AN EXAMINATION OF CONSTRAINT-INDUCED THERAPY AS A METHOD TO INTENSIFY INTERVENTION AND IMPROVE FUNCTIONAL OUTCOME DURING THE REHABILITATION PHASE OF STROKE

MICHELLE PLOUGHMAN

An Examination of Constraint-Induced Therapy as a Method to Intensify Intervention and Improve Functional Outcome During the Rehabilitation Phase of Stroke

by

© Michelle Ploughman

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ABSTRACT

Studies have shown that constraint-induced therapy (CIT) improves recovery of the impaired upper extremity and influences neuroplastic changes in the recovering brain, primarily in chronic stroke populations and when paired with six hours of additional therapy per day. A protocol of mitten constraint was developed in which subjects, during the rehabilitation phase of stroke, wore a mitten on the sound hand rather than a sling and splint as used previously, gradually increasing wearing time, without hours of additional therapy. The purpose of this exploratory study was to evaluate the effectiveness of this constraint protocol and compliance to the treatment. Subjects were randomly assigned to CIT plus conventional therapy or conventional therapy only. Upper extremity, lower extremity and trunk motor control and strength were evaluated along with shoulder pain, compliance and level of dependence on caregivers. CIT appeared to significantly improve recovery of postural control and augmented recovery of the impaired upper extremity. The constraint protocol was most effective in male subjects and subjects with left hemiplegia. Compliance varied according to level of disability on admission but was not related to overall recovery. CIT did not induce increased dependence on caregivers and was not associated with adverse events however there was a trend toward increased hemiplegic shoulder pain in some subgroups that was associated with poorer outcome. It was concluded that this constraint protocol was a clinically relevant and practical method to apply CIT in the acute rehabilitation setting.

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ANOVA	Analysis of Variance
ARAT	Action Research Arm Test
bFGF	Basic Fibroblast Growth Factor
CIT	Constraint-Induced Therapy
CIMT	Constraint-Induced Movement Therapy
CMII	Chedoke-McMaster Impairment Inventory
CPM	Continuous Passive Motion
CT Scan	Computerized Axial Tomography Scan
EMG	Electromyogram
FES	Functional Electrical Stimulation
FIM	Functional Independence Measure
fMRI	Functional Magnetic Resonance Imaging
HSP	Hemiplegic Shoulder Pain
IGF-I	Insulin-like Growth Factor-I
F	Female
M	Male
L	Left
R	Right
inpt	Inpatient

outpt	Outpatient
MCA	Middle Cerebral Artery
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MMSE	Folstein Mini-Mental Status Exam
OSI	Stroke onset to study entry interval
ORI	Stroke onset to rehabilitation interval
PET	Positron Emission Tomography
SD	Standard deviation
SE	Standard error
SMA	Supplementary Motor Area
TENS	Transcutaneous Electrical Nerve Stimulation
TMS	Transcranial Magnetic Stimulation

INTRODUCTION

Stroke is caused by transient or permanent reduction in cerebral blood flow either by emboli or thrombus formation or hemorrhage. This loss of blood supply causes a cascade of events leading to varying degrees of brain tissue loss. The nature and extent of impairment and disability depends mainly on the precise location of the stroke within the brain. Patients, post-stroke, typically suffer from a range of impairments including paresis of the body opposite to the cerebral lesion, contralateral sensory loss, expressive and/ or receptive aphasia, swallowing difficulties, and intellectual, memory and perceptual impairment.

It has been demonstrated that a coordinated approach to rehabilitation in specifically dedicated stroke units is superior to rehabilitation provided in a general hospital ward (Indredavik 1997; Langhorne 2001). There are a number of historical and philosophical approaches to the rehabilitation of the stroke patient that have been employed over the past 60 years. For example, Neuro-Developmental Treatment suggests attainment of upright postural control and skill in weight bearing positions before progressing to skilled activity whereas the Motor Learning Approach recommends beginning skilled activity using accepted motor learning principles. The Proprioceptive Neuromuscular Facilitation Approach teaches therapists to move the limbs and trunk in combinations of movements through functional ranges facilitating and providing resistance to gain motor control. None of these treatment approaches has been found to be superior to the other (Barreca 2001). There is evidence, however, that certain specific treatments such as repetitive skilled activity, constraint of the sound arm, treadmill and strength training, functional electrical stimulation, among others, have significant benefit (see review Ploughman 2002).

To complicate physical rehabilitation, stroke patients also suffer from altered muscle tone in the trunk and limbs theorized to occur as a result of release of inhibitory supraspinal control as well as other mechanisms. The hemiplegic arm and hand often adopt stereotypical postures; the arm tends to be biased toward elbow flexion, wrist and finger flexion with combination of forearm pronation or supination and shoulder flexion and medial rotation. The lower limb usually moves into extension synergy with knee extension and ankle plantarflexion making it difficult for the limb to swing freely during gait. The stroke survivor often develops shoulder subluxation due to the weight of the arm and an unprotected, mal-aligned shoulder joint. This will sometimes be related to shoulder and hand pain and swelling. It has been estimated that up to 75% of stroke patients experience hemiplegic shoulder pain and this pain has been associated with poorer functional outcome after stroke (for review see Turner-Stokes 2002).

Stroke patients with a lesion affecting the right or non-dominant hemisphere will often have spatial neglect, a perceptual impairment in which the stroke patient fails to attend to stimuli originating from the hemiplegic (contralateral) side. This phenomenon is reported in up to 85% of left hemiplegic (right brain lesion) stroke patients and has been suggested to limit stroke recovery (Paolucci 2001; Azouvi 2002).

A philosophical approach exists in rehabilitation in which patients with stroke are encouraged to compensate for unilateral impairment using the sound side. After stroke, patients are fitted with an arm sling to support the affected arm and a four-point quad cane or a wheelchair to provide safe and independent ambulation. They are taught to use the sound limb to perform activities of daily living (ADL) such as dressing, eating and are provided with devices that assist with one-handed activities. Although this approach may provide the patient with early independence, it may also impede optimal recovery of the affected side. There is also a trend especially in managed-care settings in the United States to limit the intense rehabilitation phase as an inpatient to 2 weeks followed by less intense therapy in an outpatient or day hospital setting. Accepted practice in Canada is an average rehabilitation length of stay of about 50 days (Canadian Institute for Health Information 2003). Patients who do not require nursing or medical care are often provided rehabilitation services in an outpatient or day hospital setting. The rehabilitation period is most often determined by attainable goals set by the patient and the rehabilitation team.

This thesis begins in Chapter 1 by reviewing the 'state of the art' in physiotherapy and stroke rehabilitation, specifically, the effect of physiotherapeutic techniques on plasticity of the recovering brain. The information provided in this chapter was previously published in the peer-reviewed journal Physiotherapy Canada in October, 2002. A number of questions are posed to rehabilitation professionals and researchers in the article regarding the analysis of specific physiotherapy approaches and treatments in stroke rehabilitation.

The second chapter contains the details and results of a randomized controlled exploratory study performed at the L.A. Miller Centre in St. John's between June 2001 and February 2003. This trial, approved by the Human Investigations Committee, examines the effect of a method to intensify input to the affected upper extremity during the rehabilitation phase of stroke. The study also explores the practical issues and compliance to such a treatment within a rehabilitation setting and makes recommendations for future research in the field.

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CHAPTER 1

A Review of Brain Neuroplasticity and Implications for the Physiotherapeutic Management of Stroke

1.1 Introduction

Health Canada reports that there were over 49,000 hospitalizations due to stroke in 1997 (Health Canada 2000). Hemiparesis contralateral to the side of the lesion, is the most common deficit after stroke acutely affecting 80% of patients and greater than 40% chronically (Cramer 1997). Recovery of the hemiplegic upper extremity is one of the main challenges in the rehabilitation management of stroke. For many years clinicians have held the view that brain tissue had little or no potential for recovery (Turton 1996). However, despite this belief, in the rehabilitation setting, stroke patients showed continued functional improvement beyond the 'window of recovery' often considered to be 6 months post-injury. Over the past ten years, advances in experimental techniques and brain mapping technology have shown that the adult brain continues to be modified with experience and after injury (Kolb 1992; Hallett 1999; Johansson 2000).This can be examined at a molecular or cellular level and on a larger systems level. This paper will review current brain plasticity research in humans and animals, examine the influence of rehabilitative techniques, particularly in the upper extremity, and discuss the implications in the physiotherapeutic management of stroke. This is a scientific review rather than a systematic one, so although the literature search is comprehensive, one cannot be assured that every research paper has been cited.

1.2 Neuroplasticity in the Intact Adult Brain

1.2.1 Environmental enrichment

There have been numerous studies examining the effects of sensory impoverishment and sensory and social stimulation on the rodent brain. Mice housed in enriched environments with climbing and manipulative toys (Kempermann 1997) or with free access to a running wheel (van Praag 1999) typically have increased number of neurons in the hippocampus. Voluntary running has also been shown to increase the levels of brain-derived neurotrophic factor in the rat brain (Neeper 1995). Black (Black 1990) examined the cerebellar neurons of rats placed in four housing conditions for 30 days:1) obstacle course (AC), 2) forced treadmill exercise (FX), 3) voluntary wheel running (VX) and 4) individual cages (IC). The groups with the highest activity, FX and VX, had increased capillary density in the cerebellum while the AC rats had dramatic increases in the synapses per neuron of the cerebellar Purkinje cells. Similar findings were reported by Kleim et al. (Kleim 1996) in the rat motor cortex with acrobatic training and there is reported increased number of bifurcating and multi-headed spines in neurons of the caudate nucleus of rats housed in enriched environments (Comery 1996). Others have shown that environmentally influenced neuronal modification also occurs in the brains of aged mice although to a lesser degree than adults (Kempermann 1998; Greenough 1999).

Overall, these studies indicate there is evidence in animals that various parts of the brain including hippocampus, cerebellum, cortex and striatum are changed in response to environmental stimulation and exercise.

1.2.2 Motor Learning

It is now generally accepted that the mammalian brain is capable of change throughout the lifetime in response to the environment and subsequent sensory experience. Investigators have used a number of brain mapping techniques to examine brain topography modification.

Positron Emission Tomography (PET) scanning is used to measure regional cerebral blood flow (rCBF). Specific tracers are either injected or inhaled by subjects and while they move a particular body part their brain is scanned. Increased tracer uptake reflects areas with enhanced rCBF as a result of increased metabolic activity from the movement related neural activity (Rossini 1998; Hallett 1999). Focal transcranial magnetic stimulation (TMS) typically involves using a figure-of-eight coil placed over the skull to apply a stimulus to the cortex. The motor response to this stimulus is then recorded peripherally using EMG electrodes placed on the target muscles. In this way researchers can not only map brain regions but also record amplitude and latency of the motor evoked potential (MEP). Higher MEP amplitude and short latency are indicative of efficient cortical transmission (Rossini 1998). Functional magnetic resonance imaging (fMRI) measures small changes in blood flow that accompany brain activation during performance of a task. Brain structure and blood flow can be measured simultaneously using fMRI (Cramer 2000).

Specific sensory enrichment causes plastic change in the corresponding cortical map. A number of fascinating studies investigated cortical map enlargement of preferentially used digits, specifically the index finger of Braille readers and the digits of the playing hand of string players (Pascual-Leone 1993; Elbert 1995). It appears that the cortical territory serving the preferentially used digits in these individuals expands and the enhancement is temporally dependent, since it occurs to a greater degree when the practice is initiated at an early age and for longer periods. An interesting phenomenon in the proficient Braille readers is that the representation for the reading finger appears to be enlarged at the expense of the remaining fingers. As well, the same researchers (Pascual-Leone 1995) examined cortical maps of Braille proof readers and showed that the map enlargement was larger on work days indicating the brain was capable of making a rapid change in response to input (or need).

Motor task learning can be described as specific sensory and environmental enrichment since motor tasks are accomplished using repetitive sensory feedback to learn and refine the skill. Pascual-Leone (Pascual-Leone 1994)and Karni (Karni 1995) trained adult human volunteers on finger and/or thumb repetitive movements. The training groups had progressively larger cortical outputs to the involved muscles along with improved task performance. Pascual-Leone's group had a subsequent decrease in map size back to baseline after the motor sequence was learned indicating possible contribution of other brain structures rather than primary motor cortex. This is supported by others (Jenkins 1994; Kawashima 1994) who found that after learning a complicated sequence of finger movements, rCBF shifted from cortex and cerebellum to the striatum. Several researchers have found that learning of motor skills in animals similarly increased the numbers of synapses per neuron in the motor cortex (Kleim 1996) and in the cerebellum (Anderson 1996; Kleim 1997; Kleim 1998) and in one study these findings persisted for at least four weeks after cessation of the training (Kleim 1997). These findings support the notion that motor skill practice may lead to structural brain changes that allow the skill to become "less cortical" and more automatic. This is important in relearning a skill particularly after neurological or orthopedic injury.

Sensory/environmental impoverishment also appears to induce cortical change (Sanes 1998; Coq 1999). Amputees, in particular, have been studied to determine the extent of cortical change as a result of removal of input to the cortex from the amputated body part. Cohen (Cohen 1991) and Flor (Flor 1995) used magnetic source imagery (magnetic responses to stimuli of the digit cortical representations of the amputated hand) to show change in cortex topography. They demonstrated a mean shift in cortical responsivity to facial stimulation indicating that the somatotopic representation of the missing limb was 'taken over' by that of the face. Another study by Florence (Florence 1998) used neural tracers to map the hand representation of four monkeys with chronic upper extremity injury. The findings were similar to Flor and colleagues, with the face and remaining upper limb maps expanding into the cortex representing the damaged limb.

Two studies examined the speed and topography of cortical plasticity during short term deafferentiation using a blood pressure cuff on the arm and leg of normal human subjects (Brasil-Neto 1992; Brasil-Neto 1993). Within minutes MEPs from more proximal unaffected muscles increased then returned to baseline once the cuff was removed. The cortical representation area for the muscle proximal to the tourniquet was enlarged. Is the cortical map change due to peripheral nerve impairment or decreased use of the particular muscles or both? Liepert (Liepert 1995) examined individuals with ankle immobilization following ankle injury without peripheral nerve damage. The immobilization caused a decrease in the cortical map representation for the tibialis anterior muscle, which quickly returned to baseline with muscle contraction.

These studies may indicate that cortical maps are changing on a daily and even minute-to-minute basis depending on increase or decrease in sensory input and motor activity. It suggests that when a body part is injured, immobilized or missing, there is a neuronal change along with the more readily acknowledged musculoskeletal impairments. Garraghty and Muja (Garraghty 1996) have proposed that deafferentation in primates probably occurs in two phases; in the first phase some deprived neurons immediately express new receptive fields while in the second phase the remaining majority regain responsiveness over weeks or months. These changes in cortical representation are proposed to be mediated at the synaptic level via unmasking of latent synapses or an increased responsivity of synapses in the short term and modified synaptic morphology in the long term. In summary, these research findings suggest that:

- Acquisition of motor skill is mediated by change in cortical map topography.
- An inability to move or perform a task due to physical injury causes brain topography modification. Therefore, patients with musculoskeletal injury likely have neuroplastic change as well.

- Specific skill training and practice may be integral to reacquire the skill and the corresponding cortical map representation. True intrinsic (automatic or unconscious) motor skill learning seems to occur when the activity becomes subcortical.

1.3 Neuroplasticity in the Damaged Adult Brain

If neuroplasticity occurs in the normal brain, does the damaged brain undergo similar processes and is neuroplasticity related to functional outcome? There are a number of morphological changes that have been demonstrated in cortically lesioned rats. For example, in the *intact* hemisphere there is evidence for increased cortical thickness, dendritic branching and number of synapses per neuron. These changes result from the combined effects of the lesion itself and the ensuing forelimb asymmetry (Jones 1994; Jones 1996).

1.3.1 Role of Motor Association Areas

Weiller and colleagues in two separate studies (Weiller 1992; Weiller 1993) used PET to study organizational changes after recovery from subcortical (internal capsule and striatum) stroke in ten and eight subjects, respectively, compared to controls. Regions such as the basal ganglia, thalamus, sensorimotor cortex contralateral to the recovered hand, and the ipsilateral cerebellum, had decreased rCBF indicating the dysfunction related to the ischemic lesion. Regions that had increased rCBF compared to controls were the prefrontal cortex, insula, cingulate and inferior parietal cortex of the damaged hemisphere and the premotor cortex, basal ganglia and cerebellum of the undamaged hemisphere. The patterns of activation were variable among subjects and among infarct sites but a common theme was the finding of increased activity in areas remote from the lesion and their involvement in movement of the recovered hand. Other studies have confirmed these findings (Chollet 1991; Fries 1993; Netz 1997; Seitz 1999). Notably, the structures involved during movement of the recovered hand in these studies were primarily, cortical supplementary and association areas, striatum (bilaterally) and the cerebellum contralateral to the recovered hand.

It has been suggested that different motor areas operate in parallel. Fries et al., identified in monkeys, descending pathways from multiple topographically organized cortical maps that pass through the internal capsule in an orderly manner (Fries 1993). Descending fibres from the supplementary motor area (SMA) and limbic motor fields pass through the anterior limb of the internal capsule, the premotor cortex fibres through the ventral posterior limb and primary motor fibres through the middle third of the posterior limb. The authors suggest that these parallel cortical maps are able to substitute for each other functionally. Non-primary motor areas may play an increased role in generating voluntary movement during recovery from brain injury (Schreiber 1995). This has been further supported by Seitz et al. using TMS, MRI and PET in seven patients with middle cerebral artery(MCA) infarct (Seitz 1998). These researchers found that motor recovery appeared to rely on activation of premotor cortical areas of both cerebral hemispheres. Dettmers and colleagues report similar findings and suggest that the increased recruitment of executive cortical areas in tasks that require little demand in normal subjects may be the reason many stroke patients experience an increased sense of effort and ensuing fatigue with motor task practice (Dettmers 1997). When infarcts damage either large portions of the cortex or capsule, the brain may rely on the less functional, ipsilateral pathways. The authors correlated these findings with quantitative motor recovery in 23 patients with various infarcts of the internal capsule and striatum. Ischemic lesions in the internal capsule, therefore, can have a relatively large effect on multiple motor maps. This may explain the fact that patients with subcortical (internal capsule, basal ganglia and thalamus) stroke are reported to have less favourable outcome than those with cortical stroke (Shelton 2001).

1.3.2 Role of Ipsilateral Connections

Interestingly, stroke has also been associated with both neurophysiological and functional impairments in the so-called 'unaffected' hand (Jones 1989) which may lend some evidence for the role of ipsilateral pathways in limb control and recovery from stroke.

One of the most remarkable cases for studying the role of ipsilateral pathways in recovery from brain damage is the patient with hemispherectomy (or hemidecorticate) (Rose 1992). This procedure has been performed on patients with severe epilepsy or tumor and the post-operative motor function depends largely upon the age when the surgery is performed. The functional recovery after hemispherectomy is much better in the infantile versus adult onset group (Benecke 1991). The motor recovery seen in hemispherectomy patients is proposed to be mediated via ipsilateral corticospinal projections and the cortico-reticulospinal pathway.

Benecke and colleagues used TMS to show the existence of both pathways in early and late brain damaged groups with hemispherectomy and severe hemispheric lesions but identified primarily the cortico-reticulospinal pathways in the late onset group. Both groups had more impairment (increased latency and decreased amplitude of MEPs) of the distal muscles suggesting that these ipsilateral pathways may predominantly activate proximal muscles (Benecke 1991). It is interesting that stroke patients frequently show a proximal to distal gradient with control proximal musculature returning (i.e. sitting balance, bed mobility, and gait) before dexterous limb activity.

1.3.3 Role of Map Representation Changes in the Lesioned Hemisphere

Mapping techniques have identified areas of increased activation in the lesioned hemisphere in the motor association areas and surrounding cortex (Cramer 2000). There appears to be a correlation between enlargement of the motor map of the hand and the degree of clinical improvement (Cicinelli 1997; Traversa 1997).

Using intracortical recording techniques, Jenkins and Merzenich have demonstrated that in various species of monkeys, restricted cortical lesions are followed by dramatic reorganization of cortical maps (Jenkins 1987). Regions surrounding the damaged area gain new receptive fields in which much of the skin surface formerly represented in the infarcted cortex becomes represented around the rim or penumbral zone of the infarct. This finding is supported by another study using PET to examine rCBF changes in patients with tumors occupying the hand area of the motor cortex (Seitz

1995). These patients retained their ability to use the hand and rCBF activity was identified solely around the edge of the tumor rather than at more remote sites. Other researchers have used a relatively new mapping technique, magnetoencephalography, which measures the magnetic field distribution over the scalp during peripheral nerve stimulation (Rossini 1998). This mapping method showed the same enlargement and shift of hand distribution areas in the affected hemispheres as the PET, fMRI and TMS studies.

Not all studies are in agreement however. A later study by Nudo and Milliken using intracortical mapping techniques in squirrel monkeys, showed that movements formerly represented in the infarcted zone did not appear in the cortical sector surrounding the infarct, at least in the absence of post-infarct training (Nudo 1996). They showed an apparent increase in proximal limb representations that may have accounted for the animals' recovery. In summary, motor recovery can be mediated through a number of neural pathways (Seitz 1999).

- Cortical map reorganization involving tissue surrounding the infarct mediated by unmasking of latent synapses and/or growth of new intracortical connections.
- Association motor areas in the lesioned cortex
- Association motor areas in the opposite cortex that probably have redundant collosal connections
- Uncrossed pyramidal and reticulospinal pathways in the opposite cortex.

1.4 Effect of Training on Plasticity in the Damaged Brain

1.4.1 Enhancement of Recovery in Animals

As previously discussed, environmental and sensory enrichment can induce plastic changes in the normal adult brain. Can manipulation of the environment through treatment influence plastic changes in the damaged brain? The answer is, yes, there is ample evidence in animal and human studies supporting an active role of rehabilitation in remodeling cortical maps (Nudo 1996).

Xerri and colleagues performed intracortical mapping procedures in adult owl and squirrel monkeys, trained to master small object retrieval, before and after primary somatosensory cortex lesions (Xerri 1998). Their goal was to gain insight into the specific neurophysiological processes that mediated behavioral recovery. Lesioned monkeys had the expected impairments in dexterity of the affected upper limb however they were able to accomplish the task post lesion as they were previously trained to do. Monkeys then initiated compensatory use of the opposite upper limb for the task but this resulted in a performance drop. The monkeys then reinstituted the affected limb and exhibited gradual recovery of function over several weeks. This recovery was paralleled by striking enlargement of the motor and sensory representation of the fingers in the damaged hemisphere. There was no significant change in the intact hemisphere. Nudo and Milliken used similar methods to show that map remodeling around the infarct did *not* occur (Nudo 1996). However, the studies are different in that Xerri's animals with behavioral training showed increased hand map representation while Nudo's untrained monkeys did not. In another study by Nudo and colleagues, they demonstrated that retraining of skilled hand use after infarct resulted in prevention of loss of hand territory adjacent to the lesion suggesting that rehabilitative training can indeed shape the reorganization of cortical tissue (Nudo 1996). Others have had similar findings in skilled motor activity training in animals (Jones 1999), visuospatial training in hemineglect (Pizzamiglio 1998) and aphasia training (Mimura 1998; Musso 1999) in humans.

Friel and Nudo also discuss the issue of compensation versus recovery (Friel 1998). They examined monkeys attempting to retrieve food pellets following minute ischemic cortical lesions of the primary motor cortex. Frame by frame video analysis revealed that some monkeys, although achieving pre-lesion performance levels, used slightly different movement strategies. These monkeys had slightly larger lesions and more distal limb involvement than the monkeys that made a full recovery. These authors as well as others (Levere 1980) propose that compensatory strategies in the affected limb may be a natural course of functional return but should not be equated to 'true' recovery.

Johansson and Ohllson have examined environment, social interaction and physical activity as determinants of functional outcome after cerebral infarction in rats (Ohlsson 1995; Johansson 1996). In their first study, lesioned rats were placed in three groups; Group A were in single cages, Group B were in enriched cages (elevated boards, chain, swing, blocks, etc.) and Group C were in enriched cages both before and after the lesion (Ohlsson 1995). Overall, animals with pre- and post- lesion enrichment improved sooner and to a slightly higher degree than the other rats. The rats housed in individual cages had the poorest scores on measures of functional outcome. The authors suggested that perhaps the pre-lesion environment had a neuroprotective effect. Further, the same researchers' second study attempted to differentiate between the benefits of the social group housing and the enriched environment (Johansson 1996). Group A rats were housed in groups in enriched environments, Group B rats were housed together in the same size cage with no toys and Group C rats were housed in individual cages with free access to a running wheel. In terms of recovery measured on behavioral testing (climbing, balance beam, etc.), social interaction was superior to wheel running but an enriched environment combined with social interaction resulted in the best performance. It may be that the combination of social interaction in group activities and the more intensive approach toward therapeutic activities found in typical specialized stroke units mimic these enrichment studies. Indeed, it appears that functional outcome and long term survival is significantly better in stroke units compared with general wards (Indredavik 1997; Langhorne 2001) .

An important recent study combined environmental enrichment and skilled reaching activity for two months beginning 15 days after ischemic injury in rats with the objective of enhancing dexterous limb activity (Biernaskie 2001). Despite a large ischemic injury to both cortex and striatum, animals in the treatment group had significantly greater dendritic branching of pyramidal neurons in the intact cortex and better functional outcome than the control animals. Interestingly, little spontaneous recovery was observed in animals unless they were exposed to the enrichment plus skilled reaching therapy.

All of these studies suggest that following brain injury, social interaction and complex exercise have an effect on the mechanisms underlying neural plasticity. Current evidence suggests that in animal models of brain injury and neurodegeneration, exercise induces the brain uptake of insulin-like growth factor-I (IGF-I), a neurotrophic hormone that has been shown to be neuroprotective (Carro 2001). Exercised animals perform better on behavioral tests and demonstrate neuronal preservation in a number of brain regions compared to sedentary animals. Ivanco and Greenough state, "If experience can influence plasticity (anatomical and physiological) in the injured brain, we are on strong empirical grounds to suggest behavioral therapies following brain injury" (Ivanco 2000)

The question is, what specific tasks promote plasticity and at what point in the recovery process should these be undertaken? An interesting phenomenon occurred in Johansson and Ohlsson's study (Johansson 1996). After the complete MCA occlusion, the rats displayed locomotor hyperactivity when given unlimited access to a running wheel 24 hours post surgery and only three of the nine rats survived the 13-week testing period. It was thought that the intensive exercise although voluntary, was too stressful for the animals. Recent studies have found that for about 7 days after brain lesions in rats, extreme behavioral demand placed on the affected limb (i.e.forced use) caused an exaggeration of neuronal injury and further tissue loss (Kozlowski 1996; Humm 1998; Humm 1999). It was found that the excitatory neurotransmitter glutamate was probably involved since increased levels of this neurotransmitter may cause cell death in the early post-lesion period (Choi 1990). Accordingly, glutamate receptor blockers spared the neural tissue during forced use and enhanced functional recovery. The authors suggest that although behavioral experience and therapy can enhance neuronal growth after brain injury, the region surrounding the injury may be particularly vulnerable to behavioral pressure (or stress) in the early post-lesion period.

Jones and Schallert also reported that directly following the lesion to the rat sensorimotor cortex there was an increase in dendritic arborization of the pyramidal neurons of the opposite cortex (Jones 1994). This reached a maximum about 18 days post-lesion, which closely paralleled a measured overuse of the unimpaired limb. Once the animals began to use their affected limb again, there was pruning of the dendrites and functional recovery. The researchers restricted either the ipsilateral unaffected limb or the contralateral affected forelimb to examine the effects on dendritic arborization. Restriction of the contralateral limb in the first 15 days post lesion had no effect but restriction of the ipsilateral side reduced neuronal arborization and was associated with poorer performance on tests of bilateral sensorimotor function afterwards. The authors suggest that complete restriction of the intact limb acutely post stroke may worsen overall function. There may be a specific time period when the development of compensatory strategies involving the use of the nonimpaired limb is optimal.

Bury and colleagues further investigated the effect of constraint of the unaffected forelimb on plasticity after lesions to the corpus callosum in rats (Bury 2000). Lesioned or sham operated rats were either forced to use the affected forelimb (via a plaster of paris one-holed vest) or permitted to use both forelimbs normally for 8 days directly post surgery. Histological examination of the affected sensorimotor cortex showed increased density of proteins associated with the astrocytic changes and plasticity in the lesioned-only animals and the forced-use only animals but density was greatest in the lesioned + forced-use animals. Basic fibroblast growth factor (bFGF), a neurotrophic growth factor, was also increased by lesion and forced use alone but was not further enhanced by the combinations of the conditions. These findings suggest that astrocytic reactions post cortical lesion can be shaped by behavioral demand, which may ultimately lead to enhancement of neural growth following injury. This is in contrast to the previous study by Jones and Schallert suggesting early tissue loss in response to excessive behavioral demand (Jones 1994). Perhaps this represents a balance of intensity of the rehabilitation program or shows that larger lesions are more vulnerable to excitotoxity.

In summary, environment and skill practice have an effect on neuroplasticity post-stroke. Animals exposed to enrichment, socialization and skilled activity have better functional outcome, increased complexity of neuronal branching and enhanced cortical activation. In the early days of recovery, intense use of the affected limb especially in large lesions may be contra-indicated. Therefore bilateral and reciprocal activities early post stroke may be recommended then progressing to more focused intense treatment of the impaired limb itself.

1.4.2 The Constraint- Induced Therapy Paradigm

Taub and colleagues investigated the effect of restraint of the intact upper extremity and recovery of function of primates in the late 60's and 70's (Taub 1993). They proposed that animals with chronic deficit had 'learned non-use' of the affected limb since attempts to use the hand post injury were unsuccessful and reinforced or conditioned. Taub and others then used the 'forced use' paradigm in human stroke patients (Wolf 1989; Tangeman 1990; Kunkel 1999; Miltner 1999; van der Lee 1999). In these studies patients were typically one to 20 years post left-sided infarct, right-handed with partial recovery of wrist and finger extensors and no cognitive or perceptual deficits. Patients wore either a sling, splint or both to restrict movement of the intact upper extremity for 90% of their waking hours. They engaged in 6 hours of motor relearning or ‘shaping’ therapy, five days per week, as well as using the affected extremity during ADL at home. All studies showed marked improvement on subjective and objective testing of recovery and function. The researchers suggested that this recovery was new and not associated with spontaneous recovery since so much time had elapsed post-stroke and the patients’ recovery had ‘plateaued’ pre-treatment. Further to this, with the advent of TMS mapping procedures, Taub and others have examined the cortical change resulting from this treatment (Kopp 1999; Liepert 2000; Levy 2001; Liepert 2001). Consistently, subjects had recruitment of motor areas adjacent to the lesion as indicated by increased motor output area and increased MEP amplitudes. Another study used EEG and showed an anterior shift of the hand cortical map into the supplementary motor area of the affected cortex with forced use therapy (Kopp 1999). At three month follow-up the affected hand movement source actually shifted to the opposite or ipsilateral hemisphere. The authors suggested that this may have reflected the recruitment of ipsilateral pathways. In forced use studies that had follow-up, patients maintained their acquired skill up to 2 years post-intervention (Taub 1993).

It is unknown which aspect of the treatment in these studies contributed most to recovery, the 6 hours per day spent in direct therapeutic activities or the remaining 6 – 8 hours of restraint. The former could have accounted for the significant improvement since other studies have documented the benefit of massed practice in physiotherapy (Woods Duncan 1997; Feys 1998; Lincoln 1999) or perhaps the latter, since a preliminary TMS study has demonstrated increased motor excitability with forced-use plus conventional therapy *without* the 6 hours per day of ‘shaping’ (Liepert 2001). In a review article by Taub et al., it was suggested that when 'conventional' physiotherapy is administered 6 hours per day for 10 consecutive days there is a similar increase in arm use to that seen in CI therapy (Taub 1998). The conclusion was that some chronic and subacute patients, who are able to tolerate it, could greatly benefit from physiotherapy if they received multiple hours of motor skill practice per day.

Since the CI therapy technique is useful in patients with chronic stroke, it may be even more effective in patients involved in active rehabilitation programs. In fact two recent studies have shown that cortical activation is significantly greater when forced-use therapy is combined with skilled arm training two weeks post-infarct in humans (Dromerick 2000) and primates (Friel 2000). In a recent randomized clinical trial, patients began two weeks of constraint-induced movement therapy within 14 days of their stroke versus traditional therapy. The CI group had less impairment on some outcome measures without any adverse reactions to the treatment (Dromerick 2000).

For rehabilitation professionals, forced-use offers more treatment options for patients without cognitive or perceptual problems and some motor recovery in the hand. More research needs to be undertaken in acute and rehabilitation settings since the stress of such a treatment may affect these patients as previously documented in animals[77-79]. It is also possible that the compensatory strategies learned in rehabilitation contribute to the learned non-use of the affected limb (Geer Russo 1995; Benevento 1998).

1.4.3 Motor Relearning

Cramer and Chopp suggest that in the past 10 years, research supports the hypothesis that recovery from stroke resembles stages in childhood development (Cramer 2000). They state that motor recovery follows the proximal (bilateral) to distal gradient from gross motor function to fine motor function and this is paralleled by cortical map plasticity and molecular events that resemble those in the developing brain. They suggest that different recovery stages probably call for different clinical approaches, an emphasis on bilateral activity initially and unilateral skilled activity in later rehabilitation or in mild hemiparesis. The developmental approach to management of stroke was developed by the Bobaths in the 1960's (Bobath 1990) and the motor relearning (skilled activity acquisition) approach by Carr and Shepherd in the 1970's (Carr 1987). Perhaps the approaches are not mutually exclusive but can be combined. Initially, moderately to severely affected patients would benefit from the symmetrical postural activities, especially of the trunk (Bobath) and later skilled task learning (Carr and Shepherd) (Miller 1998). In fact, a preliminary study indicates that bilateral movement activates the damaged hemisphere in acute stroke significantly more than unilateral limb activity (Staines 2001).

Interestingly, Nelles and colleagues have examined changes in rCBF post stroke (Nelles 1999; Nelles 1999). This, in itself, is not new, but whereas previous researchers studied recovered stroke patients, these investigators followed individuals for the first 12 weeks after their first cortical or subcortical stroke. Rather than patients performing a finger tapping task, the patients underwent passive elbow flexion and extension of the affected arm using a continuous passive motion (CPM) device. Remarkably these patients had activation of association cortices bilaterally as did the stroke patients moving their recovered hand actively in other studies. This is direct evidence of the benefit of passive range of movement acutely post stroke, a common treatment instituted to prevent musculoskeletal complications of immobility. An intriguing recent randomized control study by the same researchers using PET scanning investigated the effect of task-oriented arm training using motor learning techniques compared to passive ROM in 9 severe hemiplegics about 22 days post subcortical stroke (Nelles 2001). Treatment was individually applied by physiotherapists and occupational therapists for 45 minutes, four days per week for 3 weeks. Although the functional outcomes between the groups after the 3 weeks were not significant, the arm training group showed significantly more activation of the contralateral parietal cortex and primary motor area and bilateral premotor areas. This study, although small, presents compelling evidence that physiotherapy techniques influence cortical reorganization.

It appears that although passive and bilateral movement of the involved limb activates the damaged cortex (and association areas), when the patient is able to move the limb actively, active movement is the most effective method to stimulate neuroplasticity. This is confirmed in a study in which TCS mapping techniques were used to examine the effect of various physiotherapeutic techniques on MEPs of wrist and hand muscles in stroke patients (Hummelsheim 1995). The researchers compared five treatment approaches to baseline and control subjects; 1) cutaneous stimulation of wrist extensors by tapping, 2) upper extremity weight bearing, 3) proximal activation of the shoulder, 4) maximum isometric contraction of contralateral wrist extensors, and 5) attempt to activate affected wrist and finger extensors. Patients were placed in three groups by severity of hemiplegia. Group 1 had severe impairment, Group 2 was moderate and Group 3 had mild impairment. All approaches improved the frequency of occurrence of the MEPs. Attempting to isolate the affected wrist extensor in Approach 5 was overall the most effective at consistently generating MEPs in all groups. One approach, Approach 1, cutaneous tapping, was effective at raising the amplitude of the response potential in the most severe patients but had little effect in the other groups. Tapping was actually inhibitory in the healthy controls. Latencies of MEPs were diminished during the physiotherapeutic techniques and this benefit was most pronounced in the more hemiplegic groups. The exception was the cutaneous tapping techniques, which lengthened latencies in Group 3 patients and healthy controls. In summary, direct activation of the target muscle induced the most facilitory effect. In a follow-up study these researchers assessed the effect of voluntary finger flexing and extension against various loads 15 minutes twice per day compared to the Bobath method of upper extremity weight bearing on motor outcome of the hemiplegic hand (Butefisch 1995). All 27 patients were 3 – 19 weeks post stroke, had some isolated movement in the fingers and they were placed randomly in the two groups. The patients undergoing the weight bearing approach alone did not experience a significant improvement on measures of strength and contraction velocities of the hand, whereas the hand exercise group did. The problem with this study is that patients at this relatively high level of function would not receive weight bearing alone as a focused treatment strategy. Many physiotherapists use weight bearing early in the rehabilitation program before skilled activity can be performed to facilitate more proximal muscle groups. Therapists often employ an eclectic individually tailored treatment program rather than a specific philosophical 'school' approach. (Bobath, Brunnstrom, PNF, Carr and Shepherd) The important point here is that patients had good outcomes with graduated strength training with only minimal therapy time (about 30 minutes per day). Another study reports increased motor output area to the abductor pollicis muscle following one 90 minute intense physiotherapy treatment for the impaired upper extremity (Liepert 2000). It should be noted again however that patients with sensory deficits, neuropsychological deficits and complete paralysis of the hand were excluded from these studies. Further, a randomized controlled study of 132 stroke patients also demonstrated that an enhanced therapy program consisting of self directed exercise, forced-use and biofeedback improved strength and speed of movement over a weight-bearing only treatment regime and the effects were sustained at a 12 month follow-up (Sunderland 1992).

Treadmill training in stroke patients is gaining increased interest in physiotherapy. Preliminary studies show that early intense treadmill training in stroke patients improves gait velocity (Richards 1993) and measures of gait parameters (Laufer 2001). In fact, there is evidence that treadmill training with partial body weight support during the acute rehabilitation phase of stroke may be more effective with regards to restoration of gait ability and parameters than conventional gait training (Hesse 1994; Hesse 1995; Visitin 1998; Teixeira da Cunha Filho 2001). The method can be compared to both 'forced-use' and motor learning therapy since the patient is cued constantly by the moving belt during daily intense treatment sessions. It would be interesting to examine neuroplastic response to such a treatment.

In summary, there is a mounting body of evidence that indicates physiotherapeutic techniques ranging from PROM to intense motor skill training are able to directly impact cortical reorganization following stroke and that this modification is paralleled by functional recovery.

1.4.4 Functional Electrical Stimulation, Biofeedback, and Strength Training in Stroke

There is evidence that stroke patients despite having spasticity, can benefit from progressive resisted exercise. They experience a measurable improvement in strength without increases in spasticity (Engardt 1995; Teixeira-Salmela 1999). No study has shown that increased strength correlates with any neuroplastic change but one study showed that 60 to 90 minute physical training, three times per week, improved measures of overall gait speed 28% and stair climbing 37.4% in chronic stroke patients (Teixeira-Salmela 1999). The authors suggest that training specificity is required to improve functional tasks and their program incorporated actual task practice along with specific muscle strengthening. They state that since functional tasks require components of strength, balance and coordination, strength training alone is unlikely to improve functional ability. Patients in these studies had established isolated movement of the affected muscle groups before they began their training.

Studies examining the benefit of functional electrical stimulation (FES) in stroke have been equivocal. A meta-analysis of four studies revealed that FES improves strength but there is no evidence that the treatment improved function (Woods Duncan 1997). Another meta-analysis also supports that FES promotes the recovery of muscle strength after stroke and suggests that sustained improvement and functional change are promising as well (Glanz 1996). More recent examination of FES suggests upper extremity motor recovery after stroke is facilitated by FES especially during the rehabilitation stage when worn for long periods (up to 6 hours, 6 days per week), and when the stimulated movement is augmented by volitional activation of the target muscles (Faghri 1994; Francisco 1998; Chantraine 1999; Cauraugh 2000; Yu 2001). Two studies using biofeedback in combination with FES demonstrated positive effects on measures of upper extremity motor recovery (Francisco 1998; Cauraugh 2000). Hummelsheim and colleagues have found that once the stroke patient has regained functional movement, FES is not as beneficial as active hand strengthening in improving measures of hand function (Hummelsheim 1997). FES treatment does not appear to be as effective in chronic stroke deficit (Cauraugh 2000; Wang 2000). Studies examining the use of FES with or without treadmill training to restore walking in stroke patients are preliminary but promising (Hesse 1995; Wieler 1999). Presently, studies examining biofeedback have not shown a significant benefit (Moreland 1994). Task specificity and incorporation of movements into function were not employed so these results are not surprising. Researchers have yet to examine neuroplastic change during FES or biofeedback treatment.

1.5 Neuroscience Evidence-Based Practice

Physiotherapists have the skills and knowledge to influence and sculpt stroke recovery. (See Figure 1.1). They can employ rehabilitative intervention to influence the neuroplastic changes that lead to functional recovery. The efficacy of this intervention is determined by the skill of the therapist, the patient's motivation, his or her social support, and the pre and post-stroke environments. Neuroscience evidence-based practice is constantly evolving based on sound neuroscience research in humans and animals and probably incorporates the following:

- The patient, within the first few days post-stroke, may be vulnerable to a use-dependent increase in brain tissue loss especially when the infarct is severe and the therapy intense.

- In the early days and weeks post stroke, emphasis could be placed on bilateral and reciprocal activities. Passive range of motion (PROM) exercise of the affected limb likely has a direct effect on neuronal function even when the patient is unable to actively move the limbs. PROM and bilateral activity can be implemented to activate the cortex and other brain areas.

- Enrichment and exercise *pre-stroke* may have a neuroprotective effect. This is another sound reason for physiotherapists to encourage participation in an active lifestyle.

- Patients who have suffered a stroke should be in a stimulating, engaging environment with social support and physical activity to facilitate the recovery process.

- Patients in the early stages of recovery or with severe motor deficit may benefit from facilitory stimuli such as cutaneous and proprioceptive techniques such as brushing, tapping, weight bearing, and FES.

- Patients who begin to have voluntary motor activity may benefit from therapy focused on repetitive active movement of the target muscles integrated into functional tasks. Patients should engage in these activities frequently throughout the day, everyday.

- If possible, patient and caregivers should be instructed in homework that specifically targets the problematic movement. It appears that task repetition is required for neuroplasticity to occur.

- Some patients, who have consistent isolated movement, may benefit from progressive strength training and constraint-induced therapy.

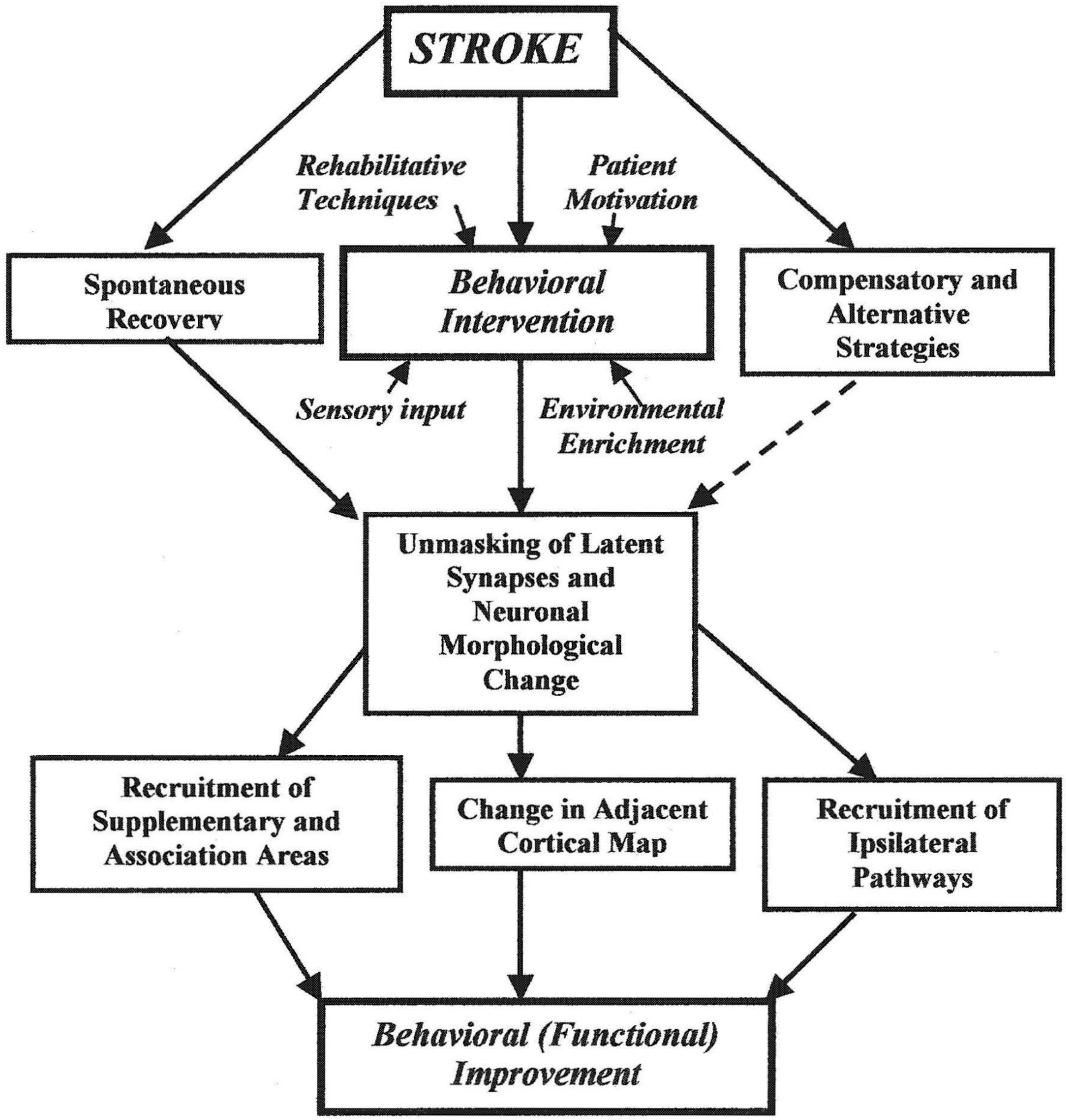

Figure 1.1: Physiotherapists can use behavioral interventions including rehabilitative strategies, sensory stimulation and environmental enrichment, to influence cortical reorganization after stroke. These interventions facilitate the recruitment of undamaged brain areas leading to functional recovery.

At this stage in our understanding of stroke recovery, there are certainly a number of unresolved questions that scientists and rehabilitation professionals may continue to contemplate.

1. Does compensatory use of the unaffected limb, likely resulting in synaptic morphological change in the intact hemisphere, occur at the expense of cortical plasticity in areas controlling the affected upper extremity?

2. In the first days or weeks after stroke in humans, is there a vulnerable period? How much intervention and what specific intervention, if any, should be employed during this period?

3. What specific rehabilitation practices should be undertaken to create an 'enriched environment' for stroke patients?

4. How much therapy is required to obtain the optimal neuroplastic effect? The evidence varies from 15 minutes twice per day to 6 hours per day. Is targeted home exercise able to induce a similar cortical change?

5. Do therapies such as strength training, FES, and biofeedback, (with adequate repetition and training specificity) induce neuroplastic changes?

6. What therapies are the most effective for moderate to severe hemiplegia and for those stroke patients with cognitive and visuospatial impairment?

7. At what point along the recovery continuum does the potential neuroplasticity end, if ever?

1.6 Conclusion

Research in animals has demonstrated that structural and functional neuroplasticity occurs in normal and damaged brains and is enhanced by enrichment and rehabilitative training. Using imaging technology, similar research is being undertaken in humans with encouraging results. The effectiveness of physiotherapy in management of stroke may be examined using standardized outcome measures as well as functional imaging techniques. It is important for physiotherapists to have a clear understanding of the science of neuroplasticity to provide rationale for specific physiotherapy practice in stroke.

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CHAPTER 2

Can Constraint-Induced Therapy Be Clinically Applied During the Rehabilitation Phase of Stroke? A Randomized Controlled Exploratory Study

2.1 Introduction

Stroke is one of the leading causes of adult disability in the United States and Canada (American Heart Association 2003, Health Canada 2000). The rate of hospitalizations for stroke in Canada has been increasing for the past 20 years and is projected to continue to increase with an aging population (Health Canada 2000). Weakness, or hemiparesis, of the body contralateral to the lesion is the most common deficit after stroke with over 50% of stroke patients suffering from residual motor impairment (Wilkinson 1997). Rehabilitation of the upper extremity is one of the foremost challenges facing rehabilitation professionals and it has been estimated that only 5% of stroke survivors who have complete paralysis regain functional use of the impaired arm and hand (Duncan 1999). Evidence suggests that focused, intensive rehabilitation of the upper extremity in both sub-acute and chronic phases of stroke improves functional outcomes and influences neuroplastic change in the recovering brain (see Ploughman 2002 for review). Rehabilitative therapy involving frequent repetitive training of the hemiplegic upper extremity increases arm and hand movement (Sunderland 1992; Butefisch 1995; Feys 1998), increases cortical motor output to the involved hand (Liepert

2000; Nelles 2001) and increases motor evoked potentials (Hummelsheim 1995). These findings are paralleled in animal studies where it has been shown that skilled reach training in a rat model of stroke improves motor recovery and enhances dendritic growth in the intact hemisphere (Biernaskie 2001). In addition to this, it has been demonstrated that in monkeys with focal ischemic infarct, retention of hand area in the primary motor cortex requires intense rehabilitation of the impaired hand (Nudo 1996; Nudo 1996; Friel 2000). Without specific arm and hand training after stroke, at least in this primate stroke model, the cortical area dedicated to the impaired hand is taken over by neighbouring proximal limb representations.

Taub has proposed that both monkeys with somatosensory deafferentation and humans with stroke, develop 'learned-nonuse' of the involved upper extremity. He has devised a program of restraint of the intact limb using a hand splint and sling for 90% of waking hours combined with 6 hours per day of intensive training or 'shaping therapy' months and years after stroke with positive results (Taub 1993). Others have demonstrated that in chronic stroke, this constraint of the uninvolved upper extremity known as Constraint-Induced Movement Therapy or CIMT applied for two weeks, improves motor recovery of the impaired upper extremity (Kunkel 1999; Miltner 1999; van der Lee 1999). The patients recruited for these studies were typically one to 18 years post-stroke, relatively high functioning with at least 10 degrees of active metacarpalphalangeal joint and interphalangeal joint extension and at least 20 degrees of active wrist extension of the impaired upper extremity and were independent ambulators. The study by van der Lee (1999) was the largest with 66 subjects having dominant side hemiplegia however the other studies were smaller ranging from 5 to 15 subjects.

Brain imaging technology in stroke patients has shown that CIMT increases cortical representation area of the affected hand (Liepert 2000), increases neuronal excitability of the damaged hemisphere (Liepert 1998) and increases activation of the undamaged cortex (Kopp 1999). However, some studies in rats suggest that restraint of the unaffected forelimb soon after stroke may exaggerate neuronal injury (Kozlowski 1996) possibly via a glutamate mediated hyperexcitability (Humm 1998; Humm 1999) or by reducing adaptive remodeling (Jones 1994). In contrast, it has been reported that forced use in rats directly following ischemic brain injury encourages neural restructuring without detrimental effects (Bury 2000).

In CIMT studies, it is not clear which aspect of the treatment regime influences the positive outcomes observed, the 6 hours per day of intense therapy or the constraint since it is likely that both can have beneficial effects. Practically, it is difficult to provide 6 hours of one-on-one therapy. Can constraint alone impact outcome? A recent study indicates patients long after stroke also benefit from constraint paired with only 3 hours of shaping therapy although the benefit is less than that with 6 hours (Sterr 2002). In that study, the standard CIMT inclusion criteria and treatment protocols were used; however, the 3 hour per day training group (n=8) were, on average, almost 20 years older than the 6 hour per day group (n=7). They modified the constraint for some subjects with balance deficits by using a half-glove on the less involved side. In a randomized controlled acute rehabilitation CIMT study by Dromerick et al. (Dromerick 2000), a mitten constraint was paired with 2 hours per day of upper extremity therapy for two weeks with positive results (n=20). Subjects wore a padded mitten rather than a splint and sling. Another feasibility study (n=6) suggests that CIMT can be successfully administered on an outpatient basis for chronic stroke patients with only one half hour of physiotherapy and occupational therapy three times per week for 10 weeks (Page 2001).

Liepert has shown that just constraint, in addition to conventional therapy, applied 4-8 weeks after stroke, enhances motor cortex excitability and improves motor performance over conventional therapy alone (Liepert 2000). Wolf demonstrated that two weeks of forced use of the impaired limb without additional therapy in patients with chronic stroke and head injury, improved measures of arm function which were maintained at one year follow-up (Wolf 1989). It has not been demonstrated if constraint of the affected upper limb without the addition of shaping therapy can be successfully incorporated into an acute rehabilitation setting and if, indeed, there is any benefit in this model.

Although one study suggests CIMT can be used for stroke patients in active rehabilitation programs (Dromerick 2000), it is not clear if constraint, because of its intensity, may worsen hemiplegic shoulder pain, a common complication post-stroke. Is sound limb constraint safe in acute stroke rehabilitation settings? Does the technique, because the sound arm is restrained, increase dependence on staff or place the patient at risk for falls? If patients with stroke develop learned nonuse, then constraint of the sound arm during the active rehabilitation phase in functional activities should prevent such a phenomenon. It is also unclear if compliance and outcomes are influenced by the side of the lesion or hand dominance. Patients, at an early stage of stroke rehabilitation, struggle to carry out activities of daily living. Can the constraint compromise an already stressed individual? In previous CIMT studies, subjects with chronic stroke volunteered for the studies and were compliant to the treatment protocol. This degree of motivation and compliance may be different and difficult to achieve in the actual rehabilitation setting. On the other hand, stroke patients spend much of the day outside of active therapy and CIMT may be a strategy to take advantage of otherwise underutilized time. Page and colleagues (Page 2001) report that preliminary findings from a survey of therapists and stroke patients examining opinions about CIMT, suggest that the majority of stroke patients would not wish to participate in two weeks of CIMT and were unlikely to be compliant to the treatment. The majority of therapists reported they did not have the resources to apply the intense shaping therapy component of the CIMT protocol.

At this stage in the development of CIMT, it is important to assess the treatment in active rehabilitation for rehabilitation specialists to evaluate its usefulness in the setting where it is actually applied. For the purpose of this study, the term Constraint-Induced Therapy or CIT will be used to differentiate constraint *without* shaping therapy from CIMT. Since this method of CIT has never been examined in this context, it is important to explore the potential benefits or difficulties with such a program.

The objectives of this exploratory study were:

1) to determine if CIT, without additional therapy, integrated into the acute rehabilitation service improves upper extremity functional outcome,
2) to determine if CIT has any negative effects 'i.e. increased hemiplegic shoulder pain, falls, increased dependence on staff',
3) to identify subgroups of patients who may benefit more from CIT 'i.e. patients with right or left hemiplegia',

4) to investigate if clients would be compliant with CIT since it would be performed with minimal supervision by the therapist.

We hypothesized that CIT, without many hours per day of 'shaping' therapy, combined with conventional rehabilitation, applied throughout the acute rehabilitation period, would lead to improved upper extremity outcomes over conventional therapy alone.

2.2 Subjects

All patients admitted to multidisciplinary rehabilitation services from June 2001 to February 2003 were screened for entry into the study. The criteria for inclusion into the study were:

1) first ischemic or hemorrhagic stroke confirmed both clinically and with CT scan or MRI,
2) receiving active physical rehabilitation services at least twice per week as an inpatient or outpatient,
3) no more that 16 weeks post stroke at time of inclusion,
4) motor control of the upper extremity of more than stage 2 on the Chedoke-McMaster Impairment Inventory (CMII) for the arm and hand but not more than stage 6.

Patients were excluded if they scored 25 or lower on the Folstein Mini-Mental Status Exam (Molloy 1998), had a history of upper extremity injury or pain, had severe sensory or language loss or hemi-neglect or were more than 75 years of age.

Of the 30 subjects who fit the criteria, three did not provide consent. Some subjects were admitted to the study up to 4 weeks after beginning rehabilitation until they achieved adequate upper extremity function (all elements of level 2 on the CMII of the arm and hand). Three subjects, who had initially provided consent, discontinued their involvement in the study during the last stages of their initial assessment processes; one 69 year old female was in the control group and two males, ages 64 and 68, were from the CIT group. These three subjects were an average of 49.3 days post-stroke. All reported they did not wish any further stress during their recovery. One other male subject from the CIT group was unable to continue due to an episode of septic arthritis of the knee requiring a transfer to an acute facility. Of the remaining 23 subjects, 10 were in the CIT group and 13 in the control group. Subjects were discharged from the inpatient units when they had reached the goals set by the team. The length of stay varied among subjects. Outpatients were discharged from the study if they were reduced to one physiotherapy treatment per week for more than two weeks.

2.3 Study Design/Methods

The study took place within a tertiary rehabilitation hospital with 36 mixed rehabilitation beds serving an urban and rural population of 500,000. The hospital also has a well-developed multidisciplinary outpatient program providing active therapy and follow-up for stroke patients discharged from both acute care and rehabilitation beds.

Patients were screened by review of the health record and discussion with the attending physiotherapist. Patients who met the inclusion criteria were admitted to the study and informed consent was obtained. Subjects were randomly assigned, using random number generation, to either conventional rehabilitation or conventional rehabilitation plus constraint. Conventional treatment for the upper extremity involved facilitation of the trunk and proximal motor control progressing to supported movement training of the limbs, then skilled task training. Subjects also received strength and endurance training, functional electrical stimulation, gait training, and education as appropriate. Constraint involved wearing a long, thick, knitted acrylic thumbless mitten extending from the fingertips to just below the elbow, on the uninvolved hand (Figure 2.1). The protocol of wear was progressive, beginning one hour per day increasing to 6 hours per day by week two of rehabilitation and continuing for the remaining rehabilitation period. We developed a thumbless mitten that discourages use of the uninvolved arm and hand but allows for bilateral activities and use of the sound arm to stabilize when walking.

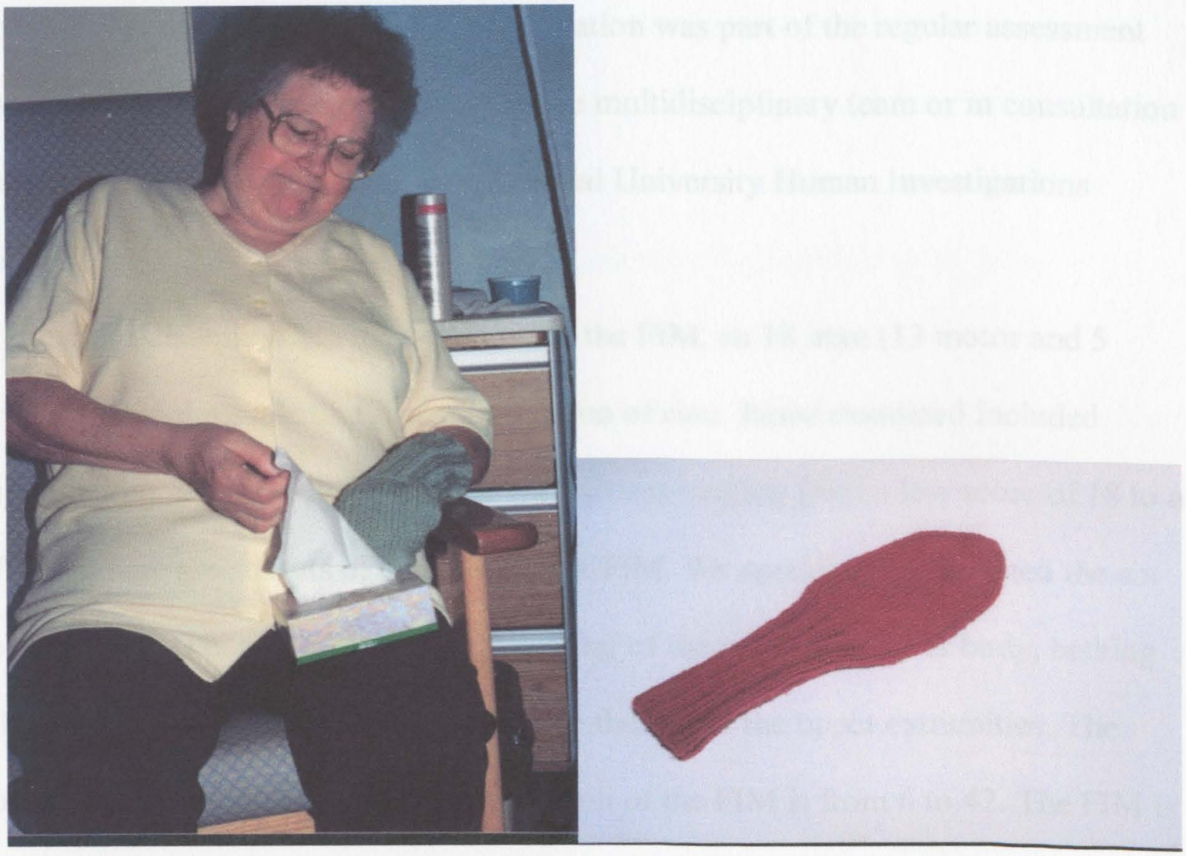

Figure 2.1: Subject with right hemiplegia wearing constraint mitten on the left hand (left) and typical constraint mitten (right)

2.4 Evaluation

On entry to the study, patient characteristics such as age, gender, lesion type, side of paresis, hand dominance, medications and co-morbid health conditions were recorded. The physical outcome measures were administered on day one and two after entry to the study and during the last two days of active rehabilitation. The treatment condition was concealed during the initial clinical evaluation performed by physiotherapists. Evaluation was performed by the attending physiotherapists on discharge, with the exception of the Action Research Arm Test (ARAT), which was performed by the investigator. The

Functional Independence Measure (FIM) evaluation was part of the regular assessment process on admission and was performed by the multidisciplinary team or in consultation with them. The study was approved by Memorial University Human Investigations Committee.

Level of disability was measured using the FIM, an 18 item (13 motor and 5 cognitive) seven-point scale that measures burden of care. Items examined included dressing, toileting, walking, and language with scores ranging from a low score of 18 to a high of 126. There are subsets of data within the FIM. We specifically examined the six items of Self-Care (i.e. eating, grooming, dressing of the upper and lower body, bathing and toileting), which would more likely involve the use of the upper extremities. The range of potential scores for the Self-Care portion of the FIM is from 6 to 42. The FIM is widely used and its validity and reliability are well documented (Segal 1994; Kidd 1995)

Impairment was measured using the Chedoke-McMaster Impairment Inventory (CMII) for arm, hand, leg, foot, postural control, and shoulder pain. The CMII is a seven-point scale ranging from one to seven representing seven stages of motor recovery with the exception of shoulder pain, which is a severity scale. At level 2, the subject is able to perform facilitated reflexive movements and a level 7 is able to perform movements of all joints out of synergistic patterns in a specified time. Its validity and reliability are well documented and it is widely used in clinical settings (Gowland 1995).

Arm and hand dexterity was measured using the Action Research Arm Test (ARAT). The ARAT consists of 19 tasks involving moving blocks, tubes, and spheres and pouring water. It uses a four-point scale, ranging from 0, indicating inability to perform any component of the task, to 3, in which the subject can perform the entire task within the specified time limit. This measurement tool has been shown to have good inter-rater and intra-rater reliability and validity (Hsieh 1998; van der Lee 2001). The ARAT testing apparatus was fabricated at Memorial University using specifications outlined in Carroll (Carroll 1965) and scored using time limits determined from performance times of healthy elderly subjects (van der Lee 2001).

Grip strength was measured using the Jamar Hand Dynamometer. Grip strength was also measured weekly by the attending therapist for the last 15 subjects in the study. Grip strength evaluation, using the Jamar Hand Dynamometer, has been shown to have good inter-rater reliability (Bohannon 1987; Riddle 1989) and accurately measures recovery after stroke (Sunderland 1989). The Jamar Hand Dynamometer was calibrated every 8 months. Consensus was reached among therapist raters, using documented guidelines (Mathiowetz 1984; Gage Richards 1996) on positioning of the subject and verbal directions. Subjects were seated without back support with the affected arm in neutral shoulder and forearm position with the elbow flexed at 90 degrees, if the subject was able. Subjects were instructed not to push against the thigh and the best score out of two attempts was recorded.

Before the study began, rehabilitation personnel were trained on the FIM and received 80% or better on the case study examination. The initial six physiotherapists involved received video training for the Chedoke-McMaster and ARAT measures and achieved 99% inter-rater reliability. All other therapist raters received video training and the instruction manual.

The principal investigator and/or the research assistant met with all subjects weekly to discuss and document rehabilitation progress, pain or discomfort, and compliance issues for subjects in the constraint group. Hours of mitten wearing per day were recorded weekly at these sessions and confirmed by family, caregivers and attending physiotherapists. Minutes of physiotherapy and occupational therapy were recorded weekly from therapists' schedule logs and verified with attending therapists.

2.5 Statistical Procedures

Data were analyzed using Statview (SAS Institute 1998). Descriptive statistics, chi-square tests and two-tailed independent t-tests were used to analyze characteristics of the control and treatment groups. Paired t-tests examined the improvement from admission to discharge for the outcomes measured. Simple and stepwise regression were used to study the effect of continuous and nominal variables on the outcome measures and correlation analysis examined the relationship between compliance to the constraint and recovery. Multivariate ANOVA, ANOVA and Scheffé's F procedure for post-hoc comparisons, determined the differences between outcome measures in control and treatment groups and subgroups. Subgroup analysis was only performed on those groups with significant differences or significant interaction effects. Measures of recovery were tested for normal distribution and significance level was set at $p=0.05$ for all statistical analyses.

2.6 Results

2.6.1 Subject Characteristics

Table 2.1 summarizes admission and rehabilitation characteristics of the CIT (treatment) and control groups. There were no significant differences in admission measures of impairment and disability, age, gender, admission status, stroke onset to study entry interval (OSI), stroke onset to rehabilitation interval (ORI), days in study, therapy time, type of stroke, cognition or side of hemiplegia. All subjects were right-handed.

Table 2.1: Subject Characteristics

Criteria	Control Mean ±SD	Treatment Mean ±SD	P-Value
Age	61.62 ±5.68	57.80 ±10.65	0.281
OSI	38.08 ±23.40	36.00 ±22.50	0.832
ORI	26.31 ±19.96	15.70 ±8.30	0.131
Days in Study	67.39 ±29.97	58.20 ±23.69	0.435
Therapy Time (hrs)	58.90 ±41.45	61.74 ±23.68	0.849
Gender	5 F/ 8 M	3 F/ 7 M	0.673
Admission Status	8 inpt/ 5 outpt	7 inpt/ 3 outpt	0.673
Side of Hemiplegia	9 L/ 4 R	4 L/ 6 R	0.161
MMSE Score	29.00 ±1.29	29.33 ±0.75	0.508
Admission Arm Score	2.77 ±0.93	3.00 ±0.94	0.563
Admission Hand Score	2.54 ±0.88	3.10 ±0.88	0.143
Admission Leg Score	4.39 ±1.77	4.10 ±0.99	0.652
Admission Foot Score	4.00 ±1.96	2.90 ±1.79	0.181
Admission Shoulder Pain	4.69 ±1.32	5.30 ±0.82	0.216
Admission Postural Control	4.92 ±1.11	4.30 ±0.95	0.172
Admission Grip Strength (kg)	3.14 ±4.70	4.95 ±6.22	0.436
Admission ARAT	16.00 ±13.64	20.70 ±15.49	0.448
Admission FIM	99.23 ±21.41	100.20 ±19.79	0.913
Admission FIM Self-Care	29.62 ±8.98	30.40 ±8.34	0.833

OSI stroke onset to study entry interval

ORI stroke onset to rehabilitation interval

F female, M male

L left, R right

Figure 2.2 depicts the location of the stroke in both the CIT and control groups. Only one subject suffered a hemorrhagic stroke (of the thalamus) while the remaining subjects experienced ischemic stroke. The subject with the hemorrhagic stroke was randomly assigned to the CIT group. Subcortical lesions were the most common stroke in the CIT group and cortical lesions were the most common type in the control subjects. Overall, 61% of the study subjects had either subcortical lesion only or subcortical lesion with cortical involvement, 26% had only cortical stroke and 8.6% had brainstem stroke.

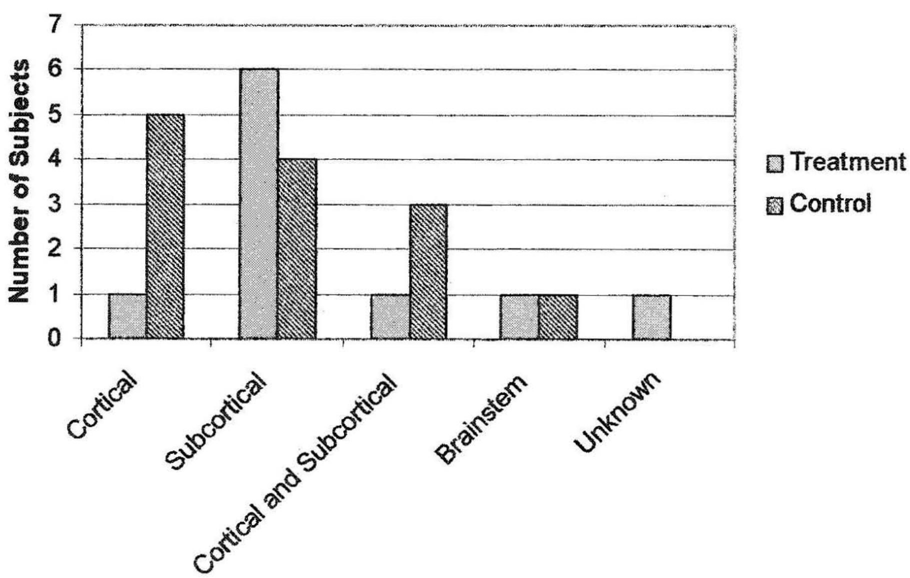

Figure 2.2: Prevalence of stroke types in each group

Figure 2.3 shows the number of subjects in each of the age categories. There was less variability in age in the control group with most subjects being between the ages of 55 and 64. The youngest subject was 37 years of age in the CIT group.

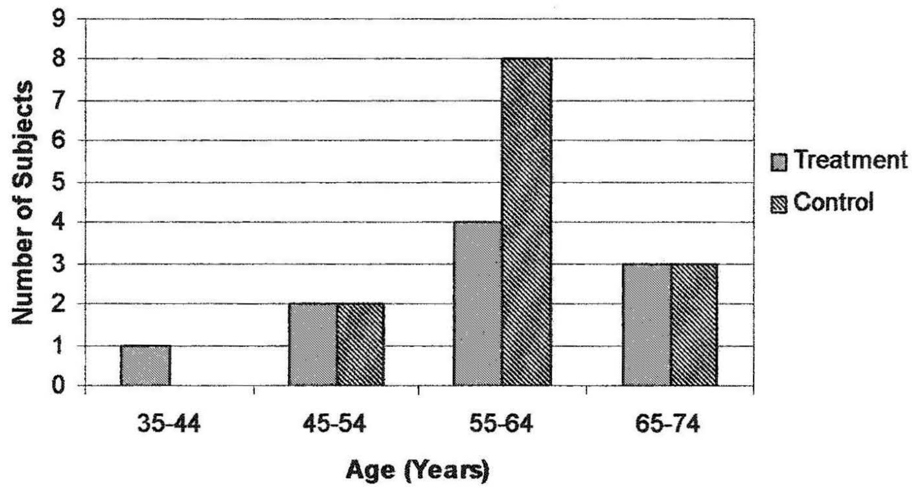

Figure 2.3: Number of subjects in age categories for both groups

Figure 2.4 depicts the interval, in days, between stroke onset and admission to rehabilitation services. Subjects in the treatment group tended to have earlier admission to rehabilitation, however, this did not reach significance.

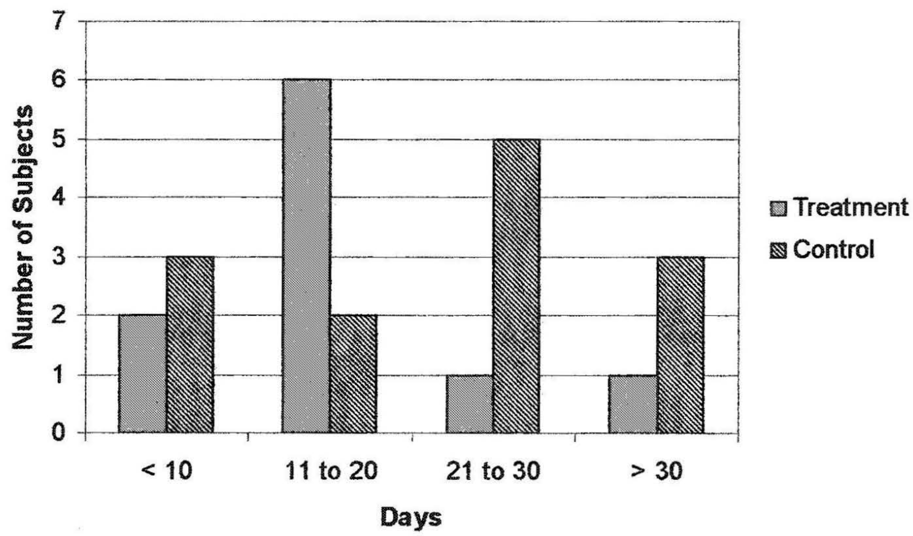

Figure 2.4: Number of subjects in categories of Stroke Onset to Rehabilitation Interval (ORI) in days

Figure 2.5 depicts the interval in days between stroke onset and admission to the study. Most subjects in both groups were between 20 and 39 days post-stroke. The most acute stroke patient was 5 days post-stroke in the control group. There were no subjects more than 100 days post-stroke when entering the study. Some subjects were delayed in entering the study until they had scored above 2 on the CMII for the arm and hand. On average, the difference between admission to rehabilitation and admission to the study was 11.8 days for control subjects and 21 days for CIT subjects.

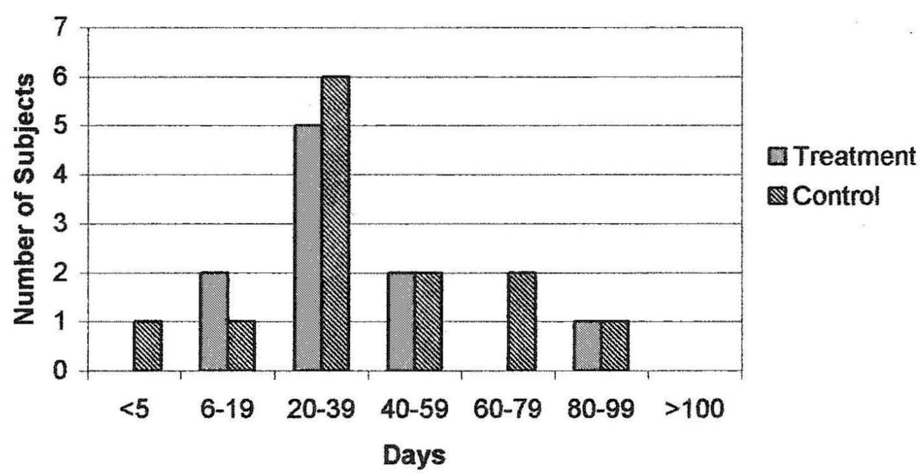

Figure 2.5: Number of subjects in categories of Stroke Onset to Study Entry Interval (OSI) in days

Figure 2.6 shows the number of subjects in each of the Therapy Time categories. Therapy Time consisted of total hours of physiotherapy and occupational therapy during the study period. There was no significant difference in average therapy time between the groups however more subjects in the control group received less than 51 hours of physiotherapy and occupational therapy.

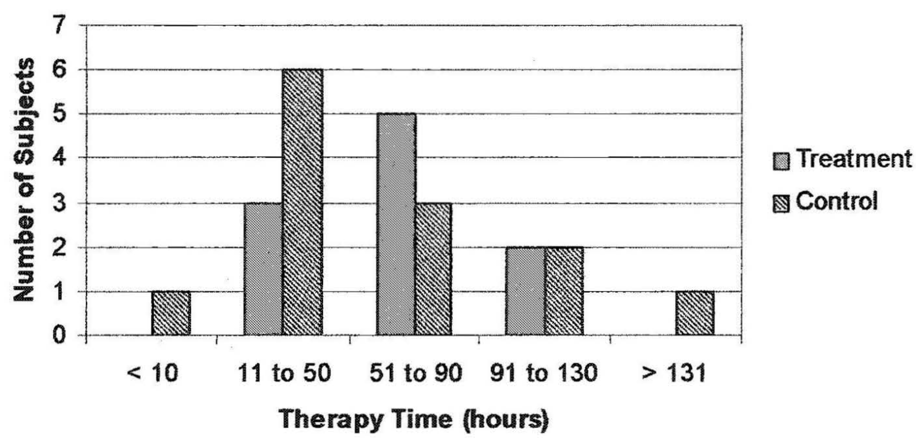

Figure 2.6: Number of subjects in Therapy Time categories in hours

Table 2.2 shows the average admission values and characteristics of the male and female subjects. There was no significant difference in therapy time, age, admission status, side of hemiplegia, admission CMII arm score or admission FIM score. There was a significant difference in the acuity of male and female subjects with females being an average of 23 days post-stroke and the males 45 days post-stroke on admission to the study. There were three times as many subjects with left hemiplegia in the male group. Seven of these male left hemiplegic subjects were randomly assigned to the control group.

Table 2.2: Admission Characteristics of Males and Females

Average	Males Mean ±SD	Females Mean ±SD	P- value
Age	58.67 ±9.70	62.38 ±3.82	0.315
OSI	44.53 ±23.35	23.38 ±13.02	0.028
ORI	25.93 ±18.22	13.75 ±9.38	0.093
Therapy time (hrs)	66.78 ±27.99	47.66 ±36.17	0.209
Side of Hemiplegia	10 L/ 5 R	3 L/ 5 R	0.179
MMSE Score	29.14 ±1.13	29.13 ±1.17	0.973
Status	10 inpt/ 5 outpt	5 inpt/ 3 outpt	0.842
Type of Stroke	*	*	0.519
Admission ARAT	18.8 ±15.05	16.63 ±13.73	0.737
Admission Arm	2.87 ±0.91	2.88 ±0.99	0.984
Admission FIM	98.2 ±22.64	102.38 ±15.86	0.649

* Males- 2 Brainstem, 4 Cortical, 3 Cort/Subcort, 6 Subcortical
Females- 2 Cortical, 1 Cort/Subcort, 4 Subcortical, 1 unknown

Table 2.3 shows the average admission values and characteristics of subjects with right and left hemiplegia. There were no significant differences between these measures and characteristics although subjects with right hemiplegia scored lower on the ARAT on admission than subjects with left hemiplegia.

Table 2.3: Admission Characteristics of Subjects with Right and Left Hemiplegia

Average	Right Mean ±SD	Left Mean ±SD	P- Value
Age	64.6 ±11.0	62.46 ±5.75	0.784
OSI	36 ±25.08	38.08 ±21.35	0.832
ORI	21.2 ±15.02	22.1 ±18.26	0.903
Therapy Time (hrs)	63.3 ±22.95	57.69 ±41.62	0.706
Gender	5 F/ 5 M	3 F/ 10 M	0.179
MMSE Score	29.3 ±1.21	29.0 ±1.06	0.547
Status	8 inpt/ 2 outpt	7 inpt/ 6 outpt	0.192
Type of Stroke	*	*	0.201
Admission ARAT	13.7 ±14.71	21.39 ±13.65	0.21
Admission Arm	2.9 ±0.88	2.85 ±0.99	0.893
Admission FIM	103.4 ±15.43	96.78 ±23.52	0.449

* Right- 1 Brainstem, 1 Cortical, 1 Cort/Subcort, 7 Subcortical
Left- 1 Brainstem, 5 Cortical, 3 Cort/Subcort, 3 Subcortical, 1 unknown

Table 2.4 shows the results of unpaired t-tests between male and female subjects and right and left hemiparetic subjects in the control group. There was a significant difference in both stroke onset to rehabilitation (ORI) and stroke onset to study interval (OSI) between females and males in the control group. Female subjects were an average 11.6 (±7.1) days ORI and 18.8 (±10.6) days OSI while male subjects entered rehabilitation an average 35.5 (±20.1) days post-stroke and entered the study an average 50.1 (±21.1) days post-stroke. Although not significant, subjects with right hemiplegia in the control group had an average score of 5.5(±1.67) on the ARAT compared to subjects with left hemiplegia who scored on average 20.67 (±14.1). Due to small subgroup sizes, analysis of differences between the types of stroke for these subgroups was not possible.

Results of unpaired t-tests between both male and female subjects and subjects with right or left hemiplegia in the *treatment* group showed no significant difference between variables (data not shown).

Table 2.4: Comparison of *Control* Subgroup Characteristics with P-values

Average	Male vs. Female	Right vs. Left
Age	0.712	0.513
OSI	0.011	0.446
ORI	0.028	0.905
Therapy Time	0.224	0.608
Side of Hemiplegia	0.071	N/A
Gender	N/A	0.071
MMSE Score	0.678	1
Status	0.207	0.506
Type of Stroke	*	*
Admission ARAT	0.969	0.06
Admission Arm	0.502	0.509
Admission FIM	0.673	0.835

* Male-1 Brainstem, 3 Cortical, 2 Cort/Subcort, 2 Subcortical
Female- 2 Cortical, 1 Cort/Subcort, 2 Subcortical
Right- 1 Cortical, 3 Subcortical
Left- 1 Brainstem, 4 Cortical, 3 Cort/Subcort, 1 Subcortical

2.6.2 Compliance with Constraint

None of the subjects in the treatment group, despite encouragement, were able to achieve 6 hours of constraint wearing per day. The average amount of constraint time per day was 2.7 hours (±2.0). However, five of 10 CIT subjects were able to tolerate the constraint 3 to 5.5 hours per day. Figure 2.6 depicts the number of subjects in the CIT group in each compliance category. Only one subject did not wear the constraint mitten at all. This subject was a 57 year old male with the lowest FIM score of 60 in the CIT group indicating severe disability.

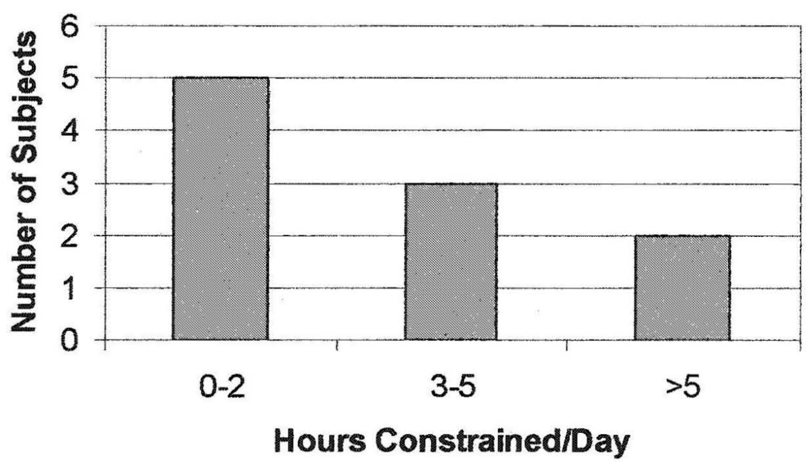

Figure 2.7: Number of subjects in the treatment group in each of the compliance categories in hours of constraint per day

Stepwise regression was performed, using a model which included all admission and rehabilitation variables of the CIT group subjects, to identify the relationship of the variables to compliance. Compliance (hours of constraint wearing per day) was not related to inpatient or outpatient status, age, side of hemiplegia, type of stroke, therapy time, ORI or OSI, or level of physical impairment on admission. There were no significant differences in average compliance between gender groups; however, male subjects wore the mitten constraint an average of 3.2 hours daily whereas female subjects were constrained on average, 1.5 hours per day. Subjects with right hemiplegia wore the mitten constraint an average of 3.4 hours per day while subjects with left hemiplegia wore the constraint for 1.6 hours per day.

Compliance (hours of wear per day) was significantly related to MMSE score on admission (R=0.902, p=0.0008). Subjects scoring lower on the MMSE wore the mitten constraint fewer hours per day (Figure 2.8).

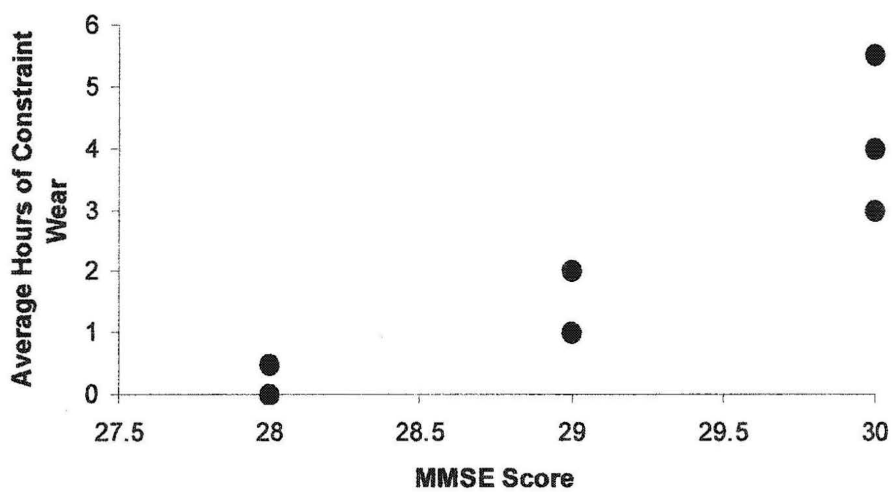

Figure 2.8: Scattergram of compliance to constraint versus admission MMSE score

Although not significant, there was a trend toward a positive correlation between admission FIM score and compliance (R=0.534, p=0.115), which appeared to suggest that subjects who entered the study with less disability tended to have better compliance to the mitten constraint. Figure 2.9 depicts the relationship between compliance to the mitten constraint (in average hours of constraint wear) and admission FIM score for each of the 10 subjects in the constraint group. The single subject who was unable to wear the constraint mitten at all had the lowest FIM score and MMSE score in the CIT group.

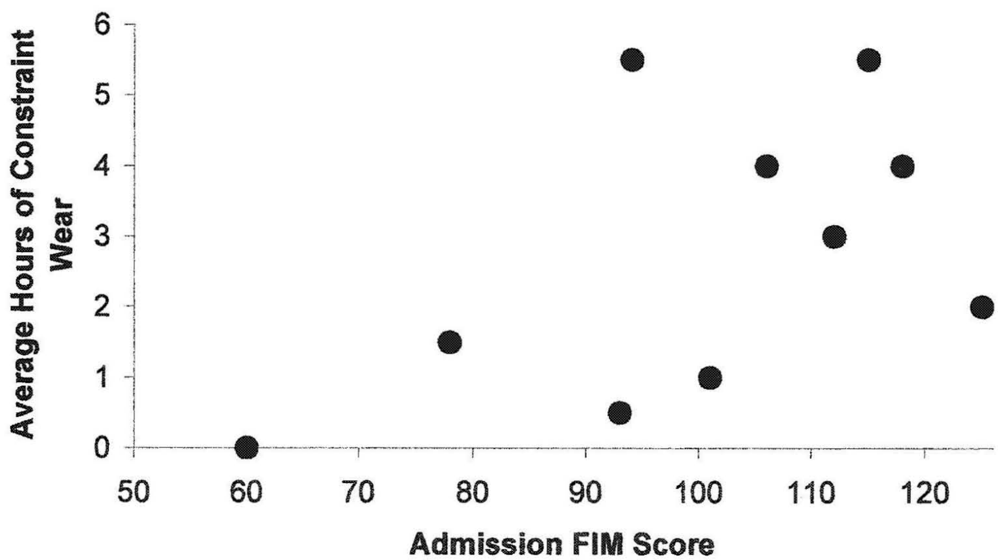

Figure 2.9: Scattergram of compliance to constraint versus admission FIM score

Table 2.5 shows the correlation between compliance to the mitten constraint and recovery (change in outcome measure score). Compliance to the mitten constraint was not correlated with change in the CMII stages of recovery, grip strength recovery, ARAT recovery or improvement of level of disability measured by the FIM in the CIT group.

Table 2.5: Correlation Between Compliance and Recovery

	Correlation	P- Value
Compliance, Arm Recovery	-0.027	0.943
Compliance, Hand Recovery	-0.171	0.647
Compliance, Shoulder Pain Recovery	0.109	0.772
Compliance, Postural Control Recovery	-0.234	0.527
Compliance, Grip Recovery	-0.105	0.781
Compliance, ARAT Recovery	0.345	0.341
Compliance, FIM Recovery	-0.431	0.223
Compliance, FIM Self-Care Recovery	-0.394	0.223

In summary, MMSE score was strongly related to hours of constraint wear. Subjects with lower scores wore the constraint mitten the least. Compliance to constraint was not related to other subject characteristics or the physical impairment level on admission except that there was a trend suggesting that the least disabled subjects (measured by FIM) were able to tolerate the most hours of constraint time. Male subjects tended to wear the mitten constraint about twice as much as female subjects. The only subject who was not able to wear the mitten at all scored the lowest on both the FIM and the MMSE in the CIT group. Hours of constraint wearing were not related to degree of improvement on any of the outcomes measured.

2.6.3 Recovery From Stroke

Figure 2.10 shows the average admission and discharge CMII scores for all the subjects. Subjects generally showed significant improvement ($p<0.001$) between admission and discharge on the CMII measures of arm, hand, leg, foot, and postural control. There was no significant difference in shoulder pain measures between admission and discharge.

On admission to the study, 82.6% of subjects had severe arm hemiparesis, scoring between 2 and 3 on the CMII for the arm, and 17.4% had moderate hemiparesis, scoring between 4 and 5. On discharge, only 8.7% made a full recovery, 8.7% had mild residual paresis of the arm while 82.6% continued to have moderate or severe arm hemiplegia. The lower extremity was less impaired with 30.4% of subjects having severe leg hemiparesis on admission, 47.8% having moderate hemiparesis and 21.9 % having either mild or no leg paresis. On discharge, 13% of subjects had complete recovery of the leg, 30.4% had mild residual hemiparesis, 43.5% had moderate hemiparesis and 13% continued to have severe lower extremity hemiparesis.

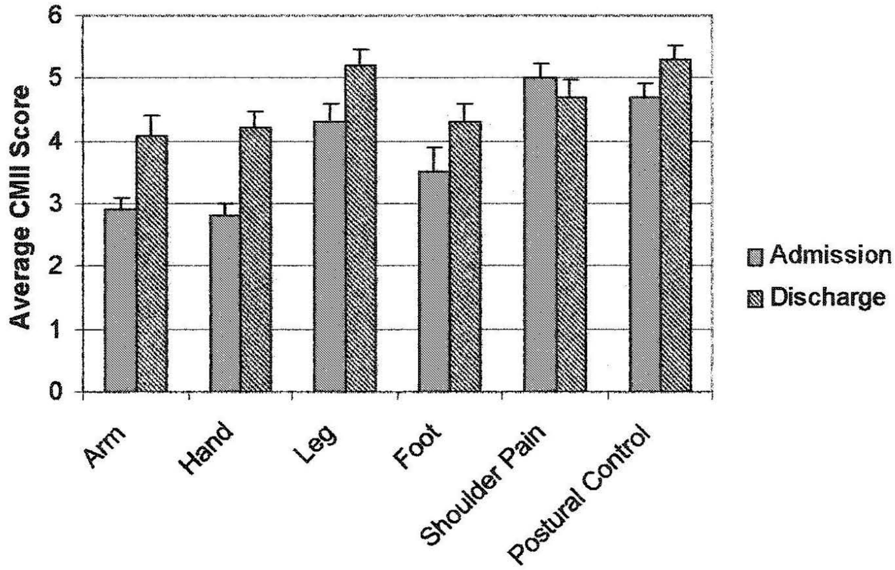

Figure 2.10: Average CMII scores on admission and discharge for all subjects (mean ±SE)

Figure 2.11 shows the average admission and discharge scores for the ARAT and the average grip strength measured in kilograms. There was a significant difference in mean values for both measures between admission and discharge ($p < 0.001$). On admission to the study, 56.5% of subjects scored less than 20 out of 57 on the ARAT suggesting clinically severe hemiparesis of the arm and hand while 30.4% scored between 20 and 34 indicating moderately severe hemiplegia. On discharge, 8.7% of subjects had full recovery scoring 55-57 on the ARAT, 17.4% had mild residual hemiparesis, 26.1% had moderate hemiparesis, 30.4% were moderately severe and 17.4% continued to have severe upper extremity hemiparesis.

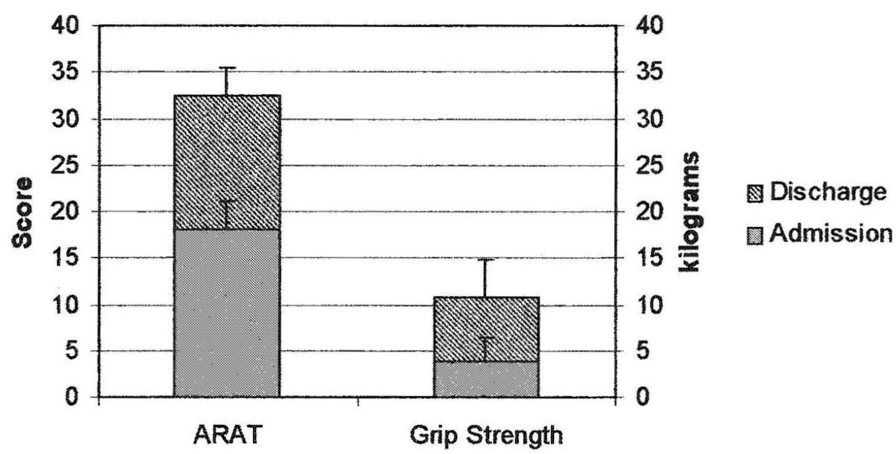

Figure 2.11: Average ARAT score and grip strength in kg on admission and discharge for all subjects (mean ±SE)

Figure 2.12 shows the average FIM and FIM Self-Care scores at admission and discharge for all subjects. Subjects had a significant improvement in level of independence on both measures ($p < 0.001$). On admission to the study 39.1% of subjects were independent with activities of daily living (ADL) with adaptations, 30.4% required supervision, 21.7% required minimal assistance for ADL, while 8.7% required either moderate or complete assistance for ADL. On discharge, 13% were completely independent, 73.9% were independent with adaptations and 13.1% required only supervision or minimal assistance of caregivers to carry out ADL.

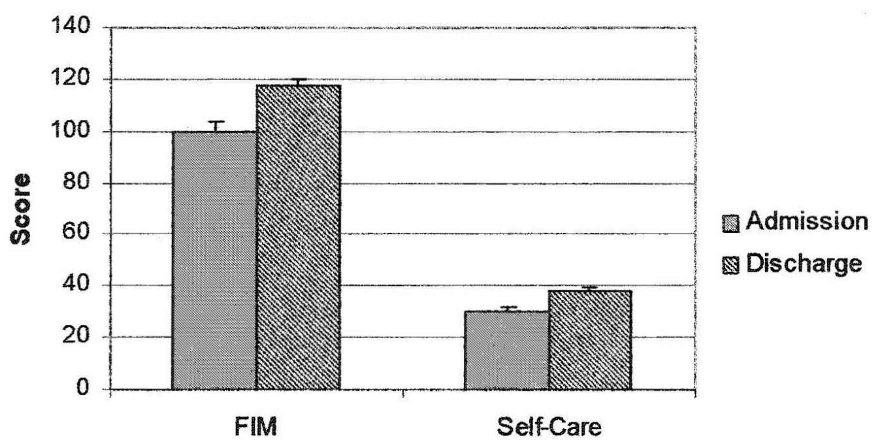

Figure 2.12: Average FIM and FIM Self-Care score on admission and discharge for all subjects (mean ±SE)

Figure 2.13 shows the average CMII score change (improvement in score from admission to discharge) for both the CIT treatment group and control subjects. There was a trend toward better recovery of function in the CIT group measured by the CMII scores of arm, leg, foot, and postural control although postural control was the only measure that reached significance. Subjects in the CIT group experienced a 53% improvement in arm function while the control group subjects had a 33% improvement. There was no difference in hand recovery between groups.

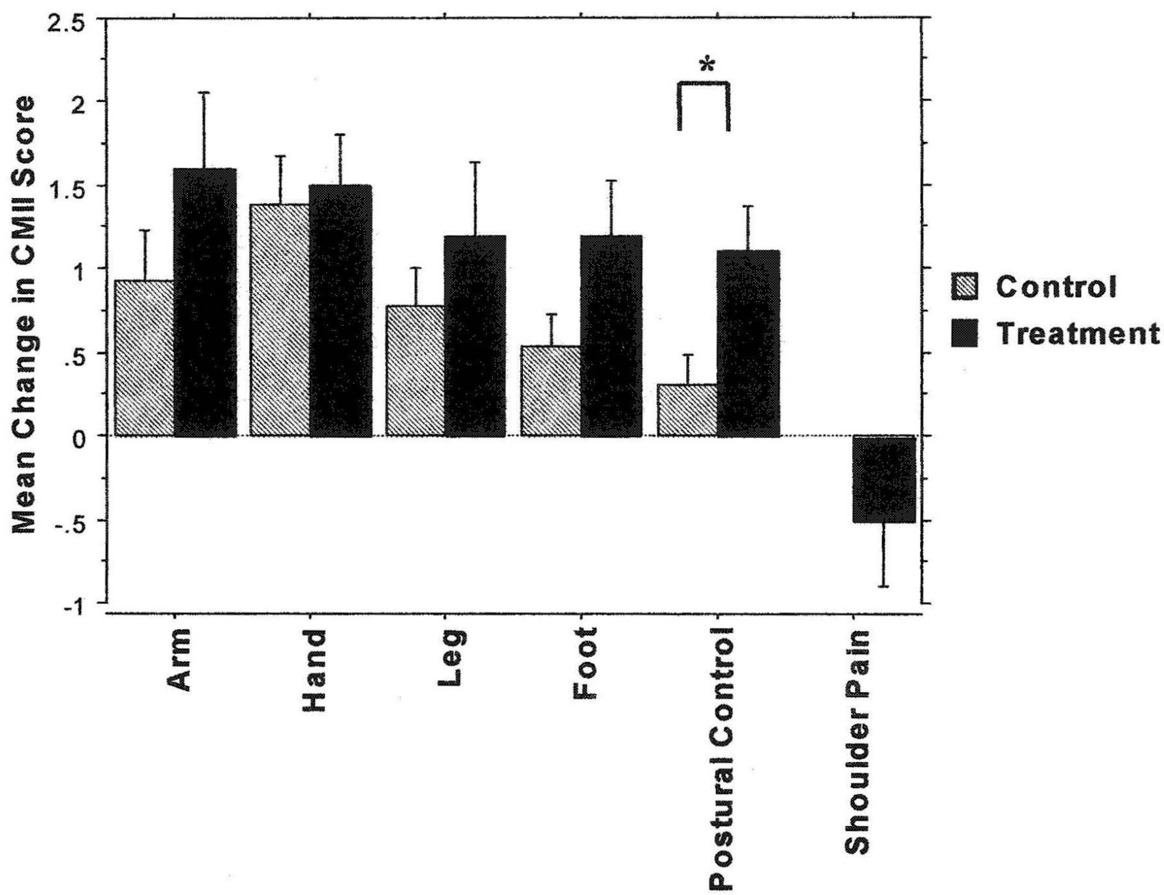

Figure 2.13: Mean change of Chedoke-McMaster Impairment Inventory score (mean ± SE); Control versus treatment group (* p= 0.019).

Although not significant, there was a trend toward worsening shoulder pain score in the CIT group compared to controls. The data indicate that 14 of 23 subjects or 61% had shoulder pain on admission to the study (scoring 5 or less on CMII). Five of the subjects with shoulder pain were in the CIT group and nine in the control. Twelve of the 14 subjects with shoulder pain had mild pain (scoring 4 or 5 on the CMII). On discharge, 15 subjects had shoulder pain, seven from the CIT group and eight from the control group. Overall, of the five subjects who had worsening shoulder pain, four were from the CIT group. Figures 2.14 and 2.15 depict the number of subjects in each group at each level of the CMII shoulder pain scale on admission and discharge. Most subjects scored between 4 and 6 on admission. Level 6 indicates scapular and shoulder mal-alignment with no pain and level 4 indicates intermittent pain localized to the shoulder only on testing. There were some subjects in both groups whose pain worsened on discharge indicated by lower shoulder pain scores. Only one subject in the control group (female, right hemiplegia, age 64) had a normal pain score of 7 on discharge.

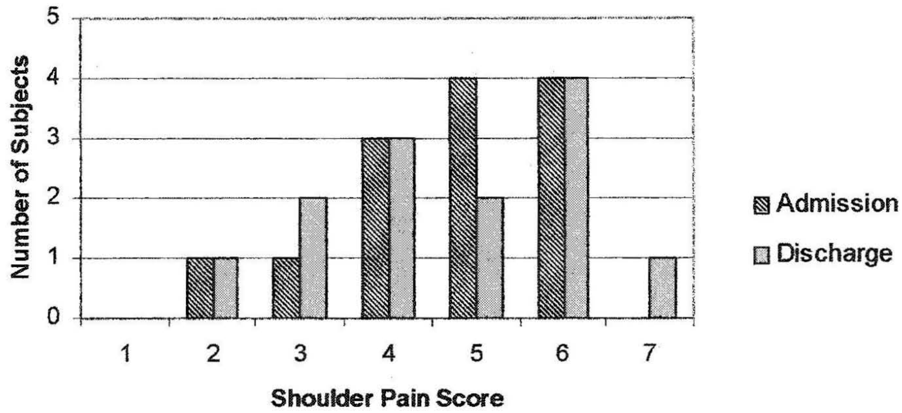

Figure 2:14: Admission and discharge shoulder pain scores for control group

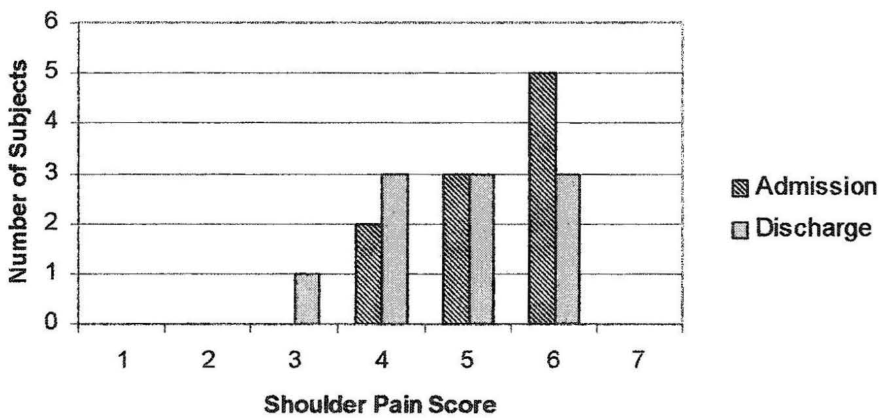

Figure 2.15: Admission and discharge shoulder pain scores for treatment (CIT) group

Figure 2.16 shows the average ARAT score change from admission to discharge for the CIT treatment group and the control group. There was a trend, albeit non-significant, toward more improvement in ARAT score in the CIT group compared to controls ($p=0.136$). Subjects in the CIT group experienced an 85% improvement in ARAT score while control subjects experienced a 74% improvement.

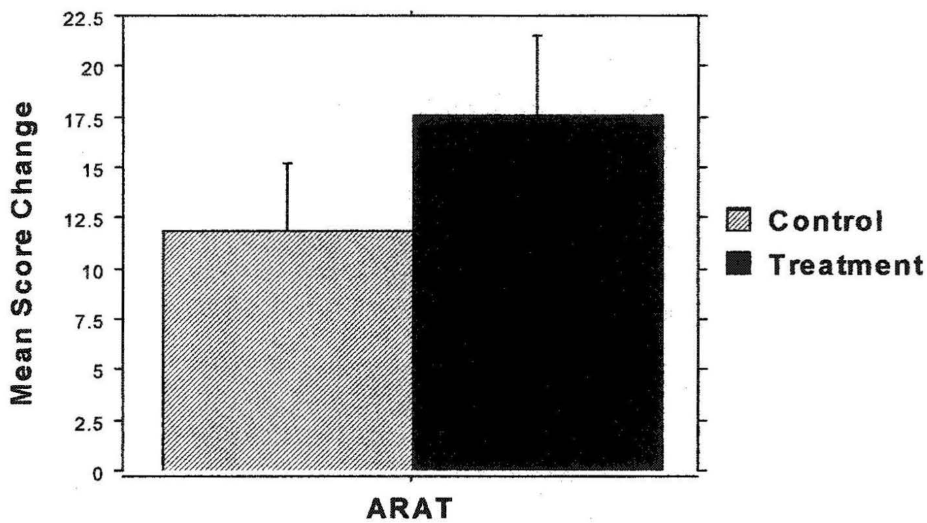

Figure 2.16: Mean change in ARAT score (mean ± SE); Control versus treatment groups.

Figure 2.17 shows the mean change in grip strength using the Jamar Hand Dynamometer for the CIT and control groups. There was no difference in recovery of grip strength.

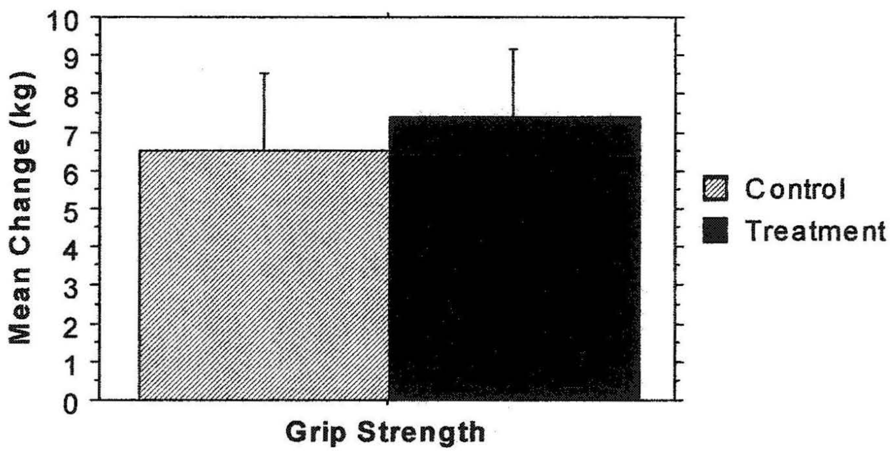

Figure 2.17: Mean change in grip strength in kg (mean ±SE); Control versus treatment groups.

Figure 2.18 shows the mean change of FIM and FIM Self-Care scores for the CIT and control groups. There was no significant difference in these variables between the CIT group and controls.

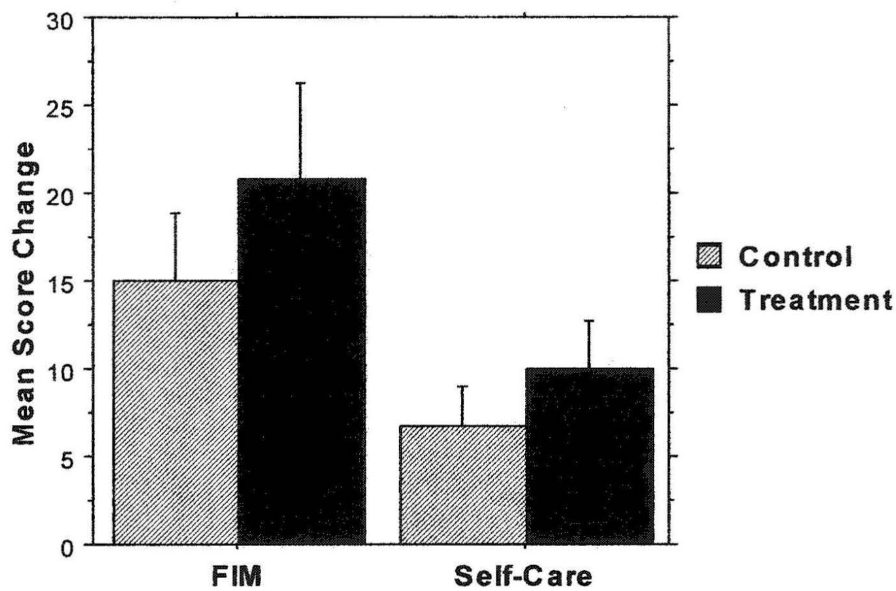

Figure 2.18: Mean change of FIM score and the Self-Care portion of FIM (mean ±SE); Control versus treatment.

In summary, it was found that subjects in the CIT group experienced more recovery of the arm, leg and trunk than control subjects although this reached significance only on the CMII measure of postural control. There was no difference between groups in recovery of grip strength or disability measured by FIM. Sixty-one percent of the subjects had shoulder pain on admission to the study and of the 5 subjects who had worsening of shoulder pain, 4 were in the CIT group.

2.6.4 Variables Affecting Recovery

All subjects characteristics and admission scores were entered into a stepwise regression model to determine the relationship of the variables to arm recovery measured by both the CMII and ARAT. Table 2.6 shows the results of regression analysis for CMII arm score change (recovery). Arm recovery was positively correlated only with admission CMII shoulder pain score (bolded). Simple regression (not bolded) suggested a negative correlation between arm recovery and stroke onset to rehabilitation interval (ORI) as well as a relationship with admission CMII hand score.

Table 2.6: Relationship Between CMII Arm Recovery and Admission and Rehabilitation Variables

	R-Value	P- Value	F- Value
Arm Recovery, Admission Shoulder Pain	**0.472**	**0.022**	**6.02**
Arm Recovery, ORI	-0.441	0.035	3.99
Arm Recovery, Admission Hand	0.437	0.036	3.21

Figure 2.19 shows the relationship between CMII arm recovery and CMII shoulder pain score. Those subjects with less shoulder pain on admission experienced more arm improvement.

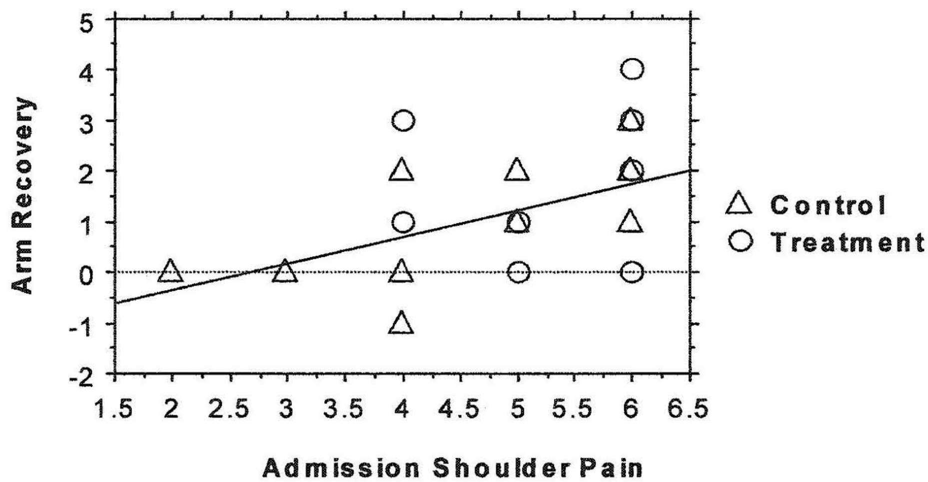

Figure 2.19: Scattergram of CMII arm recovery and admission shoulder pain for both control and treatment groups (R=0.472).

Figure 2.20 shows the relationship between arm recovery measured by the CMII for both the CIT and control groups and ORI. The outlying subject from the control is the same outlying subject in Figure 2.21. This subject had the highest admission CMII score for the hand of all subjects and one of the longest stroke onset to study entry intervals at 81 days. This subject may have experienced most of his recovery before entering the study.

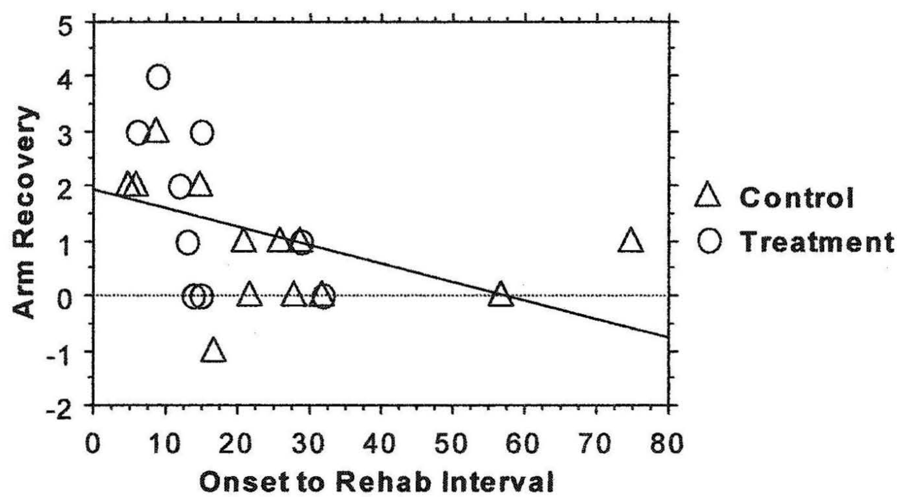

Figure 2.20: Scattergram of CMII arm recovery and Onset to Rehabilitation Interval (ORI) for both control and treatment groups (R=-0.441).

Figure 2.21 shows the relationship between CMII arm recovery and admission CMII hand score. The outlying subject from the control group scoring 5 on admission CMII for the hand, was one of the subjects with the longest OSI at 81 days.

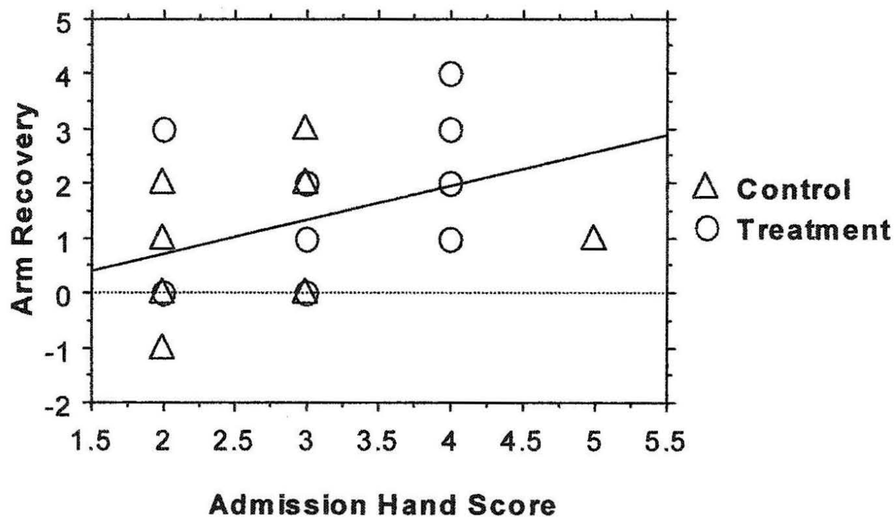

Figure 2.21: Scattergram of CMII arm recovery and CMII admission hand score for both control and treatment groups (R=0.437).

Stepwise regression showed that recovery measured by the ARAT was related only to OSI, admission hand score and admission ARAT score ($p=0.004$). No significant relationship was found between other variables, gender, inpatient or outpatient status, side of hemiplegia, or type of stroke, and recovery of the upper extremity measured by the ARAT. Table 2.7 shows the results of stepwise regression for recovery measured by the ARAT and the admission and rehabilitation variables for all subjects.

Table 2.7: Relationship-Between ARAT Score Recovery and Admission/ Rehabilitation Variables

	R- Value	P- Value
ARAT Recovery, OSI	-0.585	0.004
ARAT Recovery, Admission Hand	0.276	
ARAT Recovery, Admission ARAT	-0.305	

Figure 2.22 shows the relationship between ARAT recovery and stroke onset to study entry interval (OSI). Those subjects more than 45 days post-stroke on study entry made less impressive gains in ARAT recovery.

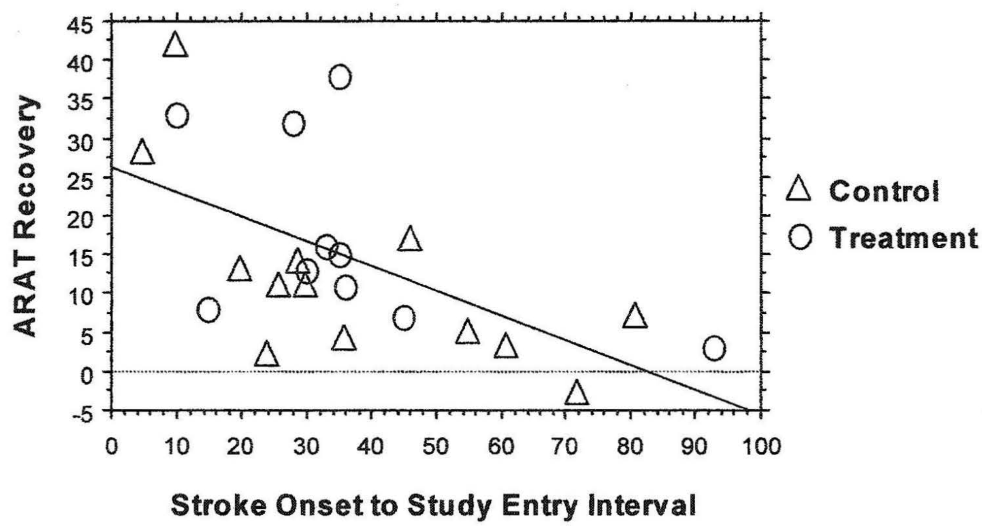

Figure 2.22: Scattergram of ARAT score recovery and OSI for both control and treatment groups.

Improved ARAT score was associated with higher CMII hand score on admission to the study (Figure 2.23) but higher admission ARAT score was associated with less ARAT score change (Figure 2.24)

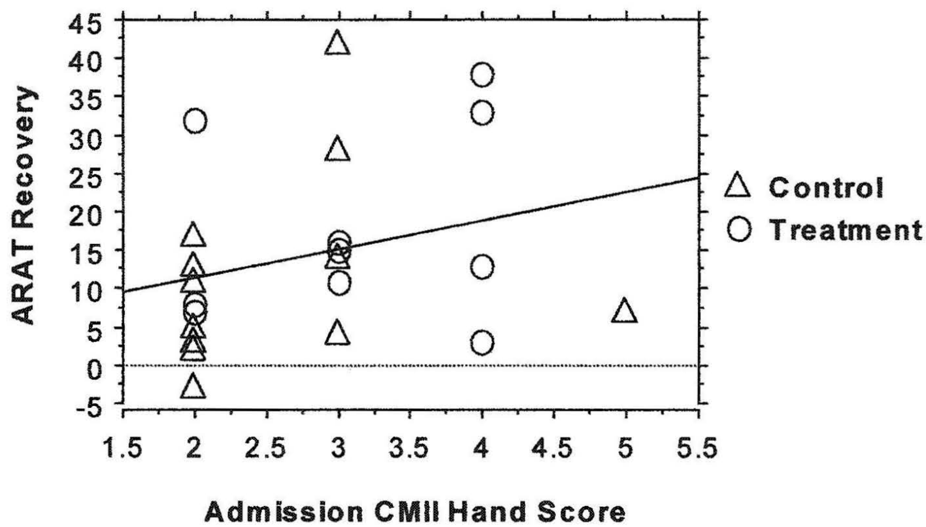

Figure 2.23: Scattergram of ARAT score recovery and admission CMII hand score for both control and treatment groups.

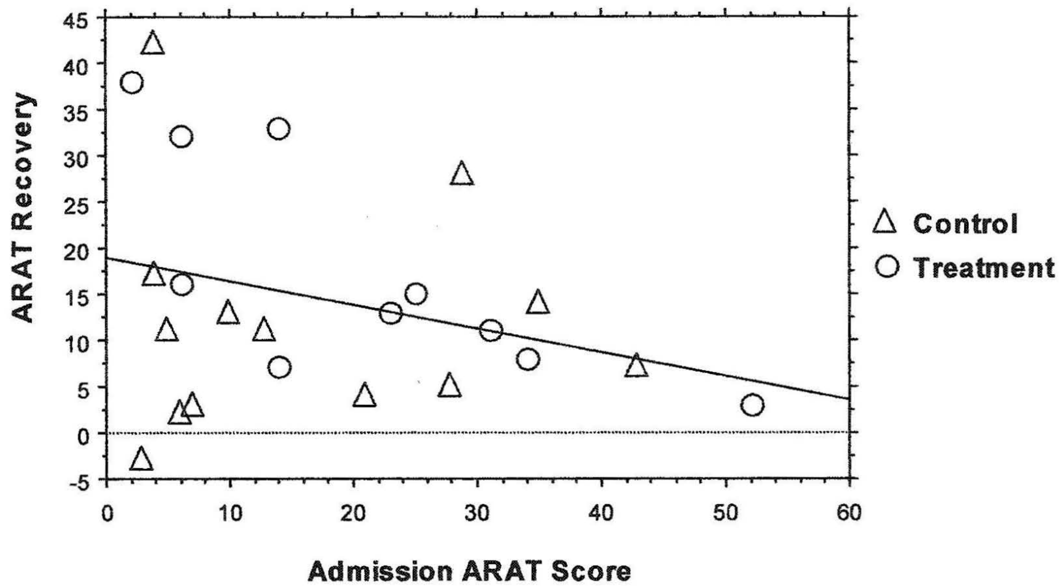

Figure 2.24: Scattergram of ARAT score recovery and admission ARAT score.

Side of hemiplegia was significantly related to arm recovery (p=0.023) with subjects with left hemiplegia having better recovery than those with right hemiplegia. Figure 2.25 shows the average improvement in CMII scores for subjects with right and left hemiplegia in the treatment and control groups. Analysis of subjects with right or left hemiplegia separately revealed a significantly greater improvement in CMII leg recovery in CIT group subjects with left hemiplegia than control subjects with left hemiplegia. Although non-significant, there was a tendency for subjects with left hemiplegia to have a more robust arm improvement with CIT than those in the control (p= 0.093). Subjects with left hemiplegia in the CIT group experienced a 44% improvement in arm score over subjects with right hemiplegia in the CIT group and left hemiplegic subjects in the control group. There was also a tendency for right hemiplegics in the treatment group to have worsening of shoulder pain over subjects in other subgroups but this did not reach significance.

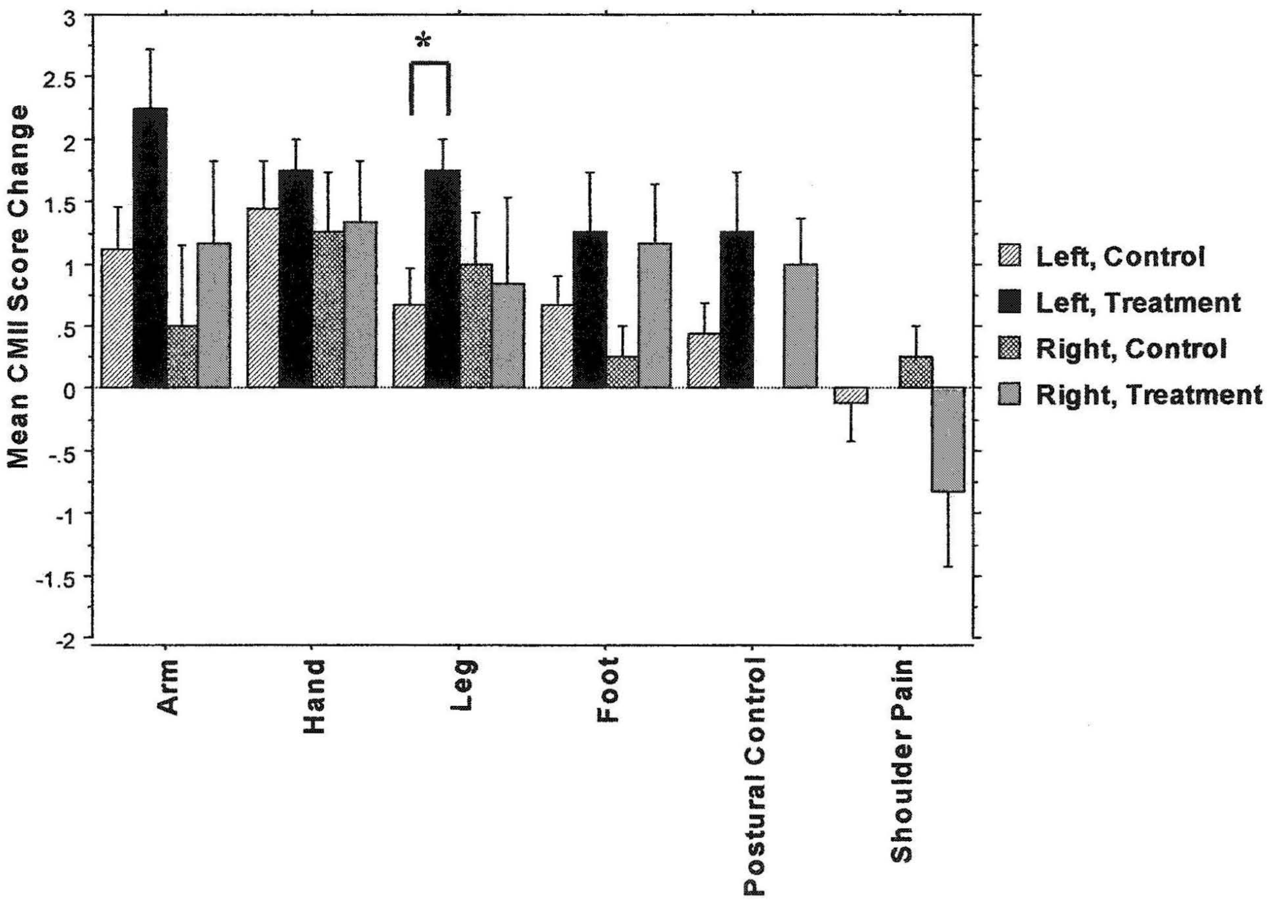

Figure 2.25: Mean change of Chedoke–McMaster Impairment Inventory score (mean ±SE); Treatment versus control and right versus left hemiplegia (* p<0.05).

Figures 2.26 and 2.27 show the average improvement in ARAT score and grip strength respectively, for subjects with right and left hemiplegia in the treatment and control groups. There were no significant differences between scores in subjects with right and left hemiplegia in the control and CIT groups.

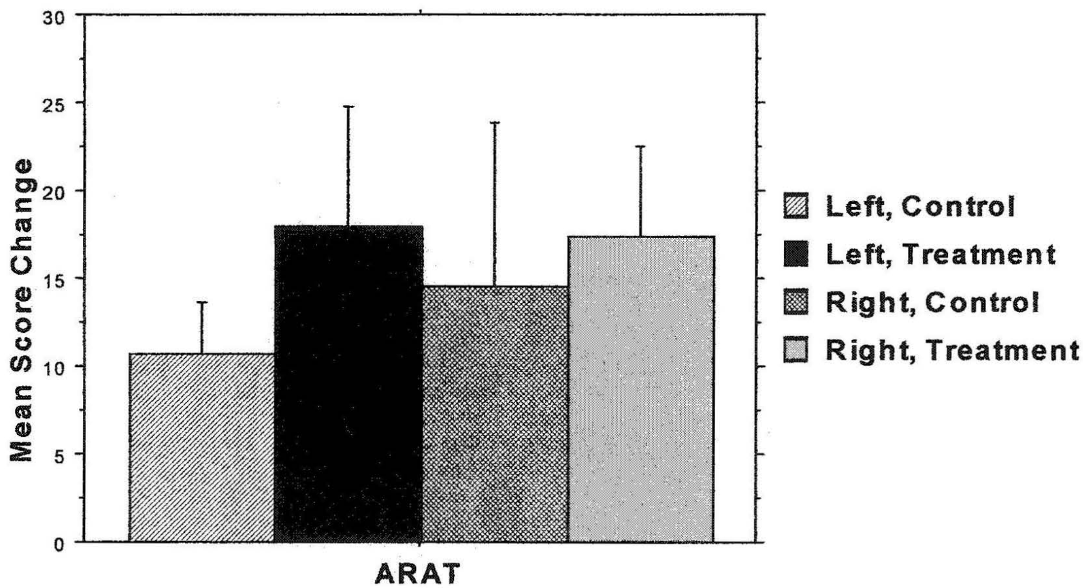

Figure 2.26: Mean ARAT score change (mean ±SE); Control versus treatment and left versus right hemiplegia.

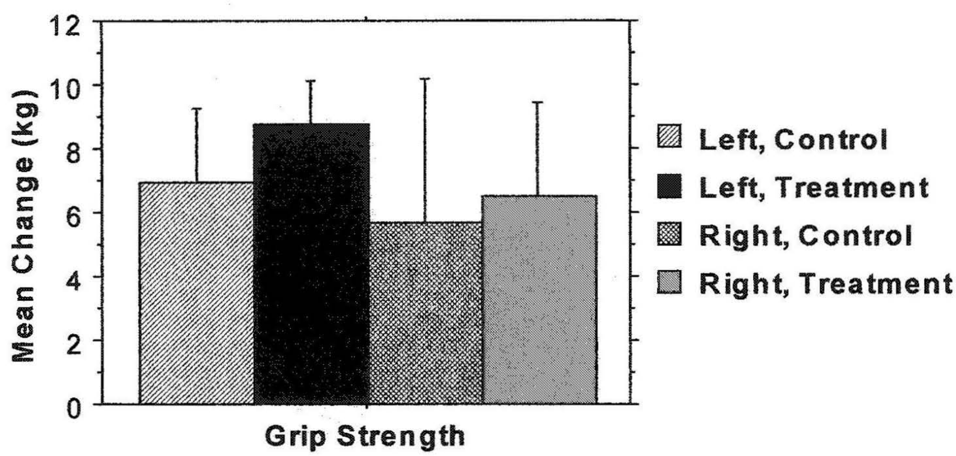

Figure 2.27: Mean change in grip strength in kilograms (mean ±SE); Control versus treatment and right versus left hemiplegia.

Figure 2.28 shows the average recovery of independence measured by the FIM for subjects with left and right-sided involvement for both study groups. Subjects with left hemiplegia in the CIT group had up to 100% more recovery than the other subgroups however this did not reach significance.

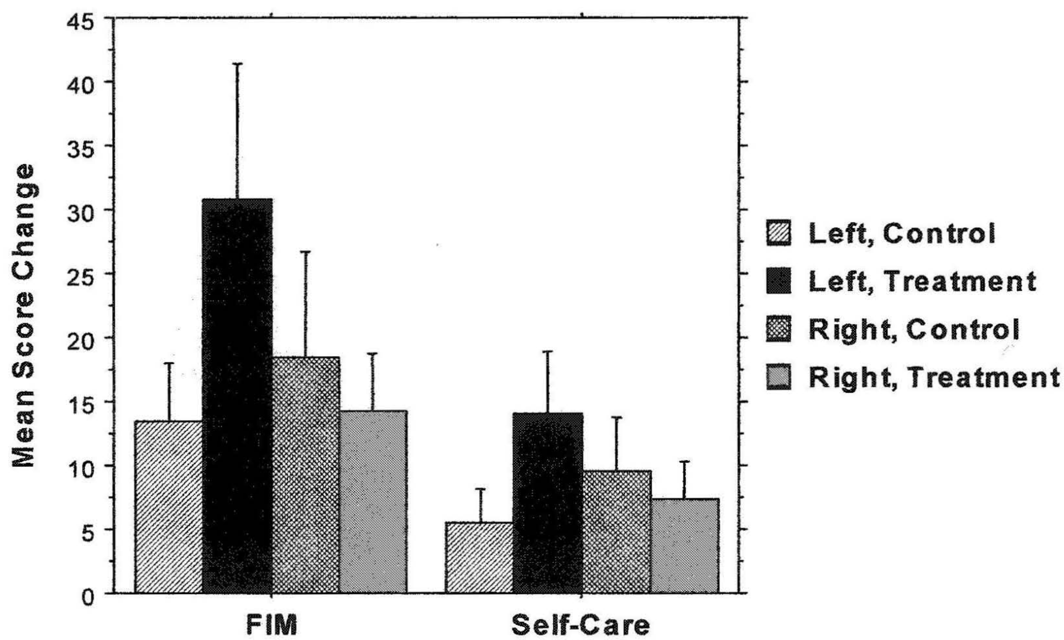

Figure 2.28: Mean change in FIM and FIM Self-Care scores (mean ±SE); Control versus treatment and right versus left hemiplegia.

There was a significant interaction effect between gender and treatment condition (control or CIT) with regard to recovery of the arm. Figure 2.29 depicts the average CMII score recovery for male and female subjects in the treatment and control groups. When female and male subjects were analyzed separately, there was a significantly greater improvement in CMII arm recovery in male subjects in the treatment group compared to controls. It should be noted that although not reaching significance, male subjects were more compliant with the mitten constraint than female subjects. There was also a significant difference in shoulder pain recovery with the females in the CIT group having significantly worse shoulder pain than females in the control group; a mean decline of 1.5 points on a seven point scale. They also developed significant worsening of shoulder pain compared to their male counterparts in the CIT group. There was a significant difference in improvement of CMII postural control in favour of females in the CIT group compared to those in the control group. Females in the control group had significantly better hand recovery than male subjects in the control group. Although not reaching significance, females in the control group demonstrated better recovery on the CMII measures of arm, hand and leg than female subjects in the treatment group.

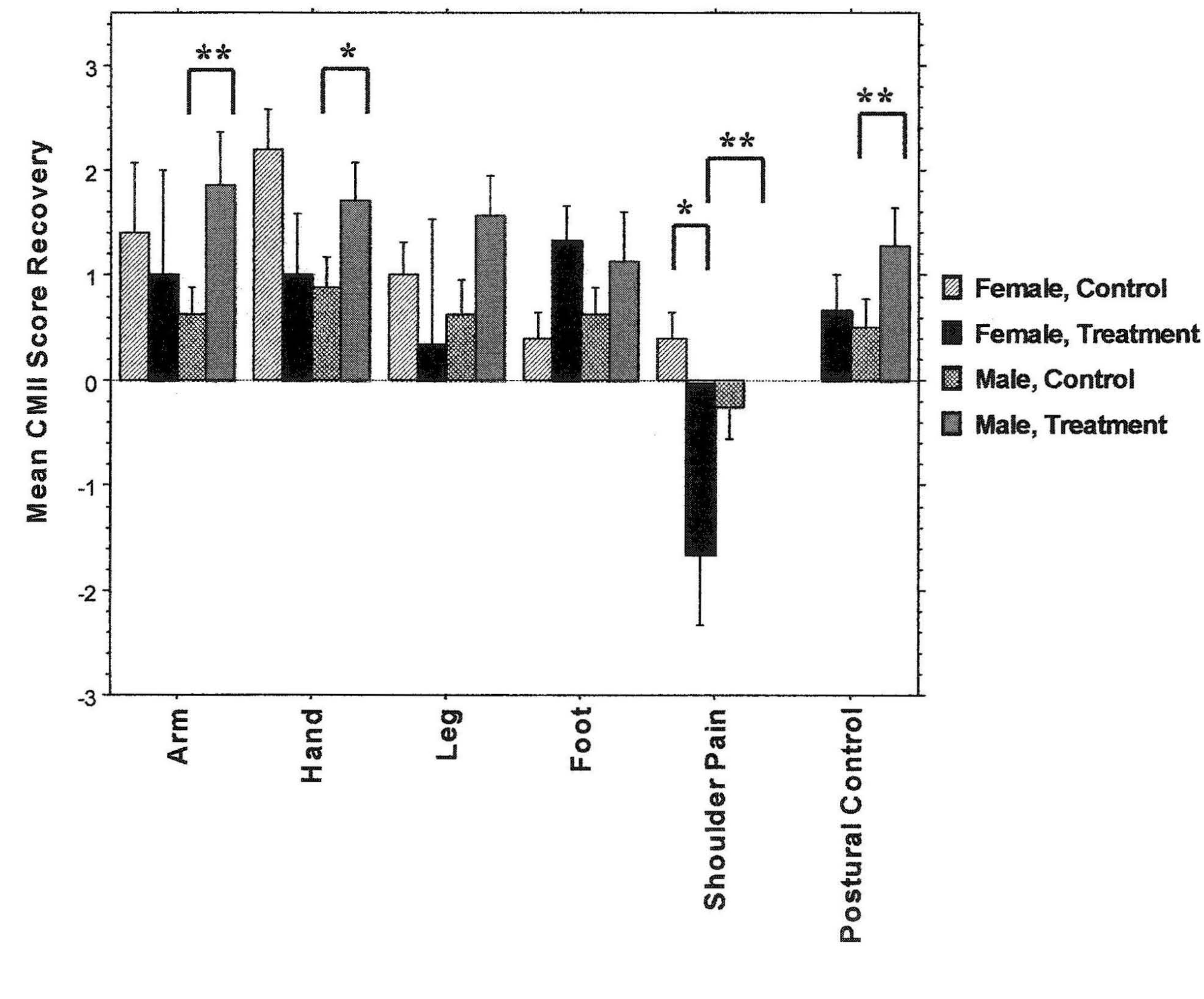

Figure 2.29: Mean CMII score change (mean ±SE); Control versus treatment and males versus females (* p<0.02, ** p<0.05).

Figures 2.30 shows the average grip strength recovery for females and males in the treatment and control groups. Male subjects in the treatment group had significantly better grip strength recovery than males in the control and females in the treatment group. There was a trend, although not significant, toward better recovery of grip strength in female subjects in the control group over females in the CIT group.

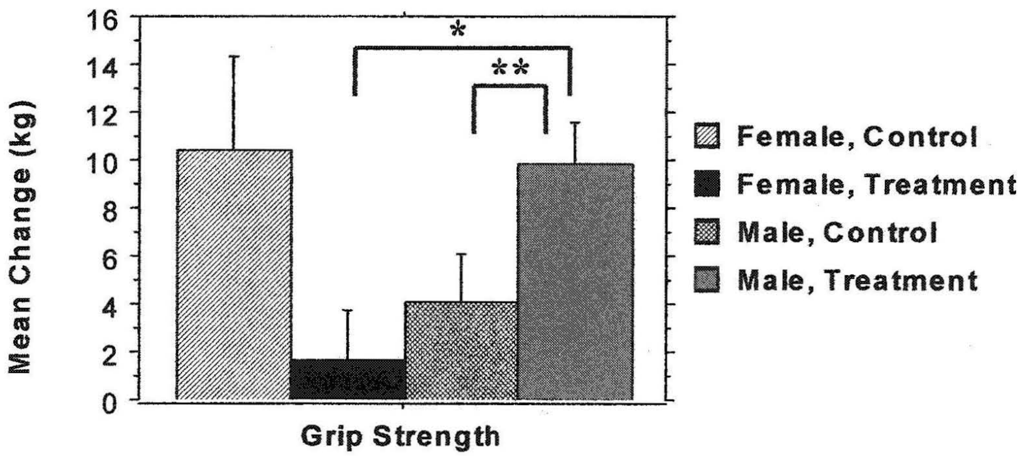

Figure 2.30: Mean change in grip strength in kilograms (mean ±SE); Control versus treatment and females versus males (* $p < 0.02$, ** $p < 0.05$).

Figure 2.31 shows the average change of ARAT score in both the female and male subjects in the treatment and control groups. Male subjects in the treatment group had significantly better recovery of hand and arm movement and coordination as measured by the ARAT than males in the control group.

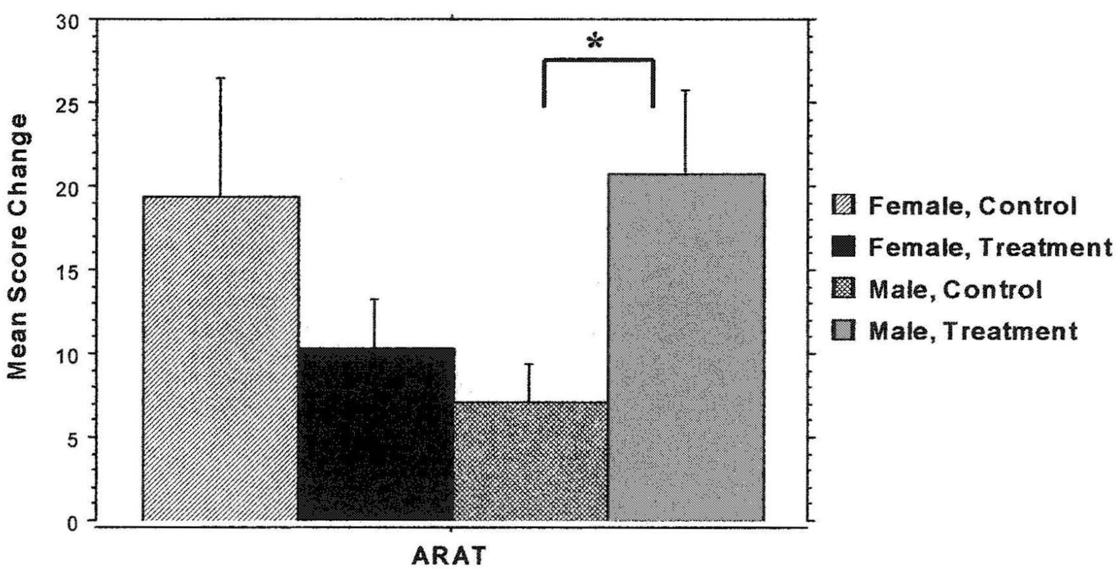

Figure 2.31: Mean ARAT score change (mean ±SE); Control versus treatment and females versus males (* p< 0.02).

Figure 2.32 shows the average FIM and FIM Self-Care score recovery for female and male subjects in the CIT and control groups. There was no significant difference between average improvement in FIM and FIM Self-Care measures between females and males in the control and treatment groups.

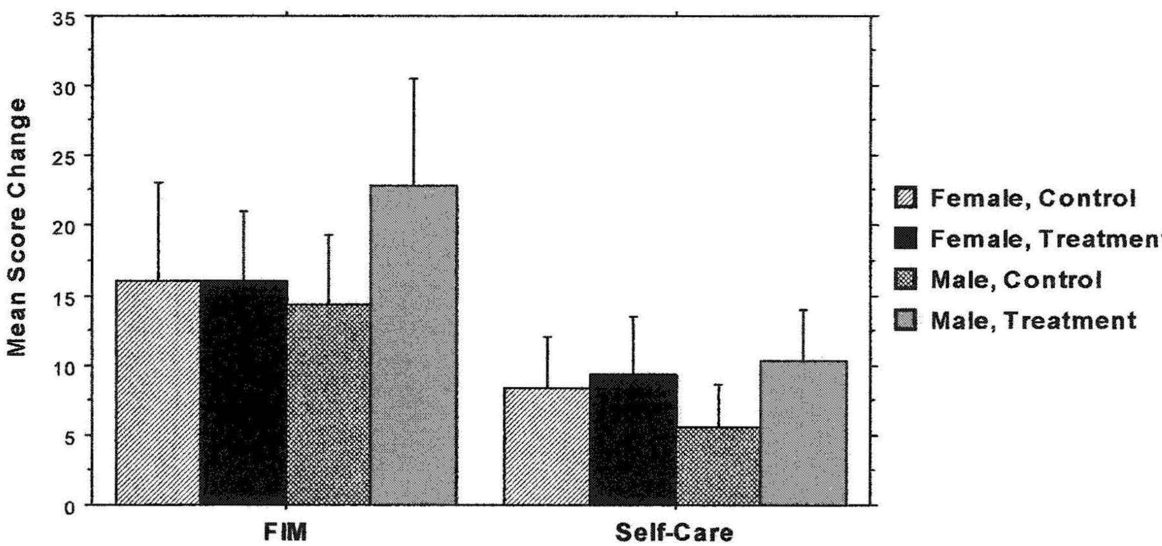

Figure 2.32: Mean FIM and Self-Care portion of FIM score change (mean ±SE); Control versus treatment and females versus males.

Figure 2.33 represents the average grip strength each week for the last 15 subjects in the study. There was a trend toward increasing grip strength in both groups from week 1 to week 8, with somewhat greater improvements in the CIT group. In weeks 9 and 10, strength decreased in both groups, corresponding to the time of peak reported shoulder pain. However it appears that the CIT subjects returned to a trend toward recovery while the control group did not.

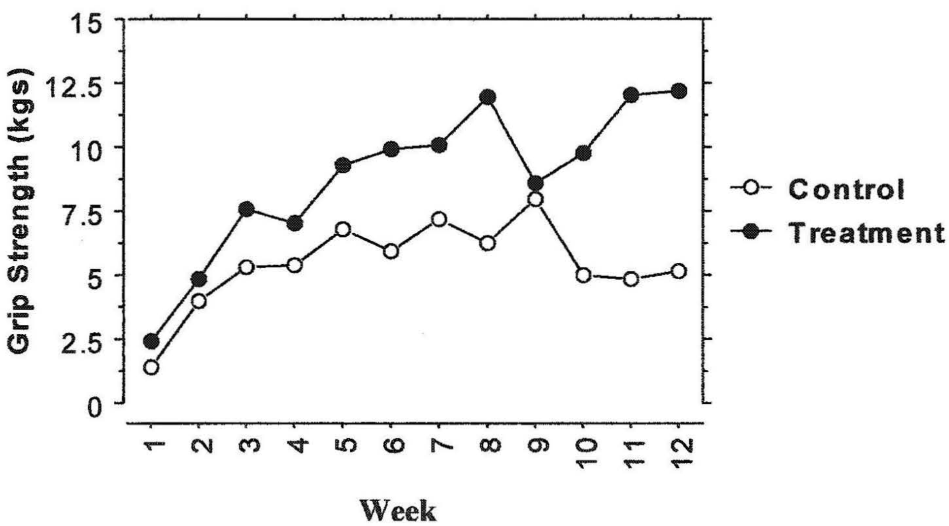

Figure 2.33: Average weekly grip strength values in kilograms for subjects in the control and treatment groups

2.6.5 Validity of Measures

Table 2.8 shows the relationship between the outcome measures used in the study. Recovery of arm function measured by the CMII was strongly correlated with improvement on other upper extremity recovery measures, grip strength recovery, ARAT recovery, and Chedoke-McMaster hand recovery. Arm recovery on the CMII was correlated with the Self-Care portion of the FIM but not the FIM in its entirety. Grip strength correlated with both ARAT recovery and hand recovery but not total FIM recovery or the Self-Care portion of FIM. The ARAT score recovery was correlated with all measures used in this study including those above as well as FIM, Self-Care, and hand recovery. Hand recovery was not correlated with either FIM or the Self-Care portion of FIM. Change in shoulder pain was correlated only with grip strength recovery and not with any of the other upper extremity measures.

Table 2.8: Relationship Between Recovery Measures

	R-Value	P- Value
Arm Recovery, Hand Recovery	0.603	0.002
Arm Recovery, Postural Control Recovery	0.459	0.026
Arm Recovery, Shoulder Pain Recovery	0.037	0.868
Arm Recovery, Grip Strength Recovery	0.559	0.005
Arm Recovery, ARAT Recovery	0.526	0.009
Arm Recovery, FIM Recovery	0.388	0.067
Arm Recovery, FIM Self-Care Recovery	0.424	0.043
Hand Recovery, Postural Control Recovery	0.302	0.164
Hand Recovery, Shoulder Pain Recovery	0.096	0.668
Hand Recovery, ARAT Recovery	0.434	0.038
Hand Recovery, Grip Strength Recovery	0.675	0.0002
Hand Recovery, FIM Recovery	0.249	0.256
Hand Recovery, FIM Self-Care Recovery	0.350	0.102
Shoulder Pain Recovery, Grip Strength Recovery	0.513	0.011
Shoulder Pain Recovery, ARAT Recovery	0.106	0.633
Shoulder Pain Recovery, FIM Recovery	-0.029	0.895
Shoulder Pain Recovery, FIM Self-Care Recovery	-0.133	0.551
Grip Strength Recovery, ARAT Recovery	0.471	0.022
Grip Strength Recovery, FIM Recovery	0.249	0.255
Grip Strength Recovery, FIM Self-Care Recovery	0.263	0.228
ARAT Recovery, FIM Recovery	0.603	0.002
ARAT Recovery, FIM Self-Care Recovery	0.551	0.006

2.7 Discussion

2.7.1 Constraint-Induced Therapy Affects Stroke Outcome

Constraint of the sound arm following stroke paired with intensive 'shaping' therapy has been shown to improve upper extremity outcome (van der Lee 1999). However, it has yet to be determined if the principles of CIT can be practically applied within the current model and resources of stroke rehabilitation. In this study, CIT applied with conventional therapy during the rehabilitation phase of stroke, appeared to augment functional recovery, although significant results were not found on most outcome measures. The constraint therapy appeared to have a significant effect on recovery of CMII scale of postural control and subjects in the CIT group had 20% greater arm recovery, measured by CMII, over control subjects.

This method of constraint encouraged bilateral, symmetrical activity and perhaps intensified the rehabilitation experience. It may be that the constraint, because of its intensity, places additional challenge on the stroke patient and has an influence on physical recovery of the trunk in addition to the impaired upper extremity. Subjects in the CIT group also had greater improvement than controls on other measures unrelated to the upper extremity, including recovery of the leg and foot. It could be suggested that more frequent attempts at use of the impaired upper extremity in functional activities would likely encourage enhanced activation of the trunk and increased loading of the lower extremities especially during reaching tasks.

The subjects in this study had greater motor impairment and were more disabled than subjects in previous studies (Taub 1993; Miltner 1999; van der Lee 1999; Dromerick

2000). Over 80% of our subjects had severe upper extremity hemiplegia on admission to the study, as indicated by CMII stage and ARAT score, which is typical of patients seen in a rehabilitation hospital. In fact, subjects in this study waited, on average, 15 days to be included in the study after entering rehabilitation because of severity of arm dysfunction. This delay was required to allow the subjects to recover at least facilitated hand grasp and release and arm flexion and extension. Studies have shown that initial paralysis is associated with poorer outcome (Harvey 1998; Macciocchi 1998; Hendricks 2002) thus these subjects were at significant disadvantage compared to more mildly affected stroke patients. In this study, it was also found that lower admission hand scores and more shoulder pain on admission to the study were associated with poorer arm recovery. Data also indicated that delayed stroke onset to study entry interval was associated with less recovery of the arm during the study period. In addition, 61% of the subjects in this study suffered subcortical lesions or lesions with both subcortical and cortical involvement. Studies indicate that patients with subcortical stroke have less favourable outcomes than patients with cortical stroke (Macciocchi 1998; Shelton 2001). Despite having factors that predict a negative outcome (i.e. severe stroke, subcortical lesions) all subjects, particularly the CIT subjects, demonstrated significant functional recovery.

The data from this study indicated that subjects in the CIT group had 11% more improvement on the ARAT and 20% more improvement on the CMII than control subjects. In the study by Dromerick et al., in an acute rehabilitation setting, subjects in the constraint plus 'shaping' group experienced an additional 36% improvement over controls measured by the ARAT, however the constraint subjects were on average 10 years younger than the control subjects (Dromerick 2000). The subjects in our study were also more impaired on admission than subjects in the Dromerick study, scoring, on average, 9.5 points out of 57 lower on the ARAT. In the study by van der Lee et al., comparing CIMT to bimanual exercise in chronic stroke, CIMT subjects experienced a 17.4% improvement on the ARAT while control subjects experienced a 6% improvement (van der Lee 1999). One of the earliest CIMT studies by Taub demonstrated that chronic stroke patients experienced approximately 18% improvement on the Arm Motor Activity Test and 26% improvement on the Emory Motor Function Test over control subjects (Taub 1993). Considering that our subjects were more impaired than those in comparable studies, the improvement found in this study may be clinically relevant and since the CIT program was performed with very little therapist intervention, it has the potential to be a cost and resource-efficient method to intensify rehabilitation.

It was also noted in this study, that although 47% and 30% of subjects in both groups had severe or moderate arm hemiplegia respectively on discharge measured by the ARAT, 80% of subjects achieved independence or adapted independence in ADL measured by the FIM score. This suggests that our subjects, despite the CIT intervention, developed compensatory strategies using the sound arm to achieve independence in ADL.

2.7.2 Compliance with the CIT Program

Previous questionnaire results have reported that the majority of patients would not be compliant with wearing the sling and splint for 90% of waking hours together with 6 hours per day of therapy (Page 2001). In contrast, the graduated program of mild constraint used in this study was generally accepted by our patient population.

Full compliance (i.e. 6 hours of constraint per day) was not achieved in this study in the acute rehabilitation setting although 3 to 5.5 hours per day was achieved by half of the treatment group. Daily wear time was not individually prescribed, and clinically, it appeared that subjects wore the mitten constraint as they were able. Because of the extent of upper extremity impairment of the subjects in our study, it may be unrealistic to expect these patients to wear the constraint for 90% of waking hours.

The two subjects from the CIT group, who discontinued their participation, did so prior to initiation of the CIT program. It was the burden of the assessment procedure, rather than the CIT protocol, that precipitated their termination. Only one subject in the CIT group did not wear the mitten constraint at all and that subject had the lowest FIM score in the group and experienced average recovery. The other CIT subjects wore it to varying degrees. The amount of wearing did not seem to be related to recovery however subjects in addition to constraint, were coached on the principles and rationale of CIT and the learned non-use theory.

It was difficult to predict which subjects would be most compliant. It was anticipated that inpatients, because of closer supervision, would be most compliant, but this was not the case. There was no evidence that compliance was related to the level of upper extremity impairment or shoulder pain on admission, as might be expected. However, compliance was related to the MMSE score on admission. This finding was unexpected since all subjects in the study were screened and scored greater than 25 on the MMSE, considered to be within normal limits, and did not demonstrate obvious cognitive deficits. It was apparent that the subjects who reached the full score of 30 were able to achieve the most hours of constraint wearing and even MMSE scores of two or three points lower than the maximum score were associated with poorer compliance. Admission FIM score was also related to compliance, albeit non-significantly. Those subjects who were most disabled and dependent on others for daily care on admission to the study tended to be least compliant with the mitten constraint. MMSE score and the cognitive subscale of FIM have been shown in previous studies to be highly correlated (Zwecker 2002), so the subjects with low MMSE scores may also be those likely to score lower on the FIM. Other constraint-induced therapy studies have not reported difficulties with compliance, however this study did not provide the individual attention and additional therapy time provided by others, and subjects were encouraged to carry out the constraint protocol independently. Some studies examining compliance to self-administration of medications have reported that MMSE scores lower than 25 predict less medication compliance in elderly subjects (Okano 2001; Salas 2001). Findings from this study may suggest that even very mild cognitive impairment may impede the stroke patient's ability to completely participate in the CIT program or that patients participating in CIT should be screened and the amount of wearing tailored to the individual's abilities.

2.7.3 Adverse Effects of the CIT Program

Examination of FIM and the Self-Care items of FIM score change revealed that CIT subjects were no more reliant on caregivers for ADL than control subjects. In fact, subjects in the CIT group tended to have more improvement of FIM and FIM Self-Care than controls. There was no evidence to suggest that CIT would be too intense for the sub-acute rehabilitation setting. There were no adverse events during the study including second stroke, falls, or worsening of status. Whereas other studies completely disallowed use of the sound arm for 90% of waking hours, this method of mitten constraint was designed to encourage bilateral activity and to act more as a 'use-cue' for the affected arm and hand rather than a total restraint. Subjects were not frustrated or uncomfortable with the mitten constraint. It could be suggested that this method of minimal constraint is more appropriate in the acute rehabilitation setting because it does not compromise independence or place excessive stress on the recovering stroke patient, on the other hand, it did not appear to prevent learned non-use as the majority of subjects despite significant hemiparesis were able to carry out ADL independently.

Sixty-one percent of the subjects experienced hemiplegic shoulder pain (HSP) on admission to the study which is consistent with other studies reporting between 5 and 85% occurrence of HSP in rehabilitation (for review see Turner-Stokes 2002). It was found that the amount of mitten wearing was not correlated with worsening of shoulder pain and shoulder pain was not correlated with recovery. Despite this, there was a trend toward less recovery in those subgroups (female subjects and subjects with right hemiplegia in the CIT group) with more shoulder pain. Although the pain was mild and did not seem to be related to the CIT treatment, it is an area warranting further investigation. There was an interesting temporal association between a reduction in grip strength and onset of peak shoulder pain in both CIT and control groups. Grip strength was the only outcome measure that was significantly related to shoulder pain. To our knowledge, this is the first study, albeit preliminary, to address the relationship between upper extremity constraint, arm recovery and hemiplegic shoulder pain.

2.7.4 Some Patients May Benefit More Than Others

Subjects with left hemiplegia in the CIT group had significantly more leg improvement and a trend toward more arm recovery than those in the control group. This subgroup of subjects experienced 44% more improvement of CMII scores than left hemiplegics in the control group and right hemiplegics in the CIT group. Since all of the subjects were right hand dominant, this finding suggests that the benefits of CIT may be greater when the dominant hand is constrained. No difference in admission and rehabilitation variables such as admission scores or therapy time were found between subjects with right and left hemiplegia or between right and left hemiplegics in the treatment group. We suspect that the phenomenon of 'learned non-use' may be more problematic when the stroke affects the non-dominant side because the patient may learn to compensate by using the sound, dominant hand. Although right hemiplegic subjects also benefited (17% more improvement in CMII arm score than controls), it appears that CIT has less of a robust effect when hemiplegia involves the dominant side. Perhaps there is an innate drive to use the dominant hand after stroke with or without constraint. As far as we are aware, there have been no previous studies that report such a phenomenon. It is difficult to draw conclusions since the sub-group sizes were small and there were no left-hand dominant subjects to compare outcomes. Alternatively, subjects with right hemispheric lesions are more likely to suffer from spatial neglect (Su 2000) and tend to have poorer functional outcomes than those with left hemispheric stroke (Macciocchi 1998). Mild stimulation such as transcutaneous nerve stimulation (TENS) can improve scanning and attention to the left side in patients with right-sided stroke (Perennou 2001) so it is possible that the CIT program serves as a cue, encouraging the right hemispheric stroke patient to use the often neglected arm and hand. Findings in this study suggest that the mitten constraint may have had a significant beneficial effect on leg recovery in the left hemiplegic group. The constraint mitten may act as a use-cue to the left side generally and holistically. It was also noted that the subjects with right hemiplegia tended to have an increase in shoulder pain over other subgroups and this may have had an influence on upper extremity outcomes in that group. Upper extremity outcomes in subjects with right or left hemiplegia were examined in the CIMT study (n=15) by Miltner and colleagues (Miltner 1999). Their findings suggested that CIMT had an equally beneficial effect in both groups. However, other studies tended to include subjects with hemiplegia on the same side. Taub et al. included subjects with either left hand dominance or left hemiplegia while van der Lee and colleagues chose only subjects with dominant side hemiplegia with equivocal benefits (Taub 1993; van der Lee 1999). This appears to be the first study to suggest a disparate effect in left versus right hemiplegia.

For those patients who would typically experience poorer outcomes, those with right hemispheric or subcortical stroke, lower admission FIM scores, and more motor impairment on admission, the CIT program appears to offer some benefit. These are issues of interest to clinicians who must determine the most appropriate CIT candidates. A larger study with subgroups of subjects with left and right hemiplegia and hand dominance would help define selection criteria.

A significant difference was found in all measures of upper extremity recovery (CMII arm, hand, shoulder pain, grip strength, and ARAT) in the male subjects in the CIT group compared to controls. Male subjects appeared to be most compliant with the mitten constraint although the rationale was not apparent. There were no differences in initial outcome scores and demographics between male and female subjects but other factors such as educational level or depression were not measured. The CIT program did not seem to have a beneficial effect for the female subjects other than in recovery of postural control, although females were underrepresented in the study. Furthermore, there was worsening of shoulder pain in the females versus males in the CIT group and versus females in the control group. In fact, females in the control group recovered to a greater degree on measures of grip strength, ARAT, Chedoke-McMaster arm and hand scores than those who were in the CIT group. This finding may have been due to differences in compliance and increased shoulder pain rather than any gender difference, since the female subjects in the CIT group were less compliant to the mitten constraint and experienced more shoulder pain. Other studies have suggested that hemiplegic shoulder pain can impede motor recovery (Teasell 1998; Turner-Stokes 2002), however, a correlation between shoulder pain and recovery of the hemiplegic arm was not found in this study. This disparity in outcome may also have been due to the fact that females in the control group entered rehabilitation significantly sooner post-stroke than males in the control, which placed them at a considerable advantage. Data from this study indicated that a shorter interval between stroke and initiation of rehabilitation was associated with improved functional recovery, a finding supported by other researchers (Harvey 1998; Musicco 2003). The numbers of subjects in these subgroups were too small to draw definitive conclusions, however, it is an area worthy of further investigation.

2.7.5 Limitations in Experimental Methods and Recommendations for Future Studies

We had difficulty maintaining concealed discharge assessment by raters. Since the research was conducted in a small facility, after randomization to treatment groups, subjects and therapists were aware of treatment group assignment. However, the discharge raters were the attending therapists who had no stated bias toward study outcomes. The ARAT admission and discharge assessments were performed by the principal investigator for which the treatment condition was concealed only on admission assessment. Bias could be suggested on this test, but we note the strong correlation between change of ARAT score and change measured by other tests. The scores on the ARAT were highly correlated with scores of tests performed by other raters. Future studies should ensure that evaluators are consistently blinded to avoid potential bias.

We did not begin weekly grip strength testing until the tenth subject had entered the study so conclusions drawn from this data, although interesting, are limited. We did not measure spatial neglect, motivation, or educational level. This information may have assisted our determination of compliance issues as well as clarified the beneficial effect in male subjects and left hemiplegics. Hours of constraint wear were recorded weekly and relied on the memory of subjects and caregivers for accuracy. It is recommended that hours of constraint wear be measured daily in subjects to avoid potential errors.

Clinical interpretation of our results is limited due to the small number of subjects especially in subgroup analysis. However we note that our subject number exceeds many of the previous CIMT and CIT studies. It will be important in future CIT studies to examine this practical method of CIT in a much larger sample of stroke patients in active rehabilitation to begin to draw definitive conclusions about its usefulness. Since this study only examined functional outcome following the active phase of stroke rehabilitation, it is not known if CIT provided any long-term benefit. Subjects should be reassessed at one and two-years post-intervention.

Because we examined CIT in a clinical setting with both inpatients and outpatients, there was variance in the lengths of stay and therapy time among subjects. The duration of intervention was not controlled. However we recorded these parameters and there was no significant difference between groups. Exposure to routine therapy in terms of duration, skill of therapists and specific techniques were not controlled therefore the contribution of these factors are not known. Any causative effects of CIT cannot be surmised with any certainty in this study due to this variability. It is recommended that researchers examining CIT attempt to control at least treatment duration and therapeutic strategies, to help determine the effects of CIT itself. It is conceivable that variations in conventional therapy could explain the results.

2.8 Summary and Conclusions

The CIT program, without additional 'shaping' therapy, appeared to have beneficial effects on recovery of postural control in the rehabilitation stage of stroke. CIT also seemed to augment functional recovery of the arm by about twenty percent.

Forced-use is not a novel approach for physiotherapists skilled in the management of the sequelae of stroke. Physiotherapists employ techniques that require the stroke survivor to direct attention and control to the affected side. For example, therapists routinely approach and treat patients from the affected side to encourage visual scanning and weight shift to that side. Despite this practice, therapeutic goals and strategies vary among caregivers and professionals and there is a definite approach in rehabilitation toward compensation, teaching patients to 'make-do' with the remaining function on the sound side. Patients are provided a wheelchair, walking cane, arm sling and one-handed devices for ADL soon after stroke. Argument can be made that these methods improve the stroke survivors' independence and self-esteem. However, it has been demonstrated that intense rehabilitation, either constraint-induced therapy or skilled task training for the upper extremity and adapted treadmill training for the lower extremity, influences neuroplastic change in the recovering brain and enhances the restoration of motor control. It could be suggested that the compensatory approach instituted directly following stroke may be counter-productive in assisting the stroke patient to achieve his or her maximal recovery.

There is nothing profound about a mitten constraint. It appears that it functions as a 'use-cue' following stroke and encourages the patient to continue to attempt to use the affected arm for even simple tasks such as stabilizing a sliding plate of food. Each movement attempt probably serves as a stimulus to the recovering brain and likely to branching neurons. Stroke patients in rehabilitation spend much of the day in non-therapeutic and usually sedentary activities when attention is not directed to the affected side. The mitten constraint may optimize this otherwise underutilized time and transform it into therapeutic time. In fact, we found that CIT seemed to be most beneficial in subjects with left hemiplegia, who are reported to more likely neglect the affected side.

This intensified rehabilitation may have other benefits, since we observed some additional improvements in other aspects of function (ie. trunk and lower extremity recovery) in subjects receiving constraint therapy.

Compliance with CIT was better in subjects with a normal MMSE score, those with less disability on admission, and male subjects. We did not specifically examine factors that may be related to compliance to CIT such as educational level, motivation or depression. Examination of these factors will be important in order to inform rehabilitation clinicians of appropriate selection criteria for the application of CIT.

Our method of CIT was safe and well-tolerated and did not increase the stroke patient's dependence on staff. We found, however, that there was a worsening of hemiplegic shoulder pain (HSP) in the female subjects in the CIT group and these subjects did not improve as much as females in the control group. The relationship between shoulder pain and CIT may be a concern for rehabilitation professionals but we found no relationship between shoulder pain recovery and upper extremity recovery. HSP was not found generally among the CIT subjects, even the most compliant, and the increase in shoulder pain was mild. This is an area worthy of further exploration. Future investigations using a larger sample will be helpful in determining more conclusively the benefits suggested in this exploratory study.

The most salient points in this study were that no additional 'shaping' therapy was added to the constraint protocol and the constraint was worn each day for the duration of the rehabilitation program once the subjects had gained at least facilitated flexion and extension of the arm and hand. The levels of impairment and disability of the subjects in our study were typical of those who participate in stroke rehabilitation, and therefore our preliminary findings have direct clinical relevance. We suggest that this CIT protocol is a practical method to apply constraint therapy principles in the acute rehabilitation phase of stroke.

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APPENDIX A

Faculty of Medicine- Memorial University of Newfoundland
And
Health Care Corporation of St. John's

Consent To Participate In Bio-Medical Research

TITLE: Effect of Constraint-Induced Therapy on Outcome during the Rehabilitation Phase in Stroke Patients

INVESTIGATORS: Michelle Ploughman, Physiotherapist
LA Miller Centre, Health Care Corporation
Of St. John's.

Dr. Dale Corbett
Faculty of Medicine
Memorial University of Newfoundland

You (or your child or ward) have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment.

Information obtained from you or about you during this study, which could identify you, will be kept confidential by the investigator(s). The investigator will be available during the study at all times should you have any problems or questions during the study.

1. Purpose of the study:

Research in humans and animals has shown that forced-use of the weak arm, months and years after stroke, improves recovery and causes changes in the brain towards normal. This study will use a thick, knitted mitten, applied to the good hand to encourage use of the weak arm and hand in every day activities. The study will attempt to show how useful this treatment is during the rehabilitation phase after stroke.

Participant's Initials___________ Page 1

2. Description of procedures and tests:

You will be assessed by a physiotherapist at the beginning and end of the study. The therapist will test the strength of your arm and hand and you will be placed randomly in one of two groups. 'Group A' will participate in the regular rehabilitation program at the Miller Centre. Group B, in addition to this, will wear a special mitten on the good hand for 6 hours per day. You will be asked to complete a daily journal of your activities. Because the group selection is random, your chance of being in one group or the other is even.

3. Duration of participant's involvement:

You will be involved in the study during your entire rehabilitation stay. Your initial and discharge assessment by the physiotherapist will take about an hour each.

4. Possible risks, discomforts, or inconveniences:

You will experience minimal or no risk or discomfort during this study. You may feel slight inconvenience or frustration when wearing the mitten on your good hand as you may find performing your daily activities, such as grooming and eating, more difficult.

5. Benefits which the participant may receive:

There is no immediate benefit to either group while participating in the study. Presently, we do not know the benefits, if any, of this type of treatment in the rehabilitation phase after a stroke.

6. Alternative procedures or treatment for those not entering the study:

If you decide not to enter this study, you will participate in the regular rehabilitation program at the Miller Centre.

7. Liability Statement.

Your signature indicates your consent and that you have understood the information regarding the research study. In no way does this waive your legal rights nor release the investigators or involved agencies from their legal and professional responsibilities.

Participant's Initials__________

Signature Page

Title of Project: Effect of Constraint-Induced Therapy on Outcome during the Rehabilitation Phase in Stroke Patients

Name of Principal Investigator: Michelle Ploughman BScP.T.

To be signed by participant

I, , the undersigned, agree to my participation or to the participation of (my child, ward, relative) in the research study described above.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee that I will benefit from my involvement.
I acknowledge that a copy of this form has been given to me.

(Signature of Participant) (Date)

(Signature of Witness) (Date)

To be signed by investigator

To the best of my ability I have fully explained the nature of this research study. I have invited questions and provided answers. I believe that the participant fully understands the implications and voluntary nature of the study

(Signature of Investigator) (Date)

Phone number

APPENDIX B

Chedoke-McMaster Stroke Assessment

SCORE FORM Page 1 of 4

IMPAIRMENT INVENTORY: SHOULDER PAIN AND POSTURAL CONTROL

POSTURAL CONTROL: Start at Stage 4. Starting position is indicated beside the item or underlined. No support is permitted. Place an X in the box of each task that is accomplished. Score the highest Stage in which the client achieves at least two Xs.

SHOULDER PAIN

1	☐	constant, severe arm and shoulder pain with pain pathology in more than just the shoulder
2	☐	intermittent, severe arm and shoulder pain with pain pathology in more than just the shoulder
3	☐	constant shoulder pain with pain pathology in just the shoulder
4	☐	intermittent shoulder pain with pain pathology in just the shoulder
5	☐	shoulder pain is noted during testing, but the functional activities that the client normally performs are not affected by the pain
6	☐	no shoulder pain, but at least one prognostic indicator is present • Arm Stage 1 or 2 • Scapula malaligned • Loss of range of shoulder movt - flexion/abduction < 90° or external rotation < 60°
7	☐	shoulder pain and prognostic indicators are absent

☐ STAGE OF SHOULDER PAIN

POSTURAL CONTROL

1		☐	not yet Stage 2
2	Supine	☐	facilitated log roll to side lying
	Side lying	☐	resistance to trunk rotation
	Sit	☐	static righting with facilitation
3	Supine	☐	log roll to side lying
	Sit	☐	move forward and backward
	Stand	☐	remain upright 5 sec
4	Supine	☐	segmental rolling to side lying
	Sit	☐	static righting
	Sit	☐	stand
5	Sit	☐	dynamic righting side to side, feet on floor
	Sit	☐	stand with equal weight bearing
	Stand	☐	step forward onto weak foot, transfer weight
6	Sit	☐	dynamic righting backward and sideways with displacement, feet off floor
	Stand	☐	on weak leg, 5 seconds ☐ sec
	Stand	☐	sideways braiding 2 m
7	Stand	☐	<u>on weak leg:</u> abduction of strong leg
	Stand	☐	tandem walking 2 m in 5 sec
	Stand	☐	walk on toes 2 m

☐ STAGE OF POSTURAL CONTROL

Chedoke-McMaster Stroke Assessment
SCORE FORM **Page 2 of 4**

IMPAIRMENT INVENTORY: STAGE OF RECOVERY OF ARM AND HAND

ARM and HAND: Start at Stage 3. Starting position: sitting with forearm in lap in a neutral position, wrist at 0° and fingers slightly flexed. Changes from this position are indicated by underlining. Place an X in the box of each task accomplished. Score the highest Stage in which the client achieves at least two Xs.

ARM

1
- [ ] not yet Stage 2

2
- [ ] resistance to passive shoulder abduction or elbow extension
- [ ] facilitated elbow extension
- [ ] facilitated elbow flexion

3
- [ ] touch opposite knee
- [ ] touch chin
- [ ] shoulder shrugging > ½ range

4
- [ ] extension synergy, then flexion synergy
- [ ] shoulder flexion to 90°
- [ ] elbow at side, 90° flexion: supination, then pronation

5
- [ ] flexion synergy, then extension synergy
- [ ] shoulder abduction to 90° with pronation
- [ ] shoulder flexion to 90°: pronation then supination

6
- [ ] hand from knee to forehead 5 x in 5 sec.
- [ ] shoulder flexion to 90°: trace a figure 8
- [ ] arm resting at side of body: raise arm overhead with full supination

7
- [ ] clap hands overhead, then behind back 3 x in 5 sec
- [ ] shoulder flexion to 90°: scissor in front 3 x in 5 sec
- [ ] elbow at side, 90° flexion: resisted shoulder external rotation

- [ ] **STAGE OF ARM**

HAND

1
- [ ] not yet Stage 2

2
- [ ] positive Hoffman
- [ ] resistance to passive wrist or finger extension
- [ ] facilitated finger flexion

3
- [ ] wrist extension > ½ range
- [ ] finger/wrist flexion > ½ range
- [ ] supination, thumb in extension: thumb to index finger

4
- [ ] finger extension, then flexion
- [ ] thumb extension > ½ range, then lateral prehension
- [ ] finger flexion with lateral prehension

5
- [ ] finger flexion, then extension
- [ ] pronation: finger abduction
- [ ] hand unsupported: opposition of thumb to little finger

6
- [ ] pronation: tap index finger 10 x in 5 sec
- [ ] pistol grip: pull trigger, then return
- [ ] pronation: wrist and finger extension with finger abduction

7
- [ ] thumb to finger tips, then reverse 3 x in 12 sec
- [ ] bounce a ball 4 times in succession, then catch
- [ ] pour 250 ml. from 1 litre pitcher, then reverse

- [ ] **STAGE OF HAND**

Chedoke-McMaster Stroke Assessment
SCORE FORM **Page 3 of 4**
IMPAIRMENT INVENTORY: STAGE OF RECOVERY OF LEG AND FOOT

LEG: Start at Stage 4 with the client in crook lying. FOOT: Start at Stage 3 with the client in supine. Test position is beside the item or underlined. If not indicated, the position has not changed. Place an X in the box of each task accomplished. Score the highest stage in which the client achieves at least two Xs. For "standing" test items, light support may be provided but weight bearing through the hand is not allowed. Shoes and socks off.

Stage	Position	LEG	Stage	Position	FOOT
1		☐ not yet Stage 2	1		☐ not yet Stage 2
2	Crook lying	☐ resistance to passive hip or knee flexion ☐ facilitated hip flexion ☐ facilitated extension	2	Crook lying	☐ resistance to passive dorsiflexion ☐ facilitated dorsiflexion or toe extension ☐ facilitated plantarflexion
3		☐ <u>abduction</u>: adduction to neutral ☐ hip flexion to 90° ☐ full extension	3	Supine Sit	☐ plantarflexion > ½ range ☐ some dorsiflexion ☐ extension of toes
4	 Sit	☐ hip flexion to 90° then extension synergy ☐ bridging hip with equal weightbearing ☐ knee flexion beyond 100°	4		☐ some eversion ☐ inversion ☐ <u>legs crossed</u>: dorsiflexion, then plantarflexion
5	Crook lying Sit Stand	☐ extension synergy, then flexion synergy ☐ raise thigh off bed ☐ hip extension with knee flexion	5	 Stand	☐ <u>legs crossed</u>: toe extension with ankle plantarflexion ☐ <u>sitting with knee extended</u>: ankle plantarflexion, then dorsiflexion ☐ <u>heel on floor</u>: eversion
6	Sit Stand	☐ lift foot off floor 5 x in 5 sec. ☐ full range internal rotation ☐ trace a pattern: forward, side, back, return	6		☐ <u>heel on floor</u>: tap foot 5 x in 5 sec ☐ <u>foot off floor:</u> foot circumduction ☐ <u>knee straight, heel off floor</u>: eversion
7	Stand	☐ <u>unsupported</u>: rapid high stepping 10 x in 5 sec ☐ <u>unsupported</u>: trace a pattern quickly; forward, side, back, reverse ☐ <u>on weak leg with support</u>: hop on weak leg	7		☐ heel touching forward, then toe touching behind, repeat 5 x in 10 sec ☐ <u>foot off floor:</u> circumduction quickly, reverse ☐ up on toes, then back on heels 5 x

☐ **STAGE OF LEG**   ☐ **STAGE OF FOOT**

APPENDIX C

ACTIVITIES AND PARTICIPATION

FIM™ instrument

	Admission	
Self-Care		
41. Eating		
42. Grooming		
43. Bathing		
44. Dressing—Upper Body		
45. Dressing—Lower Body		
46. Toileting		
Sphincter		
47. Bladder Management		
48. Bowel Management		
Transfers		
49. Bed, Chair, Wheelchair		
50. Toilet		
51. Tub, Shower		
Locomotion		
52. Walk/Wheelchair		○ Walk ○ Wheelchair ○ Both
53. Stairs		
Communication		
54. Comprehension		○ Auditory ○ Visual ○ Both
55. Expression		○ Vocal ○ Non-Vocal ○ Both
Social Cognition		
56. Social Interaction		
57. Problem Solving		
58. Memory		

FIM Levels
NO HELPER
7 Complete Independence (Timely, Safely)
6 Modified Independence (Device)

HELPER
Modified Dependence
5 Supervision
4 Minimal Assistance (Subject = 75% +)
3 Moderate Assistance (Subject = 50% +)
Complete Dependence
2 Maximal Assistance (Subject = 25% +)
1 Total Assistance (Subject = 0% +)

(NOTE: Leave no blanks; enter 1 if not testable due to risk)

APPENDIX D

Action Research Arm Test

Subject #: _____ Date: _______________

Subtest	Items	Time limit (s)	Score
Grasp	Block 2.5 cm	3.6	
	Block 5 cm	3.5	
	Block 7.5 cm	3.9	
	Ball 7.5 cm	3.8	
	Stone	3.6	
	Block 10 cm	4.2	
Grip	Tube 2.25 cm	4.2	
	Tube 1 cm	4.3	
	Place washer over bolt	4.0	
	Pour water from glass to glass	7.9	
Pinch	Large marble: first finger and thumb	3.8	
	Large marble: second finger and thumb	3.8	
	Large marble: third finger and thumb	4.1	
	Small marble: first finger and thumb	4.0	
	Small marble: second finger and thumb	4.1	
	Small marble: third finger and thumb	4.4	
Gross Movements	Move hand to mouth	2.4	
	Place hand on top of head	2.7	
	Place hand behind head	2.7	