Channel 1 - Flexors of wrist

Channel 2 - Biceps

Channel 3 - Triceps

Channel 4 - Extensors of wrist

Channel 6 - Anterior deltoid

The individualized electrode positioning makes it very easy for the patient to obtain a consistent level of contraction in each muscle group every day. The electrodes were

connected to a stimulator controller unit that delivers alternating current at a frequency of 35 Hz and a pulse width of 200 μs, intensity 10~50 mA. The stimulator was set to deliver interrupted trains of pulses with the contraction and relaxation so that to simulate the lifting of UL in a functional position.

Channel 1 was stimulated for the first 3 out of 4 portions of the whole stimulation time

Channel 2 & Channel 6 was stimulated for the 2nd portion

Channel 3 was stimulated for the 3rd portion

Channel 4 was stimulated for the 4th portion

The FES group stimulation session was given for 30 minutes for each day 3 times in a week (alternate days) for 4 weeks and it was concurrently synchronized with the physiotherapy.

3.4.3. Physiotherapy treatment protocol

3.4.3.1. Passive/Active Range of Motion (ROM)

Passive ROM: wrist/elbow/shoulder

Active/assistive ROM: wrist/elbow/shoulder bilaterally

Active ROM: wrist/elbow/shoulder in sitting and standing

Active ROM with resistance: wrist/elbow/shoulder in sitting and standing

3.4.3.2. Weight bearing and supportive reaction

Seated weight bearing (forearms on tabletop) with affected upper extremity

Extending arms, seated or standing with bilateral upper extremity weight bearing on table

Extended arms with transitional movements: side lying to sit, sit to stand, dips

Extended arms and wrist/hand on wall from anterior and lateral, progress to wall push up

Extended arms and wrist/hand on wall with change in base of support; example: weight shifting, single lower extremity support, lateral wall walking

3.4.3.3. Reaching activities

Forward supported reach bilaterally with cane on tabletop (elbow extension)

Forward supported reach with shoulder elevation, elbow/wrist extension

Reaching against gravity in frontal and sagittal planes

Reaching overhead with active wrist/hand movements

Dynamic reaching to a target; example: catch a ball

3.4.3.4. Grasping, holding and release

Maintaining digit extension with weight bearing

Grasp, hold and release containers with gravity minimized on table

Pick up and move/release small object on table

Pick up and move/release large objects without proximal support

Incorporate key and pinch grips in hold and release including stacking, lifting and overhead activity

3.4.3.5. Upper extremity ADL

Dressing, grooming

Carrying objects with bilateral upper extremities

Opening bottles, stabilizing with paretic extremity for reaching

Writing, drawing, manipulating small objects

Folding towels, sweeping, hanging towels, setting table

Self-feeding

*ROM = range of motion; ADL = activity of daily living.

Physiotherapy intervention was given for all the patients 5 days per week for 1 month. The physiotherapy intervention was individually tailored to each patient and constructed through a selection of exercises from the above mentioned protocol. The number and complexity of the exercises were adjusted by the research therapist for each patient so that he or she was able to practice independently or with assistance from a family member after the intervention and was instructed to practice 30 minutes twice a day. In addition, all patients continued to receive in-home physiotherapy 1 to 2 times per week by a home physiotherapist who was guided by the research physiotherapist. The researchers monitored the standard therapy by reviewing the study patient once in a month and modified the research-related exercise program based on patient progress. The actual amount of time that each patient exercised at home was monitored with a log book given to the patient.

3.5. Outcome measures

Outcome was assessed using Fugl Meyer Assessment for physical performance, Modified Rankin Scale, National Institute of Health Stroke Scale, Barthel Index , Modified

Ashworth Scale and TMS neurophysiological parameters like Resting Motor Threshold and Cortical Silent Period at baseline, at 1 month, and subsequently at 3 months, 6 months and 1 year. Fugl Meyer Assessment for physical performance at 01 year will be the primary outcome measures while rest of the parameters including TMS neurophysiologic parameters will be included as secondary outcome measures.

3.5.1. Fugl Meyer Assessment of Motor Performance:

The Fugl-Meyer Assessment (FMA) is a stroke-specific, performance-based impairment index. In this study we have used only the UL motor component of the FMA, which is divided into four sections like upper extremity, wrist, hand and coordination with a total score of 66.

3.5.2. Modified Rankin Scale:

The MRS is a single item, global outcomes rating scale for patients post-stroke. It is used to categorize level of functional independence with reference to pre-stroke activities rather than on observed performance of a specific task. The score ranges from 1 = no symptoms at all to 6 = dead.

3.5.3. National Institute for Health Stroke Scale

The NIHSS is a 15-item impairment scale, intended to evaluate neurologic outcome and degree of recovery for patients with stroke. The scale assesses level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory

function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect)

3.5.4. Barthel Index

This index measures the extent to which somebody can function independently and has mobility in their activities of daily living (ADL) i.e. feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing with score ranging from 0-100.

3.5.5. Modified Ashworth Scale

The Modified Ashworth Scale is considered the primary clinical measure of muscle spasticity in patients with neurological conditions and the score ranges from 0= no increase in muscle tone to 4 = affected part rigid in flexion or extension.

3.6. Statistical Test Used:

Descriptive statistics were used to present summary of data, and analyzed with SPSS version 17.0. Baseline comparability of groups was assessed with chi-square test and ANOVA. Outcome measures were analyzed using ANOVA followed by bonferroni correction and Kruskal Wallis test followed by Mann Whitney U test.

3.7. Time schedule of activities giving milestones

Months	6	12	18	24	30	36	42	48
Study design and preparation for the study								
Screening, Randomization and treatment of the patients with their follow ups								
Follow up of Patients								
Data Compilation and analysis, preparation of final thesis and submission								

Table 3.1: Time taken for achieving the various milestones.

4. Results

4.1. Introduction

Baseline comparability of groups, in terms of demographic data and baseline measurements were assessed with chi-square test and ANOVA. Non-normal data was subject to reciprocal, logarithmic and exponential transformation and Komogrov-Smirnov and Shapiro-Wilks tests were done to assess normality. Parametric measures were analyzed with ANOVA followed by post-hoc analysis with bonferroni correction. Repeated measure ANOVA was done to find out between group and within group variability. Non parametric measures were analyzed with Kruskal Wallis test followed by post hoc analysis with Mann Whitney U test. Friedmans test and Kendalls W test was done to find the changes in three groups over a period of one year.

There were no significant differences in the demographic characteristics of participants between the three intervention groups (Table: 4.1). Variables like gender and side of lesion of the participants which were categorical was assessed with chi-square test and the variables like age and days after stroke which were continuous were assessed with one way analysis of variance (ANOVA).

Treatment Groups	TBS (n=20)	FES (n=20)	PT (n=20)	Total	p[a]
Gender (male/female) %	13/7 65/35	14/6 70/30	12/6 60/40	39/21 65/35	0.80
Age (years; mean± SD)	63.55±12.67	62.25 ± 11.86	64.60 ±12.99	63.47 ± 12.34	0.84
Side of lesion (R/L) %	14/6 70/30	13/7 65/35	15/5 75/25	42/18 70/30	0.79
Days after stroke (years; mean ± SD)	17.10 ± 4.82	16.85 ± 5.14	16.40 ± 5.58	16.78 ± 5.12	0.91
FMA (mean ± SD)	14.90 ± 2.10	15.50 ± 1.99	14.30 ± 2.20		0.20
Median (range)	15 (11-19)	15.5 (12-19)	14 (11-19)		
MRS (mean ± SD)	4.05 ± 0.68	4.20 ± 0.61	4.20 ± 0.69		0.72
Median (range)	4 (3-5)	4 (3-5)	4 (3-5)		
BI (mean ± SD)	17.25 ± 12.19	16.25 ± 11.45	15.5 ± 9.30		0.78
Median (range)	20 (0-35)	17.5 (0-30)	17.5 (0-30)		

Table 4.1: Characteristics of Study Participants at baseline

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; SD, Standard deviation; %, Percentage; FMA, Fugl Meyer Assessment ; MRS, modified Rankin Scale; BI, Barthel Index; R/L, Right/Left.

p^a associated with χ^2 test for categorical variables, one-way analysis of variance for continuous variables

The mean age of study population was 63.55 ± 12.67 years in the TBS group, 62.25 ± 11.86 in the FES group and 64.60 ±12.99 in PT group. Participants were well enough to start the intervention at 17.10 ± 4.82 days (TBS group), 16.85 ± 5.14 days (FES group) and 16.40 ± 5.58

days (PT group) after stroke onset; a difference which was not significant (p=0.91) (Table 4.1). All the groups had more male (TBS group n=13, FES group n=14 and PT group n=12) than female participants (TBS group n=7, FES group n=6 and PT group n=6). Whilst the ratio of right to left sided stroke was fairly even in both groups, the TBS group had more participants with right sided infarcts (n=14) than left (n=6), FES group had more participants with right infarcts (n=13) than left (n=7) and PT group with right infarcts (n=15) and left (n=5) (Table. 4.1). None of these differences were statistically significant (p= 0.79).

4.2. Fugl Meyer Assessment of Motor Performance (FMA):

Fugl meyer assessment for motor performance scores at baseline for TBS group was 14.9 ± 2.10, FES group 15.5 ±1.99 and 14.3 ± 2.20 for PT group, a difference which was not significant (p= 0.20) which states that the groups are comparable. All 3 groups had a significant change in FMA scores from baseline over a period of one year at each point of time, when reassessed at 1 month ($p \leq 0.001$), 3 months ($p \leq 0.001$), 6 months ($p \leq 0.001$), and at 1 year ($p \leq 0.001$) (Table: 4.2) .

	Treatment Groups	n	Mean	Median	p value
Pre Treatment	TBS	20	14.9 ± 2.1	15 (11-19)	
	FES	20	15.5 ± 1.99	15.5 (12-19)	
	PT	20	14.3 ± 2.2	14 (11-19)	0.2 (ANOVA)
1 Month	TBS	20	32.65 ± 2.4	32.5 (28-38)	
	FES	20	32 ± 1.97	32 (29-36)	
	PT	20	22.05 ± 3.12	21.5 (18-31)	≤ 0.001(KW)
3 Months	TBS	20	40.2 ± 3.32	39 (37-50)	
	FES	20	39.15 ± 3.81	38 (34-50)	
	PT	20	27.8 ± 2.82	27 (24-36)	≤ 0.001(KW)
6 Months	TBS	20	49.25 ± 2.36	50 (45-53)	
	FES	20	48.6 ± 4.08	48 (42-62)	
	PT	20	35.30 ± 3.45	36 (29-44)	≤ 0.001(KW)
1 Year	TBS	20	55.55 ± 2.46	56 (50-60)	
	FES	20	55.85 ± 4.5	55.5 (46-66)	
	PT	20	43.3 ± 4.22	44 (35-54)	≤ 0.001 (ANOVA)

Table 4.2: Mean (SD) and Median (range) values of Fugl Meyer Assessment (FMA) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis

Post-hoc analysis was done to find out the difference between the groups which revealed that, as compared to PT group the mean FMA scores of TBS group was significantly higher at 1 month (22.05 ± 3.12 vs. 32.65 ± 2.4; p≤ 0.001), 3 months (27.8 ± 2.82 vs. 40.2 ± 3.32; p≤ 0.001), 6 months (35.30 ± 3.45 vs. 49.25 ± 2.36; p≤ 0.001) and at 1 year of follow up (43.3 ± 4.22 vs. 55.55 ± 2.46; p≤ 0.001). (Table: 4.3 and Table 4.2). Similarly, the mean FMA scores of FES group was significantly higher than the PT group at 1 month (32 ± 1.97 vs. 22.05 ± 3.12; p≤ 0.001), 3 months (39.15 ± 3.81 vs. 27.8 ±

2.82; p≤ 0.001), 6 months (48.6 ± 4.08 vs. 35.30 ± 3.45; p≤ 0.001) and at 1 year of follow up (55.85 ± 4.5 vs. 43.3 ± 4.22; p≤ 0.001). (Table: 4.3 and Table 4.2).

When compared to baseline status, mean FMA scores of the subjects who underwent TBS intervention showed significant increase at 1 month (26.89%; p≤ 0.001), 3 months (38.33%; p≤ 0.001), 6 months (52.05%; p≤ 0.001) and further increased by (61.59%; p≤ 0.001) at 1 year. Similarly FMA scores of subjects who underwent FES intervention also showed significant increase at 1 month (25%; p≤ 0.001), 3 months (35.83%; p≤ 0.001), 6 months (50.15%; p≤ 0.001) and further increased by (61.13%; p≤ 0.001) at 1 year.

	Between groups	p value	
1 Month	TBS& FES	0.42	(Mann Whitney U Test)
	TBS & PT	≤ 0.001	
	FES & PT	≤ 0.001	
3 Months	TBS & FES	0.19	(Mann Whitney U Test)
	TBS & PT	≤ 0.001	
	FES & PT	≤ 0.001	
6 Months	TBS & FES	0.22	(Mann Whitney U Test)
	TBS & PT	≤ 0.001	
	FES & PT	≤ 0.001	
1 Year	TBS & FES	1.00	(Bonferroni Correction)
	TBS & PT	≤ 0.001	
	FES & PT	≤ 0.001	

Table 4.3: Post-hoc analysis of Fugl Meyer Assessment (FMA) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group.

However the increase in FMA scores of subjects who underwent PT treatment showed significant increase but was not comparable to other two interventions at 1 month (11.74%; $p \leq 0.001$), 3 months (20.45%; $p \leq 0.001$), 6 months (31.82%; $p \leq 0.001$) and at 1 year of follow-up (43.92%; $p \leq 0.001$). (The percentage of change in FMA scores was calculated keeping the total score of FMA at 66 points)

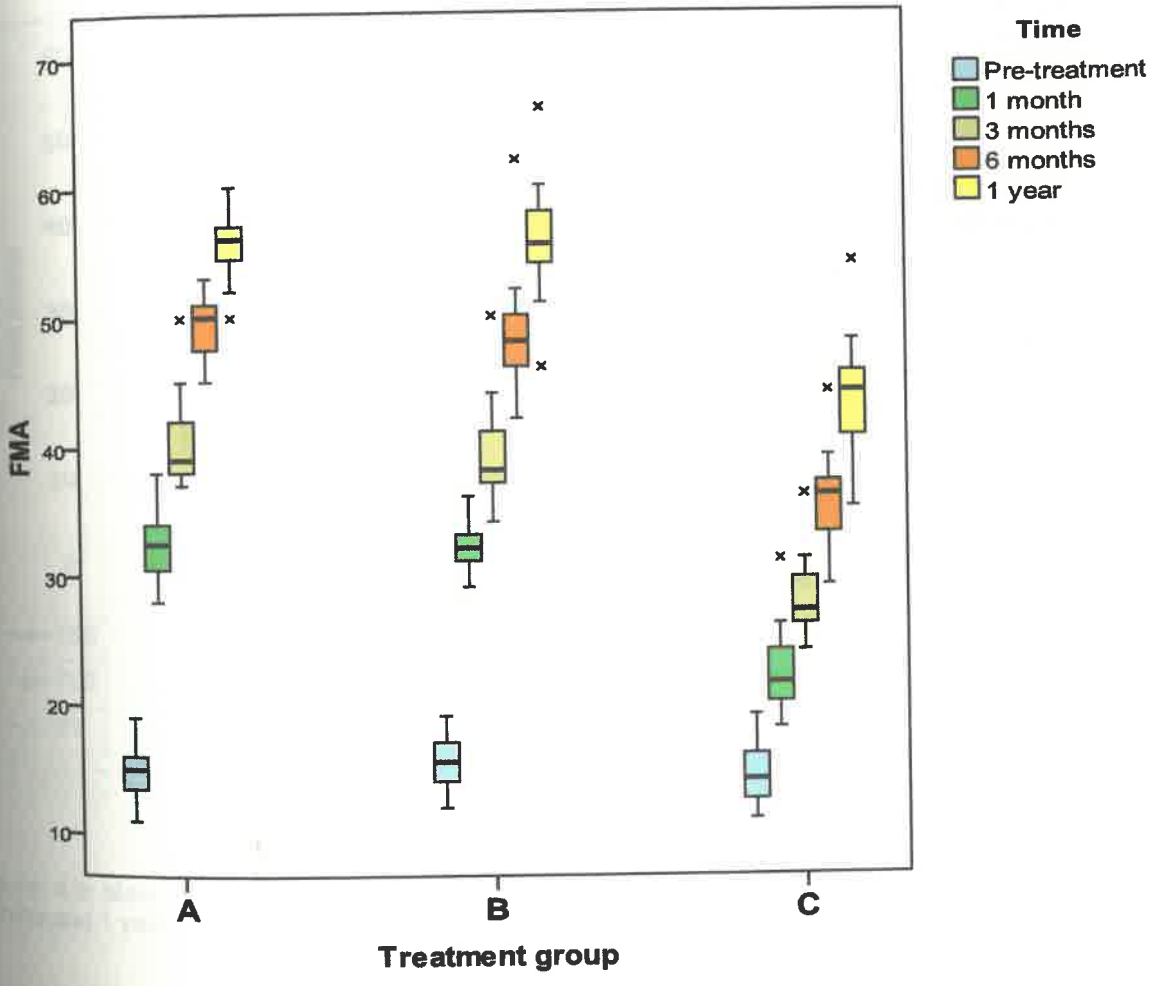
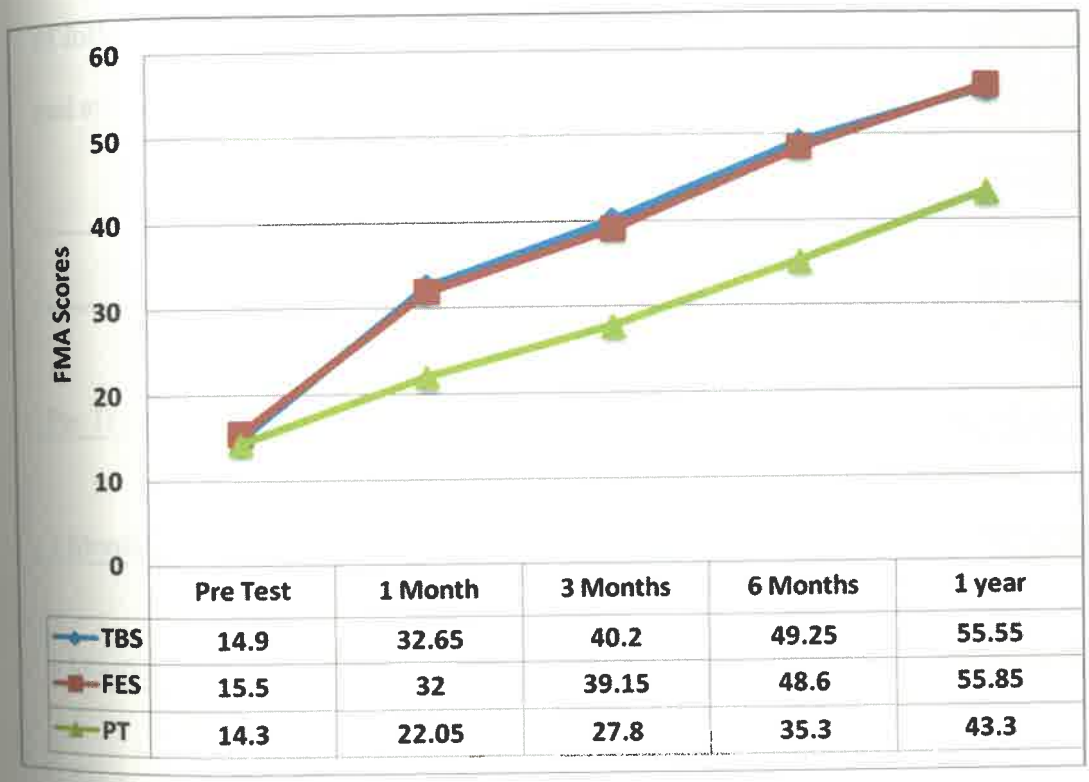


Figure: 4.1: Median Fugl Meyer Scores (FMA) of different groups
A –TBS, B –FES, C- PT

The overall analysis of the FMA scores states that, TBS intervention group and FES intervention group was significantly better than the PT intervention group at each point of time during the follow-up at 1 month, 3 months, 6 months and at 1 year, however the results showed no significant difference between the TBS group and the FES group.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	14.9	32.65	40.2	49.25	55.55
FES	15.5	32	39.15	48.6	55.85
PT	14.3	22.05	27.8	35.3	43.3

Figure: 4.2: Mean Fugl Meyer Scores (FMA) of different groups at pre-test, 1 month, 3months, 6 months and 1 year.

4.3. Modified Rankin Scale (MRS)

Scores according to modified rankin scales at baseline for TBS group was 4.05 ± 0.68, FES group was 4.20 ± 0.61 and for PT group was 4.20 ± 0.69, a difference which was not significant (p= 0.718) states that the groups are comparable at baseline. All 3 groups showed significant change in MRS scores at 1 month (p=0.003) and 3 months (p=0.002) of follow-up. There was no significant change observed at the end of 6 months (p=0.705) and at 1 year (p=0.509). (Table: 4.4).

	Treatment Groups	n	Mean	Range	P Value
	TBS	20	4.05 ± 0.68	4 (3-5)	
	FES	20	4.20 ± 0.61	4 (3-5)	
Pre Treatment	PT	20	4.20 ± 0.69	4 (3-5)	0.718 (KW)
	TBS	20	2.25 ± 0.55	2 (1-3)	
	FES	20	2.40 ± 0.50	2 (2-3)	
1 Month	PT	20	2.95 ± 0.68	3 (2-4)	0.003 (KW)
	TBS	20	1.90 ± 0.30	2 (1-2)	
	FES	20	2.00 ± 0.45	2 (1-3)	
3 Months	PT	20	2.40 ± 0.50	2 (2-3)	0.002 (KW)
	TBS	20	1.55 ± 0.51	2 (1-2)	
	FES	20	1.55 ± 0.60	2 (0-2)	
6 Months	PT	20	1.70 ± 0.55	2 (1-3)	0.705 (KW)
	TBS	20	1.30 ± 0.57	1 (0-2)	
	FES	20	1.30 ± 0.65	1 (0-2)	
1 Year	PT	20	1.50 ± 0.51	1.5(1-2)	0.509 (ANOVA)

Table 4.4: Mean (SD) and Median (range) values of modified rankin scale (MRS) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis.

As significant change was observed only at the end of 1 month and 3 months of follow-up, post-hoc analysis was done to find out the difference between the groups for the corresponding months which revealed that TBS and FES interventions produced greater improvements in the MRS scores when compared to PT. The mean MRS scores of TBS intervention group when compared to PT intervention was significant only at 1 month (2.25 ± 0.55 vs. 2.95 ± 0.68; p= 0.004). Similarly, the mean MRS scores of FES intervention group was significant than the PT intervention group at 1 month (2.40 ± 0.50 vs. 2.95 ± 0.68; p= 0.02) and 3 months (2.00 ± 0.45 vs. 2.40 ± 0.50; p= 0.05). (Table: 4.4 and Table 4.5), which states that FES group has a better outcome compared to other two groups.

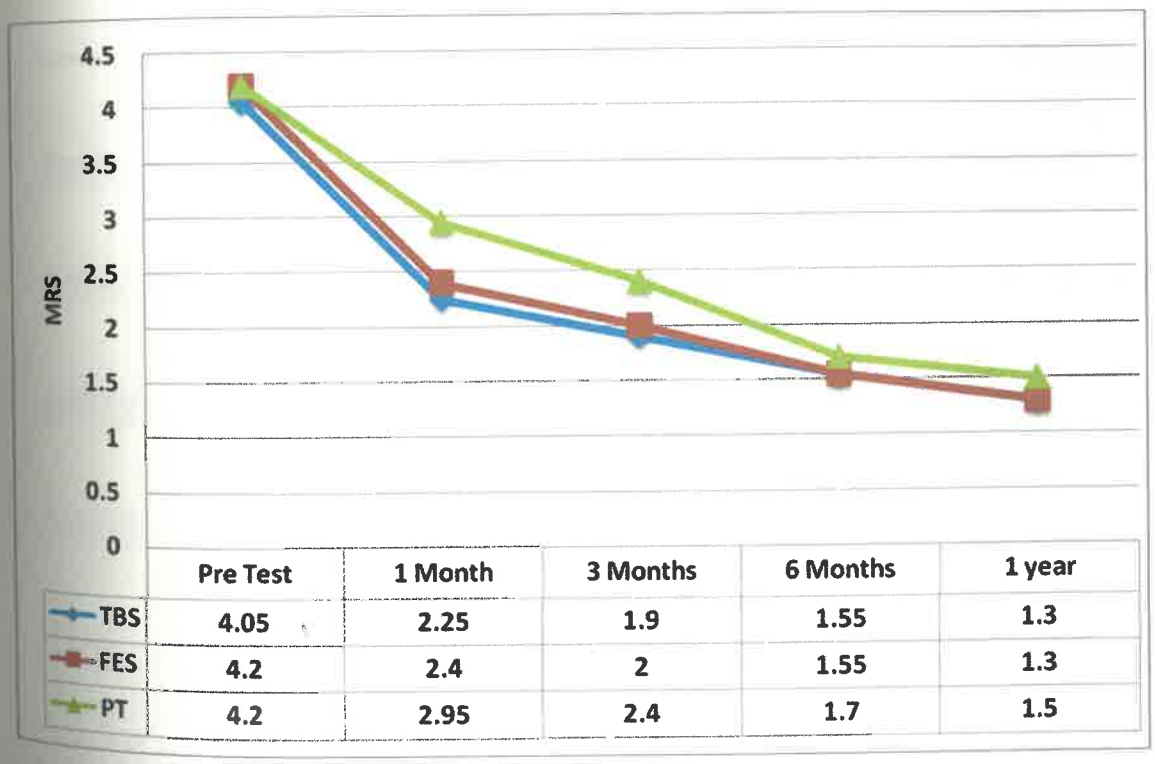
	Between groups	**p value**	
1 Month	TBS & FES	0.5	
	TBS & PT	0.004	
	FES & PT	0.02	(Mann Whitney U Test)
3 Months	TBS & FES	0.64	
	TBS & PT	0.12	
	FES & PT	0.05	(Mann Whitney U Test)

Table 4.5: Post-hoc analysis of MRS scores at 1 month and 3 months follow-up.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional Electrical Stimulation group; PT, Physiotherapy group;

When compared to baseline status, mean MRS scores of the subjects who underwent TBS intervention showed significant change at 1 month (44.44%; p≤ 0.001), 3 months

(53.09%; p≤ 0.001), 6 months (61.73%; p≤ 0.001) and (67.9%; p≤ 0.001) at 1 year. Similarly MRS scores of subjects who underwent FES intervention also showed significant change at 1 month (42.86%; p≤ 0.001), 3 months (52.38%; p≤ 0.001), 6 months (63.09%; p≤ 0.001) and (69.04%; p≤ 0.001) at 1 year respectively. However the MRS scores of subjects who underwent PT treatment also showed significant change but was not similar to other two interventions at 1 month (29.76%; p≤ 0.001) and 3 months (42.86%; p≤ 0.001), however at 6 months (59.52%; p≤ 0.001) and at 1 year (64.29%; p≤ 0.001) the difference was almost similar to other two intervention groups.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	4.05	2.25	1.9	1.55	1.3
FES	4.2	2.4	2	1.55	1.3
PT	4.2	2.95	2.4	1.7	1.5

Figure 4.3: Mean modified rankin scale scores (MRS) of different groups at pre-test, 1 month, 3months, 6 months and 1 year.

4.4. Barthel Index (BI)

Activities of daily living assessed by BI at baseline for TBS intervention group was (17.25 ± 12.19), FES group was (16.25 ± 11.45) and for PT group was (15.5 ± 9.30), a difference which was not significant (p= 0.78) indicates that the groups are comparable. All 3 groups showed significant change in BI scores from baseline after 1 month (p≤0.001) and 3 months (p≤0.001) of follow-up. However no significant change was observed at the end of 6 months (p=0.14) and 1 year (p=0.90). (Table: 4.6)

	Treatment Groups	n	Mean	Median	p value
Pre Treatment	TBS	20	17.25 ± 12.19	20(0-35)	
	FES	20	16.25 ± 11.45	17.5(0-30)	
	PT	20	15.5 ± 9.30	17.5(0-30)	0.78 (KW)
1 Month	TBS	20	52.5 ± 11.18	52.5(35-70)	
	FES	20	51.75 ± 10.54	52.5(35-70)	
	PT	20	40.25 ± 8.80	40(25-55)	≤0.001(ANOVA)
3 Months	TBS	20	72.25 ± 9.52	72.5(55-85)	
	FES	20	72.25 ± 9.24	70(60-90)	
	PT	20	62.25 ± 8.50	60(45-85)	≤0.001 (KW)
6 Months	TBS	20	87.00 ± 9.23	87.5(70-100)	
	FES	20	87.00± 7.67	85(75-100)	
	PT	20	82.50 ± 7.34	82.5(70-100)	0.14 (ANOVA)
1 Year	TBS	20	89.50 ± 7.76	90(75-100)	
	FES	20	89.75 ± 6.17	90(80-100)	
	PT	20	88.75 ± 7.23	90(75-100)	0.90 (ANOVA)

Table 4.6: Mean (SD) and Median (range) values of Barthel Index (BI) at 1 month, 3 months, 6 months and 1 year.
Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis

Post-hoc analysis results shows that the mean BI scores of TBS intervention group was significantly higher at 1 month when compared to PT intervention group (52.5 ± 11.18 vs. 40.25 ± 8.80; p= 0.001) and at 3 months (72.25 ± 9.52 vs. 62.25 ± 8.50; p= 0.001) (Table: 4.6 and Table 4.7). Similarly, the mean BI scores of FES group was significantly higher than the PT group at 1 month (51.75 ± 10.54 vs. 40.25 ± 8.80; p=0.001), and 3 months (72.25 ± 9.24 vs. 62.25 ± 8.50; p= 0.001). (Table: 4.6 and Table 4.7). The results reveal that TBS intervention and FES intervention produced greater improvements in the BI scores when compared to PT intervention, it also suggest that there is no significant difference between the TBS intervention groups and the FES intervention groups at 1 month (52.5 ± 11.18 vs. 51.75 ± 10.54; p=0.84) and at 3 months (72.25 ± 9.52 vs. 72.25 ± 9.24; p= 0.99). (Table: 4.6 and Table 4.7).

	Between groups	**p value**	
1 Month	TBS & FES	0.84	(Bonferroni correction)
	TBS & PT	0.001	
	FES & PT	0.001	
3 Months	TBS & FES	0.99	(Mann Whitney U Test)
	TBS & PT	0.001	
	FES & PT	0.001	

Table 4.7: Post-hoc analysis of BI scores at 1 month and 3 months follow-up.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group.

When compared to baseline status, mean BI scores of the subjects who underwent TBS intervention showed significant change at 1 month (35.25%; p≤ 0.001), 3 months

(55%; p≤ 0.001), 6 months (69.75%; p≤ 0.001) and further increased by (72.25%; p≤ 0.001) at 1 year. Similarly BI scores of subjects who underwent FES intervention showed significant change at 1 month (35.5%; p≤ 0.001), 3 months (56%; p≤ 0.001), 6 months (70.75%; p≤ 0.001) and further increased by (73.5%; p≤ 0.001) at 1 year. However the increase in BI scores of subjects who underwent PT intervention also showed significant change but was not similar to other two interventions at 1 month (24.75%; p≤ 0.001) and 3 months (46.75%; p≤ 0.001), but at 6 months (67%; p≤ 0.001) and at 1 year (73.25%; p≤ 0.001) the difference was almost similar to other two intervention groups (The percentage of change in BI scores was calculated keeping the total score of BI at 100 points).

	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	17.25	52.5	72.25	87	89.5
FES	16.25	51.75	72.25	87	89.75
PT	15.5	40.25	62.25	82.5	88.75

Figure 4.4: Mean Barthel Index scores (BI) of different groups at pre-test, 1 month, 3months, 6 months and 1 year.

4.5. National Institute of Health Stroke Scale (NIHSS)

Global stroke outcome was assessed by NIHSS, there was no significant difference (p= 0.131) between the 3 groups at baseline (14.10 ± 1.92; TBS), (15.30 ± 1.46; FES) and (14.95 ± 2.42; PT) which indicates that the groups are comparable. All 3 groups showed significant change in NIHSS scores from baseline after 1 month (p≤0.001), 3 months (p≤0.001) and at 6 months (p=0.029) of follow-up. However there was no significant change observed at the end of 1 year (p=0.169). (Table: 4.8)

	Treatment Groups	n	Mean	Median	p value
	TBS	20	14.10 ±1.92	14(10-18)	
	FES	20	15.30 ± 1.46	15(13-18)	
Pre Treatment	PT	20	14.95 ± 2.42	15(10-19)	0.131 (KW)
	TBS	20	8.05 ± 1.85	8(4-11)	
	FES	20	8.10 ± 1.59	8(6-12)	
1 Month	PT	20	10.85 ± 1.98	11(8-14)	≤0.001(KW)
	TBS	20	4.20 ± 1.36	4(2-6)	
	FES	20	4.10 ± 1.37	4(2-7)	
3 Months	PT	20	6.05 ± 1.67	6(4-9)	≤0.001(KW)
	TBS	20	2.55 ± 0.69	2(2-4)	
	FES	20	2.25 ± 0.79	2(1-4)	
6 Months	PT	20	3.15 ± 1.14	3(2-5)	0.029 (KW)
	TBS	20	2.05 ± 0.61	2(1-3)	
	FES	20	2.05 ± 0.61	2(1-3)	
1 Year	PT	20	2.40 ± 0.68	2(1-4)	0.169 (KW)

Table 4.8: Mean (SD) and Median (range) values of National institute for health stroke scale (NIHSS) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis.

Post-hoc analysis was done to find out the difference between the groups at 1 month, 3 months and 6 months. The mean NIHSS scores of TBS intervention group when compared to PT intervention group were significant at 1 month (8.05 ± 1.85 vs. 10.85 ± 1.98; p≤ 0.001) and 3 months (4.20 ± 1.36 vs. 6.05 ± 1.67; p= 0.002), the results did not show significant difference between the TBS group and PT group at 6 months (2.55 ± 0.69 vs. 3.15 ± 1.14; p= 0.12), (Table: 4.8 and Table 4.9). Similarly, the mean NIHSS scores of FES group were significant than the PT group at 1 month (8.10 ± 1.59 vs. 10.85 ± 1.98; p≤ 0.001), 3 months (4.10 ± 1.37 vs. 6.05 ± 1.67; p= 0.001) and 6 months (2.25 ± 0.79 vs. 3.15 ± 1.14; p= 0.018), (Table: 4.8 and Table 4.9).

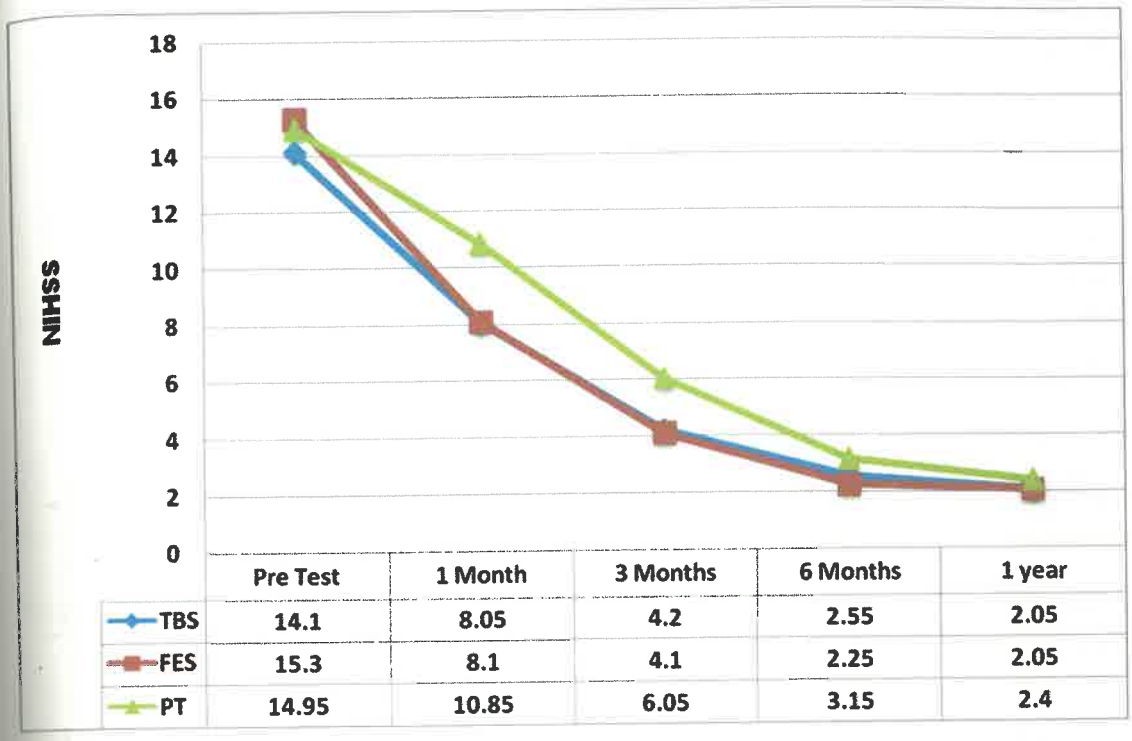
	Between groups	**p value**	
1 Month	TBS & FES	0.93	
	TBS & PT	≤ 0.001	
	FES & PT	≤ 0.001	(Mann Whitney U Test)
3 Months	TBS & FES	0.74	
	TBS & PT	0.002	
	FES & PT	0.001	(Mann Whitney U Test)
6 Months	TBS & FES	0.3	
	TBS & PT	0.12	
	FES & PT	0.018	(Mann Whitney U Test)

Table 4.9: Post-hoc analysis of NIHSS scores at 1 month, 3 months and 6 months of follow-up.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group.

The results reveal that TBS intervention and FES intervention produced greater improvements in the NIHSS scores when compared to PT intervention, it also suggest that there is no significant difference between the TBS intervention groups and the FES intervention groups at 1 month (8.05 ± 1.85 vs. 8.10 ± 1.59; p=0.93), 3 months (4.20 ± 1.36 vs. 4.10 ± 1.37; p= 0.74) and at 6 months (2.55 ± 0.69 vs. 2.25 ± 0.79; p=0.30). (Table: 4.8 and Table 4.9).

When compared to baseline status, mean NIHSS scores of the subjects who underwent TBS intervention showed significant change at 1 month (42.9%; p≤ 0.001), 3 months (70.21%; p≤ 0.001), 6 months (81.91%; p≤ 0.001) and further decreased by (85.46%; p≤ 0.001) at 1 year. Similarly NIHSS scores of subjects who underwent FES intervention also showed significant change at 1 month (47.05%; p≤ 0.001), 3 months (73.21%; p≤ 0.001), 6 months (85.29%; p≤ 0.001) and further decreased by (86.6%; p≤ 0.001) at 1 year. However the decrease in NIHSS scores of subjects who underwent PT intervention showed significant change but was not similar to other two interventions at 1 month (27.42%; p≤ 0.001) and 3 months (59.53%; p≤ 0.001), but at 6 months (78.93%; p≤ 0.001) and at 1 year (83.95%; p≤ 0.001) the difference was almost similar to other two intervention groups.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	14.1	8.05	4.2	2.55	2.05
FES	15.3	8.1	4.1	2.25	2.05
PT	14.95	10.85	6.05	3.15	2.4

Figure 4.5: Mean NIHSS of different groups at pre-test, 1 month, 3 months, 6 months and 1 year.

4.6. Resting Motor Threshold.

4.6.1. Resting Motor Threshold- Ipsilesional Hemisphere (RMT-IH)

RMT from the ipsilesional hemisphere was elicited only from 10 subjects of TBS intervention group, 8 subjects of FES intervention group and 9 subjects of PT intervention group. There was no significant change when the RMT-IH values were analyzed at each point of time at 1 month, 3 months, 6 months and at 1 year post stroke (Table: 4.10). So the post hoc analysis was not warranted for finding out the between group differences. However the RMT-IH values showed a significant difference ($p<0.001$) when Friedmans test and Kendalls W was done to find the difference over

period of 1 year, mean values of RMT-IH at baseline were 90 ± 7.07 for TBS group, 92.5 ± 6.54 for FES group and 90.56 ± 7.26 for PT group, which reduced to 81.33 ± 11.87 for TBS group, 85.38 ± 11.80 for FES group and 88.08 ± 9.47 for PT group respectively at the end of 1 year of follow-up.

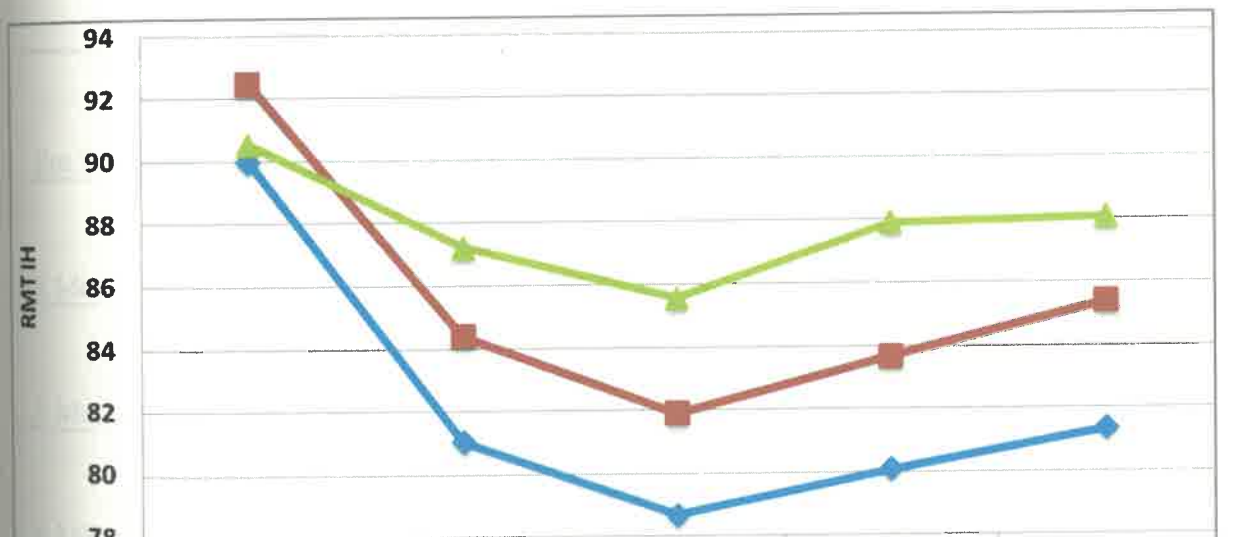
	Treatment Groups	n	Mean	Range	p value
	TBS	10	90.00 ± 7.07	(80-100)	
	FES	8	92.50 ± 6.54	(85-100)	
Pre Treatment	PT	9	90.56 ± 7.26	(80-100)	0.67 (KW)
	TBS	10	81.00 ± 8.43	(70-95)	
	FES	8	84.38 ± 10.15	(70-100)	
1 Month	PT	9	87.22 ± 7.12	(80-100)	0.27 (KW)
	TBS	10	78.64 ± 9.24	(65-95)	
	FES	8	81.88 ± 11.63	(70-100)	
3 Months	PT	9	85.56 ± 5.83	(80-95)	0.21 (KW)
	TBS	10	80.00 ± 11.18	(65-100)	
	FES	8	83.64 ± 11.85	(65-100)	
6 Months	PT	9	87.92 ± 8.10	(75-100)	0.19 (KW)
	TBS	10	81.33 ± 11.87	(60-100)	
	FES	8	85.38 ± 11.80	(65-100)	
1 Year	PT	9	88.08 ± 9.47	(75-100)	0.30 (KW)

Table 4.10: Mean (SD) and range values of resting motor threshold – ipsilesional hemisphere (RMT-IH) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis.

When compared to baseline status, mean RMT-IH scores of the subjects who underwent TBS intervention showed significant decrease at 1 month (10%; $p \leq 0.001$), 3 months (12.6%; $p \leq 0.001$), 6 months (11.11%; $p \leq 0.001$) and (9.63%; $p \leq 0.001$) at 1 year.

Similarly RMT-IH scores of subjects who underwent FES intervention showed significant decrease at 1 month (8.78%; p=0.002), 3 months (11.4%; p=0.001), 6 months (9.58%; p≤ 0.001) and (9.63%; p≤ 0.001) at 1 year. However the change in RMT-IH scores of subjects who underwent PT intervention also showed significant change but was not similar to other two interventions at 1 month (3.69%; p=0.004), 3 months (5.52%; p≤ 0.001), 6 months (2.92%; p≤ 0.001) and at 1 year (2.74%; p≤ 0.001). The percentage change in all the 3 groups in their mean values in RMT-IH scores showed there was a decrease in motor threshold after the 1 month and 3 months of follow-up and this decrease was not consistent after the 6 months and at 1 year of follow-up.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	90	81	78.64	80.06	81.33
FES	92.5	84.38	81.88	83.64	85.38
PT	90.56	87.22	85.56	87.92	88.08

Figure 4.6: Mean RMT-IH values of different groups at pre-test, 1 month, 3 months, 6 months and 1 year.

4.6.2. Resting Motor Threshold- Contralesional Hemisphere (RMT-CH)

Unlike ipsilesional hemisphere all the 60 subjects contralesional hemisphere was excitable for RMT. There was no significant change when the RMT-CH values were analyzed at each point of time at 1 month, 3 months, 6 months and at 1 year post stroke (Table: 4.11). So the post hoc analysis was not warranted for finding out the between group differences. However the RMT-CH values showed a significant difference ($p<0.001$) when Friedmans test and Kendalls W was done to find the difference over period of 1 year.

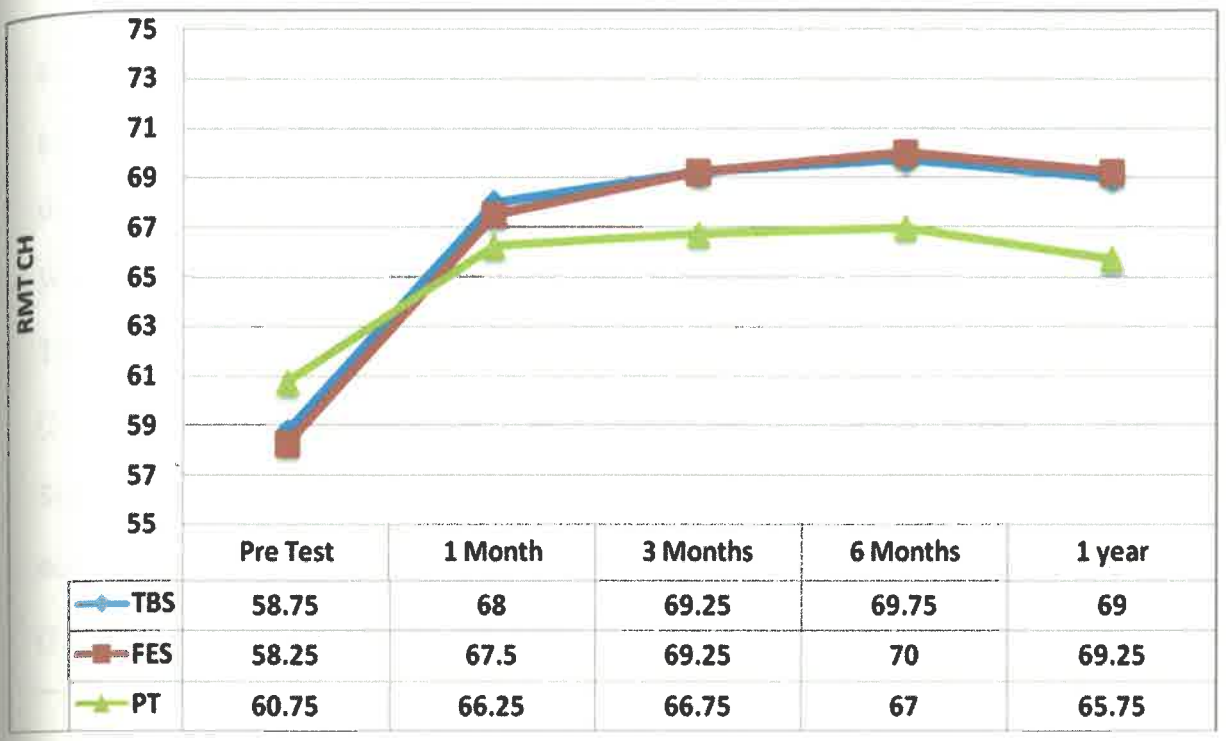
	Treatment Groups	n	Mean	Range	P Value
	TBS	20	58.75 ± 9.44	(45-75)	
	FES	20	58.25 ± 9.07	(40-75)	
Pre Treatment	PT	20	60.75 ± 8.30	(45-75)	0.64 (KW
	TBS	20	68.00 ± 9.37	(55-80)	
	FES	20	67.50 ± 8.81	(55-85)	
1 Month	PT	20	66.25 ± 8.09	(50-80)	0.82 (KW)
	TBS	20	69.25 ± 8.32	(55-80)	
	FES	20	69.25 ± 8.32	(55-85)	
3 Months	PT	20	66.75 ± 7.48	(55-80)	0.51 (KW)
	TBS	20	69.75 ± 8.35	(55-80)	
	FES	20	70.00 ± 7.95	(60-85)	
6 Months	PT	20	67.00 ± 7.51	(50-80)	0.52 (KW)
	TBS	20	69.00 ± 7.88	(55-85)	
	FES	20	69.25 ± 6.74	(55-85)	
1 Year	PT	20	65.75 ± 7.30	(50-75)	0.29 (KW)

Table 4.11: Mean (SD) and range values of resting motor threshold – contralesional hemisphere (RMT-CH) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group; KW, Kruskal Wallis.

Mean values of RMT-CH at baseline were (58.75 ± 9.44) for TBS group, (58.25 ± 9.07) for FES group and (60.75 ± 8.30) for PT group, which increased to (69.00 ± 7.88) for TBS group, (69.25 ± 6.74) for FES group and (65.75 ± 7.30) for PT group respectively at the end of 1 year of follow-up.

When compared to baseline status, mean RMT-CH scores of the subjects who underwent TBS intervention showed significant increase at 1 month (15.74%; p≤ 0.001), 3 months (17.87%; p≤ 0.001), 6 months (18.72%; p≤ 0.001) and (17.44%; p≤ 0.001) at 1 year. Similarly RMT-CH scores of subjects who underwent FES intervention showed significant increase at 1 month (15.87%; p p≤=0.001), 3 months (18.88%; p≤0.001), 6 months (20.17%; p≤ 0.001) and (18.88%; p≤ 0.001) at 1 year. However the change in RMT-CH scores of subjects who underwent PT intervention also showed significant change but was not similar to other two interventions at 1 month (9.05%; p= p≤ 0.001), 3 months (9.88%; p≤ 0.001), 6 months (10.29%; p≤ 0.001) and at 1 year (8.23%; p≤ 0.001). The percentage change in all the 3 groups in their mean values in RMT-CH scores showed that there was an increase in motor threshold after the 1 month, 3 months and 6 months of follow-up and this increase was not consistent at 1 year of follow-up.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	58.75	68	69.25	69.75	69
FES	58.25	67.5	69.25	70	69.25
PT	60.75	66.25	66.75	67	65.75

Figure 4.7: Mean RMT-CH values of different groups at pre-test, 1 month, 3 months, 6 months and 1 year.

4.7. Cortical Silent Period

4.7.1. Cortical Silent Period-Ipsilesional Hemisphere (CSP-IH)

CSP from the ipsilesional hemisphere was elicited only from 10 patients of TBS group, 8 patients of FES group and 9 patients of PT group. There was no significant change when the CSP-IH values were analyzed at each point of time at 1 month, 3 months, 6 months and at 1 year post stroke (Table: 4.12). So the post hoc analysis was not warranted for finding out the between group differences. However the CSP-IH values showed a significant difference ($p<0.001$) when repeated measure ANOVA was done to find within group and between group differences over a period of 1 year (Table: 4.13). Mean values of CSP-IH at baseline were (278.50 ± 18.86) for TBS group, (282.50 ± 20.87) for FES

group and (260.00 ± 10.00) for PT group, which reduced to (226.79 ± 73.27) for TBS group, (224.23 ± 62.84) for FES group and (232.31 ± 52.74) for PT group respectively at the end of 1 year of follow-up.

When compared to baseline status, mean CSP-IH scores of the subjects who underwent TBS intervention showed significant decrease at 1 month (26%; p≤ 0.001), 3 months (26.39%; p≤ 0.001), 6 months (26.69%; p≤ 0.001) and (18.56%; p≤ 0.001) at 1 year. Similarly CSP-IH scores of subjects who underwent FES intervention showed significant decrease at 1 month (24.78%; p p≤=0.001), 3 months (24.6%; p≤0.001), 6 months (23.25%; p≤ 0.001) and (20.60%; p≤ 0.001) at 1 year.

	Treatment Groups	**n**	**Mean**	**Range**	**p value**
Pre Treatment	TBS	10	278.50 ± 18.86	(250-310)	
	FES	8	282.50 ± 20.87	(245-310)	
	PT	9	260.00 ± 10.00	(245-275)	0.03 (ANOVA)
1 Month	TBS	10	206.00 ± 23.31	(175-250)	
	FES	8	212.50 ± 32.40	(170-250)	
	PT	9	220.56 ± 13.79	(200-240)	0.43 (ANOVA)
3 Months	TBS	10	205.00± 38.92	(160-300)	
	FES	8	213.00 ± 32.34	(170-270)	
	PT	9	213.89 ± 10.54	(200-230)	0.77 (ANOVA)
6 Months	TBS	10	204.17 ± 35.47	(150-275)	
	FES	8	216.82 ± 55.51	(160-360)	
	PT	9	222.73 ± 42.45	(190-320)	0.60 (ANOVA)
1 Year	TBS	10	226.79 ± 73.27	(150-425)	
	FES	8	224.23 ± 62.84	(160-370)	
	PT	9	232.31 ± 52.74	(190-340)	0.95(ANOVA)

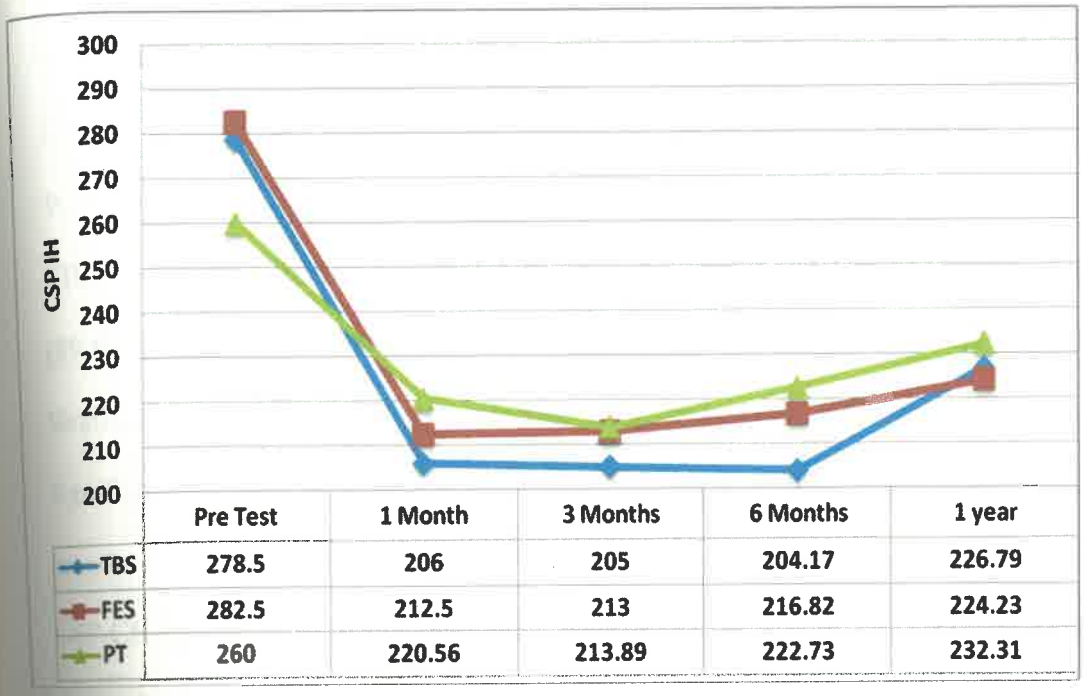
Table 4.12: Mean (SD) and range values of cortical silent period – ipsilesional hemisphere (CSP-IH) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group.

However the change in CSP-IH scores of subjects who underwent PT intervention also showed significant change but was not similar to other two interventions at 1 month (15.17%; p= p≤ 0.001), 3 months (17.75%; p≤ 0.001), 6 months (14.33%; p≤ 0.001) and at 1 year (10.65%; p≤ 0.001). The mean change in CSP-IH values of all the 3 intervention groups showed that after the sudden decrease of CSP-IH values at 1 month i.e. immediately after the intervention, there was moreover no change in the cortical silent period until the end of follow-up at 1 year.

Tested variables	**p value**
Between treatment Groups (1,2,3)	.752
Within groups - between each round of follow up (Spheracity assumed – Mauchly's test)	<0.001
Between treatment group and between each round of follow up (Spheracity assumed – Mauchly's test)	<0.001

Table 4.13: Repeated measure ANOVA to find between group and within group differences for cortical silent period – ipsilesional hemisphere (CSP-IH) from baseline to 1 year of follow-up



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	278.5	206	205	204.17	226.79
FES	282.5	212.5	213	216.82	224.23
PT	260	220.56	213.89	222.73	232.31

Figure 4.8: Mean CSP-IH values of different groups at pre-test, 1 month, 3 months, 6 months and 1 year.

4.7.2. Cortical Silent Period-Contralesional Hemisphere (CSP-CH)

Unlike ipsilesional hemisphere all 60 subjects contralesional hemisphere was excitable for CSP. There was no significant change when the CSP-CH values were analyzed at each point of time at 1 month, 3 months, 6 months and at 1 year post stroke (Table: 4.14). So the post hoc analysis was not warranted for finding out the between group differences. However the CSP-CH values showed a significant difference ($p<0.001$) when repeated measure ANOVA was done to find within group and between group differences over a period of 1 year (Table: 4.15). Mean values of CSP-CH at baseline were (162.72 ± 27.06) for TBS group, (172.65 ± 24.49) for FES group and (182.80 ± 38.79) for PT group,

which increased to (208.00 ± 40.44) for TBS group, (210.40 ± 28.68) for FES group and (195.90 ± 41.46) for PT group respectively at the end of 1 year of follow-up.

When compared to baseline status, mean CSP-CH scores of the subjects who underwent TBS intervention showed significant increase at 1 month (24.12%; p≤ 0.001), 3 months (29.67%; p≤ 0.001), 6 months (31.73%; p≤ 0.001) and at 1 year (27.83%; p≤ 0.001). Similarly CSP-CH scores of subjects who underwent FES intervention showed significant increase at 1 month (18.47%; p≤=0.001), 3 months (21.72%; p≤0.001), 6 months (22.59%; p≤ 0.001) and (21.86%; p≤ 0.001) at 1 year. However the change in CSP-CH scores of subjects who underwent PT intervention also showed significant change but was not similar to other two interventions at 1 month (6.94%; p= p≤ 0.001), 3 months (7.90%; p≤ 0.001), 6 months (5.82%; p≤ 0.001) and at 1 year (7.16%; p≤ 0.001). The mean change in CSP-CH values of all the 3 intervention groups indicates that, after the sudden increase of the cortical silent period at 1 month i.e. immediately after the intervention, there was moreover no change in the cortical silent period until the end of follow-up at 1 year.

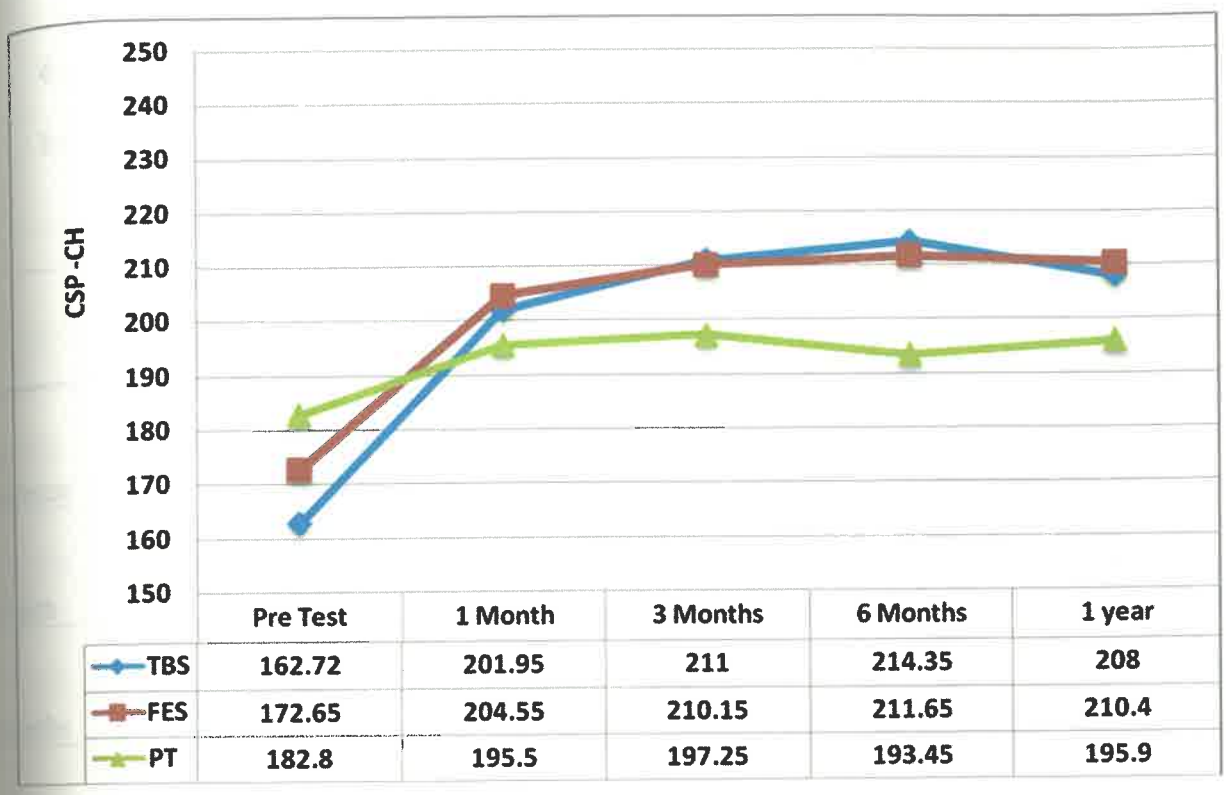
	Treatment Groups	n	Mean	Range	P Value
Pre Treatment	TBS	20	162.72 ± 27.06	(123-224)	
	FES	20	172.65 ± 24.49	(129-225)	
	PT	20	182.80 ± 38.79	(113-286)	0.13 (ANOVA)
1 Month	TBS	20	201.95 ± 31.62	(167-268)	
	FES	20	204.55 ± 28.68	(156-267)	
	PT	20	195.50 ± 37.60	(132-288)	0.67 (ANOVA)
3 Months	TBS	20	211.00± 29.79	(175-275)	
	FES	20	210.15 ± 28.31	(161-270)	
	PT	20	197.25 ± 37.28	(131-290)	0.32 (ANOVA)
6 Months	TBS	20	214.35 ± 31.90	(175-285)	
	FES	20	211.65 ± 28.39	(161-270)	
	PT	20	193.45 ± 38.83	(132-298)	0.11 (ANOVA)
1 Year	TBS	20	208.00 ± 40.44	(95-280)	
	FES	20	210.40 ± 28.68	(160-270)	
	PT	20	195.90 ± 41.46	(123-312)	0.43(ANOVA)

Table 4.14: Mean (SD) and range values of cortical silent period – contralesional hemisphere (CSP-CH) at 1 month, 3 months, 6 months and 1 year.

Abbreviations: TBS, Theta burst stimulation group; FES, Functional electrical stimulation group; PT, Physiotherapy group.

Tested variables	p value
Between treatment Groups (1,2,3)	.665
Within groups - between each round of follow up (Spheracity assumed – Mauchly's test)	<0.001
Between treatment group and between each round of follow up (Spheracity assumed – Mauchly's test)	<0.001

Table 4.15: Repeated measure ANOVA to find between group and within group differences for cortical silent period – contralesional hemisphere (CSP-CH) from baseline to 1 year of follow-up.



	Pre Test	1 Month	3 Months	6 Months	1 year
TBS	162.72	201.95	211	214.35	208
FES	172.65	204.55	210.15	211.65	210.4
PT	182.8	195.5	197.25	193.45	195.9

Figure 4.9: Mean CSP-CH values of different groups at pre-test, 1 month, 3 months, 6 months and 1 year.

4.8. Modified Ashworth Scale.

4.8.1. Modified Ashworth Scale – Elbow flexors.

Kendall's tau c test was performed to find out the significance in change of spasticity between the study groups, the values were interpreted as concordant and discordant and the significance mentioned as p value. Chi square test was not applicable as each cell needs 5 expected values. The results states that there was no significant difference between the 3 groups in ashworth scores at different point of time at 1 month, 3 months,

6 months and after 1year of follow-up (Table: 4.16). There showed a slight discordance between the study groups at 6 months post stroke, but the p value was not significant.

	Treatment Groups	Ashworth scores						Significance
		0	1	1+	2	3	4	
Pre Treatment	TBS	90%	10%	-	-	-	-	Kendall's tau c=+0.071
	FES	85%	15%	-	-	-	-	P=0.076
	PT	80%	15%	5%	-	-	-	Concordant-not significant
1 Month	TBS	85%	10%	-	5%	-	-	Kendall's tau c=+0.070
	FES	85%	10%	5%	-	-	-	P=0.086
	PT	75%	10%	15%	-	-	-	Concordant-not significant
3 Months	TBS	70%	20%	5%	5%	-	-	Kendall's tau c=+0.098
	FES	60%	15%	15%	10%	-	-	P=0.102
	PT	60%	10%	20%	10%	-	-	Concordant-not significant
6 Months	TBS	30%	35%	10%	20%	5%	-	Kendall's tau c=-0.009
	FES	35%	40%	-	20%	5%	-	P=0.117
	PT	35%	25%	15%	20%	5%	-	Discordant-not significant
1 Year	TBS	20%	25%	-	45%	10%	-	Kendall's tau c=+0.011
	FES	25%	15%	15%	35%	10%	-	P=0.117
	PT	15%	15%	30%	25%	15%	-	Concordant-not significant

Table 4.16: Kendall's tau c test for modified ashworth scale (elbow flexors) at Pre treatment, 1 month, 3 months, 6 months and 1 year.

4.8.2. Modified Ashworth Scale – Wrist flexors.

The results states that there was no significant difference between the 3 groups in ashworth scores at different point of time at 1 month, 3 months, 6 months and after 1year of follow-up (Table: 4.17). There showed a slight discordance between the study groups at 1 year post stroke, but the p value was not significant.

	Treatment Groups	Ashworth scores						Significance
		0	1	1+	2	3	4	
Pre Treatment	A	80%	20%	-	-	-	-	Kendall's tau c=+0.108
	B	70%	30%	-	-	-	-	P=0.094
	C	65%	30%	5%	-	-	-	Concordant-not significant
1 Month	A	70%	20%	-	5%	-	-	Kendall's tau c=+0.06
	B	75%	10%	15%	-	-	-	P=0.100
	C	65%	10%	25%	-	-	-	Concordant-not significant
3 Months	A	60%	20%	15%	5%	-	-	Kendall's tau c=+0.11
	B	55%	10%	20%	15%	-	-	P=0.105
	C	50%	10%	25%	15%	-	-	Concordant-not significant
6 Months	A	30%	35%	10%	20%	5%	-	Kendall's tau c=+0.087
	B	30%	35%	10%	20%	5%	-	P=0.118
	C	25%	25%	15%	30%	5%	-	Concordant-not significant
1 Year	A	15%	25%	5%	45%	10%	-	Kendall's tau c=-0.056
	B	25%	20%	15%	30%	10%	-	P=0.115
	C	20%	10%	35%	25%	10%	-	Discordant-not significant

Table 4.17: Kendall's tau c test for modified ashworth scale at Pre treatment, 1 month, 3 months, 6 months and 1 year.

4.9. Correlation

Spearman's Rank correlation was done between (i) Fugl meyer assessment scale which is an UL motor performance scale and Barthel index which is an measure for activities of daily living (ii) Fugl meyer assessment scale and modified rankin scale to know the relation between the UL motor performance and the disability, (iii) Fugl meyer assessment scale and modified ashworth scale for elbow flexors and wrist flexors to know the relation between the UL motor performance and spasticity.

4.9.1. Correlation between Fugl Meyer Assessment and Barthel Index

Spearman's Rank correlation showed a positive correlation between UL motor performance assessed by fugl meyer assessment scale and activities of daily living by barthel index with a significant correlation at 1 month (r = 0.327; p = 0.011) and 3 months (r = 0.312; p = 0.015) of follow-up (Table: 4.18).

	Pre Treatment	1 Month	3 Months	6 Months	1 year
Correlation Coefficient	-0.008	0.327	0.312	0.084	-0.41
Sig. (2-tailed)	0.954	0.011	0.015	0.523	0.758

Table 4.18: Correlation between FMA and BI

4.9.2. Correlation between Fugl Meyer Assessment and Modified Rankin Scale

Spearman's Rank correlation showed a negative correlation between UL motor performance assessed by fugl meyer assessment scale and post stroke disability assessed by modified rankin scale with a significant correlation at 1 month (r = -0.451.; p≤0.001) and 3 months (r = -0.426; p = 0.001) of follow-up (Table: 4.19).

	Pre Treatment	1 Month	3 Months	6 Months	1 year
Correlation Coefficient	-0.076	-0.451	-0.426	-0.111	-0.117
Sig. (2-tailed)	0.565	≤0.001	0.001	0.398	0.371

Table 4.19: Correlation between FMA and MRS

4.9.3. Correlation between Fugl Meyer Assessment and modified Ashworth Scale (Elbow)

Spearman's Rank correlation showed a negative correlation between UL motor performance assessed by fugl meyer assessment scale and spasticity of flexors of elbow assessed by modified ashworth scale with no significant correlation noted during the 1 year follow-up. (Table: 4.20).

	Pre Treatment	1 Month	3 Months	6 Months	1 year
Correlation Coefficient	-0.186	-0.127	-0.218	-0.008	0.002
Sig. (2-tailed)	0.155	0.333	0.095	0.95	0.987

Table 4.20: Correlation between FMA and MAS (Elbow)

4.9.4. Correlation between FMA and mAS (Wrist)

Spearman's Rank correlation showed a negative correlation between UL motor performance assessed by fugl meyer assessment scale and spasticity of the flexors of wrist assessed by modified ashworth scale with no significant correlation noted during the 1 year follow-up. (Table: 4.21).

	Pre Treatment	1 Month	3 Months	6 Months	1 year
Correlation Coefficient	-0.178	-0.052	-0.155	-0.80	0.047
Sig. (2-tailed)	0.173	0.695	0.238	0.545	0.724

Table 4.21: Correlation between FMA and MAS (Wrist)

5. Discussion

The present study was done to find the efficacy of TBS and FES as compared to Physiotherapy in stroke rehabilitation, and it is one of its first kind where TBS and FES are compared head to head for the rehabilitation of upper limb in post stroke patients, in which TBS was used for 12 sessions over a period of one month. FES which is used to stimulate the paralyzed muscle in post stroke patients was applied in a different pattern compared to the previous studies; the researcher had applied FES for the whole upper limb muscles with six channels to stimulate the upper extremity in a functional pattern.

Both TBS and FES interventions showed a greater improvement in the UL scores to a greater extent than the PT intervention. The TBS and FES interventions demonstrated unique benefits in reducing UL deficits. Even though the PT group showed significant improvement in UL functions but it was not as comparable to the TBS and FES groups.

Various studies have shown that the impaired coticospinal excitability following an ischemic stroke can be increased at least transiently by transcranial electrical or magnetic stimulation (Khedr *et al* 2005; Mansur *et al* 2005; Takeuchi *et al* 2005; Fregni *et al* 2006; P Talelli, R J Greenwood and J C Rothwell 2007; Kim *et al* 2006) This increase in the cortical excitability induced by transcranial stimulation has been shown to correlate with improvement in motor functions of paretic hand. TBS with its low intensity of stimulation has been found to be safe and effective way of increasing the cortical excitability which can last beyond the duration of stimulation (Huang *et al* 2005; P Talelli, R J Greenwood and J C Rothwell 2007; Di Lazzaro *et al* 2008a)

In agreement with the previous studies done by (Mansur *et al* 2005; Khedr *et al* 2005; Kim *et al* 2006; P Talelli, R J Greenwood and J C Rothwell 2007; Ackerley *et al* 2010) TBS intervention group demonstrated greater improvement in the performance of the overall UL functions than the PT intervention group in post stroke patients. Beneficial effects of TBS intervention does not corroborate with some previous studies (Ackerley *et al* 2010; Talelli *et al* 2012).

In the present study TBS led to greater improvements in FMA scores, there reported a 27% increase in FMA scores at 1 month, followed by 38% at 3 months, 52% at 6 months and 62% at 1 year of follow-up respectively when compared to the baseline. Similar results were reported from studies done by (Khedr *et al* 2005) where 52 acute stroke patients underwent high frequency rTMS to the ipsilesional hemisphere showed improvements in the scandinavian stroke scale scores when compared with the sham rTMS. In a similar study done by (Mansur *et al* 2005) ten chronic stroke were administered with 1 Hz low frequency rTMS to the contralesional hemisphere showed reduction in simple reaction time and four choice reaction time which was correlated with the functional performance of upper extremity by purdue peg board which showed increase in number of correctly placed pegs after the real rTMS.

The study results does not corroborate with the study done by (Ackerley *et al* 2010), where 10 chronic sub-cortical stoke patients were given iTBS to ipsilesional hemisphere and cTBS to contralesional hemisphere and was compared with sham stimulation assessed by action research arm test which showed a deterioration of the median scores (46 vs. 41) after cTBS and was unchanged after iTBS and sham stimulation. Similar

results were also shown by (Talelli *et al* 2012), where 41 chronic stroke patients underwent iTBS to ipsilesional hemisphere and cTBS to the contralesional hemisphere combined with conventional physiotherapy and assessed with nine hole peg test, jebson taylor test and grip dynamometry at 4 days, 30 days and 90 days after the treatment showed no significant change in any of the outcome measures.

In the present study FES group also led to greater improvement in FMA scores, there reported a 25% increase in FMA scores at 1 month, followed by 36% at 3 months, 50% at 6 months and 61% at 1 year of follow-up respectively when compared to the baseline scores. The results were similar to the studies done by (Alon *et al* 2007) where FES was administered to 15 acute stroke patients for 12 weeks which showed an 52% increase in modified FMA scores when compared to the control intervention which had shown only 34% increase, the box and block test for hand function also showed an greater improvement in the FES groups supported by the jebsen taylor light object lift test which showed a 91% increase in FES group compared to the 83% increase in the control group. Similar study done by (Mangold *et al* 2009) also showed an positive trend towards the FES group when compared to the conventional physiotherapy, where 23 acute stroke patients were given FES for 4 weeks (12 sessions) which was similar to our protocol, showed improvements in FES group assessed by chedoke McMaster stroke assessment scales.

Cauraugh and colleagues published several studies in which electromyographic-triggered NMES was used in combination with task-specific exercises to train chronic stroke survivors (Cauraugh *et al* 2000; Cauraugh and Kim 2003b; Cauraugh and Kim 2003a).

The authors used the Box & Block test as a main outcome measure. Taken together, these studies showed that 2 weeks of training resulted in an increase in the number of blocks transferred in 60 seconds, from as little as 1 block in one study to 8 blocks in another study.

Similar results were documented by (Kimberley *et al* 2004) who investigated home-based NMES training over a 3-week period. Whereas the increase in blocks transferred after training was statistically significant, transferring a few additional blocks may not represent clinically meaningful improvement in upper extremity function. Two groups of investigators initiated NMES in the acute/subacute phase of rehabilitation to promote recovery of the paretic upper extremity following ischemic stroke. (Chae *et al* 1998) stimulated the wrist-finger extensors for only 3 weeks, whereas (Powell *et al* 1999) stimulated the same muscle groups for 8 weeks in a randomized controlled trial. Chae and colleagues reported gains of 13.1 (NMES) versus 6.5 (control) points in upper extremity FMA score, reflecting significant recovery of motor control but not actual functional use of the upper extremity. Powell and coauthors showed significant effects of their NMES program on hand function (measured by ARAT); however, these benefits were no longer evident at the 24- week follow-up.

Physiotherapy intervention group also showed significant difference but not similar to the other two groups, the FMA scores increased by 12% at one month, 20% at 3 months, 32% at 6 months and 44% at 1 year of follow-up which was similar to the results of the studies done by (Alon *et al* 2007), 34% increase in the FMA scores after 12 weeks of

conventional physiotherapy intervention, and (Lin *et al* 2009) showed a 3% increase in FMA scores after 3 weeks of intervention.

In the present study FMA was the primary outcome measure used for assessing the UL functions. FMA scores in the present study were significantly improved for all the three intervention groups notably there was a greater improvement in the TBS and FES groups compared to the PT group throughout the 1 year of follow-up. This difference might be due to the additive effects of TBS and FES on physiotherapy, where the iTBS might have produced a facilitatory effect on the ipsilesional cortex and the cTBS a inhibitory effect on the contralesional cortex which inturn might have reduced the intracortical inhibition and facilitated the cortico spinal outflow. However when FES is applied to the muscles of UL, it would have increased the afferent input from the peripheral muscles and might have influenced the excitability of the corresponding motor areas on the contralateral hemispheres.

The other postulates for the improvement might be due to the Long Term Potentiation (LTP) of the ipsilesional hemisphere and Long Term Depression (LTD) of the contralesional hemisphere by the non-invasive stimulation both by central (TBS) and peripheral (FES). The LTP and LTD effects vary according to the difference in patterns of Ca2+ influx through the postsynaptic NMDA receptor. When there is a high level of Ca2+ influx which leads to desensitization of Inositol triphosphate receptors leading to phosphorylation of calcium calmodulin dependent protein kinase II (CaMKII) which leads to LTP. On contrary when there is moderate levels of Ca2+ influx which leads to dephosphorylation of cyclic AMP dependent protein kinase (PKA) which leads to LTD.

The neurophysiological assessments with RMT and CSP also showed a greater improvement in the TBS and FES groups when compared to the PT group. The RMT-IH of TBS group after iTBS decreased by 10% at one month, 13% at 3 months, 11% at 6 months and 10% at 1 year of follow-up, rather the RMT-CH of TBS group after cTBS increased by 16% at one month, 18% at 3 months, 19% at 6 months and 17% at the end of 1 year of follow-up. Whereas the CSP-IH of TBS group after the iTBS decreased by 26% at one month, 27% at 3 months and 6 months, and 19% at the end of 1 year of follow-up. The CSP-CH after cTBS increased by 24% at one month, 30% at 3 months, 32% at 6 months and 29% at the end of 1 year of follow-up. The decrease in RMT and CSP of the ipsilesional hemisphere was at the maximum at 3 months of follow-up, however the excitability was not maintained and the decrease was not consistent after 6 months. Similarly the RMT and CSP of the contralesional hemisphere where the inhibitory stimulation (cTBS) was applied, the effect was greatest at 6 months of follow-up. Though the TBS intervention was given only for 1 month the neurophysiological effects lasted consistently till 3 months at ipsilesional hemisphere where facilitatory stimulation (iTBS) was applied and till 6 months at the contralesional hemisphere where inhibitory stimulation (cTBS) was applied, which states that the inhibitory stimulation to the contralesional hemisphere was long lasting rather compared to the facilitatory stimulation to the ipsilesional hemisphere supported by (Huang *et al* 2011). The results of the present study was similar in accordance with the previous studies where it was found that the excitability of the ipsilesional hemisphere was significantly depressed as compared to contralesional hemisphere and this reduced excitability could be improved

with iTBS-IH and cTBS-CH. There was significant decrease in RMT and CSP values of ipsilesional hemisphere following iTBS-IH and cTBS-CH. Our results are similar to those reported by (Di Lazzaro *et al* 2008a) who found significant increases in MEP amplitudes and decreases in RMT of ipsilesional hemisphere following iTBS-IH and cTBS-CH in 12 patients with acute stroke. On the other hand, (P Talelli, R J Greenwood and J C Rothwell 2007) studied six patients with chronic stroke and found that excitatory TBS of the ipsilesional hemisphere resulted in improvement in motor parameters and simple reaction time of paretic hand while inhibitory TBS of contralesional hemisphere was ineffective. Similarly, (Ackerley *et al* 2010) reported decrease in MEP amplitudes of ipsilesional hemisphere following cTBS of contralesional hemisphere in chronic stroke patients which correlated with deterioration of paretic UL functions. Various methodological differences in previous studies especially with regard to the number of patients, duration and type of stroke, variable stimulation parameters and use of training program in conjunction with TBS may explain the differences in the results.

The RMT-IH of FES group decreased by 9% at one month, 11% at 3 months, 10% at 6 months and 10% at 1 year of follow-up, rather the RMT-CH of FES increased by 16% at one month, 19% at 3 months, 20% at 6 months and 19% at the end of 1 year of follow-up. The CSP-IH of FES group decreased by 25% at one month and 3 months, 23% at 6 months, and 21% at the end of 1 year of follow-up. The CSP-CH increased by 19% at one month, 22% at 3 months, 23% at 6 months and 22% at the end of 1 year of follow-up. The change in the neurophysiological parameters of FES group was greater till the end of intervention at 1 month, later on the RMT and CSP values does not show a consistent

change. This effect might be due to the effect of FES on the cortical excitability and later on when the intervention was stopped the cortical excitability was not consistent because, thereafter the therapy does not include a FES program rather conventional physiotherapy was followed till the entire follow-up period of 1 year. The change in the RMT at contralesional hemisphere was more compared to the ipsilesional hemisphere; this proves that the inhibitory effect at the contralesional hemisphere dominated the facilitatory effect at the ipsilesional hemisphere. The inhibitory effect which was shown might be due to the repeated and overuse of the contralateral upper limb which might have resulted in the reduction of intracortical inhibition and increase in intracortical facilitation.

Few patients from all the three intervention groups were not excitable for MEP, the probable reasons might be due to tissue loss in the descending cotico-spinal tract or the associated cortical and subcortical structures. Not always that MEP is a good prognostic indicator, because motor activity is generated by a plastically altered motor system including alternative pathways. Other probable mechanism might be that stroke patients might recruit an extended network comprising premotor and sensory motor structures normally reserved for the performance of complex movements for even the simplest of gestures this is likely to have indirectly increased the threshold of the excitatory interneurons and cortico-spinal neurons in the affected hemisphere needed to induce MEP activity after single pulse TMS stimulation.

There are only a few studies which have assessed the neurophysiological parameters after the FES intervention, the results of the present study is in agreement with the study done

by (Barsi *et al* 2008) which has showed an 15% increase in mean MEP area of flexor muscles and 19% increase in the mean MEP of flexor digiti profundus muscle after applying FES combined with voluntary activity in 25 healthy volunteers, this intervention also showed shortening of silent period when compared with voluntary muscle contraction and FES given alone.

Physiotherapy intervention group which was assumed to be the control intervention also showed improvements in the motor cortex excitability when assessed with single pulse TMS. In the present study the RMT-IH decreased by 4% at one month, 6% at 3 months, 3% at 6 months and at 1 year of follow-up, rather the RMT-CH increased by 9% at one month, 10% at 3 months and 6 months and 8% at the end of 1 year of follow-up. In the present study the CSP-IH of PT group decreased by 15% at one month, 18% at 3 months, 14% at 6 months, and 11% at the end of 1 year of follow-up, on contrary the CSP-CH increased by 7% at one month, 8% at 3 months, 6% at 6 months and 7% at the end of 1 year of follow-up. The change in the neurophysiological parameters was not similar to the TBS and FES intervention groups. However the summary of results of the RMT and CSP values shows that the TBS group has slightly greater advantage on these scores even though not significant statistically, this difference might be due to the reason that the TBS stimulates the corresponding motor cortex directly which would have influenced the motor cortex excitability. The results of RMT values have shown a greater increase in the motor threshold and thereby reduced excitability of the contralesional hemisphere in all the three intervention groups stating a reduction in the trans callosal inhibition from the contralesional to the ipsilesional hemisphere.

The secondary outcome measures were modified rankin scale, NIHSS and Barthel index. The median MRS scores of all the groups at baseline were 4, however it decreased significantly to 2 in TBS, 2 in FES and 3 in PT groups respectively after the intervention at one month, even though the median scores were 2 for all the three intervention groups at 3 months it had shown a significant difference between the FES and the PT groups, rather there showed no significance when MRS scores were compared between the TBS vs. PT and between TBS vs. FES. This signifies a slight advantage of FES group over the TBS and PT groups in the global outcome at 3 months of follow-up. The median scores were similar for all the three groups thereafter till the end of one year follow-up and did not show any significance, stating that there is no much difference in global outcome of post stroke patients between the three interventions in long term follow-up.

The barthel index scores of the TBS group increased by 35% at one month, followed by 55% at 3 months, 70% at 6 months and 72% at 1 year. The results of the present study were similar to the study done by (Khedr *et al* 2005) on 52 acute stroke patients who were administered with 3 Hz high frequency rTMS for 10 consecutive days which showed improvements in the BI scores after intervention and 10 days thereafter at follow-up when compared to sham stimulation. The FES group BI scores of the present study increased by 36% at one month, 56% at 3 months, 71% at 6 months and 74% at 1 year of follow-up, the present study results were in agreement with the study done by (Mangold *et al* 2009) in 23 acute and sub acute stroke patients where FES was given for 4 weeks (12 sessions) and was compared with physiotherapy which showed significant improvement in FES group with a moderate effect size of 0.53 on extended barthel index

sub score. Similar results were also shown by (Thrasher *et al* 2008) on 21 acute stroke patients who were administered with FES for 12 weeks and compared with conventional physiotherapy exercises also had shown significant difference between the groups ($p<0.05$) when assessed with BI scores after 12 weeks of intervention. In the present study PT group also showed significant change in BI scores throughout the 1 year of follow-up with a change of 25% at one month, 47% at 3 months, 67% at 6 months and 73% at 1 year. The significant change was evident between the groups only till 3 months, and later on the changes were not significant and this might be due to the reason that some aspects such as bowel, bladder and transfers representing some part of the BI total score are possibly not expected to change as a result of physical rehabilitation of the UL. NIHSS also had a corresponding change in all the three intervention groups, were TBS group had a change of 43% at one month, 70% at 3 months, 82% at 6 months and 73% at 1 year which was in agreement with the previous study done by (Khedr *et al* 2005). Corresponding changes were seen in the FES group, which showed a change of 47% at one month, 73% at 3 months, 85% at 6 months and 87% at 1 year of follow-up. The change which was noted at the PT group was not similar to the TBS and FES intervention groups, where it has shown a change of 27% at one month, 60% at 3 months, and 78% at 6 months, and at 1 year it was 84% which was almost similar to the TBS and FES groups. The between group scores were significant at 1 month, 3 months and at 6 months which also specified that TBS group and the FES group had a greater improvement than the PT group at 1 month and 3 months, however at 6 months of follow-up the FES group showed a significant improvement compared to the TBS and PT groups.

This comparative trial extended prior research on stroke motor rehabilitation by studying TBS, FES and PT intervention with intensive treatment schedule for 1 hour/day for 1 month. To our knowledge no prior studies have used similar protocols with similar treatment intensity for comparison among these rehabilitation therapies. Some previous studies have compared TBS with PT (Ackerley *et al* 2010; Talelli *et al* 2012), but with different treatment intensity and protocols. In the present study the researcher has used TBS for 1 month (12 sessions) which has been not yet used in any of the previous studies and also it was combined and compared with physiotherapy for a period of 1 month. Some previous studies have compared FES with physiotherapy (Alon *et al* 2007; Thrasher *et al* 2008; Mangold *et al* 2009) with the same treatment intensity but did not contrast TBS with FES. Furthermore, these studies on TBS employed less treatment intensity, or adopted a combination with physiotherapy which was not aimed in functional training, which were different from the present study. With respect to study design and sample size, previous studies (P Talelli, R J Greenwood and J C Rothwell 2007; Di Lazzaro *et al* 2008a; Ackerley *et al* 2010) used either nonrandomized controlled trial or a randomized controlled trial with less participant number. The present study employed 20 participants for each group well more than the participant number in most of the previous studies.

6. Conclusion

Thus the results of present study rejects the Hypothesis 1, Hypothesis 2 and Hypothesis 3 and states that there is significant improvement in rehabilitation of stroke patients receiving Theta Burst Stimulation along with Physiotherapy, Functional Electrical Stimulation along with Physiotherapy and Physiotherapy alone. On contrary the results of present study partially accepts the hypothesis 4 and states that there is no significant difference between stroke patients receiving Functional Electrical Stimulation along with Physiotherapy compared to those patients receiving Theta Burst Stimulation along with Physiotherapy, However there is a significant difference between stroke patients receiving Theta Burst Stimulation along with Physiotherapy compared to those patients receiving Physiotherapy alone and Functional Electrical Stimulation along with Physiotherapy compared to those patients receiving Physiotherapy alone

The overall findings of this study suggest that both TBS and FES might be a more compelling approach for improving the UL motor functions than the PT alone. However the FES could be an optimal approach if improving the global outcome following stroke, moreover if the concern is activities of daily living then all the three groups have performed equally. Even though the nuerophysiological outcome was slightly better in the TBS group, it did not transfer into functional performance. So to brief out, both TBS and FES can be used as to facilitate neuroplasticity and thereby improving the UL performance in post stroke patients when combined with physiotherapy.

A few limitations to this study warrant consideration. First the study findings were based on a small percentage of all eligible patients. Caution should be exercised when generalizing the results beyond the study. Further research should recruit a larger sample to validate the findings of the present study. Second the neurophysiological parameters were not excitable from the ipsilesional hemisphere of around 50% of the patients, future research should include only those patients whose motor cortex is excitable with single pulse TMS. Neurophysiological parameters should also include the intracortical facilitation and intracortical inhibition. Third, there should have been one more group combining FES and TBS to know the combined or additive effects of both interventions. The major delimitation which should be mentioned is that the sub scores of FMA were not included in the performa so the researcher was not able to analyze hand, wrist and upper extremity components separately.

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Abstracts

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