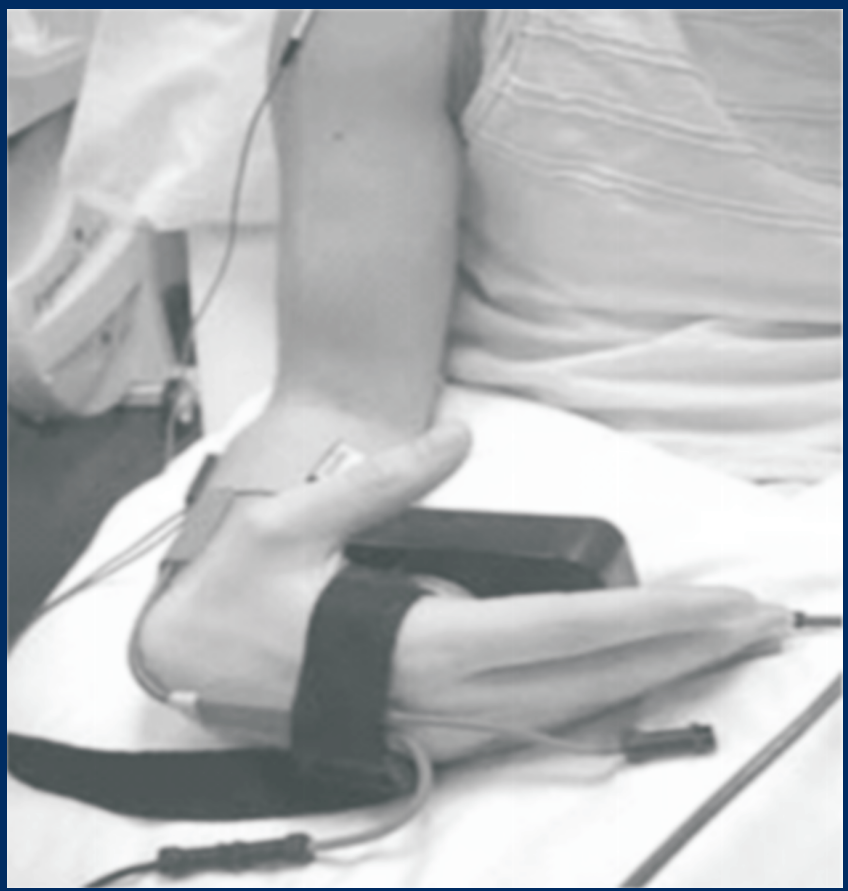
DOES SPASTICITY INTERFERE WITH FUNCTIONAL RECOVERY AFTER STROKE?

A novel approach to understand, measure and treat spasticity after acute stroke.



Shweta Malhotra

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A NOVEL APPROACH TO UNDERSTAND, MEASURE AND TREAT SPASTICITY AFTER ACUTE STROKE.

Shweta Malhotra

Address of Correspondence:

Shweta Malhotra
Roessingh Research and Development
P O Box 310
7500 AH Enschede
The Netherlands
switipi@hotmail.co.uk

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Chapter 1

GENERAL INTRODUCTION

Introduction

A stroke or acute ischemic cerebrovascular syndrome is a medical emergency that causes permanent neurological damage, complications or death. Stroke is both a leading cause of death and disability worldwide.[1] Half of all the patients who survive a stroke have impairments that lead to loss of upper limb function.[2, 3] Spasticity, contractures and pain are common impairments that may develop rapidly after stroke [4,5,6] and are considered to be major contributors to secondary complications, which cause limited mobility, chronic disability, delays in recovery of the paretic limb and problems in rehabilitation.

In the field of rehabilitation medicine, spasticity is classified as a positive phenomenon characterized by an exaggerated sensory-motor response, elicited during passive stretch. Despite the importance of spasticity; there is as yet no single agreed definition of this phenomenon. Moreover, there is no consensus on a valid technique used for measuring spasticity. Post stroke spasticity may be maladaptive and interfere with a person's ability to perform functionally useful movement.[7, 8] However, there is little evidence to prove that either a clinically important association between spasticity and secondary complications exists or that spasticity interferes with functionally useful movement.

Pathophysiology of spasticity:

The continuous reconsideration and revision of the definition of spasticity, reflects the diversity of its manifestations and that its pathophysiology, is still debated and not completely understood.[9] Spasticity is usually associated with a lesion (or lesions) involving both the ''pyramidal'' and ''parapyramidal'' systems (the cortico-reticular pathways at the level of the cortex or internal

capsule, and the reticulospinal and vestibulospinal tracts at the level of the spinal cord). [8] The location of the lesion also plays a role in determining the character of spasticity. [9, 10, 11]

It would appear that activity in other afferent pathways (e.g. cutaneous), supraspinal control pathways (or systems) and even changes in the a-motor neurone may also contribute to the signs and symptoms associated with spasticity and other positive features of the UMN syndrome. [12] Moreover, the onset of spasticity is likely to be contingent upon a plastic rearrangement in the central nervous system, and possibly the sprouting of axonal fibers.[10, 13] This may result in overactivity of the muscles and exaggerated reflex responses to peripheral stimulation. [11] In spastic people, a further decrease of presynaptic inhibition and reciprocal inhibition has not been found during contraction.[14]

Objectives and outline of thesis

The focus of this thesis was on identifying if spasticity on the wrist after an acute stroke interferes with functional recovery of the upper limb. To achieve this objective, it was crucial to have a clear understanding of the phenomenon of spasticity, identify a valid measurement technique and investigate a recognized method to treat spasticity.

In C**hapter 2**, a systematic review is described on whether there is a consistent definition and unified assessment framework for the term 'spasticity'. The congruence between the definitions of spasticity and the corresponding methods of measurement were also explored. The review included search of publications with keywords spasticity and tone between the years 1980 to 2006.

Chapter 3 quantifies the agreement between the three clinically usable methods of measuring spasticity. Patients with a first stroke who had no useful functional movement in the upper limb within six weeks from stroke onset were enrolled in the study. Spasticity at the wrist joint was simultaneously measured using a common clinical measure (modified ashworth scale), a

biomechanical measure (resistance to passive movement) and a neurophysiological measure (muscle activity).

The trial in **Chapter 4** reports the time course of development of spasticity and contractures at the wrist after stroke. This chapter also explores the association between spasticity and functional recovery of the upper limb. Spasticity was measured by quantifying muscle activity during passively imposed stretches at two velocities. Contractures were measured by quantifying passive range of movement and stiffness. Upper limb functional movement was assessed using the ARAT. All assessments were conducted at baseline, and at 6, 12, 24 and 36 weeks after recruitment.

Chapter 5 reports the results of the randomized controlled trial that investigates whether treatment with surface neuromuscular electrical stimulation to the wrist extensors improves recovery of arm function in severely disabled patients with stroke. Patients were randomized to surface neuromuscular electrical stimulation using surface electrical stimulators for 30 minutes twice in a working day for 6 weeks in addition to standardized upper limb therapy or just standardized upper limb therapy.

Chapter 6 reports secondary analysis findings from the phase II, randomized controlled single-blinded study. This study investigated the effects of surface neuromuscular electrical stimulation applied early after acute stroke to the wrist and finger extensor muscles on upper limb pain, spasticity and contractures in patients with no functional arm movement.

Finally **Chapter 7** presents a general discussion by integrating and discussing findings of different studies. Implications of scientific work of present thesis for clinical practice are presented and suggestions for further research are proposed.

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Chapter 2

SPASTICITY, AN IMPAIRMENT THAT IS POORLY DEFINED AND POORLY MEASURED.

S Malhotra , A Pandyan, C Day, PW Jones, H Hermens

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Abstract

Objective: To explore, following a literature review, if there was a consistent definition and a unified assessment framework for the term 'spasticity'. The congruence between the definitions of spasticity and the corresponding methods of measurement were also explored.

Data sources: The search was performed on the electronic databases of Web of Science, Science Direct and Medline.

Review methods: A systematic literature search of publications written in English between the years 1980 to 2006 was performed with the following keywords: spasticity and tone. The search was limited to the following keywords stroke, hemiplegia, upper, hand and arm.

Results: Two hundred and fifty references contributed to this review [190 clinical trials, 46 literature reviews, and 14 case reports]. Seventy-eight used the Lance definition; 88 equated spasticity with increased muscle tone, 78 provided no definition and six others used their own definitions for spasticity. Most papers used a single measure some used more than one. Forty-seven papers used neurophysiological methods of testing, 228 used biomechanical methods of measurement or assessment, 25 used miscellaneous clinical measures (e.g. spasm frequency scales) and 19 did not explicitly describe a measure.

Conclusion: The term spasticity is inconsistently defined and this inconsistency will need to be resolved. Often, the measures used did not correspond to the clinical features of spasticity that were defined within a paper (i.e. internal validity was compromised). There is need to ensure that this lack of congruence is addressed in future research.

Introduction

Following an upper motor neurone (UMN) lesion, a patient can present with a variety of sensory-motor and cognitive problems. The sensory motor problems can be broadly classified as "positive features" (i.e. abnormal reflex responses, spasticity, spasms, clonus and dyssynergic movement patterns) and "negative features" (i.e. muscle weakness, loss of dexterity and fatigability). Although both positive and negative features contribute to the resulting functional loss, in patients with an UMN lesion, there is a substantial focus on one particular positive feature "spasticity". This focus on spasticity results from the premise that spasticity interferes with functional recovery and lead to secondary complications such as contractures, weakness, and pain.[1, 2]

Spasticity was originally associated with a soft yielding resistance that appeared only towards the end of a passive stretch and an increased amplitude stretch reflex.[3] Two decades later, during a post conference discussion, it was suggested that spasticity could be defined as "*a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) and increased tendon jerks resulting from disinhibition of the stretch reflex, as one component of an upper motor neurone lesion*". [4-6] The North American Task Force for Childhood Motor Disorders, attempting to improve the precision of the above definition, have suggested that spasticity should be redefined as "*a velocity dependent increase in hypertonia with a catch when a threshold is exceeded*".[7] More recently, the members of the SPASM consortium, putting forward the argument that the existing definition were to narrow for clinical purposes, suggested that the definition be widened to "*disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles*".[8] This latter definition purports to shift the focus of the definition to encompass current understanding of pathophysiology and clinical practice.

For research into spasticity to be valid it is important that the measures or outcome measures of spasticity are also valid and reliable. A prerequisite for identifying valid and reliable measurement(s) is either precise definition(s) or an unambiguous description(s). The aims of this work were to explore whether such a definition existed and, if one did, where the measures used were congruent to the same definition. As the literature related to the measurement and treatment of spasticity in the upper motor neurone syndrome is vast and all measurements developed for the lower limb have also been adapted for use in the upper limb, the search to support this review was limited to the articles related to upper limb spasticity post stroke from (Web of Science, Science Direct and Medline) between the periods 1980 and 2006.

Methods

A search was performed by a single reviewer on published articles between 1980 (following the first formal definition by Lance) and 2006 on the following three electronic databases: Web of Science, Science Direct and Medline, with keywords:

1) spasticity
2) tone
3) stroke
4) hemiplegia
5) upper
6) hand
7) arm

Search combinations were:

8) 1 or 2
9) 3 or 4
10) 5 or 6 or 7
11) 8 and 9 and 10

Exclusion Criteria:

Animal studies, duplicates and references that were written in languages other than English were excluded from this review.

Inclusion criteria:

Published references were fully reviewed if they fell into one of the following categories:

- characterization of spasticity
- measurement of spasticity
- treatment of spasticity
- modeling any association between spasticity and function, and
- literature reviews on any of the above

Subsequent to having identified a suitable article from the title and abstract, the whole paper was read and scanned to extract the necessary data for the paper. These were definition and outcome measures used to assess spasticity. All the data including author details, year of publication, title of article, the definition of spasticity and the measures used were stored on a excel spreadsheet.

Results

The searches identified 272 papers from Medline, 53 from Science Direct and 279 from Web of Science. After excluding duplicates and applying the inclusion criteria, 250 references contributed to the review. There were 190 clinical trials, 46 literature reviews, and 14 case reports. (The list of references not cited in this paper can be found at: ftp://ftp.keele.ac.uk/pub/pta38/Clinical_Rehabilitation)

Results for definition of spasticity:

Much of the research has not worked to a common definition (Table 1). Thirty one percent of the articles did not define spasticity. 31% percent of the articles cited the definition proposed by Lance in 1980 [4] and 35% percent of the articles equated spasticity with *increased muscle tone* but no specific definition of altered muscle tone was provided. Other terms that were used within this context were "abnormal tone", "hypertonia" and "hyperreflexia" however these terms were also not defined explicitly. Two examples to illustrate the variability of definitions are cited below

A condition of paralysis or muscular weakness associated with hyperreflexia, the symptoms of which include increased resistance to manipulation, exaggeration of the deep reflexes, and clonus. [9]

An exaggerated activity of the stretch reflex loop with a length-dependent increase in tonic reflexes and a velocity-dependent increase in phasic reflexes.[10]

Three percent of the articles equated spasticity with abnormal and involuntary muscle activity. [8]

Table 1: This table illustrates that majority of the articles have either used muscle tone to define spasticity or have not used any definition.

Measures used:	***Definitions used:***			
	Lance	**Muscle Tone**	**None**	**Others**
Clinical Trials	59	69	58	4
Literature Reviews	16	13	15	2
Case Reports	3	6	5	0
Total	**78 (31%)**	**88 (35%)**	**78 (31%)**	**6 (3%)**

Results for measurement of spasticity:

Although most papers subscribed to a single definition (the others did not cite any specific definition), 314 different outcome measures were identified from the 250 papers (some articles used more than one outcome measure for spasticity). These measures could be clustered as described below:

15% (47 articles) attempted to measure aspects of spasticity directly, i.e. neurophysiological testing methods were used (37 used surface electromyographic (EMG) activity to quantify the muscle response to stretch, 9 either used the H-reflex response or the H-reflex standardized to the M-wave max, 1 used F-wave response).

71% percent used biomechanical measures/assessment (228 articles) to quantify spasticity indirectly. The perturbations and measurement methods varied:

a) instrumented measurement of stiffness during a controlled motorized perturbation (controlled velocity, controlled torque).
b) instrumented measurement of stiffness during a manual perturbation (uncontrolled velocity).
c) assessment of stiffness using clinical scales following manual perturbation (Ashworth Scale, Modified Ashworth Scale, Tardieu Scale, Clinical score for tone, Tone Assessment Scale, or Global assessment scale).

8% (25 articles) used miscellaneous methods consisting of a combination of clinical scales (e.g. [11]) and routine clinical tests (spasm frequency score, biceps tendon reflex, postural changes, passive range of movement or drawing test).

6% (19 articles) did not use/describe the outcome measure (Neurological consultation or none).

Results for congruence between definition and measurement of spasticity:

Table 2: This table illustrates the congruence between the number of each definition and each measurement used:

Measures used:	***Definitions used:***		
	Lance	**Muscle Tone**	**Others(Spasm)**
Clinical Scales using an externally imposed stretch	33	60	2
Instrumented biomechanical measures	7	3	0
Neurophysiological	8	4	1
Hybrid (a combination of neurophysiological & biomechanical)	13	3	0
Posture	1	3	0
No measure described	0	2	1
Total	**62**	**75**	**4**

Congruence between definition and measurement was explored using the data from case reports and controlled clinical trials. Of the 204 such articles, 63 could not be used, as these did not define spasticity.

Amongst the 75 articles that defined spasticity as increased muscle tone; 60 used clinical scales to quantify stiffness, three used biomechanical measures of stiffness, four used neurophysiological measure, three used a combination of both biomechanical and electrophysiological measures, three used clinical measures of posture/range of movement and two did not describe the measure.

Amongst the 62 articles that cited Lance's definition; 33 used clinical scales to quantify aspects of stiffness, seven used instrumented biomechanical methods to quantify stiffness, eight used neurophysiological measures and 13 used a combination of both a biomechanical and electrophysiological measures and one measured resting posture.

Among the four articles that defined spasticity as muscle overactivity; one used muscle activity response to an external perturbation, two the Modified Ashworth Scale /Ashworth Scale and one did not describe a measure.

Discussion

The key findings from this review are that (a) the term spasticity is inconsistently defined and (b) the (outcome) measures often did not correspond to the definition (or the description of the key clinical features). Incongruence between definition(s) and measurement(s) can significantly compromise the internal validity of research and will need to be robustly addressed. This discussion will consist of two major sections; the first will critically evaluate the validity of existing definition and the second will make recommendations on how to select an appropriate measure from the 'basket of measures' identified. While the focus of this paper is on spasticity it is important to note other such anomalies can be found throughout the rehabilitation literature a typical example being "core stability".

A critical evaluation of existing definitions

There are two broad approaches taken with respect to definitions of spasticity. The majority attempt at providing narrow and precise description of spasticity. Whilst this approach is probably the most valid it has not worked as well as it should have as these narrow definitions often do not conform to common clinical presentations.[1,12]

The second type of definition takes the diametrically opposite approach, i.e. the definitions attempts to provide an umbrella statement to catch all possible variable interpretations of the phenomenon (the spasm definition is the only one in this category). [8] Whilst the latter type of definition is scientifically weaker it does provide a framework from which narrow and precise definitions can be further developed. With respect to spasticity a decision has to be made as to whether the scientific

community continues subscribing to traditional narrow definitions or take a step backwards to using broader definitions. Based on this review it would appear that the time has come to move away from the existing narrow definitions as our current understanding does seem to challenge the validity of most of these definitions as discussed below.

The first formal definition for the term spasticity was proposed by Lance [4 – 6] and there is one important assumption being made, i.e. the increase in stretch reflex mediated muscle activity could be reliably measured by quantifying/assessing muscle tone (i.e. the stiffness) encountered when stretching a relaxed muscle during an externally imposed perturbation. Since the publication of this definition our understanding of the pathophysiology associated with spasticity has significantly progressed and some of the early assumptions made in the original definitions will need to be reconsidered.

In addition to increased stretch reflex activity, the abnormal muscle activity may result from changes in the membrane properties of the alpha-motor neurone and/or changes in the threshold of activation of the alpha-motor neurone.[13] The latter is influenced by a variety of pathways these are - group Ia presynaptic inhibition, group Ia reciprocal inhibition (from antagonist), recurrent Ib inhibition, group II afferents, group III & IV cutaneous afferents, and decreased recurrent renshaw inhibition.[13-15]

Both Denny-Brown and Lance seem to suggest that hyperexcitable deep tendon reflexes are a discerning feature of spasticity. [3-7]Current evidence suggests that this may not be the case and that the variability of the reflex response in people with spasticity is high[15, 16] and may not be dissimilar to that of a population with no spasticity.

Indirectly measuring muscle activation by quantifying/assessing resistance to an externally imposed movement is fundamentally flawed as this is confounded measure. The factors that can confound measurement of stiffness are the mechanical properties of the musculoskeletal structures being stretched, the compliance of the patient (i.e. the ability to relax) and muscle activity at rest. These confounding factors can contribute to substantial inter and intra subject variations. A further confounder of modeling the impact of muscle activity on stiffness is related to modeling the force generation during an eccentric contraction.[8]

To exclusively attribute a velocity dependent increase in resistance to an externally imposed movement to spasticity may also be inaccurate. The muscle-tendon complex behaves as a visco-elastic material and will inherently demonstrate the same velocity dependent behavior in the absence of any muscle activation.[17]

A substantial proportion of the literature, ignoring the Lance Definition[4], defines spasticity as an increase in muscle tone (i.e. an increase in the resistance to an externally imposed passive movement). Although it would appear to be a pretty straightforward definition, there is a potential source of ambiguity in this definition also. The word "tone" can also be defined as state of readiness to act/contract (i.e. innervation status) [e.g. 18]. Inferring as to which of these two definitions are used is normally easy in papers discussing adult spasticity. However, this may not necessarily be the case in papers discussing spasticity in cerebral palsy. Using the same logic as previously discussed, the validity of using increased stiffness as an indicator of spasticity is flawed.

The North American Task for Childhood Motor Disorders attempts at making the Lance definition[4] more precise by adding additional details.[7] This modification has further confounded the original definition by introducing a new term [described as a "catch"] and one precondition [the catch occurs

when a threshold has been exceeded]. The key differentiating feature of spasticity, as per this definition, is the occurrence of a catch when some arbitrary (velocity) threshold is exceeded. Therefore, one has to conclude that the modifications do not provide any additional benefit to the original Lance definition.

The SPASM consortium attempted to widen the definition of spasticity in order to be able to reflect the vagaries in both research and clinical practice. This definition shifts the focus away from measurement of stiffness to the measurement of the "abnormal" muscle activity. By doing this the term "spasticity" can now be used to described most of the "positive features" associated with the UMN syndrome. However, this definition may exclude abnormal movement patterns triggered during voluntary movement[*], and will exclude all the negative features associated with the upper motor neurone syndrome. Whilst such a definition may be clinically relevant the term can lose usefulness if researchers fail to identify which particular aspect of spasticity is being measured or studied.

In summary, it is reasonable to conclude that there is no adequate definition of the phenomenon of spasticity. Of the definitions currently available the broader definition proposed by the SPASM consortium provides a starting point for the development of future clinically usable definition.

Recommendations for measurement

To add to this problem of variable definitions, the framework used to underpin the measurement of spasticity is also substantially variable. Based on the international classification of functioning, disability and health (ICF) framework[19], spasticity can be classified as an impairment. So any attempt at using indirect measures of activity (e.g. measures of function) or participation (i.e. quality

[*] **NB**: The phenomenon of associated reactions can also be observed in neurologically intact subjects when attempting

of life) is flawed. The main reason for this is that there is as yet insufficient evidence of a causal relationship between the impairment (i.e. spasticity) and the various measures of activity limitation and/or participation restrictions. The currently available measures of impairment can be classified as neurophysiological or biomechanical measures. These methods have been extensively reviewed in the literature [8,16, 20 - 22] and will only be described in brief to set the scene for identifying optimal measurement.

Neurophysiological measures provide the most direct way of studying (i.e. quantifying and classifying) spasticity. Most existing measures, i.e. the H-reflex, F-wave, response of a muscle (measured using electromyography) to an externally imposed perturbation, only measure aspects of spasticity. The H-reflex bypasses the spindle and measures excitability in the reflex arc. The F-wave is primarily a measure of excitability of the α-motor neurone. Studying the muscle response tap (or vibration) will provide a measure of excitability in the stretch reflex pathway. Studying the muscle response to an externally imposed passive stretch of the joint also provides information on the excitability of the stretch reflex pathways especially. Ideal measures, when studying the muscle response to an externally imposed perturbation are threshold angles and patterns of muscle activation. All of the above measures can be confounded by the resting levels of muscle activity [which is commonly described as "spastic dystonia"], [23] the ability to relax, pain, temperature and other environmental conditions, and cognitive capabilities[24]. Not surprisingly, most of these measures demonstrate a high degree of variability.[8]

Biomechanical measures can at best only provide an indirect method of measuring spasticity. Depending on the primary assumptions made one can measure aspects of spasticity by quantifying stiffness, posture at rest, range of movement. The one common assumption in all these cases is that biomechanical measures provide a valid reflection of the underpinning neurophysiological

phenomenon (abnormal muscle activation to the externally imposed perturbation). Biomechanical measures can be administered in a variety of ways and these have also been extensively reviewed in the literature.[20] If instrumented methods are used either interval level (instrumented hand held measures) or ratio level (e.g. threshold angle measures using controlled displacement methods) measurement of spasticity is possible. If clinical scales are used either ordinal level (e.g. Ashworth scale) or nominal level (e.g. Tardieu method of measurement) measurement of spasticity is possible. It is crucial to recognize that changes in the biomechanical properties of the musculo-tendenous and joint structures can significantly confound all biomechanical measurement and therefore significantly compromise validity of these measurements [25].

The key problem in the current literature is the lack of congruence between definition and measurement and this can lead to a compromise of internal validity [e.g. 26]. The solution to this problem is fairly simple, i.e. both researchers and clinicians will need to ensure that any outcome measures used in spasticity related research is valid and congruent to the definition. Furthermore, when measurements are selected it is essential to minimize the effect of confounding factors not related to the definition in use. This would mean that wherever possible the aim should be on standardizing to neurophysiological measures (as described above) or valid clinical scales (e.g. spasm frequency scale, myotatic reflex scale, original Tardieu scale) to classify spasticity. As most biomechanical measures are confounded using them in isolation is not advisable or recommended. However, using biomechanical measures in conjunction with simultaneous measurement of muscle activity (using surface or needle electromyography) may be recommended. In addition to control of the environmental conditions and time of testing, if the methods of measurement are dependent on an externally imposed biomechanical perturbation the following will also need to be considered.

- Controlling the velocity of the externally imposed perturbation is not equivalent to controlling the stimulus to the afferent system. The main reasons for this are the polyaxial nature of the wrist

joint, the variations in the radius of rotation of the muscle-tendon units about a variable centre of rotation and the variability in the orientation of the ensemble of stretch receptors.

- The efferent response to any externally imposed perturbation will be influenced by the resting length of the muscle, the range of movement employed during the test, the acceleration and the amount of support provided to the limb segment under test.

There were a few limitations to this systematic review. Firstly, our search terms and database were narrow. Although unlikely, it is also possible that the spasticity related literature within the field of stroke rehabilitation may not be representative of the spasticity related literature in other conditions. In spite of these limitations we are of the view that the literature sampled for this review reflects the current state of the art with respect to spasticity related research in all neurological conditions. There is also a potential bias in this paper, i.e. two of the authors involved in this paper (ADP & HH) played a key role within the SPASM consortium.

Clinical Message:

- Define the term "spasticity" precisely (even if this does not conform to any published definition)
- Select a valid measure/outcome measure that is congruent with the cited definition
- Internal validity of research can be significantly compromised if measures are not congruent to definition

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Chapter 3

AN INVESTIGATION INTO THE AGREEMENT BETWEEN CLINICAL, BIOMECHANICAL AND NEUROPHYSIOLOGICAL MEASURES OF SPASTICITY.

S Malhotra, E Cousins, AB Ward, C Day, P Jones, C Roffe, A Pandyan

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Abstract:

Objective: To quantify agreement between three clinically usable methods of measuring spasticity.

Methods: Patients with a first stroke who had no useful functional movement in the upper limb within six weeks from stroke onset were eligible to participate. Spasticity at the wrist joint was simultaneously measured using three methods, during an externally imposed passive stretch at two (uncontrolled) displacement velocities. The measures used were a common clinical measure (modified Ashworth Scale), a biomechanical measure (resistance to passive movement) and a neurophysiological measure (muscle activity).

Results: One hundred patients (54 men and 46 women) with a median age of 74 years (range 43-91) participated. Median time since stroke was 3 weeks (range 1-6), the right side was affected in 52 patients and the left in 48 patients. Based on muscle activity measurement, 87 patients had spasticity. According to the modified Ashworth score 44 patients had spasticity. Sensitivity of modified Ashworth score, when compared to muscle activity recordings, was 0.5 and specificity was 0.92. Based on muscle activity patterns, patients could be classified into five sub-groups. The biomechanical measures showed no consistent relationship with the other measures.

Conclusion: The presentations of spasticity are variable and are not always consistent with existing definitions. Existing clinical scales that depend on the quantification of muscle tone may lack the sensitivity to quantify the abnormal muscle activation and stiffness associated with common definitions of spasticity. Neurophysiological measures may provide more clinically useful information for the management and assessment of spasticity.

Introduction

Spasticity is a clinical condition that can develop after stroke.[1] The prevalence of post stroke spasticity is estimated to be 19% and 38% at three months and one year respectively.[2, 3] Spasticity is considered to be a major contributor to secondary complications such as contractures, weakness and pain.[3, 4] Spasticity may also impede voluntary movement and therefore can have a detrimental impact on the patient's ability to achieve functional goals and carry out activities essential for daily living. [4]

Despite the importance of spasticity there is as yet no single agreed definition of this phenomenon. There are at least four definitions for this phenomenon.[1, 5-7] A common construct underpinning all of these definitions is that spasticity is characterised by abnormal muscle activity. All but one of these definitions, i.e. the SPASM definition 1, suggests that this abnormal muscle activity will clinically present as an increase in muscle tone (which is defined as resistance encountered during an externally imposed passive stretch of a relaxed muscle). [5-7]

Much of our current understanding of spasticity in stroke has primarily resulted from studies that have assessed spasticity by measuring stiffness about a joint.[8, 9] Although these clinical measures of stiffness are easy to use, there is some evidence that these may have limited validity and reliability in terms of quantifying (abnormal) muscle activity, the primary pathophysiological manifestation of spasticity.[1, 10]

The aim of this study was to quantify the agreement between three clinically usable measures of spasticity that reflected the constructs that underpinned the definitions identified in the literature. Spasticity was quantified during an externally imposed passive stretch of a relaxed joint using two (uncontrolled) displacement velocities. The three measures used were the modified Ashworth scale

(a common clinical method for measuring muscle tone), the resistance encountered during passive stretching (biomechanical method), and, the quantity and patterns of electrical muscle activity during the passive movement (neurophysiological method).

Methods

Data for this convenience sample, observational study was obtained from the baseline measurement taken as a part of two existing studies that had full approval from the local research ethics committee (LREC approval 04/Q2604/1 and 03/34).

Patients within six weeks of a first stroke were eligible to participate if they scored zero in grasp section of the Action Research Arm Test.[11] (This test contains four domains of functional movement i.e. grasp, grip, pinch and gross movements and the maximum score a person can achieve is 57). Patients were excluded if they were medically unstable, had a previous medical history of osteoarthritis, rheumatoid arthritis or soft tissue injuries that resulted in contractures or had reduced range of movement in the wrist and fingers. No other selection criteria were used.

This study was based at the local stroke unit and recruitment was between the years 2005 – 2007. Eligible patients were recruited as study participants with valid signed consent or with signed assent from the next of kin (if the patient was not competent to sign the consent form). Patients and relatives were informed of the option to withdraw from the study of their own accord at any point. All measurements were taken by the clinical scientist (trained on the use of the modified Ashworth scale). The measurements were carried out at the patient's bedside on the acute stroke ward or stroke rehabilitation unit.

Outcome measures

Details of the medical history including age, gender, affected side and stroke subtype were established by interview and consultation of medical notes. Patients were examined neurologically and their stroke was classified as total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) and posterior circulation syndrome (POCS). [12] None of the selected patients had a haemorrhagic stroke.

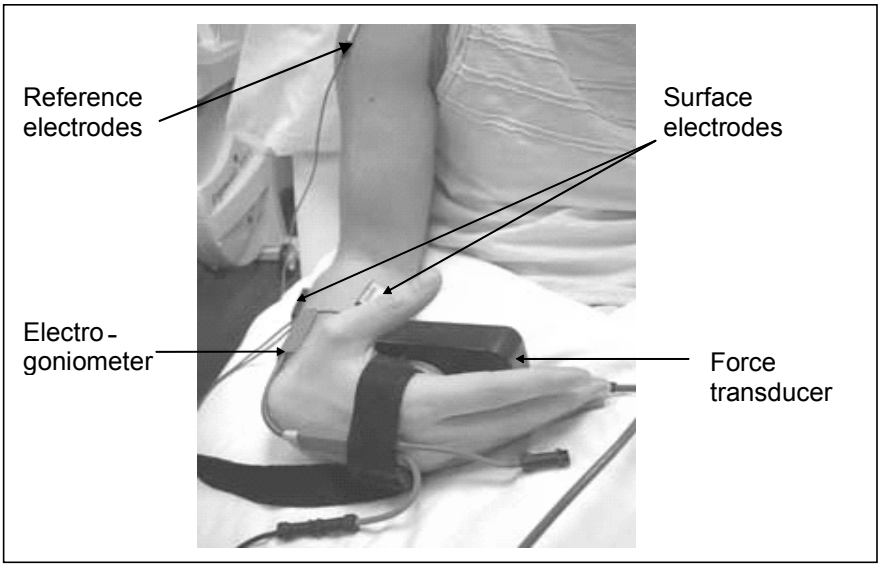
Spasticity was measured at the wrist flexors. For this, the participants were seated on a bed or chair with the forearm resting on their side. The participant's forearm was fully supported and positioned in a parallel direction to the ground, with the forearm in mid pronation-supination, the elbow flexed to approximately 90° and the shoulder slightly abducted (<10° estimated visually) during the tests. The long wrist flexors and extensors were identified.[13] The locations were cleaned with an alcohol wipe. Surface bipolar electromyography electrodes[a] were placed over the identified muscles [13] and the reference electrode was placed over the acromion. A flexible electrogoniometer[b] was placed across the lateral aspect of the wrist joint for measuring displacement. The transducers were then connected to the DataLink[c] for display and data collection purposes.

Figure 1: Experimental set up showing the forearm fully supported and positioned in a parallel direction to the ground, with the forearm in mid pronation-supination and the elbow flexed to approximately 90°. Surface bipolar electromyography electrodes[a] were placed over the long wrist flexors and extensors and the reference electrode was placed over the acromion. A flexible

[a] SX230 active surface electrodes for bipolar recording of muscle activity, Biometrics Ltd, UK
[b] SG 110 electrogoniometer, Biometrics Ltd, UK
[c] DLK900 dataLink, Biometrics Ltd, UK

[a] SX230 active surface muscle activity electrodes for bipolar recording, Biometrics Ltd, UK

electrogoniometer[b] was placed across the lateral aspect of the wrist joint for measuring displacement. For measuring spasticity, the wrist was first flexed as far as comfortable for the subject. Applying a force transducer on the palmar surface of the hand, the wrist was passively extended using a slow stretch from maximum flexion into maximum extension. The wrist was once again returned into flexion and the movement was repeated using a brisk stretch as per guidance for modified Ashworth scale.



The patient was instructed to completely relax and a 20 second recording of the baseline muscle activity was recorded. For measuring spasticity, the wrist was first flexed as far as comfortable for the subject. Applying a force transducer (to measure force used for stretching the forearm manually) on the palmar surface of the hand (Figure 1), the wrist was passively extended using a slow stretch from maximum flexion into maximum extension (manual count for three seconds). The wrist was once again returned into flexion and the movement was repeated using a brisk stretch as per

[b] SG 110 electrogoniometer, Biometrics Ltd, UK

guidance for modified Ashworth scale (duration of stretch being one second). [14] Force (measured Newtons), range of movement (measured in degree) and muscle activity (measured in millivolts - mV) were taken simultaneously during both the externally imposed passive extension. (**NB**: The modified Ashworth score was graded during the brisk stretch only.)

The data from the transducers were sampled at 1000Hertz and stored in a personal computer for analysis. As force (applied to produce the displacement), range of movement and duration of displacement were measured, it was possible to quantify both stiffness and velocity. The quantity of muscle activity was quantified from surface electromyography recordings.

Data was processed and analysed using a customised programme[c]. The raw electromyography data was notch filtered (50 Hertz) and smoothed using a root mean square procedure (window width 20 ms). [4] Instantaneous velocity for slow and fast movement, were calculated using the first difference approximation. From this the 'average velocity' was calculated. For each individual, wrist angles and muscle activity data were graphed as an XY scatter plot to classify muscle action (Figure 2). Then the area under the angle muscle activity plot was calculated to quantify muscle activity.

The angle versus force data was also presented as an XY scatter plot to determine the resistance to passive extension (stiffness) of muscle. The resistance to passive extension was calculated as the slope of the force angle curve between 10% - 90% available range of movement using standard linear regression techniques and the coefficient of determination (R^2). [15] Curves were classified as negligible stiffness if resistance to passive extension was less than 0.07 Newton/degree.[15] If resistance to passive extension was greater than 0.07 Newton/degree then the curve shapes were classified as linear if R^2 was greater than 0.6. Non-linear if R^2 was less than 0.6 (non-linear curves were further split into clasp knife phenomenon and non linear curve, depending on the shape).[15] The

[c] MathCAD 12, Mathsoft, USA

method of classification was used for the resistance encountered during the fast and slow movement respectively.

Statistical methods

Spasticity was described using the modified Ashworth score, stiffness and quantity of muscle activity. These measures produced different types of data i.e. nominal, ordinal, and interval/ratio data therefore a series of differing approaches had to be used to explore relationships.

- Descriptive data was used to present the quantification and patterns of muscle activity. Paired sample t-test was used to investigate if the muscle activity and resistance to passive extension differed between slow and fast movement.
- The analysis of variance (ANOVA) was used to explore if stiffness was significantly different between the various levels of the modified Ashworth grades. The paired sample t-test was also used to investigate if the differences in stiffness recorded between slow and fast changed with each modified Ashworth score.
- The association between the modified Ashworth score and muscle activity was explored with a 5x6 cross tabulation. The association between resistance to passive extension and muscle activity was explored by a 5x4 cross tabulation. A paired sample t-test was used to investigate if stiffness differed between slow and fast movement within subgroup created using the muscle activity patterns.

All procedures were carried out using SPSS for windows version 14 (SPSS Inc., Chicago, IL, USA).

Results:

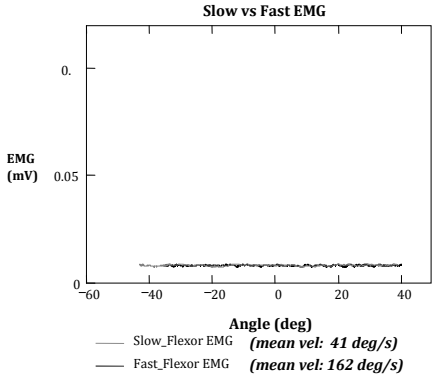
One hundred participants (54 men and 46 women; 52 with right side affected and 48 with left side affected) were recruited for the study. The median age was 74-years (range: 43-91) and the median time from stroke onset to recruitment was 3-weeks (range: 1-6). The stroke in 67 patients was

classified as TACS, 21 as PACS, 11 as LACS and one as POCS 12. All patients had negligible recovery of arm function scoring zero in the grasp section of Action Research Arm Test. The total scores were "0" in 97 patients, "1" in two patients and "3" in one patient respectively. The three patients, who had a score of more than "0" in total, did so because they were partially able to carry out one or more of the movements required in the gross movement section of the Action Research Arm Test.

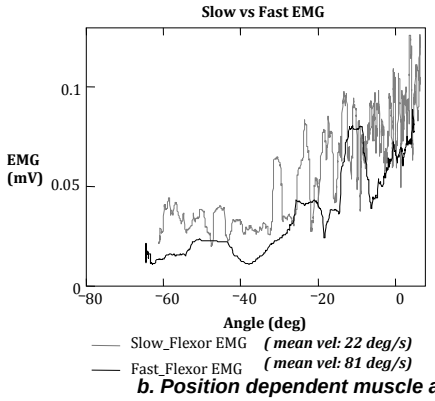
There was virtually no muscle activity at rest in most patients (mean = 0.006 mV, range = 0 – 0.02). The testing protocol was carried out as planned i.e. the velocity during the fast movement was always faster than that of the slow movement. The mean difference in the average velocity was 87 degree/second (SD = 36; range = 10 to 190). There were substantial inter subject variations.

Figure 2:

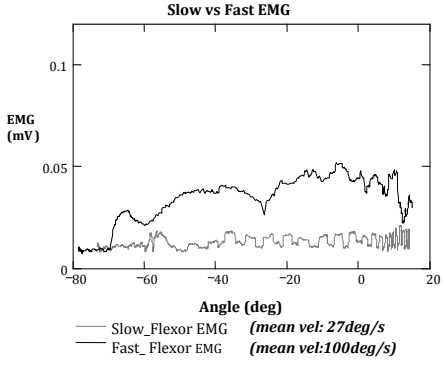
Muscle activity response (annotated as **EMG** on graphs) to an externally imposed passive extension movement about the wrist joint. The angle is plotted on the x-axis and flexor muscle activity on the y-axis. The muscle patterns demonstrated: a. negligible activity, b. Initiation of flexor muscles at -30 degrees as the muscle is stretched at a slow speed of 22 degrees/s, c. Flexor muscle being predominantly active at only a fast stretch of 100degrees/s, d. Increase in flexor muscle activity at 42 degrees during a slow stretch and at -17 degrees during a fast stretch, e. Early manifestation of the flexor muscles at -60 degrees which dies down during end range of movement.



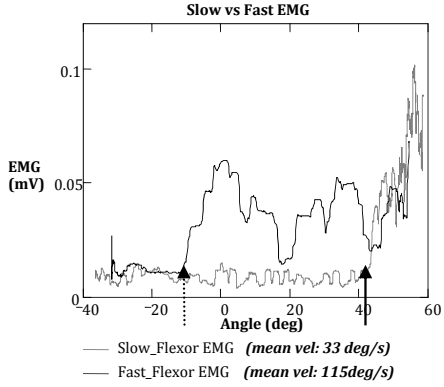
a: No/Negligible muscle activity



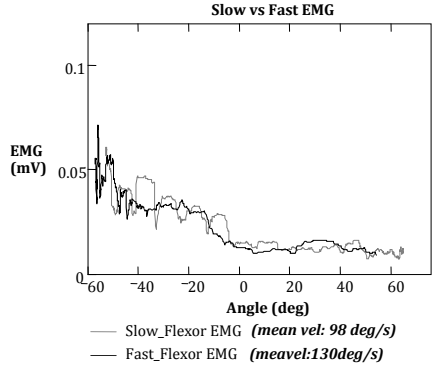
b. Position dependent muscle activity



c: Velocity dependent muscle activity



d. Both (Position+Velocity) muscle activity



e: Early Catch

Thirteen patients showed no abnormal activity during an externally imposed stretch but 87 did (Figure 2). Abnormal muscle activity was seen from as early as one week after stroke (see Appendix). Depending on muscle activity, pattern responses were classified into five groups.

1. No/negligible muscle activity: Negligible muscle activity during both the slow and the fast stretch (Figure 2a) was seen in 13% of the sample (estimated 95% confidence interval (CI) for the population 7% to 21%).
2. Position-dependent muscle activity: The muscle activity increased as the muscles are stretched and the activity continued even when movement was stopped (at end range of stretch). The increase in muscle activity appeared to be independent of the velocity of stretch (Figure 2b). This was seen in 27% of the sample (estimated 95% CI for the population 19% to 36%).
3. Velocity dependent muscle activity**:** During slow stretch there is negligible muscle activation but there was a subsequent increase in muscle activity during the fast stretch (Figure 2c). This was seen in 22% of the sample estimated 95% CI for the population 15 % to 31%.
4. Position and velocity dependent muscle activity**:** Increased abnormal muscle activity during both slow and fast stretch. Figure 2d shows an example of this pattern in which movement related increase in flexor muscle activity is evident during the end range of movement (around 42 degrees 'unbroken arrow'). This increase is independent of velocity. In addition during the fast stretch the muscle activity was trigged in the early part of the movement (around -10 degrees 'dotted arrow'). This was seen in 37% of the sample estimated 95% CI for the population 28% to 47%.
5. Early Catch**:** Early activation of the flexor muscles just as the joint is extended and this activity reduces as the muscle lengthens (Figure 2e). This was seen in 1% of the sample estimated 95% CI for the population 0.1% to 5%.

The muscle activity during the slow stretch was 0.013 mV (Range = 0.001 to 0.16), and during fast stretch was 0.02 mV (range = 0.001 to 0.2). The difference in the quantity of muscle activity between slow and fast stretch was statistically significant ($p < 0.01$, 95% CI = 0.005 to 0.01) for the whole group. Significant differences were mainly observed within the "velocity" subgroup and the "position + velocity" subgroup (Table 1).

Table I: A table summarising the paired sample t-test used to investigate if the muscle activity and stiffness differed between slow and fast movement. The differences in the quantity of muscle activity during slow and fast were only significant within two groups (position + velocity, velocity) of the muscle activity patterns whereas that of stiffness were not significant within each group of the muscle activity patterns.

Muscle activity Patterns	**Mean quantity of muscle activity during stretch mV (Standard Deviation)**			**95% Confidence Interval mV**	**Mean stiffness during stretch Newton/degree (Standard Deviation)**			**95% Confidence Interval Newton/ degree**
	Slow	**Fast**	**Mean diff**		**Slow**	**Fast**	**Mean diff**	
no/negligible spasticity	0.005 (0.00)	0.008 (0.01)	0.003 (0.01)	(-0.003)-(0.008)	0.01 (0.49)	0.03 (0.19)	0.02 (0.21)	(-0.15) - (0.10)
position dependent	0.01 (0.03)	0.02 (0.04)	0.01 (0.01)	(-0.005)-(0.01)	0.06 (0.14)	0.08 (0.15)	0.02 (0.06)	(-0.05) - (0.05)
velocity dependent	0.008 (0.01)	0.02 (0.01)	0.01 (0.01)	(0.045)-(0.015)	0.02 (0.32)	0.04 (0.18)	0.02 (0.17)	(-0.09) - (0.06)
position+ velocity dependent	0.01 (0.02)	0.02 (0.03)	0.01 (0.02)	(0.005)-(0.018)	0.07 (0.19)	0.11 (0.20)	0.04 (0.14)	(-0.09) - (0.03)

There was weak-to-moderate association between the curve shapes observed during the slow and the fast movement respectively ($\kappa = 0.332$, SE = 0.073, $p<0.01$) (Table 2).

Table II: Comparison of the curve shapes between slow and fast movement. Cohen's Kappa was used to study agreement between the curve shapes obtained during the slow and fast stretch respectively. There is a fair association in the curve shapes between the slow and the fast movement.

		Curve shapes during fast stretch				Total
		linear	no stiffness	clasp knife phenomenon	non linear	
Curve shapes during slow stretch	linear	**42**	7	0	4	**53**
	no stiffness	7	**13**	1	3	**24**
	clasp knife phenomenon	0	0	**1**	0	**1**
	non linear	9	9	0	**4**	**22**
Total		**58**	**29**	**2**	**11**	**100**

Stiffness during the fast movement did not systematically increase with an increase in the modified Ashworth scale scores ($F= 1.6$, $p= 0.2$). The stiffness for modified Ashworth scale grades "3" and "1+" were similar. Modified Ashworth scale score "0", "1" and "2" were similar. The mean stiffness during the slow stretch was 0.05 Newton/degree (range = -0.4 to 1), and during fast stretch was 0.08 Newton/degree (range = -0.2 to 1.1). The difference in stiffness between slow and fast stretch was statistically significant ($p = 0.047$, 95% CI = -0.056 to 0.000) for the whole group. (NB: The negative values may have occurred if subjects voluntarily assisted the movement. However, differences between stiffness during slow and fast stretch were not significant within each modified Ashworth grade (Table 3)

Table III: A summary of stiffness within each score of modified Ashworth scale. The analysis of variance was used to explore if stiffness was significantly different between the various levels of the modified Ashworth scale scores. The differences in stiffness between slow and fast stretch were not significant within each score of the modified Ashworth scale.

modified Ashworth scale scores	**Mean stiffness during stretch Newton/degree (Standard Deviation)**			**95% Confidence Interval Newton/degree**
	Slow	**Fast**	**Mean difference**	**p value**
0	0.03 (0.93)	0.06 (0.16)	0.03 (0.14)	(-0.65) - (0.10) 0.15
1	0.04 (0.08)	0.05 (0.11)	0.01 (0.06)	(-0.39) - (0.19) 0.49
1+	0.09 (0.32)	0.18 (0.34)	0.09 (0.20)	(-0.22) - (0.39) 0.15
2	0.06 (0.03)	-0.01 (0.11)	-0.07 (0.14)	(-0.15) - (0.29) 0.38
3	0.12 (0.12)	0.17 (0.19)	0.05 (0.18)	(-0.23) - (0.11) 0.57

Eighty seven patients had spasticity as identified by (abnormal) muscle activity but the modified Ashworth scale only identified 44 as having spasticity (table IV). Of the 56 patients who showed no spasticity on the modified Ashworth scale, 44 (79%) demonstrated involuntary muscle activity, a marker for spasticity. As a majority of the cells had a count of less than five, measures of association were not calculated. With reference to muscle activity recordings the modified Ashworth scale had a sensitivity of 0.5 and a specificity of 0.92.

Table IV: Comparison of muscle activity patterns with modified Ashworth scale scores. There were no statistically significant associations between muscle activity patterns and modified Ashworth scale Scores

Modified Ashworth scale scores	**Muscle activity patterns**					**Total**
	no/negligible spasticity	position dependent	velocity dependent	position + velocity dependent	early catch	
0	12	15	14	15	0	**56**
1	0	6	5	9	1	**21**
1+	0	1	3	8	0	**12**
2	1	1	0	2	0	**4**
3	0	3	0	3	0	**6**
4	0	1	0	0	0	**1**
Total	**13**	**27**	**22**	**37**	**1**	**100**

There was no significant association between the curve shapes during a fast stretch and muscle activity patterns (Table V). The only association that was observed was that linear patterns of stiffness were associated with some form of position dependent activation. As a majority of the cells had a count of less than five, measures of association were not calculated.

Table V: A summary of the curve shapes during fast flexion in comparison to muscle activity patterns. There was no significant association between the curve shapes during a fast stretch and muscle activity patterns. The linear curve shapes were normally seen to be associated with position dependent muscle activation.

		Muscle activity patterns					**Total**
		no/ negligible spasticity	position dependent	velocity dependent	position + velocity	early catch	
Curve shapes during fast flexion	linear	3	**21**	8	**25**	1	**58**
	no stiffness	6	3	11	9	0	**29**
	clasp knife phenomenon	1	0	0	1	0	**2**
	non linear	3	3	3	2	0	**11**
Total		**13**	**27**	**22**	**37**	**1**	**100**

Discussion:

The present study was carried out on one hundred comparable stroke patients who were homogenous in terms of functional performance, i.e. all had no useful functional movement in their upper extremity. There was evidence that the abnormal muscle activity, the primary pathophysiological presentation of spasticity, was observed in a significant proportion of the severely disabled stroke survivors. This abnormal increase in muscle activity does not necessarily produce a proportional (or consistent) change in muscle tone as suggested by a majority of existing definitions [16]. There is now a need to resolve the inconsistancy between the clinical presentations of this phenomenon and existing definitions. Whether existing definitions are adequate to describe the patterns of muscle

activation observed during the course of this study is a moot point. Of the various definitions available in the literature [1, 5-7] the one that defines *spasticity as disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles* [1] is the most appropriate to cover the variations in muscle activity patterns observed. However, even this definition is inadequate, as it does not help with describing the variations observed within this sample. The inconsistency between the definitions of spasticity and the clinical presentations needs to be resolved but the emphasis must be on the development of definitions that have clinical relevance.

Position dependent spasticity (Figure 2b), may result from changes in the gain / threshold of group Ia and group II muscle spindle afferents. The fact that the activation levels were similar for both fast and slow movement would suggest that group II afferents may have played a bigger role. The patients who show this pattern could be possibly at a higher risk for developing contractures at the wrist, as the muscle activity patterns would encourage the joints to be held in a shortened position. Also, from a clinical perspective it may be that the position of the joint and the range in which it is tested may confound the assessment of spasticity.

The velocity dependent spasticity (Figure 2c) is consistent with the Lance definition of spasticity[6] and it may result from changes in the spinal networks influenced by the Ia afferent pathway, or a change in the threshold/gain of the stretch reflex pathway. Some patients demonstrated a combination of both velocity and position dependent muscle activity (Figure 2d). This pattern similar to that described by Lance (1980)[6] and the pathophysiology of this pattern is possibly similar to that described earlier. These patients are also at a risk of developing early contractures.

The Early Catch (Figure 2e) that we observed is similar to the clasp knife phenomenon as described by Burke.[17] This would suggest that spasticity might have an acceleration component. It is unlikely that Ib inhibition plays any role in this phenomenon. [4]

It is likely that the lack of any abnormal activation could be consistent with paralysis or with an ability to relax with the former being more likely in this group. It was not possible to explore the exact pathophysiological basis for the variation in muscle activity patterns that were recorded.

There were no clear patterns of association between muscle activation patterns and resistance to passive movement (assessed by modified Ashworth scale or measured as stiffness). Based on the cross tabulations, it is possible to infer that muscle activation patterns may contribute to the variation in stiffness between fast and slow movement in an unpredictable way. This further strengthens the argument that the indirect measurement of stiffness is confounded by a variety of factors, e.g. muscle and joint visco-elastic properties, muscle activation patterns and possibly the ability to relax.[18] The impact of using confounded measures in routine clinical practice can be far reaching. There are three particular areas of concern. These are related to (a) time course of development of spasticity, (b) the prevalence estimates for spasticity in stroke, and (c) effect size calculations associated with common antispasticity treatment. Using current clinical measures of muscle tone it is possible that we have overestimated the time taken for spasticity to develop and underestimated both prevalence of spasticity and "effect size" associated with common antispasticity treatment.[15, 19]

The findings from this study are consistent with some previous research demonstrating that the modified Ashworth scale has limited sensitivity when it is used as a measure of stiffness [20]. There is now evidence that the modified Ashworth scale also lacks the sensitivity to measure changes in abnormal muscle activation patterns. There are some claims that the modified Ashworth scale can provide a valid and sensitive measure of spasticity [21]. However, it is not possible to compare the

findings of such previous studies with this one as there was one vital methodological difference (i.e. previous studies did not take concurrent measurements of stiffness, muscle activity and the modified Ashworth scale).

The device used in this study is portable, non invasive and easy to use. The total time required for spasticity measurement (that also included placing sensor over the identified locations) took a maximum of only 15 minutes. Although the measuring device and techniques used in this study are uncomplicated and user-friendly, the sensitivity and accuracy of this hybrid technique has as yet only been fully studied under laboratory conditions, additional work is required to detect errors of measurement in routine clinical practice.

The homogenous sample used for this study was not fully representative of the stroke population and a more comprehensive cross sectional study will need to be done to obtain true prevalence estimate of spasticity. This study demonstrates that presence and severity of muscle response to an external imposed stretch may vary depending on limb position, emotional state, and awareness. These were not controlled in the study. The effect of these variables on reliability needs to be explored. The velocity used during stretching was uncontrolled and whether the future protocols would require velocity standardization also need to be explored in a separate study. Although, the position by application of force was standardized, there may be a need to standardize the moments/torque (the turning effect of force) in the future studies. Sampling frequency used for data processing was 1000 Hertz, whereas the minimum synaptic time delay in spinal cord is 1millisecond, therefore we did not quantify time based threshold. Despite these limitations it is important to point out that there are no easy solutions to the problems posed. If one were to take a fully controlled perturbation approach the complexity of the measurement device and protocols make clinical measurements impractical and irrelevant. More work is therefore required to compare manual uncontrolled measurement

techniques, such as those developed in this study, against more controlled perturbation methods to identify the minimum controls that are required to reliably study the phenomenon of spasticity.

Clinical message to take away from this study:

- There is a lack of concordance between the clinical presentations of spasticity and existing definitions of this phenomenon.
- Using measures of muscle activity to quantify and/or classify spasticity in routine clinical and research practice may be more useful than using indirect measures of muscle tone.

Acknowledgements

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Online only: A summary of the muscle activity patterns in comparison to the total number of weeks post stroke. The muscle activity patterns were seen from as early as one-week post stroke.

Weeks post stroke	**Muscle activity patterns**					
	no/negligible muscle activity	**Position dependent muscle activity**	**Velocity dependent Muscle activity**	**Position + velocity dependent muscle activity**	**Early catch**	**Total**
1	2	3	6	1	0	12
2	2	11	6	9	1	29
3	8	7	4	17	0	36
4	1	4	4	5	0	14
5	0	1	2	4	0	7
6	0	1	0	1	0	2
Total	13	27	22	37	1	100
Proportion of patients exhibiting the problem (Estimated 95% CI for population)[†]	0.13 (0.7 - 0.2)	0.27 (0.19-0.36)	0.22 (0.15-0.31)	0.37 (0.28-0.47)	0.01 (0.001-0.05)	**N = 100**

[†] calculation based on statistics with confidence, proportions and their differences by Newcombe R and Altman D.

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Chapter 4

SPASTICITY AND CONTRACTURES AT THE WRIST AFTER STROKE: TIME COURSE OF DEVELOPMENT AND THEIR ASSOCIATION WITH FUNCTIONAL RECOVERY OF THE UPPER LIMB.

S Malhotra, AD Pandyan, C Roffe, S Rosewilliam, H Hermens

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Abstract

Objective: To investigate the time course of development of spasticity and contractures at the wrist after stroke and to explore if these are associated with upper limb functional recovery

Design: Longitudinal observational study using secondary data from the control group of a randomized controlled trial.

Setting: The Acute Stroke Unit at the University Hospital of North Staffordshire.

Subjects: Patients without useful arm function (Action Research Arm Test – ARAT) score of 0 within 6 weeks of a first stroke.

Main Measures: Spasticity was measured by quantifying the muscle activity during passively imposed stretches at two velocities. Contractures were measured by quantifying the passive range of movement and stiffness. Upper limb function was assessed using the ARAT. All assessments were conducted at baseline, and at 6, 12, 24 and 36 weeks after recruitment.

Results: Thirty patients (43% male, median age 70 (range 52–90) years, median time since stroke onset 3 (range 1–5) weeks) were included. Twenty- eight (92%) demonstrated signs of spasticity throughout the study period. Participants who recovered arm function (n=5) showed signs of spasticity at all assessment points but did not develop contractures. Patients who did not recover useful arm function (n=25) had signs of spasticity and changes associated with contracture formation at all time points tested.

Conclusion: In this group of patients who had no arm function within the first 6 weeks of stroke, spasticity was seen early but did not necessarily hinder functional recovery Contractures are more likely to develop in patients who do not develop arm function.

Introduction:

Stroke is a leading cause of death and severe adult disability. Approximately 110,000 strokes occur in England every year[1] and around half of all the patients who survive a stroke have impairments that lead to loss of upper limb function[2]. Spasticity and contractures are two common impairments that affect the muscle and joints of the upper limb[3, 4] and may significantly contribute to this functional loss and restrict social participation[5].

Spasticity is defined as disordered sensori-motor control, resulting from an upper motor neuron lesion and presenting as intermittent or sustained involuntary activation of muscles[6, 7]. It is a common neurological impairment which may develop within a week following a stroke[8]. Post-stroke spasticity may be maladaptive and interfere with a person's ability to perform functionally useful movement[9, 10]. Contractures are more likely to develop if the abnormal muscle activity, resulting from spasticity, holds a joint in either shortened position and/or prevents active movement[7].

Contracture is a pathological condition of soft tissues characterised by stiffness. It is usually associated with loss of elasticity and fixed shortening of the involved tissues resulting in both loss of range of movement and increased stiffness around a joint[11]. Many authors report the development of contractures in hemiplegic limbs following a stroke[12-15]. However, there is little information on the prevalence of contractures in the hemiplegic population. The two joints most prone to contractures are the wrist and ankle[3] with a higher incidence in the upper limb[3,4]. Contractures, in the upper limb joints, can lead to significant problems with cosmesis, hygiene and active movement capabilities, thereby resulting in significant participation restrictions. Spasticity may contribute to contracture formation[11] and clinical texts suggest that such a causal association exist[10, 12-15].However, there is

little evidence to prove either a clinically important association between spasticity and contractures exists or that spasticity interferes with functionally useful movement.

The first steps in the exploration of these relationships are:

- to study the time course of development of both spasticity and contractures at the wrist in patients with stroke who do not have arm function at recruitment
- to also assess whether spasticity impedes function and contributes to contractures.

Methods:

Secondary anonymous data for this longitudinal analysis was obtained from the control group of a randomized controlled trial (RCT) conducted between 2004 and 2008. This study had full approval from the local research ethics committee (LREC approval 04/Q2604/1). Only those patients from the control group with a complete set of relevant measures associated with spasticity, contractures, pain and arm function were selected for this secondary analysis.

Patients within 6 weeks of a first stroke were eligible to participate in the RCT if they had a score of 0 in the Action Research Arm Test[16,17]. Patients were excluded if they were medically unstable, had a previous medical history of osteoarthritis, rheumatoid arthritis or soft tissue injuries that resulted in contractures or had a reduced range of movement in the wrist and fingers. The control group received routine physiotherapy for 30-minutes each day for six weeks from recruitment to the study (5-day week). The study therapist provided standardised routine upper limb therapy to all the participants and this therapy was a reflection of local practice[18]. Overnight splints were not used.

Following a baseline assessment repeated measurements were taken at 6, 12, 24 and 36 weeks after recruitment. Measurements were taken at the patient's bedside on the acute stroke unit and the stroke rehabilitation ward. Follow-up measures were also done in the community e.g. in the patients' own homes, sheltered housing, and in nursing-or residential homes.

Clinical Measures:

Demographic details including age, gender, affected side of the body, and stroke subtype were taken at recruitment. Patients were examined neurologically and classified as total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) and posterior circulation syndrome (POCS)[19].

Spasticity was quantified neurophysiologically by measuring the muscle activity during passive extension of wrist[8]. Wrist contractures were characterized biomechanically by measuring the passive range of movement and stiffness at slow stretch at the wrist[20]. These measurements were taken using a custom built device[20]. The measurement procedure, in brief, was as follows:

The participant's forearm was fully supported and positioned in a direction parallel to the ground, with forearm in mid pronation-supination, the elbow flexed to approximately 90° and the shoulder slightly abducted (<10° estimated visually) during the tests. The wrist was first flexed as far as comfortable for the subject. Applying a force transducer (to measure force used for stretching the forearm manually) on the palmar surface of the hand, the wrist was passively extended using a slow stretch from maximum flexion into maximum extension (manual count for three seconds). The wrist was once again returned into flexion and the movement was repeated using a brisk stretch as per guidance for modified Ashworth scale (duration of stretch being one second)[21]. Force (measured in Newtons), passive range of movement (measured in degree) and muscle activity (measured in

millivolts - mV) were simultaneously taken during the externally imposed passive extension. The data from the transducers were sampled at 1000 Hz and stored in a personal computer for analysis.

Muscle activity was quantified from surface electromyography recordings using a customised programme[c]. The raw electromyography data was notch filtered (50 Hertz) and smoothed using a root mean square procedure (window width 20 millisecond)[20]. For each individual, wrist angles and muscle activity data were graphed as an XY scatterplot to classify muscle action[8]. Then the area under the angle muscle activity plot was calculated to quantify muscle activity[8]. To be consistent with current definitions, the assumption was that greater spasticity was associated with greater (EMG) activity.

As force (in Newtons) (applied to produce the displacement), range of movement (in degrees) and duration of displacement (in seconds) were measured, it was possible to quantify stiffness (as Newtons/degree) and velocity (as degrees/second). The angle versus force data was also presented as an XY scatter plot to determine the stiffness (resistance to passive extension) of muscle. The resistance to passive extension was calculated as the slope of the force angle curve between 10% - 90% available range of movement using standard linear regression techniques and the coefficient of determination (r^2). Contractures are associated with an increase in stiffness and a reduction in range of movement. Instantaneous velocity for slow and fast movement was calculated using the first difference approximation. From this the "average velocity" was calculated.

Severity of disability was measured using the Barthel Index (BI)[22]. Upper limb functional movement was assessed using the Action Research Arm Test[16, 17]. Pain was measured using a five point verbal rating scale (ranging from "0" had no pain to "5" had pain that could not be any worse).

[c] MathCAD 12, Mathsoft, USA

Statistical methods:

Data are reported for the whole group and for two pre-defined subgroups. Patients who recovered arm function (defined as Action Research Arm Test score of ≥ 6) at any time during the study were allocated to the functional group and those who did not to the non-functional group. The mean and the standard error (standard deviation divided by square root of the sample size) were used to summarize the results at each time point.

Change over time within the sample and the respective subgroup was studied (using the Friedman's test). The differences between the functional group and non-functional group were studied using the Mann Whitney U test. Mean differences and 95% Confidence Intervals (CI) are reported where appropriate. In addition, the change over time was analyzed using an approach recommended by Matthews et al[23]. All the statistical procedures were carried out using SPSS version 15.

The approach recommended by Matthews et al[23] is briefly described below. The change in each individual was modeled using a method of linear regression (y=a + bx), minimising for least square error, with the outcome measure as the dependent variable (y) and time (in weeks) of measurement as the independent variable. The slope (b) from this equation was used to quantify change over time. The comparisons between slopes of the functional and non-functional groups were studied using the Mann Whitney U test.

Results:

Thirty patients were eligible (13 males and 17 females) to participate in the study. The median age was 70.5 years (range 52-90) and the median time from stroke onset was 3 weeks (range 1-5). Fourteen (47%) patients had right and 16 (53%) patients had left hemiparesis. Twenty (67%)

patients had a total anterior circulation syndrome (TACS), 8 (26%) had a partial anterior circulation syndrome (PACS), and 2 (7%) had a lacunar syndrome (LACS). The baseline characteristics for individual groups are presented in Table 1

Table I: Baseline characteristics of the study group (30 patients).

Characteristics	*Non Functional group (n=25)*	*Functional Group (n=5)*
Gender - Male : Female	11 : 14	2 : 3
Side of body affected - Left : Right	15 : 10	1 : 4
Median age in years (range)	70 (52 -88)	78 (67- 90)
Median time post stroke in weeks (range)	3.0 (1 - 5)	4.0 (2 - 5)
Oxfordshire Community Stroke Project Classification System		
Total anterior circulation syndromes (TACS)	17	3
Partial anterior circulation syndrome (PACS)	7	1
Lacunar syndrome (LACS)	1	1
Posterior circulation syndrome (POCS)	0	0

The descriptive data obtained from the whole group analysis is presented in Table 2. There was a significant decrease in the passive range of movement ($p < 0.01$) (Table 2). The mean rate of decrease in passive range of movement was -0.5 degrees/week (95% CI = -0.9 to -0.16). There was no significant increase in resistance to passive movement ($p > 0.1$) (Table 2). The mean rate of increase in joint stiffness was 0.002 N/degrees/week (95% CI = -0.00 to 0.005). There was no significant change in the EMG activity during slow or fast stretch ($p > 0.1$) over the study period (Table 2). The testing protocol was carried out as planned (i.e velocity during fast movement was always faster than the slow movement.) The mean difference in the average velocity over the study

period was 76 degrees/s (SD = 39; range = 10 - 190). There was a significant increase in pain ($p = 0.01$) (Table 2), the mean rate of increase was 0.1 units/week (95% CI = - 0.01 to 0.3). There was significant increase in the Barthel Index ($p < 0.01$) (Table 2), the mean rate of improvement was 0.2 units/week (95% CI = 0.15 to 0.27).

Table 2: This table shows a summary of results for whole group, where Mean +/- Standard Error is used to describe the data. Friedman's test was used to determine significant differences in the group.

Outcome Measure	wk 0 M (SE)	wk 6 M (SE)	wk 12 M (SE)	wk 24 M (SE)	wk 36 M (SE)	p-value for the change over time	Mean slope (i.e. b) (95%CI)
PROM at slow stretch deg	99.0 (3.6)	79.6 (4.6)	77.2 (3.7)	72.5 (4.9)	75 (5.3)	<0.01	- 0.5 deg/wk (-0.9 to -0.16)
Stiffness at slow stretch N/deg	.047 (0.12)	.08 (.02)	.05 (.02)	.08 (.02)	0.13 (.04)	0.14	0.002 N/deg/wk (-.0001 to .005)
EMG at slow stretch mV	1.1 (0.19)	0.99 (0.24)	0.85 (0.16)	0.75 (0.95)	0.87 (0.15)	0.68	- 0.08 mV/wk (-0.2 to 0.006)
EMG at fast stretch mV	1.2 (0.21)	1.1 (0.23)	0.95 (0.2)	0.78 (0.1)	1.0 (0.16)	0.36	- 0.01 mV/wk (-0.3 to 0.07)
Pain	0.43 (0.18)	1.4 (0.29)	1.3 (0.29)	1.2 (0.28)	1.1 (0.29)	0.01	0.1 units/wk (-0.01 to 0.3)
Barthel Index range: 0-20	2.6 (0.55)	6.5 (0.93)	8.2 (1.0)	9.5 (1.1)	10.3 (1.2)	0.00	0.2 units/wk (0.15 to 0.27)

CI, confidence interval; deg, degree; EMG, electromyography; F, functional; HV, higher values; LV, lower values; mV, millivolts; N, Newton; NF, non functional; PROM, passive range of movement; wk, week.

The descriptive data obtained from the subgroup group analysis (i.e. with the group split as functional and non-functional) are presented in Table 3. Out of 30 control subjects, five subjects had recovered arm function by the end of the study and 25 did not. The 95% confidence interval showed that between 7% and 34% proportion of people who had no arm function at 6 weeks after a stroke, are likely to start recovering within 12 to 24 weeks after a stroke.

Table 3: This table shows a summary of the results for individual groups, where Mean +/- Standard Error is used to describe the data. Friedman's test was used to determine significant differences in each group. Mann Whitney U test was used to determine significant differences between the functional and non functional group over time and also used for comparing the slopes between groups.

Outcome Measure	Group NF= 25 F=5	Wk 0 M(SE)	Wk 6 M (SE)	Wk 12 M (SE)	Wk 24 M (SE)	Wk 36 M (SE)	p-value for change over time	Mean slope (i.e. b0) (95%CI)
PROM at slow stretch deg HV: better movement	NF	100.3 (4)	80.8 (4.8)	74 (4.1)	65.1 (4.4)	67.7 (5.3)	<0.01	-0.8 deg/wk (-1.1 to -0.49)
	F	92.9 (9.5)	73.7 (15)	93.1 (5.1)	110 (7.6)	112 (2.4)	0.12	0.9 deg/wk (-0.06 to1.77)

LV: worse movement	**p-value comparing groups**	***0.55***	***0.67***	***0.03***	***0.01***	***0.00***	**Not applicable**	**0.00**
Stiffness at slow stretch N/deg	**NF**	**0.05 (.02)**	**0.08 (.02)**	**0.06 (.02)**	**0.09 (.03)**	**0.15 (.05)**	**0.12**	**0.002 N/deg/wk (0.000 to 0.005)**
LV: better movement	**F**	**0.046 (.01)**	**0.09 (.03)**	**0.025 (.02)**	**0.03 (.03)**	**0.04 (.02)**	**0.3**	**-0.0006 N/deg/wk (-0.002 to 0.001)**
HV: worse movement	**p-value comparing groups**	***0.55***	***0.50***	***0.50***	***0.40***	***0.28***	**Not applicable**	**0.12**
Stiffness at fast stretch N/deg	**NF**	**0.07**	**0.08**	**0.10**	**0.12**	**0.2**	**0.00**	**0.002 N/deg/wk (0.00 to 0.008)**
LV: better movement	**F**	**0.05**	**0.05**	**0.09**	**0.09**	**0.01**	**0.8**	**0.002 N/deg/wk (-0.005 to 0.001)**
HV: worse movement	**p-value comparing groups**	***0.66***	***0.70***	***0.66***	***0.12***	***0.00***	**Not applicable**	**0.5**
EMG at slow stretch mV	**NF**	**1.1 (0.2)**	**0.97 (0.3)**	**0.73 (0.2)**	**0.74 (0.2)**	**0.7 (0.1)**	**0.9**	**0.01mV/wk (-0.03 to 0.07)**

HV: more abnormal activity	**F**	**1.1 (0.4)**	**1.1 (0.5)**	**1.4 (0.6)**	**0.82 (0.2)**	**1.7 (0.6)**	**0.6**	**0.02mV/wk (-0.03 to 0.07)**
LV: less abnormal activity	**p-value comparing groups**	***0.96***	***0.60***	***0.25***	***0.60***	***0.03***	**Not applicable**	**0.4**
EMG at fast stretch mV	**NF**	**1.2 (0.3)**	**1.1 (0.3)**	**0.9 (0.2)**	**0.7 (0.1)**	**0.8 (0.1)**	**0.5**	**- 0.08mV/wk (-0.2 to 0.006)**
HV: more abnormal activity	**F**	**1.0 (0.4)**	**1.3 (0.6)**	**1.3 (0.7)**	**1.1 (0.3)**	**1.9 (0.7)**	**0.6**	**0.02 mV/wk (-0.03 to 0.07)**
LV: less abnormal activity	**p-value comparing groups**	**0.83**	**0.90**	**0.60**	**0.20**	**0.07**	**Not applicable**	**0.2**
Pain LV: improved HV: worsened	**NF**	**0.52 (0.3)**	**1.7 (0.3)**	**1.4 (0.3)**	**1.4 (0.3)**	**1.3 (0.3)**	**0.01**	**0.12 units/wk (-0.01 to0.03)**
	F	**0.0 (0.0)**	**0.0 (0.0)**	**0.8 (0.8)**	**0.0 (0.0)**	**0.2 (0.2)**	**0.4**	**0.003 units/wk (0 to 0.003)**
	p-value comparing groups	**0.4**	**0.02**	**0.3**	**0.05**	**0.2**	**Not applicable**	**0.7**

BI **range: 0-20**	**NF**	**2.8** **(0.6)**	**5.8** **(1.0)**	**7.1** **(1.0)**	**7.9** **(1.2)**	**8.6** **(1.3)**	**0.00**	**0.2 units/wk** **(0.1 to 0.2)**
HV: better functionality	**F**	**1.4** **(1.4)**	**10.0** **(2.1)**	**13.6** **(1.9)**	**17.2** **(0.58)**	**18.4** **(0.50)**	**0.00**	**0.4 units/wk** **(0.3 to 0.5)**
LV: worse functionality	**p-value compare groups**	**0.20**	**0.12**	**0.03**	**0.00**	**0.00**	**Not applica ble**	**0.00**

CI, confidence interval; deg, degree; EMG, electromyography; F, functional; HV, higher values; LV, lower values; mV, millivolts; N, Newton; NF, non functional; PROM, passive range of movement; wk, week.

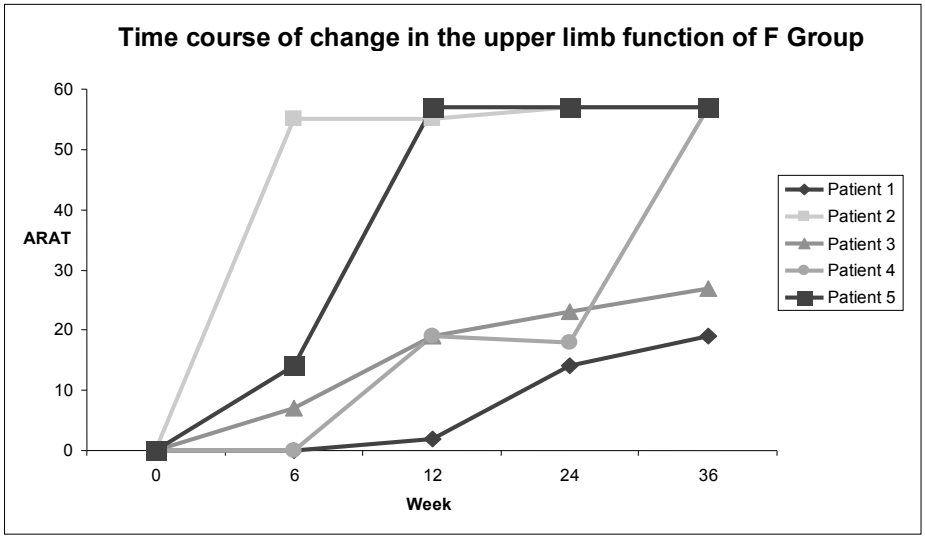
In the functional group, both the passive range of movement and stiffness did not change significantly ($p > 0.1$) (Table 3). The mean rate of increase in passive range of movement was 0.9 degrees/week (95% CI = -0.06 to 1.77) and stiffness was < 0.0001 N/degrees/week (95 % CI = -0.002 to 0.001). However, in the non-functional group the passive range of movement deteriorated significantly ($p < 0.01$) but stiffness did not change significantly ($p>0.1$). The mean rate of decrease in passive range of movement was -0.8 degrees/week (95% CI = -1.1 to -0.49) and mean rate of increase in stiffness was 0.002 N/degrees/week (95 % CI = 0 to 0.005).

The EMG activity during slow and fast stretch remained unchanged over time in both the functional and non-functional groups ($p > 0.1$) (Table 3). The mean rate of change of EMG activity in the functional group during both slow and fast stretch was 0.02 mV/week (95% CI= -0.03 to 0.07). The mean rate of decrease of EMG activity in the non functional group during slow and fast stretch was -0.01 mV/week (95% CI= -0.03 to 0.07) and -0.08 mV/week (95% CI= -0.2 to 0.006) respectively.

Abnormal muscle activity was evident in 29 out of 30 (24/25 in the non-functional group and 5/5 in the functional group) patients at recruitment. At the end of the study abnormal activity was seen in 28 of the 30 patients (23/25 in the non-functional group and 5/5 in the functional group).

Pain remained unchanged in the functional group ($p > 0.1$), while it significantly increased in the non-functional group ($p = 0.01$) (Table 3). The mean rate of change of pain was 0.003 units/week (95% CI = 0 to 0.003) in the functional group and 0.12 units/week (95% CI = -0.01 to 0.03) in the non-functional group. The BI significantly increased in both the groups ($p < 0.01$), the mean rate of improvement was 0.4 units/week (95% CI = 0.3 to 0.5) in the functional group and 0.2 units/week (95% CI = 0.1 to 0.2) in the non-functional group. The mean rate of improvement was 1 unit/week (95% CI = 0.5 to 1.6) in the functional group and 0.03 units/week (95% CI = 0.01 to 0.04) in the non-functional group. Out of the five patients in the functional group, three recovered some arm function by week 6 and the remaining two between week 6 and week 12 (Figure I).

Figure I: A summary of time course of change in the upper limb function (action research arm test) in all 5 patients of the F group.



Discussion:

Spasticity was quantified using passive testing protocols, in a way congruent to our current understanding of spasticity [6, 8, 11]. Almost the entire sample, even those who recovered arm function, demonstrated signs of spasticity at all time points of measurement. The presentation of spasticity varied with time. All those patients who recovered function always showed some form of position dependent spasticity[8]. The data suggests that spasticity, as measured using passive testing protocols, may not interfere with recovery of useful functional movement contrary to the general perception that it does[10].

The functional group, demonstrating position dependent spasticity showed an increase in muscle activity as the muscles were passively stretched and even continued when the movement was stopped (at end range of movement). It has been previously hypothesised that the position dependent spasticity may be a marker for activity in the long latency cortical pathways[8] and if true, then one possible reason for functional recovery may be the existence of activity in the pathways connecting the muscles of the arm to the cortex. If this can be proved to be the case then position dependent spasticity, early after stroke, may be a prognostic marker for functional recovery. Further research need to be conducted to verify this hypothesis.

Changes consistent with contracture formation were observed in the study population as a whole. Contractures mainly developed in those who did not recover arm function and were not evident in those who recovered function. Significant reduction in passive range of movement was seen prior to observing increase in joint stiffness. Contractures were completely established between 6-weeks and 12-weeks following a stroke despite the subjects receiving routine treatment. The people who developed contractures had both spasticity and no function. From first principles, the primary

hypothesis would suggest that immobilisation caused due to lack of functionally useful movement was the most likely cause of contractures [8,11,24]. Spasticity may not have contributed to contracture formation, as people who developed arm function did not develop contracture. The one anomaly in this study was a patient in the functional group who appears to have developed stiffness despite not losing range of movement. The most probably cause for the increase in stiffness is likely to be a reduced use of the hand or oedema but more work is required to explore this behavior.

Although less likely, contracture formation may be dependent on pain as the pain profiles differed between the groups and pain significantly worsened in the non-functional group. Pain can be a barrier to active movement and this loss of movement could exacerbate the formation of contractures. This would further encourage fixed positioning and thereby lead to the formation of contractures.

This is a novel study exploring the time course of development of both spasticity and contractures, but it lacks statistical power. The sampling frame was limited to a homogenous sample that was not fully representative of the stroke population; however this was intentional as there is evidence that people who show early signs of functional recovery get better naturally[11], so there was a need to explore the time course of change associated with the two significant barriers of recovery in stroke. For findings to be generalizable, a more comprehensive longitudinal study is required.

The 15 patients who were unable to complete the assessments may have demonstrated different patterns with respect to functional recovery, spasticity and contractures. It was not possible to identify what was different in the people who regained function when compared to those who did not. The lack of premorbid data on status of joints was also likely to be a confounding factor in this study: It was not possible to confirm whether those who recovered function had joints that were

normal nor was it possible to confirm if those who developed contractures had pre-existing problems that exacerbated the formation of contractures. Incorporating information on premorbid status in any prospective longitudinal study will be recommended.

Two methods were used to analyse the repeated measure data. The application of Matthews et al[23] approach in studying time course of change in stroke is relatively new. We think that the Matthews et al[23] method is superior, as there is a possibility that some of the serial measures in stroke related impairments are not strictly independent and the data can be analyzed in a way that is appropriate to the question. A further advantage of the Matthews et al[23] approach is that repeated serial measures can be reduced to a single variable that can then be analysed using a single test – this is likely to reduce errors associated with multiple comparison. Even though it might be more labour intensive, it is recommended for future use

EMG can vary over time but the consistency within the data would suggest that the signal to noise ratio is sufficiently high so as not to change our interpretation. Therefore, despite the limitations, the key findings need to be considered within clinical practice.

Clinical message:

- Spasticity appears not to be a barrier to functional recovery
- Wrist contractures develop rapidly after a stroke
- Loss of function, and not spasticity, may be the primary contributor to contracture formation.

Acknowledgments:

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Chapter 5

Can Surface Neuromuscular Electrical Stimulation Of The Wrist And Hand Combined With Routine Therapy Facilitate Recovery Of Arm Function?

S Rosewilliam, S Malhotra, C Roffe, P Jones, A Pandyan

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Abstract

Objective: To investigate whether treatment with surface neuromuscular electrical stimulation (sNMES) to the wrist extensors improves recovery of arm function in severely disabled patients with stroke.

Design: Single blinded randomized controlled trial

Setting: Acute stroke unit and stroke rehabilitation wards of a University Hospital.

Participants: Patients with no upper limb function (Action Research Arm Test (ARAT) score 0) were recruited to the study within 6 weeks of stroke. Ninety patients were recruited, 23 died, 67 completed the study and were included in the analysis (mean age 73 years).

Interventions: Participants were randomized to sNMES using surface electrical stimulators for 30 mins twice in a working day for six weeks in addition to standardised upper limb therapy or just standardised upper limb therapy.

Main Outcome measures: The primary outcome measure was ARAT. Assessments were made at baseline, 6, 12, 24 and 36 weeks after recruitment.

Results: There were statistically significant improvements in measures of wrist extensor (mean difference was 0.5; 95% CI 0.0 to 1.0) and grip strength (mean difference 0.9; 95% CI 0.1 to 1.7) over the treatment period. Arm function (ARAT score) was not significantly different between the groups over the treatment period at 6 weeks (mean difference was 1.9; 95% CI -2.9 - 6.8) or over the study period at 36 weeks (mean difference 6.4; 95% CI -1.8 to 14.7) and rate of recovery was not significantly different (mean difference 0.7; 95% CI -0.2 to 1.6).

Conclusion: In patients with severe stroke, with no functional arm movement electrical stimulation of wrist extensors improves muscle strength for wrist extension and grip and larger studies are required to study its influence on arm function.

Introduction

Most patients who survive a stroke will regain the ability to walk independently, but only less than 50% will recover arm function. [1,2] Recovery of arm function after a stroke follows a predictable pattern, yet the time course of recovery is variable.[3] Delays in recovery of function increase the risk of secondary complications such as spasticity, contractures and pain, [3] and these affect normal movement and further interfere with rehabilitation. [3, 4]

There is a growing body of evidence to suggest that some adjunct therapies such as neuromuscular electrical stimulation (NMES), biofeedback, and constraint induced therapy, have the potential to either facilitate recovery of arm function or prevent the formation of secondary complications. [5-10] Amongst these NMES has been the most widely researched. [6, 8] In spite of encouraging results from randomised controlled trials. [6,9] there is still no definitive evidence to support the use of NMES as routine adjunct treatment. [5]

It was previously shown that treatment with sNMES of the wrist extensors for 8 weeks leads to a transient improvement in arm function, not maintained 24 weeks after cessation of treatment. [9] However, secondary analysis of the data from this RCT suggests that results may have been confounded by heterogeneity in the study population at recruitment. Subgroup analyses showed that patients with no upper limb function at recruitment had a greater chance of regaining arm function when treated with sNMES, and these benefits were maintained until the end of the study, 24 weeks after discontinuation of sNMES.[4, 11]

This phase II study was set up to investigate whether treatment with sNMES to the wrist extensors in combination with standardised rehabilitation therapy improves the recovery of arm function in people with poor prognostic indicators of arm function.

Methods

This single blind randomised controlled trial with an independent assessor was carried out at a University Hospital between 2004 and 2008.

All adult patients with a first stroke who had no arm function (defined as a score of 0 in the Grasp sub-section of the ARAT) [11] within six weeks of onset and who had no contraindications to sNMES were considered for trial inclusion. Participants were excluded if they were medically unstable, if they had a previous history of osteoarthritis, rheumatoid arthritis or soft tissue injuries resulting in contractures or a reduced range of movement in the wrist and fingers, and if informed consent or relatives' assent could not be obtained.

The study was approved by the North Staffordshire Local Research Ethics Committee (Ref no.04/Q2604/1) and conducted to the principles of Good Clinical Research Practice (GCP).

Participants were randomised into two groups, i.e. a control group and a treatment group, using a method of concealed random allocation (a pseudo random computed sequence in blocks was generated and the codes were stored by an independent person not involved in recruitment or measurement). Baseline measures were taken by an independent assessor who was blinded to the allocation of participants. Participants in both groups were given a defined module of upper limb

physiotherapy that reflected current local clinical practice [12] for a period of six weeks in addition to the routine treatment on the stroke unit.

Intervention

Participants in the treatment group were treated with sNMES for 6 weeks. SNMES was delivered by CE marked electrical stimulators developed by Odstock Medical Limited customised for the study. Patients received 30 minute sessions of sNMES to the wrist and finger extensors at least twice a day for 5 days a week. Treatment was delivered by surface electrodes positioned on the dorsal surface of the forearm (inactive electrode placed slightly inferior to the common extensor origin below the elbow and the active electrode posterior and few inches above the wrist). [10] The stimulation parameters required to produce slow movement through the full range at maximum patient comfort were as follows: Pulse width = 300μs; ON time = 15s; OFF time= 15s. [13] The ON time included a ramp up time of 6s and a ramp down time of 6s [13] to provide smooth movements. The frequency of stimulation was set to 40 Hz. [9,13] The intensity of stimulation was adjusted to obtain maximum possible range of wrist and finger extension with an intensity that was tolerated by the patient and without inducing fatigue. On completing the initial treatment session the patient or their carer (relative) was trained on using the sNMES system and delivering treatment. Treatment compliance in both groups was monitored using a patient record.

Assessments were done at baseline, at the end of the treatment period (6-weeks), 3, 5, and 9 months after stopping treatment. The primary outcome measure was recovery of arm function (ARAT). [14] Secondary outcomes were independence in activities of daily living assessed by the Barthel index (BI), [15] active range of movement (AROM) in wrist flexion and extension, wrist flexor and extensor

strength, and grip strength. Basic demographic data and details of the stroke were taken from the case notes.

Sample Size Estimation

A sample size of 72 participants (36 in each arm) is required to reject the null hypothesis, i.e. treatment with sNMES will not facilitate recovery of arm function, with 80% power and a 2-tailed significance level of 5%. For sample size estimation, return of useful arm function was defined as a 9 point improvement in the ARAT score; standard deviation was 8 and 17 in the control and treatment arms respectively. [4] Allowing for attrition 45 patients were recruited in each arm. However, at the end of this study a full data set was only obtained in 66 participants (31 in the treatment arm and 35 in control arm). Post study power calculation was done to examine the internal validity of the study and it yielded a power of 75%.

Statistical Analysis

The data collected was analysed using SPSS version 15. Missing values were imputed in 2 ways; when an intermediate assessment was missed, the mean of the 2 adjacent values was used and when someone dropped out of the study the last value was carried over. We adopted a conservative approach, carrying forward last value/means for middle missing values, even though it tends to suppress the slope as other methods (e.g. regression analysis for predicting the missing values) was found to overestimate the level of recovery (e.g. giving scores higher than maximum possible in ARAT). One patient improved between consent and baseline assessment, and no longer met the inclusion criteria and he was therefore excluded from the inferential analysis.

The analyses included:

1. The differences between the groups in ARAT scores (primary outcome) and other secondary outcome measures over the study period for participants who were alive till the end of the study (study completers) using the independent sample t-test. The results from the study completers has only been reported and discussed within the main text as there were significant baseline differences in age and functional ability (BI) between them and those who died. However intention to treat analysis for all including those who died (n=89) is reported in supplemental table 1 (available online only at http://www.archives-pmr.org/). The mean differences have been reported to show the effectiveness of the treatment.

2. The rate of recovery of outcome measures [16,17] for each individual for the treatment period (0-6 weeks), the follow up period (12-36 weeks) and the entire study period (zero to 36 weeks). This was done to assess whether there is any corresponding improvement in the recovery rate with treatment.

No corrections were made for multiple testing despite possibility of alpha inflation, as this was considered to add to the limitations in the study power.

Statistical test results for description and analysis of baseline differences in data are given in the text and tables.

Results

Of the 90 participants recruited 23 patients died during the course of the study due to study-unrelated causes such as respiratory infections, recurrent stroke and cardiac arrest (recalculated power is reported in the sample size estimation section). This resulted in the study having 5 patients less than originally calculated. The data from 1 participant who refused baseline measurements (because of stress) after randomisation was still included in the analysis. The reasons for loss of

follow up data were inability to contact participants, participants moving away from the accessible geographical area, or refusal of repeat measurements. The consort flow chart (fig 1) for the study gives further detail of the progression of participant numbers.

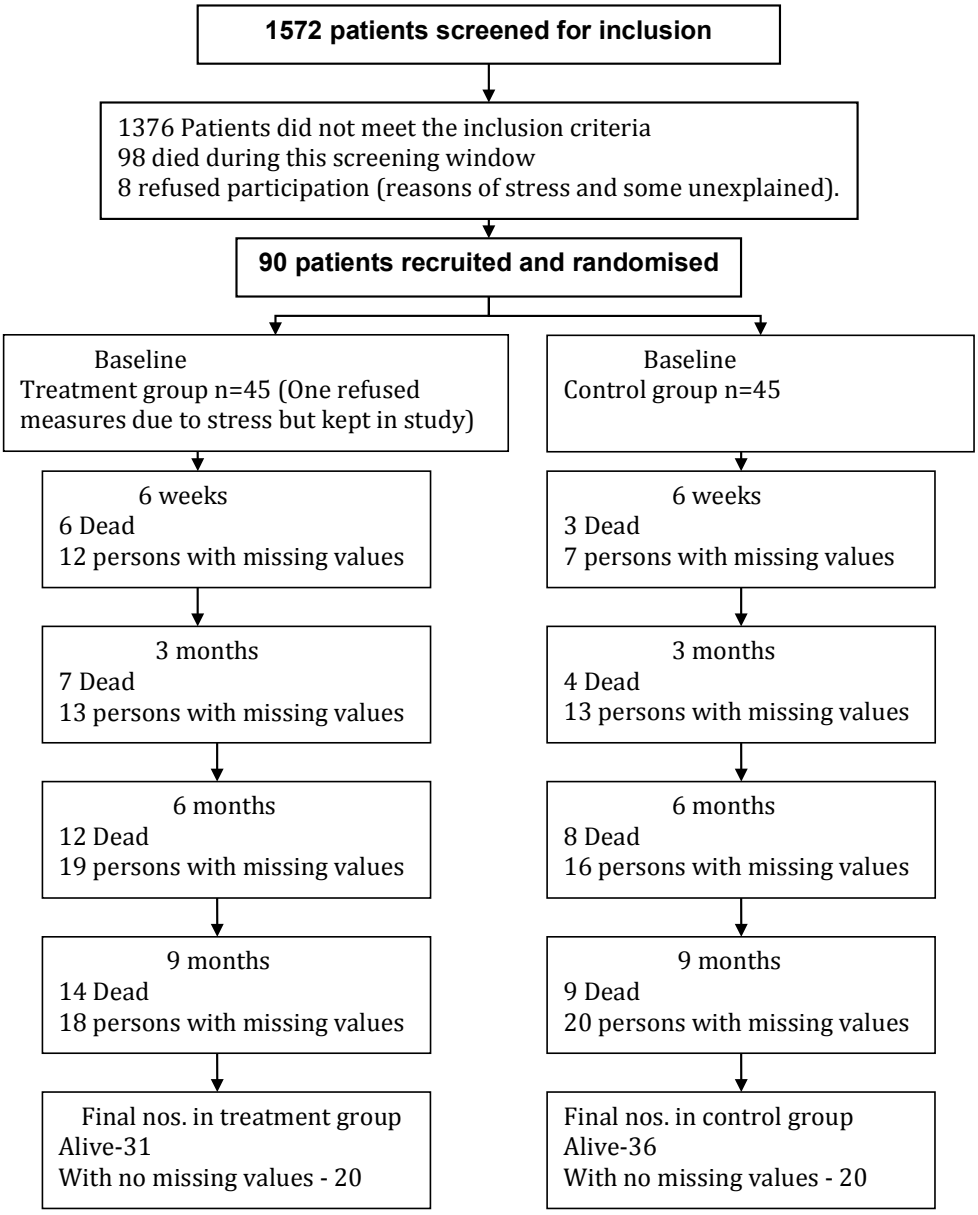

Fig 1. Flow of participants in the study

The descriptive demographic data, baseline characteristics of all 90 participants, those who were alive till the end of the study (n=67-Treatment and control group differences) and of those who died during the course of the study (n=23) are shown in table 1. Patients who died within the first nine months were older (p = 0.003) and more disabled (p = 0.004). Because there were potentially confounding differences at the baseline between those who survived and those who died the results and the discussion will focus on those who were alive at the end of the study.

Table 1. Baseline characteristics of participants

	The entire sample N_{total} = 90	**Participants who died before the end of the study N_{dead} = 23**	**Participants who were alive at the end of the study N_{alive} = 67**	
			Treatment	Control
Sex: men, n (%)	44(49%)	13(57%)	15(48%)	16(52%)
Total anterior circulation syndrome, n (%)	61(68%)	17(74%)	19(62%)	25(69%)
Partial anterior circulation syndrome, n (%)	19(21%)	5(22%)	5(16%)	9(25%)
Lacunar syndrome, n (%)	9(10%)	1(4%)	6(19%)	2(6%)
Posterior circulation syndrome n (%)	1(1%)	0	1(3%)	0(0%)
Hemiparesis (n, % right)	46(51%)	13(57%)	17(25%)	16(23%)
Age (y)	74.6(11.0)	80.4 * (9.3)	72.4(12.1)	72.7(9.9)
ARAT	0.2 (2.3)	0.0(0.0)	0.0(0.0)	0.6(3.5)
Barthel Index	2.8 (3.3)	1.1 (1.4)*	4.4 † (3.9)	2.5(2.9)
AROM-Wrist max flexion (deg)	3.1 (13.8)	-1.5 (13.8)	5.9 (13.1)	3.5 (14.2)
AROM-Wrist max extension (deg)	0.8 (8.2)	0.3 (1.5)	2.2 (12.3)	0.0 (6.1)
Isometric muscle strength wrist flexors (N)	0.1 (0.5)	0.0 (0.1)	0.3 (0.8)	0.06 (0.2)
Isometric muscle strength wrist extensors (N)	0.1 (0.4)	0.0 (0.0)	0.2 (0.6)	0.06 (0.2)
Grip strength (N)	0.1 (1.0)	0.0 (0.0)	0.47 (1.7)	0.0 (0.0)

Values with star indicate that t-test showed significant difference for these variables at baseline. Values are n, %, or mean Values are n, %, or mean +/- SD or as otherwise noted. Abbreviation:

AROM, active range of movement. (*p≤ 0.05 t-test for comparison between alive versus dead) and († p=0.03 t-test for comparison between treatment and control group)

Primary outcome measures

ARAT measure was not significantly different between the groups over the treatment period at six weeks or over the study period at 36 weeks (p = 0.4 and 0.1, respectively). Though ARAT scores improved more in the treatment group than in the control group over the treatment period and over the whole study period, this was not significant [Table 2].

Table 2. Mean +/- (SD) and t-test results for participants who were alive over the weeks with ITT.

Outcome Measure	Group	Week 6 T (n=39) C (n=41)	Week 12 T (n=38) C (n=40)	Week 24 T (n=33) C (n=36)	Week 36 T (n=31) C (n=35)
ARAT total score	T	5.0 (11.7)	7.7 (14.6)	10.1(17.1)	11.6 (18.9)
	C	3.1(10.2)	3.3(12.6)	4.8(13.9)	5.2 (14.3)
	Mean diff (95% CI) P Value	1.9 (-2.9 - 6.8) 0.4	4.3 (-1.8 -10.5) 0.2	5.4 (-2.1 -12.8) 0.2	6.4 (-1.8- 14.7) 0.1
Barthel Index Total	T	5.4 (4.0)	7.3(5.3)	9.4 (5.9)	10.5(5.8)
	C	5.8 (5.2)	6.9 (5.7)	8.1(6.7)	8.9(7.1)
	Mean diff (95% CI) P Value	-0.4 (-2.5- 1.7) 0.7	0.4 (-2.1 -2.9) 0.8	1.3 (-1.7- 4.3) 0.4	1.5 (-1.7- 4.7) 0.4
WRIST FLEXION AROM measured in Degrees	T	10.1(16.8)	9.8 (15.1)	17.0 (21.3)	15.7(18.9)
	C	8.2(13.4)	8.9 (11.9)	16.6 (20.9)	13.6 (19.3)
	Mean diff (95% CI) P Value	1.9 (-4.8- 8.7) 0.6	0.9 (-5.1 -7.1) 0.8	0.4 (-9.8-10.6) 0.9	2.2 (-7.3-11.6) 0.7
WRIST EXTENSION AROM measured in Degrees	T	10.2 (16.2)	8.7 (15.5)	10.2 (18.9)	16.3 (22.8)
	C	6.3(10.3)	5.8(12.8)	7.5 (19.1)	10.6(19.0)
	Mean diff (95% CI) P Value	3.9 (-2.1-9.9) 0.2	2.9 (-3.5-9.4) 0.4	2.7 (-6.4- 11.8) 0.6	5.7 (-4.6-15.9) 0.3

Isometric muscle strength wrist flexors	T	1.0 (2.6)	1.1 (2.2)	1.7 (2.7)	1.4 (1.9)
	C	0.4 (0.9)	0.6 (1.1)	1.1(1.6)	1.3 (1.7)
	Mean diff (95% CI) P Value	0.6 (-0.3 -1.5) 0.2	0.5 (-0.2- 1.3) 0.2	0.6 (-0.5 -1.7) 0.3	0.2 (-0.7-1.1) 0.7
Isometric muscle strength wrist extensors (Newton)	T	0.7(1.5)	0.9(1.7)	1.2(1.9)	1.4(1.9)
	C	0.2(0.5)	0.5 (1.0)	0.7(1.1)	0.9(1.4)
	Mean diff (95% CI) P Value	0.5 (0.0-1.0) 0.04	0.5 (-0.2-1.1) 0.2	0.6 (-0.2-1.2) 0.12	0.5 (-0.3-1.4) 0.2
Grip Strength (Newton)	T	1.0 (2.5)	1.5 (3.2)	2.2(3.9)	3.2(5.3)
	C	0.2(0.7)	0.7(2.5)	1.5(3.7)	1.4(3.2)
	Mean diff (95% CI) P Value	0.9 (0.1-1.7) 0.03	0.7 (-0.5-2.1) 0.2	0.8 (-1.0-2.7) 0.4	1.74 (-0.4-3.9) 0.1

Abbreviations: AROM, active range of movement; C, control group; CI, confidence interval; MD, mean difference at each point of measurement; T, treatment group.

The difference in rate of recovery was not statistically significant between the groups during the treatment phase (p=0.1) and over the entire study period (p= 0.2). The rate of recovery in the treatment group was higher than in the control group, during the treatment phase and over the entire study period [Table 3]. Patients in the treatment group were more likely to recover clinically important ARAT $\geq$6 compared to those in control group (Odds ratio 2.3; 95% CI 0.7-7.2); but that was not statistically significant.

Table 3. Mean +/- (SD) and t-test for rate of recovery for difference between the groups for the participants who were alive with ITT.

Outcome Measure	Group T (n=31) C(n=35)	Week 0-6	Week 12-36	Week 0-36
ARAT total score	T	1.1(2.1)	0.1(0.5)	0.3(0.5)
	C	0.4(1.6)	0.1(0.2)	0.1(0.4)
	Mean diff (95% CI) P Value	0.7 (-0.2-1.6) 0.1	0.04 (-0.1-0.2) 0.7	0.2 (-0.1-0.4) 0.2
Barthel Index Total	T	0.3(0.5)	0.1(0.1)	0.2(0.1)
	C	0.6(0.7)	0.1(0.1)	0.2(0.2)
	Mean diff (95% CI) P Value	-0.2 (-0.5-0.1) 0.1	0.1 (-0.1-0.1) 0.8	0.01 (-0.1-0.1) 0.9
WRIST FLEXION AROM (Degrees)	T	1.2(2.5)	0.2(0.6)	0.3(0.4)
	C	0.7(2.8)	0.2(0.6)	0.3(0.5)
	Mean diff (95% CI) P Value	0.5 (-0.8-1.8) 0.5	-0.01 (-0.3-0.28) 0.9	-0.1 (-0.3-0.2) 0.6
WRIST EXTENSION AROM (Degrees)	T	1.7(2.9)	0.2(0.6)	0.3(0.5)
	C	0.6(1.2)	0.2(0.6)	0.2(0.5)
	Mean diff (95% CI) P Value	1.1 (0.03-2.2) 0.04	0.04 (-0.3-0.3) 0.8	0.04 (-0.2-0.3) 0.8
Isometric muscle strength wrist flexors (Newton)	T	0.2(0.4)	0.002(0.1)	0.03(0.05)
	C	0.1(0.2)	0.02(0.05)	0.03(0.04)
	Mean diff (95% CI) P Value	0.1 (-0.03-0.3) 0.1	-0.02 (-0.05-0.01) 0.2	-0.01 (-0.03-0.02) 0.6
Isometric muscle strength wrist extensors (Newton)	T	0.1(0.2)	0.01(0.04)	0.03(0.05)
	C	0.02(0.1)	0.01(0.03)	0.02(0.05)
	Mean diff (95% CI)	0.11 (0.03-0.2)	-0.003 (-0.02-0.02)	0.01 (-0.01-0.03)

	P Value	0.0	0.7	0.5
Grip Strength (Newton)	T	0.1(0.4)	0.06(0.1)	0.06(0.1)
	C	0.02(0.1)	0.03(0.1)	0.1(0.1)
	Mean diff (95% CI) P Value	0.12 (-0.02-0.3) 0.1	0.03 (-0.02-0.1) 0.2	0.0 (-0.1-0.1) 0.9

Abbreviations: AROM, active range of movement; C, control group; CI, confidence interval; MD, mean difference at each point of measurement; T, treatment group.

Secondary outcome measures

Results for secondary outcome measures are shown in table 2. The Barthel Index improved in both groups during the treatment and the follow-up periods, but there was no difference in the level of improvement between the treatment groups. AROM at the wrist (flexion and extension) improved more in the treatment than the control group but the difference in improvement was not statistically significant at any point ($p>0.2$). Wrist extension strength and grip improved significantly in the treatment group over the study period ($p=0.04$ and 0.03 respectively). Although the treatment group remained stronger at the end of the study the difference was not statistically significant ($p=0.2$ and 0.1 for wrist extension strength and grip strength respectively).

The rate of improvement was three times faster for AROM in extension ($p=0.04$) and six times faster for wrist strength in extension ($p<0.01$) in the treatment group than in controls during the treatment period [Table 3]. There were no significant differences in the rate of recovery for any of the other secondary outcomes at any other time point.

Discussion

The main findings of this study are that surface neuromuscular stimulation of forearm muscles significantly improves wrist extension strength and grip strength in patients with stroke who had no active movement at the start of treatment. We also found non-significant improvements in complex functional arm movements (ARAT). Wider activities of daily living (Barthel Index) did not improve. The effect of treatment ceased after discontinuation of the intervention. This could be due to reduced focus on upper limb therapy in routine stroke care [18] and loss of translation of this effect of treatment into activities of function in daily life. Significant improvement of direct measures of function (muscle strength, grip strength) suggests that the treatment is effective at reducing impairment. It is likely that a larger study, with routine therapy as control, would have shown significant improvements in complex arm function.

Normally, the focus of routine therapy in patients with severe levels of disability (as recruited for this trial) will focus on retraining trunk control and mobility. However, in this study, patients in both groups, i.e. control group and the treatment group, received 30 minutes of physiotherapy focused on the rehabilitation of the upper limb. This additional therapy may have led to a greater than normal level of improvement in the control group. As a result the differences between the groups would not have been significant. There is some evidence from the literature, [9, 19] and data from our secondary analysis (mean improvements in the control group were 2.0 ARAT units sd 8.0) that supports the argument that the improvements in the control group of this study were better than patients who get an undefined form of routine treatment. More work will be required

to test the hypothesis that a daily structured program of upper limb rehabilitation in acute stroke will lead to improvements in hand function of a severely disabled stroke population.

The duration of treatment followed in this study was limited to 6 weeks. The evidence was that the rate of recovery in the relevant impairments and recovery of function were highest during the period when active treatment was applied. However, as soon as this therapy was discontinued the rate of recovery between groups almost equalised. It is possible that in such a severely disabled group of patients the duration of treatment may need to be longer than that followed in this trial. Whilst it is not possible to comment on how long the duration would normally be required, it can be hypothesised that any treatment should be continued until the patient achieves a threshold of function that can be built on by the patients and therapist. Again here is a need for much more work to elucidate the minimum duration of treatment. It is possible the high attrition rate (nearly 30%) and the resultant reduction in the sample size may have also contributed in part to the lack of significance.

It is not clear if these improvements that we have observed in this study are associated with systemic effects of electrical stimulation, in particular effects associated with increased cortical excitability and the resultant neural plasticity [20] and/or effects on muscle physiology, [21] or the additional therapy time in the treatment group. There is some suggestion that the effects in this study could have been attributed to the effects of sNMES on muscle physiology as there is clear evidence that patients in the treatment group had got stronger extensors following treatment when compared to the control group. Improved extensor strength can lead to more efficient gripping which is essential for activities of daily living [22]. It is also possible that the systemic effects

associated with increased cortical excitability may have improved the long term functional outcome in some of the patients and this could explain the continued long term functional benefits seen in the treatment group [23]. More research is required to tease out the time effects from the systemic effects of treatment.

This study has demonstrated that for a homogenous group of severely disabled patients small but meaningful improvement is possible. The improvement reported in study are likely to be clinically relevant as they have included a full data set of patients who were alive at 9-months after recruitment to the study and included patients who had both left and right hemispheric strokes. In this regards this is probably one of the largest, clinically relevant, studies that have been conducted exploring the effects of an acute upper limb rehabilitation protocol in severely disabled patients with stroke.

Study Limitations

A significant limitation in this study protocol was that the electrical stimulation was limited to a cyclical movement of one single limb segment (the wrist). There can be criticism that the movement used in this study may not be functionally relevant and could explain the small effect size. There is some pilot evidence in the published literature that that simultaneous stimulation of multiple limb segments may have a bigger treatment effect [24]. Again more work will be needed to elucidate the relative merits of multiple channel stimulation.

Conclusions

In patients with severe stroke and no functional arm movement electrical stimulation of wrist extensors improves muscle strength and grip strength, but there were no significant improvement in terms of improvements in range of movement. There is some evidence that this treatment facilitated recovery of arm function. It is not clear as to whether this functional improvement was a direct result of plasticity or was secondary to strength gains. The functional improvement, although clinically important, did not reach levels of statistical significance. There are 3 potential reasons for not achieving statistical significance: (1) the sample size was inadequate, (2) the treatment duration was inadequate, and (3) the control group received additional treatment lasting between 30 minutes a day (this is not equivalent to conventional therapy). To address the first point, a larger sample study will need to be carried out. To address the latter 2 points, more fundamental work is needed to identify the optimal duration of treatment and also the interaction effects between treatment with electrical stimulation and other potential concomitant therapies.

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Chapter 6

A randomized controlled trial of surface neuromuscular electrical stimulation applied early after acute stroke: effects on wrist pain, spasticity, contractures.

S Malhotra, S Rosewilliam, H Hermens, C Roffe, P Jones, AD Pandyan

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Abstract

Objectives: To investigate effects of surface neuromuscular electrical stimulation applied early after stroke to the wrist and finger extensor muscles on upper limb pain, spasticity and contractures in patients with no functional arm movement.

Design: Secondary analysis from a Phase II randomized controlled single blind study.

Setting: An acute hospital stroke unit

Subjects: Patients with no useful arm function within six weeks of a first stroke.

Intervention: Patients were randomized to treatment (30-minute sessions of surface neuromuscular stimulation to wrist and finger extensors and 45 minutes of physiotherapy) or control (45 minutes of physiotherapy) groups. All patients had access to routine care. Treatment was given for six weeks from recruitment.

Results: Ninety patients (49% male, median age 74-years (range 32-98), median time since stroke onset 3-weeks (range one to six weeks)) were included. Treatment compliance was variable (mean 28%). The treatment prevented the development of pain (mean difference in rate of change 0.4 units/week, 95% confidence interval (CI) 0.09 to 0.6). Treatment may have prevented a deterioration in contractures (quantified by measuring passive range of movement) in severely disabled patients (mean rate of deterioration -0.5 deg/week; 95% CI -0.9 to -0.06). There were no significant changes in stiffness and spasticity.

Introduction:

Half of all the patients who survive a stroke have impairments that lead to loss of upper limb function.[1] Pain, spasticity and contractures are common impairments that develop rapidly after stroke [2-6] and are considered to be a major contributor to secondary complications which causes limited mobility, delays in recovery of the paretic limb and problems in rehabilitation. The current methods of treatments or therapies for pain, spasticity and contractures [7-10] are unsatisfactory. Despite a threefold increase in treatment interventions for these conditions over 10 years, "best practice" for the rehabilitation of the paretic upper limb is still unclear[11.]

In stroke, therapeutic surface neuromuscular electrical stimulation has been used to facilitate return of function and prevent complications in the upper limb [12-16]. Surface neuromuscular electrical stimulation has been recommended as a safe method to improve upper limb outcomes after stroke.[12-14] However, robust evidence for efficacy of electrical stimulation is lacking, especially in relation to the treatment of spasticity, development of contractures or prevention of pain.[17, 18] We have recently shown that early application of functional electrical stimulation to wrist and finger extensors in patients with severe stroke and no functional movement in the upper limb improves muscle strength for wrist extension and grip, but has a small effect on arm function ((effect size 0.35 (95% CI is -0.20 to 0.91))[19]. The aim of this study is to investigate whether treatment, given for six weeks, prevents the development of upper limb pain, wrist flexor spasticity and contractures in severely disabled acute stroke patients.

Methods:

This was a secondary analysis of data from a recently published single blind randomised controlled trial aimed at investigating the effects of surface neuromuscular electrical stimulation of the wrist combined with routine therapy on recovery of arm function in patients with stroke.[19] The study was approved by the North Staffordshire Local Research Ethics Committee (Ref no.04/Q2604/1). Ninety stroke patients participated in this trial. Stroke patients admitted to the University Hospital of North Staffordshire within six weeks of a first stroke were eligible to participate if they had no useful hand function, defined as a score of 0 in the grasp subsection of the Action Research Arm Test (ARAT) [20, 21], and if they had no contraindication to surface neuromuscular electrical stimulation. [22] Patients were excluded if they were medically unstable, had a previous medical history of osteoarthritis, rheumatoid arthritis or soft tissue injuries that resulted in contractures or had reduced range of movement in the wrist and fingers or were unwilling to take part in the study.

Patients were randomised into two arms, i.e. a control arm and a treatment arm, using a method of concealed random allocation. A pseudo random computed sequence in blocks was generated and the codes were stored by an independent person not involved in recruitment or measurement. Patients in the treatment arm received 30 minute sessions of surface neuromuscular electrical stimulation to the wrist and finger extensors at least twice a day (a maximum of three times a day) for five days a week. Surface neuromuscular electrical stimulation was delivered by surface electrodes (inactive electrode placed just below the common extensor origin and active electrode placed such that the stimulation produced balanced extension of the wrist, i.e. extension without ulnar and radial deviation) positioned on the dorsal surface of the forearm.[16] The stimulation

parameters were set to produce slow movement through the full range at maximum participant comfort (pulse width = 300μs; ON time = 15s; OFF time= 15s). The ON time included a ramp up time of 6s and a ramp down time of 6s and the frequency of stimulation was set to 40 Hz. The intensity of stimulation was adjusted to obtain maximum range of wrist and finger extension without inducing pain or fatigue. After completing the initial treatment session, the patient or their carer (relative) were trained to apply the surface neuromuscular electrical stimulation system and delivering the treatment independently. Patients in the control group were not given electrical stimulation. Their care was otherwise the same as that of patients in the intervention group. Patients in both the control and treatment arms were given a defined module of routine physiotherapy, with interventions which reflected local clinical practice, [19] for a period of six weeks in addition to the usual clinical treatment on the stroke unit. The protocol classified therapies based on therapy input as passive, active assisted, active/strengthening and functional.[19] Treatment compliance in both arms was monitored using a patient record. Both groups also had usual care.

Clinical Measures:

Details of the medical history were established by interview and consultation of medical notes. Demographic details including age, gender, and affected side of the body and stroke subtype were taken at recruitment. Patients were examined neurologically and classified as total anterior circulation syndrome, partial anterior circulation syndrome, lacunar syndrome and posterior circulation syndrome. [23]

Outcomes were assessed by an independent assessor blinded to the study protocol (separate from the physiotherapist who administered the surface neuromuscular electrical stimulation and study related physiotherapy). Following a baseline assessment, which was conducted within 3 days of recruitment, repeated measurements were taken at 6, 12, 24 and 36 weeks after recruitment. Measurements were taken at the patient's bedside on the acute stroke ward, the stroke rehabilitation unit or at various discharge destinations including nursing home, sheltered housing or residential homes.

Pain was measured using a numerical five-point verbal rating scale (ranging from 0 (no pain) to 5 (pain that could not be any worse)).[24] Spasticity was quantified neurophysiologically by measuring muscle activity during passive extension of wrist.[4, 24] Wrist contractures were characterized biomechanically by measuring the passive range of movement (PROM) and stiffness at slow stretch at the wrist.[4, 24, 25] These measurements were taken using a custom built device.[26] The full measurement procedure has been described previously.[24]

Motor performance in the impaired arm was, for classification purposes, assessed using the Action Research Arm Test (ARAT). [20, 21] Patients who recovered arm function (defined as an improvement in the ARAT score by six points) at any time during the study were allocated to the Functional and those who did not, to the Non-functional group. An improvement of six points is likely to have resulted in a person progressing from not being able to do a task to be able to completing a task, but with difficulty.

Statistical methods:

To compare significant baseline differences in demographics between the control and treatment arms, Mann-Whitney U test were preformed on age and time post stroke while Chi squared test were performed on gender, side of body affected, type of stroke and mortality (over the entire study period).

Data are reported on all those who survived (with intention to treat) - the numbers gradually decreased during follow-up with 67 surviving the end of the study. Missing values were interpolated in two ways; a) The mean of 2 adjacent values was used when an intermediate assessment was missed and b) The last value was carried forward when someone dropped out of the study. Data is presented in Tables 2 (for the whole group), Table 3 (for the subgroup of patients who did not recover functional movement of the upper limb: the non-functional group), Table 4 (for the subgroup of patients who did recover functional movement of the upper limb: the functional group) and Table 5 (rate of change of outcome measures).

The change over time was analyzed using the summary measures approach recommended by Matthews et al [1990].[27] By using this method, changes over time between the control arm and treatment arm could be compared directly with a single comparison as opposed to individually studying the within group changes.[24]

The mean and the standard error were used to summarize the results at each time point. Statistical significance of the differences between the control and treatment arms and the Functional and Non-functional groups was assessed using the Mann Whitney U test. Mean differences and 95%

Confidence Intervals (CI) are reported where appropriate. All the statistical procedures were carried out using SPSS version 15 (SPSS Inc, Chicago, IL, USA). No correction was applied for multiple testing, as the 95% CI are reported and this descriptive statistic informed the discussion more than the P-values per se.

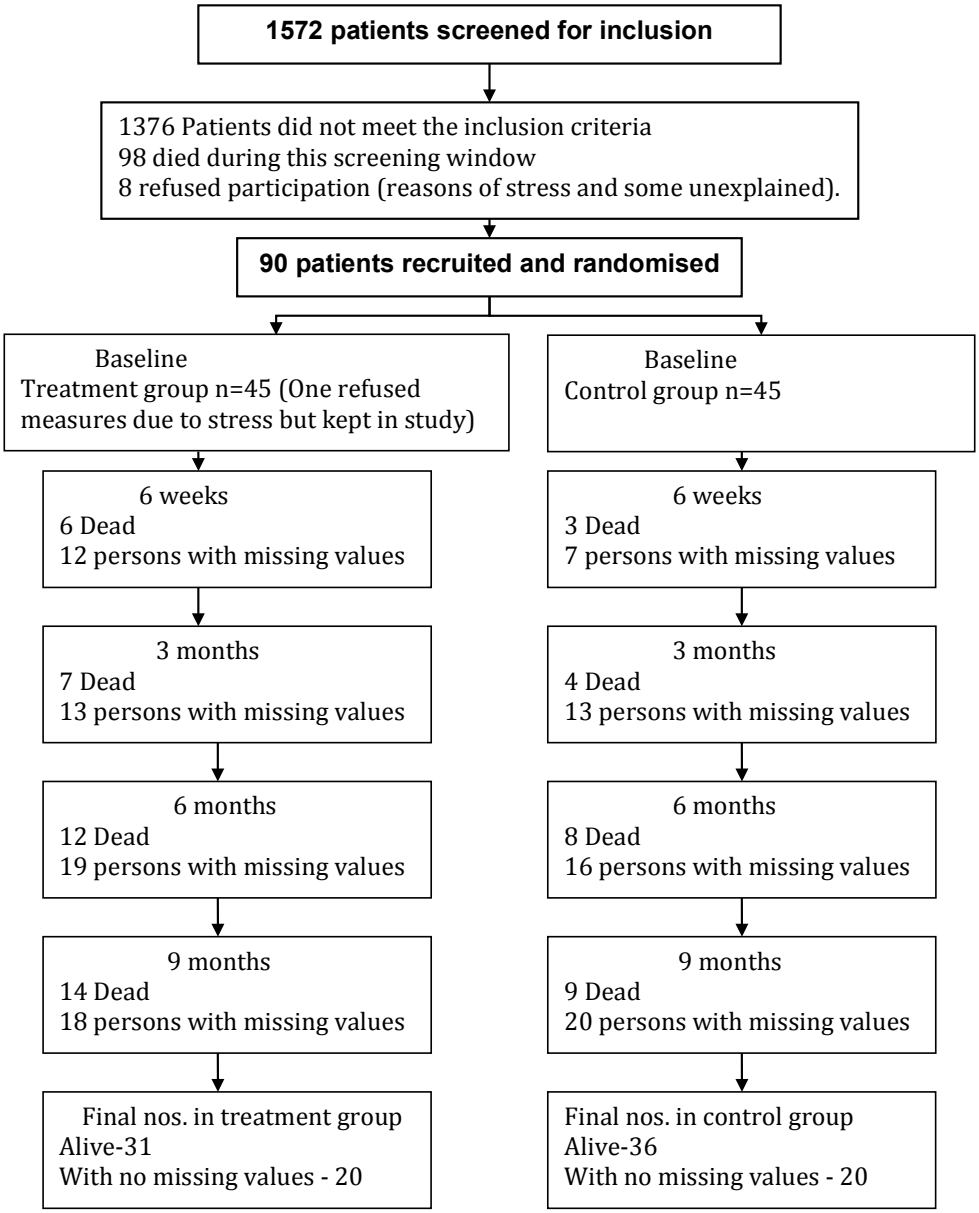
Results:

The treatment and control arms were well matched at baseline in terms of age, gender, neurological impairment and other clinical characteristics (Table 1). The consort flowchart (Figure 1) gives details on progression of participant numbers. Out of 90 patients (one patient recovered full function within three days of being screened and recruited, thus was not included in the final analysis), 19 patients recovered some upper limb function within six to 36 weeks after stroke whereas 70 others demonstrated no functional recovery. The treatment group showed a mean compliance of 28% (Range 0-100%)

Table 1: Baseline characteristics of patients included in the study.

	Control arm (n=45)	*Treatment arm (n=45)*	*P-value*
Gender (% male)	**47%**	**51%**	**0.8**
Side of body affected (% left)	**51%**	**42%**	**0.5**
Age in years [Median (range)]	**74 (52 - 90)**	**74 (32 – 98)**	**0.7**
Time post stroke in weeks [Median (range)]	**3.0 (1- 6)**	**3.0 (1- 6)**	**0.06**
Patients dead by the end of the study (n)	**9 (20%)**	**14 (31%)**	**0.3**
Total anterior circulation syndrome [n (%)]	**31 (69%)**	**30 (67%)**	**0.51**
Partial anterior circulation syndrome [n (%)]	**11 (24%)**	**8 (18%)**	
Lacunar syndrome [n (%)]	**3 (6.7%)**	**6 (13%)**	
Posterior circulation syndrome [n (%)]	**0 (0%)**	**1 (2%)**	

Figure 1: Consort Diagram



Results for the whole group are presented in Table 2, and results for the non-functional and functional groups in table 3 and 4 respectively (data from those who died are excluded at each time point). The rate of change of the outcome measures (between 0-6 weeks, 12-36 weeks and 0-36 weeks in both the functional and non-functional group) for those who survived are presented in Table 5. The results are described below:

Table 2: **Results for all patients**

	Control Treatment	Wk 0 Baseline Mean (SE) n=44 n= 45	Wk 6 End of Intervention Mean (SE) n= 42 n = 39	Wk 12 Follow up Mean (SE) n = 41 n = 38	Wk 24 Follow up Mean (SE) n = 37 n = 33	Wk 36 Follow up Mean (SE) n = 36 n = 31
PROM at slow stretch deg/wk	**Control**	95.3 (3.2)	79.5 (4.1)	77.1 (3.5)	73.7 (4.5)	77 (4.9)
	Treatment	92.4 (3.8)	83.9 (3.8)	72.6 (3.3)	80 (5.0)	81 (5.8)
	p-value mean diff (95%CI)	0.7 2.9 (-6.84 to 12.64)	0.7 -4.4 (-15.36 to 6.56)	0.4 4.5 (-4.93 to13.93)	0.4 -6.3 (-19.48 to 6.88)	0.8 -4 (-18.9 to 10.9)
Stiffness at slow stretch N/deg/wk	**Control**	0.05 (0.01)	0.08 (0.01)	0.04 (0.02)	0.07 (0.02)	0.1 (0.04)
	Treatment	0.05 (0.02)	0.06 (0.01)	0.11 (0.05)	0.08 (0.02)	0.08 (0.04)
	p-value mean diff (95%CI)	0.8 0 (-0.04 to 0.04)	0.7 0.02 (-0.01 to 0.05)	0.07 -0.07 (-0.18 to 0.04)	0.7 -0.01 (-0.07 to 0.05)	1.0 0.02 (-0.09 to 0.13)
EMG at slow stretch mV/wk	**Control**	1.1 (0.25)	1.1 (0.21)	1.0 (0.19)	1.0 (0.18)	1.1 (0.2)
	Treatment	1.3 (0.2)	1.9 (0.4)	1.1 (0.28)	1.4 (0.3)	1.1 (0.24)
	p-value mean diff (95%CI)	0.5 -0.2 (-0.83 to 0.43)	**0.09** -0.8 (-1.69 to 0.09)	0.8 -0.1 (-0.76 to 0.56)	0.5 -0.3 (-0.99 to 0.39)	0.9 0 (-0.61 to 0.61)
Pain units/wk	**Control**	0.4 (0.15)	1.1 (0.23)	1.2 (0.25)	1.1 (0.24)	1.0 (0.27)
	Treatment	0.5(0.17)	0.5 (0.16)	0.8 (0.2)	0.4 (0.18)	0.4 (0.18)
	p-value mean diff (95%CI)	0.6 -0.1 (-0.54 to 0.34)	**0.02** 0.6 (0.05 to 1.15)	0.1 0.4 (-0.23 to 1.03)	**0.02** 0.7 (0.11 to 1.29)	**0.07** 0.6 (-0.04 to 1.24)

Table 2: shows a summary of the results for all patients (except B06 Pt N= 89) and for those who were alive with Intention to treat (omitting those who died at each week), where M+/-SE is used to describe the data. Mann Whitney U test was used to determine significant differences between the control and treatment arm over time. Bold values in tables represent statistically significant results. CI, confidence interval; EMG, electromyography; deg, degree; mV, millivolts; N, Newton; PROM, passive range of movement; Wk, week.

Table 3: Results for the Non-Functional Group

	Control Treatment	Wk 0 Baseline Mean (SE) n=37 n= 33	Wk 6 End of Intervention Mean (SE) n= 34 n = 27	Wk 12 Follow up Mean (SE) n = 34 n = 27	Wk 24 Follow up Mean (SE) n = 31 n = 22	Wk 36 Follow up Mean (SE) n = 30 n = 20
PROM at slow stretch deg/wk	**Control**	96.6 (3.4)	80 (4.3)	74.4 (3.9)	67.9 (4.2)	70.6 (4.8)
	Treatment	91 (4.1)	78 (4.1)	69.2 (3.9)	69.6 (5.2)	76 (7.9)
	p-value mean diff (95%CI)	0.3 5.6 (-4.84 to16.04)	0.6 2.0 (-9.65 to 13.65)	0.3 5.2 (-5.61 to 16.0)	0.7 -1.7 (-14.8 to 11.4)	0.5 -5.4 (-23.5 to 12.7)
Stiffness at slow stretch N/deg/wk	**Control**	0.05(0.01)	0.07 (0.01)	0.04 (0.02)	0.07 (0.03)	0.13 (0.05)
	Treatment	0.03(0.01)	0.06 (0.01)	0.15 (0.07)	0.09 (0.03)	0.08 (0.06)
	p-value mean diff (95%CI)	0.5 0.02 (-0.01 to 0.05)	0.9 0.01 (-0.02 to 0.04)	0.5 -0.11 (-0.25 to 0.03)	0.9 -0.02 (-0.1 to 0.06)	0.8 0.05 (-0.1 to 0.2)
EMG at slow stretch mV/wk	**Control**	1.2(0.3)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)
	Treatment	1.1(0.2)	1.3 (0.4)	0.6 (0.12)	0.9 (0.2)	1.0 (0.3)
	p-value mean diff (95%CI)	0.9 0.1 (-0.61 to 0.81)	0.4 -0.3 (-1.18 to 0.58)	0.6 0.4 (-0.06 to 0.86)	0.9 0.2 (-0.35 to 0.75)	0.9 0 (-0.71 to 0.71)
Pain units/wk	**Control**	0.48(0.18)	1.5 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
	Treatment	0.42(0.19)	0.6 (0.2)	0.9 (0.3)	0.5 (0.3)	0.5(0.2)
	p-value mean diff (95%CI)	0.9 0.06 (-0.45 to 0.57)	**0.04** **0.9** (0.19 to 1.61)	0.3 0.4 (0.43 to 1.23)	**0.02** 0.8 (-0.03 to 1.63)	**0.09** 0.7 (-0.01 to 1.41)

Table 3: shows a summary of the results of Non Functional Group at measurement points *for all patients* (except B06 Pt N= 89) and *for those who survived* till the end of the study with missing values replaced where M+/-SE is used to describe the data. Mann Whitney U test was used to determine significant differences between the control (C) and treatment (T) arm over time. Bold values in tables represent statistically significant results.
CI, confidence interval; EMG, electromyography; deg, degree; mV, millivolts; N, Newton; PROM, passive range of movement; Wk, week.

Patients did not demonstrate pain at baseline. However, by six weeks, pain developed in the control arm, but not in the treatment arm ($p=0.02$) and the effect on pain persisted to the end of the study. The functional group showed negligible change in pain over time (Table 4). In the non-functional group, the rate of deterioration of pain in control arm was significantly higher ($p=0.04$) than that in the treatment arm within first six weeks (Table 5).

Passive range of movement was not significantly different between the control and treatment arms at any time point of measurement over the entire study period ($p > 0.2$; Table 2). For the non-functional and functional groups there was no significant difference between both arms in all but the final measurement point ($p > 0.2$; Tables 3 and 4 respectively). Over the treatment period the rate of recovery in passive range of movement was significantly better in the treatment arm in both the non-functional and functional groups. In the non-functional group the mean rate of deterioration in the treatment arm was smaller than that in the control arm. In the functional group the mean rate of recovery indicated an improvement in the treatment arm as opposed to the deterioration in the control arm. Over the entire study period the gains made by the treatment arm of the non-functional group were maintained and those made by the functional group were lost (Table 5). There was a significant difference favoring treatment for the non-functional group (Table 5). There was a no difference in the functional group.

Stiffness in the wrist flexors was not significantly different between control and treatment at any time point during the entire study period, in the whole group ($p > 0.2$ Table 2) or in the non-functional and functional groups individually ($p > 0.2$; Tables 3 and 4 respectively). The rate of change in stiffness from 0-36 weeks, in the control arm was not significant ($p> 0.2$) (Table 5).

The rate of change in stiffness over time decreased in both the treatment and control arms for the Functional group over the entire study period.

Spasticity, as indicated by abnormal muscle activity on electromyography during slow stretch was seen in majority of the patients (85 out of 90) at baseline (44/45 in the control and 41/45 in the treatment arm), and this abnormal muscle activity persisted until the end of the study (in 64 out of 67 patients with 34/36 in the control and 30/31 in the treatment arm). Electromyography (in the wrist flexors) was not significantly different between the control and treatment arms at any time point of measurement over the entire study period ($p > 0.2$; Table 2). When the group was split into a non-functional and a functional group there was also no significant difference between treatment and control ($p > 0.2$; Tables 3 and 4 respectively). The rate of recovery also showed no specific pattern of change but the treatment arm of the Functional group showed an increase over the treatment period (Table 5).

Table 4: Results for the Functional Group

	Control Treatment	Wk 0 Baseline Mean (SE) n=7 n=12	Wk 6 End of Intervention Mean (SE) n= 7 n = 12	Wk 12 Follow up Mean (SE) n = 6 n = 11	Wk 24 Follow up Mean (SE) n = 5 n = 11	Wk 36 Follow up Mean (SE) n = 5 n = 11
PROM at slow stretch in deg/wk	**Control**	88.6 (7.4)	77.4 (10.6)	92.4 (4.2)	109.6 (7.6)	112.1 (2.4)
	Treatment	95.9 (8.4)	96.9 (6.5)	80.7 (6.3)	99.5 (9.6)	88.8 (7.6)
	p-value mean diff (95%CI)	0.2 -7.3 (-29.24 to 14.64)	0.3 -19.5 (-43.9 to 4.87)	0.2 11.7 (-3.4 to 26.5)	0.2 10.1 (-13.9 to 34.1)	0.05 23.3 (7.68 to 38.92)
Stiffness at slow stretch in N/deg/wk	**Control**	0.05 (0.09)	0.08 (0.03)	0.02 (0.02)	0.03 (0.02)	0.04(0.01)
	Treatment	0.1 (0.05)	0.07 (0.03)	0.04 (0.04)	0.03 (0.03)	0.08 (0.03)
	p-value mean diff (95%CI)	0.8 -0.05 (-0.25 to 0.15)	0.4 0.01 (-0.07 to 0.09)	0.9 -0.02 (-0.11 to 0.07)	0.1 0 (-0.07 to 0.07)	0.3 -0.04 (-0.10 to 0.02)
EMG at slow stretch in mV/wk	**Control**	0.86 (0.3)	1.2 (0.4)	1.4 (0.5)	0.8 (0.2)	1.7 (0.6)
	Treatment	1.8 (0.6)	3.2 (0.9)	2.3 (0.8)	2.3 (0.8)	1.3 (0.4)
	p-value mean diff (95%CI)	0.4 -0.94 (-2.25 to 0.37)	0.1 -2.0 (-3.93 to -0.07)	0.6 -0.9 (-2.75 to 0.95)	0.3 -1.5 (-3.12 to 0.12)	0.3 0.4 (-1.01 to 1.81)
Pain in units/wk	**Control**	0.0 (0.0)	0.0 (0.0)	0.8 (0.6)	0.14 (0.14)	0.29 (0.18)
	Treatment	0.17(0.17)	0.18 (0.18)	0.3 (0.24)	0.3 (0.22)	0.3 (0.22)
	p-value mean diff (95%CI)	0.4 0.17 (-0.5 to 0.16)	0.4 -0.18 (-0.53 to 1.17)	0.6 0.5 (-0.77 to 1.77)	0.3 -0.16 (-0.67 to 0.35)	0.9 -0.01 (-0.57 to 0.55)

This table shows a summary of the results of Functional group at measurement points *for all patients* (except B06 Pt N= 89) and for *those who survived till* the end of the study with missing values replaced where M+/-SE is used to describe the data. Mann Whitney U test was used to determine significant differences between the control (C) and treatment (T) arm over time. CI, confidence interval; EMG, electromyography; deg, degree; mV, millivolts; N, Newton; PROM, passive range of movement; Wk, week.

Table 5: Rate of Recovery

		Functional Group			Non-Functional Group		
Outcome Measure		**Wk 0-6 Mean (95%CI) C = 5 T = 11**	**Wk 12-36 Mean (95%CI) C = 5 T = 11**	**Wk 0-36 Mean(95%CI) C = 5 T = 11**	**Wk 0-6 Mean(95%CI) C = 30 T = 20**	**Wk 12-36 Mean (95%CI) C = 30 T = 20**	**Wk 0-36 Mean (95%CI) C = 30 T = 20**
PROM at slow stretch deg/wk	**Control**	-3.2 (-7.2 to 0.9)	0.8 (0.5 to 1.5)	0.9 (-0.06 to 1.8)	-2.7 (-4.2 to -1.3)	-0.3 (-7.4 to 0.1)	-0.8 (-1.1 to -0.5)
	Treatment	1.0 (-2.9 to 4.9)	0.4 (-0.6 to 1.2)	-0.07 (-0.5 to 0.3)	-1.3 (-2.8 to 0.3)	0.1 (-0.4 to 0.6)	-0.3 (-0.6 to 0.06)
	p-value mean diff (95%CI)	0.1 -4.2 (-10.5 to 1.8)	0.5 0.4 (-0.8 to 1.7)	**0.03** 0.97 (0.2 to 0.65)	0.1 -1.4 (-3.6 to 0.64)	0.3 -0.4 (-1.06 to 0.24)	**0.04** -0.5 (-0.9 to -0.06)
Stiffness at slow stretch N/deg/wk	**Control**	0.008 (-.007 to .23)	0.0006 (-.038 to .04)	-0.0006 (-.002 to.001)	0.005 (-.002 to .01)	0.004 (0 to 0.009)	0.002 (-0.01 to 0.005)
	Treatment	-0.007 (-0.04 to 0.02)	0.001 (-.003 to .006)	-0.0005 (-.003 to .02)	0.04 (-.002 to .01)	-0.001 (-.01 to .01)	0.001 (-.022 to .005)
	p-value mean diff (95%CI)	0.5 0.015 (-0.02 to 0.05)	1.0 .0005 (-0.006 to .005)	0.6 -.001 (-0.004 to .004)	0.8 - 0.035 (-0.08 to 0.01)	0.6 .005 (-0.005 to 0.015)	0.9 0.001 (-0.004 to 0.004)
EMG at slow stretch mV/wk	**Control**	-0.006 (-.17 to .16)	-0.0008 (-0.1 to 0.1)	0.01 (-0.03 to .05)	-0.03 (-.14 to .08)	-0.001 (-.02 to .02)	-0.008 (-0.02 to .007)
	Treatment	0.2 (-0.07 to 0.5)	-0.02 (-0.1 to 0.05)	-0.02 (-.07 to .03)	-0.001 (-0.1 to 0.1)	0.02 (-.01 to .05)	-0.007 (-0.03 to 0.02)
	p-value mean diff (95%CI)	0.3 - 0.206 (-0.6 to 0.2)	0.8 0.0192 (-1.0 to 0.15)	0.5 0.03 (-0.04 to 0.11)	0.9 -0.029 (-0.19 to 0.12)	0.5 -0.021 (-0.05 to 0.014)	0.7 -0.001 (-0.02 to 0.02)
Pain units/ wk	**Control**	0 (0 to 0)	-0.1 (-0.5 to 0.2)	.001 (-.002 to.005)	0.4 (0.23 to 0.5)	-.007 (-0.08 to .06)	0.02 (-0.008 to 0.04)
	Treatment	- .08 (-0.2 to 0.06)	0 (0 to 0)	-.003 (-.02 to .02)	0 (-0.4 to 0.4)	-.05 (-0.1 to 0.03)	-0.007 (-0.05 to 0.04)
	p-value mean diff (95%CI)	0.6 -0.08 (-0.12 to 0.27)	0.1 -0.1 (-0.03 to 0.005)	0.6 0.004 (-0.02 to 0.03)	**0.04** 0.4 (0.09 to 0.6)	0.5 0.04 (-0.07 to 0.15)	0.6 0.027 (-0.02 to 0.07)

Table 5: shows the rate of recovery for the Functional and Non-Functional groups for those who survived till the end of the study with missing values replaced (Total = 66; F=16; NF=50) where M (95% CI) is used to describe the data. Mann Whitney U test was used to determine significant differences between the control (C) and treatment (T) arms over time. Bold values in tables represent statistically significant results. CI, confidence interval; EMG, electromyography; deg, degree; mV, millivolts; N, Newton; PROM, passive range of movement; Wk,week

Discussion:

We found that patients with severe stroke who do not recover functional movement in the upper limb are more likely to have pain than patients who recover arm function. Surface neuromuscular electrical stimulation to the wrist and finger extensors started within six weeks of stroke onset and continued for six weeks prevented pain in patients who did not regain functional movement in the upper limb. This effect was maintained till the end of the study, 30 weeks after discontinuation of the intervention. There was some evidence that contracture formation was transiently reduced during the treatment period in patients who had not regained functional movement in the upper limb. Treatment had no effect on spasticity.

Upper limb pain is a severe and disabling problem after stroke. While appropriate handling of the upper limb has reduced its incidence, it remains a common problem. There is some evidence that shoulder pain caused by spasticity may respond to Botulinum toxin injections. [26] Conventional analgesics are largely ineffective, and electrical stimulation of shoulder muscles has previously been shown to be ineffective in relieving pain. [28] When the protocol was designed we assumed that spasticity and contractures were factors in the aetiology of pain, and that effective treatment of spasticity and prevention of contractures would therefore reduce post stroke upper limb pain. Our research shows that surface neuromuscular stimulation prevented the development of pain without significant effects on spasticity and contractures. It can be hypothesized that sensory motor stimulation combined with mobilization of the upper limb may have prevented the development of pain. This is consistent with the neuromodulation literature, which demonstrates that treatment with surface neuromuscular electrical stimulation has the potential to increase

excitability of the central nervous system via antidromic signal transmission in sensory nerves.[29] This may have reduced pain via gating mechanisms, [30] release of endorphins[31] and/or prevention of maladaptive plastic changes in the brain. As our measures of pain were subjective records of the presence and severity of pain in the upper limb we are unable to confirm the exact location of the pain. Therefore we are unable to determine the mechanisms responsible for the observed treatment effect, particularly with respects to whether therapeutic effects were specifically associated with the segment stimulated or whether the effects were extrasegmental. It is important to note that we started treatment relatively early after the stroke, before clinical evidence of pain was documented. Further research should address whether this protocol for providing surface neuromuscular stimulation and mobilization is effective in treating established post stroke upper limb pain.

Surface neuromuscular electrical stimulation showed no effects on spasticity. There was evidence of spasticity (as seen by stretch induced muscle activity) at every time point from the baseline to the end of the study. Stimulation of an antagonistic muscle group (wrist extensors in this case) with surface electrical stimulation has previously been shown to reduce spasticity temporarily via spinal inhibition during the period of stimulation. However such effects cease as soon as the stimulation is terminated.[18] In this study we measured spasticity at least 24 hours after treatment was discontinued and it is possible that any transient treatment effect, if it had existed, has been missed. However, our findings do confirm that there are no long-term effects of treatment on spasticity.[18] This may or may not be relevant for the development of contractures, as debate continues as to whether spasticity reduction is useful.[24]

Patients who did not recover arm function were at more risk for the development of contractures. This is consistent with previous findings.[6,24] The repeated mobilisation associated with treatment may have been the most likely cause for the short- term prevention of contractures. This effect was lost as soon as treatment was discontinued. This might suggest that if surface neuromuscular electrical stimulation is to have a role in the treatment of stroke patients with no functional recovery, the treatment may need to be provided until functional recovery occurs if the aim was prevention of contractures. There is also the possibility that the treatment was ineffective in the prevention of contractures because the intensity or duration was insufficient. With regards to intensity we did not attempt to increase the intensity to stretch to end range of movement but we had set the intensity at the level to provide pain free range of movement. This might not have been adequate to prevent tendon and/or muscle shortening. Different protocols may be required to obtain a better outcome in relation to spasticity and contractures. More work is needed for example a stretch to the end of the range of movement followed by a period of hold at end range of movement stimulus (as opposed to a simple cycling through the pain free range of movement). More fundamental work is needed to identify a protocol that will be effective for contracture prevention and/or management.

The present study was carried out on 90 acute stroke patients who were homogeneous in terms of functional performance (i.e. all had no useful functional movement in their upper extremity during recruitment). Patients in both the control and treatment arms were well matched at baseline in terms of age, sex, side affected and stroke type. Twenty-five percent of patients died before the end of the trial. As all patients included in the study had severe disabling strokes, and were included early after the stroke, where mortality is highest rather than in the chronic stable phase,

this morality rate is within the expected range. As there was no significant difference in mortality between the two treatment groups, this is unlikely to have introduced a systematic bias. The compliance with treatment was variable and the mean compliance was low. This was expected as many patients were unable to self administer treatment. We have not carried out any per protocol analysis to confirm whether response to treatment was influenced by compliance to treatment as the sample size was small.

This secondary analysis is under powered. Although based on current practice, the protocol showed limited benefit in terms of spasticity and contracture. There is a need to revisit our protocol and fundamental hypothesis related to the treatment of contractures.

Clinical Message:

- Patients without functional movement in the arm are likely to develop upper limb pain.
- Surface neuromuscular electrical stimulation for six weeks started within six weeks of stroke prevents pain in this group of patients.
- This intervention has no long term effect on spasticity.

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Chapter 7

GENERAL DISCUSSION

General Discussion

The focus on spasticity results from the common belief that spasticity significantly interferes with functional recovery and leads to secondary complications such as contractures, weakness and pain.[1, 2] However, there is minimal evidence to prove either a clinically important association exists between spasticity and contractures or that spasticity interferes with functionally useful movement.

The objective of this thesis was to identify if spasticity on the wrist after an acute stroke interferes with functional recovery of the upper limb. For further research into spasticity, it is crucial to understand and explore whether there is a consistent definition and a unified assessment framework for spasticity. In this chapter of discussion, the main findings are integrated and evaluated within the context of existing literature.

Understanding and measuring spasticity:

From the systematic literature review in **Chapter 2**, it is clear that the term spasticity is inconsistently defined and this inconsistency needs to be resolved. On critical evaluation, two broad approaches were taken with respect to definitions of spasticity. The majority attempted at providing a narrow and precise description of spasticity. While being the most valid approach, it has not worked as well as it should have as these narrow definitions [3, 4, 5] do not conform to common clinical presentations.[1, 6] On the other end, the broader definition that attempts to provide an umbrella statement to catch all possible variable interpretations of this phenomenon

"*disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles"* proposed by the SPASM consortium[7] seems to provide a starting point for the development of future clinically usable definition.

To add to the problem of variable definitions, the review in **Chapter 2** identified that the frameworks used to underpin the measurement of spasticity is also substantially variable. It was proven that the measures used did not correspond to the critical features of spasticity that were defined within the papers. Incongruence between definitions and measurements can significantly compromise the internal validity of research and will need to be robustly addressed. The **SPASM** definition shifts the focus from measurement of stiffness to measurement of 'abnormal' muscle activity.

An investigation on the clinical, biomechanical and neurophysiological measures of spasticity in **Chapter 3** demonstrated that biomechanical measures show no consistent relationship with other measures and that the existing clinical measures depending on the quantification of muscle tone may lack sensitivity to quantify the abnormal muscle activation and stiffness associated with common definitions of spasticity. On the other hand neurophysiological measures may provide more clinically useful information for the management and assessment of spasticity.

It is evident by **Chapter 3** that abnormal muscle activity, the primary pathophysiological presentation of spasticity, is presented in a significant proportion of the severely disabled stroke survivors. Moreover, the presentations of spasticity (quantity and patterns of electrical activity during passive movement) are variable and are not always consistent with existing definitions.

Depending on muscle activity, pattern responses of spasticity are identified and classified into five groups 1) No/Negligible 2) Position Dependent 3) Velocity Dependent 4) Position and Velocity Dependent and 5) Early Catch.

Natural history of spasticity after stroke

Using current clinical measures of muscle tone, it was possible to have overestimated the time taken for spasticity to develop and underestimated both prevalence of spasticity and 'effect size' associated with common anti-septic treatment.[7] Quantifying spasticity by passive testing protocols in a way congruent to current understanding of spasticity [8, 9] in **Chapter 4**, it is evident that spasticity develops early, within first six weeks of a stroke.

The results of this novel study also suggested that contrary to the general perception[1], spasticity (measured using passive testing protocols) may not interfere with recovery of useful functional movement. Also, spasticity may not be the primary contributor to contracture formation. Instead, loss of function and pain could exacerbate formation of contractures.

Treatment with surface neuromuscular electrical stimulation:

Surface neuromuscular electrical stimulation [sNMES] has been recommended as a safe method to improve upper limb outcomes after stroke.[10, 11, 12] However, robust evidence for efficacy of electrical stimulation is lacking, especially in relation to the treatment of spasticity, development of contractures or prevention of pain. [13, 14]

Chapter 5 discusses probably one of the largest, clinically relevant, studies that has been conducted exploring the effects of an acute upper limb rehabilitation protocol in severely disabled patients with stroke. This study showed that in patients with severe stroke and no functional arm movement, electrical stimulation of the wrist extensors improves extensor muscle strength and grip strength, but there were no significant improvements in in the range of movement. There is some evidence that this treatment facilitated recovery of arm function. It is not clear as to whether this functional improvement was a direct result of plasticity or was secondary to strength gains.

Chapter 6 demonstrated that sNMES to the wrist and finger extensors, started within six weeks of stroke onset and continued for six weeks, prevented the development of pain in patients who did not regain functional movement in the upper limb. There was some evidence that contracture formation was transiently reduced during the treatment period in the same group of patients.

sNMES treatment showed no effects on spasticity. Stimulation of an antagonistic muscle group (wrist extensors in this case) with surface electrical stimulation has previously been shown to reduce spasticity temporarily via spinal inhibition during the period of stimulation. However, such effects cease as soon as the stimulation is terminated.[14] In this study we measured spasticity at least 24 hours after treatment was discontinued and it is possible that any transient treatment effect, if it existed, was missed. However, our findings do confirm that there are no long-term effects of treatment on spasticity.[14]

Limitations and Topics for Future Research:

Although unlikely, it may be possible that the spasticity-related literature, as reviewed within the field of stroke rehabilitation may not be representative of the spasticity-related literature in other conditions. Inspite of this limitation, we are of the view that the literature sampled for this review reflects the current state of the art with respect to spasticity related in research in all neurological conditions.

In the conducted studies, although intentional, the homogenous sample used was not fully representative of the stroke population. For findings to be more generalizable, a more comprehensive cross-sectional longitudinal study is required however the big problem with needing ethical approval will naturally lead to a self-selecting sample. Also, it was not possible to confirm whether those who recovered function had joints that were normal nor was it possible to confirm those who developed contractures had pre-existing problems that exacerbated the formation of contractures. Incorporating information on premorbid status in any prospective longitudinal study is recommended. Moreover, the effect of limb position, emotional state and awareness on presence and severity of muscle response to an external imposed stretch, should be explored.

More work is required to compare manual uncontrolled measurement techniques such as those developed in these studies, against more controlled perturbation methods to identify the minimum controls required to practically and reliably study the phenomenon of spasticity.

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Summary:

In **Chapter 1** the pathophysiology of spasticity is described and the objective of this thesis is formulated. The principal aim of this thesis is on identifying if spasticity on the wrist after an acute stroke interferes with functional recovery of the upper limb.

Chapter 2 presents the results of a systematic review performed on two hundred and fifty articles (190 clinical, 46 literature reviews and 14 case reports) over a period of two decades. Seventy-eight used the Lance definition, 88 equated spasticity with increased muscle tone, 78 provided with no definition and six others used their own definitions for spasticity. It was proven that not only is spasticity inconsistently defined but also the measures of spasticity are incongruent to the definitions used.

Furthermore, to quantify the agreement between the three (clinical, biomechanical and neurophysiological) measures of spasticity that reflected the constructs that under-pinned the definitions identified in the literature, a study was performed, described in **Chapter 3** of this thesis. This convenience sample study (with one hundred stroke patients having no upper limb function) showed that there was a lack of concordance between the clinical presentations of spasticity and existing definitions of this phenomenon. It also demonstrated that using measures of muscle activity to quantify and/or classify spasticity in routine clinical and research practice may be more useful than using indirect measures of muscle tone.

Chapter 4 focuses on spasticity and contractures at the wrist after stroke to determine the time course of development and their association with functional recovery after stroke. Spasticity was measured by quantifying muscle activity during passively imposed stretches at two velocities, contractures were measured using passive range of movement and stiffness while upper limb

function was measured using action research arm test. All assessments were conducted at baseline and at 6, 12, 24 and 36 weeks after recruitment. The entire sample demonstrated signs of spasticity at all time points of measurement and these presentations varied with time. Spasticity did not seem to be a barrier to functional recovery. Wrist contractures seemed to have developed rapidly after stroke.

Chapter 5 and **Chapter 6** describe the effects of surface neuromuscular electrical stimulation (sNMES) applied to the wrist for six weeks after acute stroke. This randomized study demonstrated that sNMES treatment along with standardized upper limb therapy improves muscle strength for wrist extension and grip and prevents the development of pain in severely disabled stroke patients. There was some evidence that treatment with electrical stimulation was beneficial in reducing contractures however it had no effect on spasticity. Larger studies are required to study sNMES treatment influence on arm function.

The thesis is concluded with a general discussion in **Chapter 7**, in which the findings of the different studies are discussed and are integrated.

Samenvatting

Het doel van dit proefschrift was om te onderzoeken in hoeverre spasticiteit van de pols interfereert met het functionele herstel van de bovenste extremiteit bij mensen na een acuut cerebro vasculair accident (cva).

In **hoofdstuk 1** wordt eerst ingegaan op de pathofysiologie van spasticiteit en wordt verder ingegaan op het doel van het onderzoek.

In **hoofdstuk 2** worden de resultaten beschreven van een systematisch review uitgevoerd op 250 artikelen (190 klinisch onderzoek, 46 reviews en 14 case reports) over een periode van 20 jaar. In 78 artikelen werd de definitie van Lance gebruikt, in 88 artikelen werd spasticiteit getypeerd als een verhoogde spierspanning en in 78 artikelen werd geen duidelijke definitie gegeven, terwijl er in 6 artikelen nieuwe definities warden geformuleerd. Aangetoond kon worden dat niet alleen spasticiteit inconsistent werd gedefinieerd maar ook dat de maten van spasticiteit, incongruent zijn aan de gehanteerde definities.

Om de samenhang tussen de drie verschillende benaderingen van spasticiteit, klinisch, biomechanisch en neurofysiologisch te onderzoeken werd een studie opgezet die in **hoofdstuk drie** is beschreven. Hierbij werden 100 CVA patiënten onderzocht die geen functie in de aangedane bovenste extremiteit hadden. Uit het onderzoek bleek dat er weinig samenhang was tussen de klinische manifestaties van spasticiteit en de bestaande definities van spasticiteit. Ook werd aangetoond dat het gebruik van kwantitatieve maten van spier activatie om spasticiteit te kwantificeren in dagelijkse klinische praktijk en in onderzoek nuttiger zijn dan de indirecte variabelen die spierspanning kwantificeren.

Hoofdstuk 4 richt zich op spasticiteit en contracturen rond de pols en met name hoe deze zich na een acuut cva ontwikkelen in de tijd en hoe de samenhang tussen deze is en hoe beiden samenhangen met het functionele herstel na het cva. Spasticiteit werd hierbij gemeten door de spieractiviteit te kwantificeren tijdens het strekken van de pols met twee verschillende snelheden. Contracturen warden gemeten door de passieve bewegingsmogelijkheden te bepalen en de hierbij optredende stijfheid en de functie werd gemeten met de Arma test (Action Research arm test). Al deze metingen werden op baseline gemeten en 6, 12, 24 en 36 weken na de initiële rekrutering. Enige vorm van spasticiteit werd gemeten bij alle personen en de mate varieerde in de tijd. Het optreden van spasticiteit bleek geen hindernis te zijn voor functioneel herstel. Contracturen van de pols ontwikkelden zich vaak snel na het CVA.

Hoofdstuk 5 en **Hoofdstuk 6** beschrijven de effecten van de toepassing van oppervlakte elektrostimulatie gedurende 6 weken na het acute cva. Deze gerandomiseerde studie toont aan dat elektrostimulatie gecombineerd met gestandaardiseerde training van de bovenste extremiteit de spierkracht van polsextensie en greep verhoogt en bovendien de ontwikkeling van pijn remt bij de ernstig aangedane patiënten. Er was ook enig aanwijzing dat de behandeling met elektrostimulatie een positief effect heeft op de ontwikkeling van contracturen maar geen effect op spasticiteit. Grotere studies zijn nodig om het effect op arm functie te bepalen.

Tenslotte wordt in **hoofdstuk 7** de bevindingen uit de verschillende studies besproken en in hun samenhang geïntegreerd.

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Curriculum vitae

Shweta Malhotra was born in Kuwait, in 1981. After completing her Masters in Biomedical Engineering from University of Strathclyde, she was employed by Keele University as a Researcher under the supervision of Dr Anand David Pandyan. She worked on her PhD in collaboration with University of Twente under the guidance of Dr Hermie Hermens. The present thesis is the result of her PhD research. Her research interest is in the area of investigation of upper limb spasticity after stroke.

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