Electrical stimulation of the upper extremity in stroke: Cyclic versus EMG-triggered stimulation

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Therapeutic electrical stimulation of the upper extremity in stroke

Joke de Kroon

Therapeutic electrical stimulation of the upper extremity in stroke

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Twente
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volgens besluit van het College voor Promoties
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Paranimfen:

Cor de Kroon
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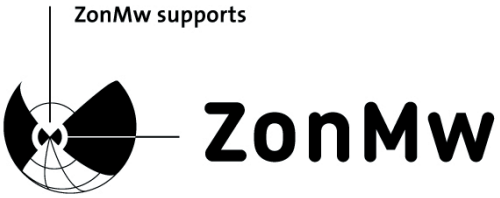

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Electrostimulatie,

een stimulerend onderwerp

dat prikkelt tot onderzoek.

Contents

1

Introduction and outline of the thesis

Introduction

Worldwide more than 40,000 people are struck by stroke every day.[1] The figures for the Netherlands show a daily incidence of 80, based on an incidence of approximately 30,000 per year.[2] About 20% of the patients do not survive the acute phase. The stroke survivors suffer from motor impairments, cognitive deficits and behavioral problems. The most prominent consequence of stroke in the acute phase is hemiparesis, which is present in 80-90% of all stroke patients.[3] Fortunately most subjects surviving stroke experience some degree of motor recovery, which occurs most rapidly in the first 30 days after stroke.[4] However, 3 months after stroke, only 20% has regained an entirely normal function of the affected arm, leaving a great number of subjects with either a non-functional or impaired arm.[5]

The patterns of recovery are similar for upper and lower extremities.[4] But whereas a subject may be able to walk independently with limited motor recovery of the lower extremity, functional use of the upper extremity requires finer motor control and therefore a higher level of recovery.[6] Residual functional impairments have considerable impact on ADL activities, hobbies and work. As a consequence the majority of stroke survivors considers the impaired arm function as a major problem,[7] and functional impairment of the arm is associated with a low level of subjective well-being.[8] These implications of impaired arm function after stroke emphasize the importance of therapeutic options to improve upper extremity function beyond natural recovery. One of the therapeutic modalities employed in clinical practice is electrical stimulation.

Historical aspects of electrical stimulation

Electrical stimulation has been applied for many centuries. As early as 400 A.D. torpedo fish was recommended as a therapeutic agent. This species has specific organs to produce electrical charge to shock its prey. In 46 A.D. Scribonius Largus, a Roman physician, reported successful treatment of chronic headache and gout by placing fish over the painful body parts.[9] Although not a very convenient treatment modality, the electric fish were used throughout the years.

In the 18th century it became possible to generate electricity artificially and the application of stimulation expanded enormously. Successful treatment of hemiplegia, epilepsy, kidney stones, sciatica, gout, rheumatism and angina pectoris was reported and electrical stimulation was claimed to be a cure-all for a wide variety of disorders.[10] The positive effect of electrical therapy on hemiplegia is illustrated in the following case report by practitioner Samual Quelmalz in 1753.[10]

> "A young man of 18 with hemiplegia of two years duration was unable to stand or walk and has lost his speech. His fingers were held in flexion so that he was unable to put on his shoes by himself. His arm was motionless, and his hand cold.
> I applied some shocks to his hand in the morning and again in the afternoon. After a few days he returned and was able to move the arm more freely and also to speak with greater ease. Electric shocks were given once or twice a week. Soon he recovered so much function that he no longer complained of inability to finger the violin as he had previously."

Stimulation developed from the application of shocks towards provocation of muscle contraction. In 1961 Liberson reported correction of foot-drop in a hemiplegic patient by stimulating the peroneal nerve during the swing phase of gait, thereby improving gait.[11] The first publication about electrostimulation of the upper extremity in 1963 described an electrophysiologic splint for the hand.[12]

Electrical stimulation of the upper extremity in stroke

Application of electrical stimulation of the arm in stroke started as functional electrical stimulation (FES). In FES, muscle contraction is provoked in order to assist the performance of functional activities during stimulation. FES is an aid for continuous use. An example of FES is a peroneal stimulator to assist walking in patients with impaired gait due to stroke. Throughout the years, attention shifted from functional to therapeutic electrical stimulation (TES). TES is a therapeutic strategy aimed at improving impairments after stimulation. Nowadays the main application of ES in the upper extremity is therapeutic electrical stimulation, and therefore the scope of this thesis is TES.

Since the first publication of Long in 1963 many articles have described positive effects of TES on the affected upper extremity. TES is claimed to result in reduction of spasticity[13] and improvement of range of motion,[14,15] muscle strength,[14,16] voluntary movement[17,18] and functional abilities.[16,19] Electrostimulation seems a cure-all once more.

However, the scientific evidence for the effect of TES is limited since the claims are based on small case studies, a few randomized controlled trials (RCTs), a meta-analysis of four RCTs of which only one focussed on the upper extremity[20] and critical reviews which might be biased since they were not performed systematically.[21,22]

Moreover, there is a wide variety in stimulation paradigms. Clinical trials thus far report on various methods of therapeutic electrical stimulation. And the setting of stimulation parameters such as, amongst others, frequency, amplitude and pulse duration is different from study to study. At this stage it is not known if one method is better than the other,

and if there is one particular parameter setting which is most effective. This lack of clarity is connected to indistinctness with respect to the mechanism of action of ES.

The serious burden of the affected arm after stroke indicates the need of an effective treatment modality. In this respect the positive results of electrical stimulation thus far are encouraging. However, a firm scientific basis with respect to effectiveness and optimal stimulation paradigms is required before recommendations on the use of TES to facilitate motor recovery of the upper extremity can be formulated for clinical practice.

Outline of the thesis

The aim of this thesis is to progress towards evidence based application of TES. In order to reach this goal it is necessary to evaluate the available evidence on the effectiveness of ES, to explore the relative value of the different methods of stimulation and parameter settings and gain more insight in the underlying mechanisms of action of TES.

The question of effectiveness of TES of the upper extremity in stroke is addressed in a systematic review, which is described in **chapter 2**. Since the selected studies were heterogeneous with regard to patient characteristics and stimulation strategy, it was decided to refrain from performing a pooled analysis in this review.

The heterogeneity with respect to stimulation paradigms raises the question if there is a relation between the characteristics of the specific stimulation applied and the therapeutic benefit gained. This issue was investigated in a second systematic review which is described in **chapter 3**. The characteristics under study were method of stimulation, duration of stimulation, stimulation frequency, amplitude and pulse duration, stage after stroke and target muscles.

With respect to target muscles, TES of the extensor muscles of the wrist and alternate stimulation of wrist flexors and extensors are most commonly applied. The results of a RCT to compare these strategies are described in **chapter 4**.

The review described in chapter 3 concluded that EMG-triggered ES may be more effective than cyclic ES in facilitating upper extremity motor recovery following stroke. **Chapter 5** reports the results of a RCT in which both methods were directly compared to explore if EMG-triggered ES is indeed more effective than cyclic ES.

The specific mechanism of action of ES is still unclear. The trial described in **chapter 6** evaluated if ES evokes changes in central motor activation parameters and whether there is a difference in central changes between cyclic and EMG-triggered stimulation.

Implications of the scientific work of this thesis for daily clinical practice and future research are discussed in **chapter 7**.

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2

Therapeutic electrical stimulation to improve motor control and functional abilities of the upper extremity after stroke: a systematic review

JR de Kroon
JH van der Lee
MJ IJzerman
GJ Lankhorst

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Abstract

Background: Therapeutic electrical stimulation (TES) is a therapeutic strategy aimed at improving impairments of the upper extremity in stroke.

Objective: Assessment of the available evidence on the effect of TES of the affected upper extremity in improving motor control and functional abilities after stroke.

Methods: A systematic literature search was performed to identify randomized controlled trials (RCT) studying the effect of TES on motor control and functional abilities. The methodological quality of the studies was systematically assessed by two raters. The reported outcomes were examined to evaluate the effect of TES and to identify a possible relationship with patient characteristics, method of stimulation and methodological quality. When possible, effect sizes were calculated (Hedges' g).

Results: Six RCTs were included. The methodological scores ranged from 7 to 16 (maximum 19). All studies assessed the effect on motor control, and four reported a positive effect. Effect sizes calculated in three studies ranged from 0.55 to 1.46. Only two studies assessed the effect on functional ability, one reported a positive effect.
Sub-group analyses in two studies suggest a better response to stimulation in less severely affected patients. Apart from this, no relationship between effect and patient characteristics, method of stimulation or methodological quality could be detected.

Conclusions: The present review suggests a positive effect of electrical stimulation on motor control. No conclusions can be drawn with regard to the effect on functional abilities.

Introduction

One of the disabling consequences of a stroke is functional impairment of the affected upper extremity. It has been reported that three months after a stroke only 20 % of all stroke survivors have an entirely normal arm function,[1] leaving a great number of patients with either a non-functional or an impaired arm. The majority of stroke patients report that the impaired arm function is a major problem.[2] To improve the impaired arm function, various therapeutic strategies can be applied, one of which is electrical stimulation.

Functional versus therapeutic electrical stimulation

Electrical stimulation can be broadly divided in two categories: functional (FES) and therapeutic electrical stimulation (TES).[3,4] In FES, muscle contraction is provoked in order to assist the performance of functional activities during stimulation. FES is an aid for continuous use. An example of FES is a peroneal stimulator to assist walking in patients with impaired gait due to stroke.[4] TES, however, is a therapeutic strategy aimed at improving impairments after stimulation. Since the main application of electrical stimulation for the upper extremity in stroke patients is therapeutic instead of functional, this review focussed on TES.

Therapeutic Electrical Stimulation

With regard to TES, several methods of application can be distinguished (see Table 1). NeuroMuscular Electrical Stimulation (NMES), EMG-triggered electrical stimulation (EMG-stim), Positional Feedback Stimulation Training (PFST) and Transcutaneous Electrical Nerve Stimulation (TENS) are applied by different devices, with different possibilities for the adjustment of stimulation parameters. The specific setting of the parameters determines the type of reaction provoked by the stimulation.

The background of these different methods is not exactly the same. Whereas patients passively receive NMES, they are actively involved in EMG-triggered and positional feedback stimulation. It is suggested that in EMG-triggered and positional feedback stimulation the effect of the repetitive muscle contractions in NMES is maximized by adding cognitive feedback to electrical stimulation.[3,10] TENS was originally used for the treatment of pain by evoking a sensory reaction without muscle contraction. With TENS, however, muscle contractions can be evoked in addition to a sensory reaction by adjusting the stimulation parameters.

The specific mechanism of action of these different stimulation methods is not clear. It is not known which neurophysiological principles account for the reported effects of TES.[3]

Table 1. Classification of applied methods of therapeutic electrical stimulation

	Characteristics of stimulating device	Characteristics of stimulation	Triggering of stimulation
neuromuscular electrical stimulation (NMES)	stimulation parameters like frequency, amplitude, pulse duration, ramp-up[1], ramp-down[2] and duty cycle[3] can be adjusted independently	cyclic stimulation	pre-programmed scheme, started by pushing trigger button, no voluntary muscle contraction of target muscle
EMG-triggered electrical stimulation (EMG-stim)		cyclic stimulation	when EMG-signal of voluntary contraction of the target muscle passes preset threshold
positional feedback stimulation training (PFST)		cyclic stimulation	when joint angle passes preset threshold due to voluntary muscle contraction
transcutaneous electrical nerve stimulation (TENS)	frequency, amplitude and pulse duration can be adjusted; no ramp-up[1], ramp- down[2] or duty cycle[3]	continuous or burst stimulation	pre-programmed scheme, started by pushing trigger button, no voluntary muscle contraction of target muscle

[1] ramp-up is the time-period needed for the stimulus to reach peak intensity; [2] ramp-down is the time-period needed for the stimulus to return to zero; [3] to prevent fatigue, the stimulus is automatically turned 'on' and 'off' (cyclic stimulation); duty cycle is the ratio of the 'on' time and the total cycle time.

Effect of TES

In general, TES is claimed to be effective in the reduction of spasticity[5] and the improvement of muscle strength,[6] range of motion,[6,7] motor control[8] and function.[8] However, the claims are mainly based on small case studies and a limited number of randomized controlled trials (RCTs). A meta-analysis of four RCTs supported the use of electrical stimulation to promote the recovery of muscle strength after stroke,[9] but only one of the four RCTs focussed on the upper extremity.[10] Subsequently two critical reviews[3,11] have been published. Both reviews discussed the effect of TES on the upper and lower extremity, but neither presented a distinct conclusion with regard to the effect on the arm. The overall conclusion was that TES may facilitate motor recovery in stroke, but the effect on functional recovery remains unclear. This conclusion might be biased, since the reviews were not performed systematically.[12] In both reviews, recommendations were given for future trials. The authors advocate large multicentre trials of good methodological quality, with clearly described patient characteristics to assess the effect of the different methods of stimulation. However, the currently available evidence has not yet been systematically and explicitly evaluated.

Research questions

The present systematic review was performed to address the following research questions:

1. What is the effect of therapeutic electrical stimulation on motor control and functional abilities of the affected arm in stroke patients? Motor control is defined as the ability to perform voluntary movements (lack of motor control refers to focal impairment), whereas functional ability is defined as the ability to perform purposeful activities (lack of functional ability refers to focal disability).[13]
2. Is there a relationship between reported effects and patient characteristics, method of stimulation or methodological quality?

Methods

Literature search

A systematic literature search up to December 2001 was conducted in Medline, Embase, CINAHL, and the database of the Cochrane Field "Rehabilitation and Related therapies". The following keywords were used: electrical stimulation, electrical stimulation therapy, neuromuscular stimulation, stroke, cerebrovascular disorders, hemiplegia, hemiparesis, arm, upper extremity, rehabilitation. The Medline search strategy is described in Appendix 1. In addition, the references of relevant publications were carefully checked.

Selection criteria

Studies that met the following criteria were included:

1. therapeutic electrical stimulation applied to the affected upper extremity in stroke patients, aiming at improvement of motor control and/or functional abilities, 2. application of stimulation with surface electrodes, 3. relevant outcome measures with respect to motor control and functional abilities, 4. randomized controlled trial, 5. full-length publication in English, German, French or Dutch.

The application of these criteria resulted in the exclusion of studies which focussed on invasive techniques, such as electro-acupuncture or implanted electrodes.

Assessment of methodological quality

The methodological quality of the selected studies was assessed by two raters independently (JHvdL and IS), based on a list of 19 criteria concerning patient selection, intervention, outcome measurements and statistics (see Appendix 2).[14] In case of disagreement, consensus was reached by discussion or, if necessary, by consulting a third rater.

Data-extraction and data-analysis

In order to address the research question, the reviewers selected the outcome measures they considered most relevant for motor control and for functional ability in each study. For these 'primary' outcome measures, the effect of electrical stimulation, as reported by the author in the original article, was assessed as positive (in favour of the electrical stimulation group, $p \leq 0.05$), negative (in favour of the control group, $p \leq 0.05$), or no difference. Effect sizes were calculated by dividing the difference in gain between both treatment groups by the pooled standard deviation (Hedges' g).[15] If necessary, authors were contacted and requested to supply missing data.

The results were examined in order to identify a possible relationship between the reported effect and patient characteristics (acute or chronic, severity of stroke), intervention (method of stimulation, contrast between the two treatment groups) and methodological quality.

Results

Selection of literature

The systematic literature search in Medline resulted in the identification of 11 RCTs. The searches in Embase, CINAHL and the database of the Cochrane Field "Rehabilitation and Related therapies" did not yield additional RCTs. Seven articles, describing six RCTs, fulfilled the selection criteria and were included in the present review (Table 2).[10,16-21]

Characteristics of selected studies

The characteristics of the selected studies are presented in Table 2.

Patients: The number of patients included in a study ranged from 11 to 60, resulting in a total of 207 patients in the six studies. Due to drop-out during the treatment period, the data of 177 patients were eligible for determination of the treatment effect immediately after the intervention period (short-term effect).

Three studies included patients in the acute stage after stroke,[16,17,19] sub-acute patients were included in one study,[10] and the remaining two studies[18,20] included patients in the chronic stage. With respect to the severity of stroke, the study populations were heterogeneous.

Intervention: The method of TES varied between the studies. Effects of neuromuscular electrical stimulation,[16,19] EMG-triggered electrical stimulation,[17,20] positional feedback stimulation[10] and transcutaneous electrical stimulation[18] were described. With regard to the control groups, sensory stimulation was used in one study.[16] In two studies[10,18] the experimental and the control group received the same standard therapy, but the

experimental group also received electrical stimulation. This implies that the intensity of therapy was higher in the experimental group. In an attempt to compensate for the additional stimulation therapy in the experimental group, the control group also received additional therapy in three studies.[17,19,20] These additional treatments were: extra individual therapy consisting of range of motion and strengthening exercises of the impaired wrist,[17] trials of voluntary wrist-lifting,[20] and a visit from the intervention physiotherapist 3 times a week to discuss progress in rehabilitation.[19]

Outcome measures: As many as 25 different outcome measures were used in the six studies to assess the effect of electrical stimulation on the upper extremity (see Table 2). All studies used at least two outcome measures, but none of them distinguished between primary and secondary outcome measures. All studies measured motor control (i.e. active range of motion,[10,19] isometric strength,[10,19] grip strength,[19] Fugl-Meyer Motor Assessment [upper extremity part],[16,17,18,20] and Motor Assessment Scale[20]), and two assessed functional abilities (Action Research Arm test,[19] 9-hole peg test[19] and box & block test[20]).[13]

Methodological quality

There was disagreement on 15.8 % of the items assessing methodological quality. Consensus on these items was reached by discussion. The scores for methodological quality ranged from 7[10,20] to 16[19] out of 19 (Table 2).

In only one study sufficient information was reported to consider both groups similar with regard to the most important prognostic indicators.[19] Blinding of the outcome assessor was reported in four studies,[10,16,17,19] but none of the studies reported blinding of the care-provider or double-blinding. Concealed treatment allocation was reported in one study.[19] One study reported on patient compliance[19] and two on adverse effects.[16,19] None of the studies described an intention-to-treat analysis.

Table 2. Characteristics of included studies and methodological score

	Powell 1999[19]	Chae 1998[16]	Sonde 1998&2000[18,21]	Francisco 1998[17]	Bowman 1979[10]	Cauraugh 2000[20]
patients included (drop-out) [a]	30E/30C (3E/2C)	25E/21C (11E/7C)	26E/18C (none)	16 total (7 total)	15E/15C (not stated)	7E/4C (not stated)
age in years mean (sd)						
experimental	69.0 (10.8)	59.4 (11.1)	71 (6.0)	60.3 (15.6)	no data available	61.6 (2.6)
control	66.4 (12.2)	60.0 (15.1)	73 (3.5)	69.6 (16.2)		mean of both groups
stage[b]	acute	acute	chronic	acute	sub-acute	chronic
time post stroke mean (sd)						
experimental group	23.9 days (7.7)	13.6 days (7.1)	9.1 months (2.2)	17.5 days (2.4)	3 weeks to 4 months	3.49 years (2.56)
control group	22.9 days (5.5)	17.8 days (5.9)	8.3 months (2.1)	18.2 days (2.3)	for both groups	mean of both groups
severity	median (range)	mean (sd)	mean (sd)	mean (sd)		
experimental group	ARA 6 (0;18)	FM 11.1 (10.1)	FM 24.8 (14.5)	FM 12.5 (9.0)	min 5° to max 30°	no data available
control group	ARA 0 (0;39)	FM 8.3 (8.8)	FM 25.9 (16.8)	FM 21.2 (7.8)	active wrist extension	
intervention						
experimental group	standard + NMES	standard + NMES	standard + TENS	standard + EMG-stim	standard + PFST	standard + EMG-stim
control group	standard + visits to PT	standard + sens stim	standard	standard + add therapy	standard	standard + wrist ext
target muscles in experimental group	ext dig communis ext carpi radialis ext carpi ulnaris	ext dig communis ext carpi radialis	wrist extensors (in 21 patients also elbow ext or shoulder abductors)	ext carpi radialis	wrist extensor muscles	ext dig communis ext carpi ulnaris
duration[c]						
experimental group	3x30 min. a day 8 weeks	60 min. a day 15 sessions	60 min. a day, 5 days a week, 3 months	2x30 min. a day, 5 days a week, mean 33.0 days (7.5)	2x30 min. a day, 5 days a week, 4 weeks	2x30 pos trials a day 3 days a week, 2 weeks
control group	3x10 min. a week, 8 weeks	60 min. a day 15 sessions		2x30 min. a day, 5 days a week, mean 25.8 days (8.2)		2x30 trials a day, 3 days a week, 2 weeks

outcome measures	resting wrist angle, isom strength, pROM, aROM, mAshw, grip strength, ARA, 9HPT, VAS local discomfort, Rankin, Barthel Index star cancelation	FM self-care FIM	mAshw sensibility FM Barthel Index VAS spasticity VAS shoulder pain	FM self-care FIM	aROM patterned motion aROM selective motion isom strength flexors isom strength extensors	reaction time sustained contraction FM MAS box&block
methodological score						
total (max 19)	16	13	8	8	7	7
patient selection (max 4)	4	2	2	2	2	2
intervention (max 5)	3	3	0	2	1	1
outcome measures (max7)	7	6	4	3	4	3
statistics (max 3)	2	2	2	1	0	1

[a] drop-out during treatment period. [b] time post stroke: acute is < 1 month, sub-acute between 1 and 6 months, chronic > 6 months. [c] duration of therapy in addition to standard therapy.

add therapy: additional therapy (i.e. strengthening exercises of the wrist); ARA: Action Research Arm test; aROM: active range of motion; C: control; dig: digitorum; E: experimental; EMG-stim: EMG-triggered electrical stimulation; ext: extensor; FM: Fugl-Meyer Motor Assessment; 9HPT: 9 hole peg test; isom strength: isometric strength; mAshw: modified Ashworth scale; MAS: Motor Assessment Scale; NMES: Neuromuscular Electrical Stimulation; PFST: positional feedback stimulation training; pos trials: positive trials, i.e. trials in which threshhold is achieved, thereby triggering TES; pROM: passive range of motion; PT: physiotherapist; self-care FIM: self-care components of the Functional Independence Measure; sens stim: sensory stimulation; VAS: Visual Analogue Scale; wrist ext: voluntary wrist extension exercise.

Effect of electrical stimulation

Table 3 shows the selected primary outcome measures and the effect reported in the original study. Four of the six trials reported a positive effect on motor control,[10,16,17,18] and one of the two studies in which functional abilities were assessed reported a positive effect.[20] The effect sizes for motor control ranged from 0.55 to 1.46. It was not possible to calculate effect sizes for all primary outcome measures due to insufficient data presentation. Correspondence with the authors failed to provide all missing data. A pooled analysis was not performed because of heterogeneity of the included studies.

In two studies, a post-hoc sub-group analysis was performed.[18,19] One revealed a significantly better effect on motor control in the less severely affected group than in the more severely affected group,[18] and the other reported a significant effect on functional abilities in the less severely affected sub-group, but no effect in the whole group.[19] Follow-up measurements were performed in three studies.[16,18,19,21] In one study the effect was still positive 4 weeks after the end of the treatment.[16]

Table 4 shows that there is no relationship between the reported effect and the stage after stroke, the method of TES or the contrast in intensity of therapy. There is no reason to suspect that the overall methodological score or the specific item on blinding of the outcome assessor biased the results.

Discussion

In this systematic review, the results of six RCTs were analyzed in order to assess the effect of therapeutic electrical stimulation on motor control and functional abilities of the affected arm in stroke patients and to identify a possible relationship between reported effects and patient characteristics, method of stimulation or methodological quality.

With regard to the first research question, it was not possible to draw conclusions concerning the effect of electrical stimulation on functional abilities, because this was only assessed in two out of the six studies included. However, the findings of this review suggest a positive effect of electrical stimulation on motor control. A statistically significant effect appeared in four studies.

However, no firm conclusions can be drawn, because only six RCTs fulfilled the selection criteria. Reports of many more trials on electrical stimulation have been published, but these are predominantly case series or non-randomized trials. A pooled analysis of separate effect sizes can increase power,[12] but because the selected studies were heterogeneous with regard to patient characteristics and method of stimulation, it was

Table 3. Effect on motor control and functional abilities

	Primary outcome measures	Gain experimental	Gain control	Reported effect[a]	Effect size[b]
motor control					
Powell[19]	grip strength (kg)	2 (0;3)#	1 (0;4)#	0	
Chae[16]	FM	13.1 (10.3)^	6.5 (6.1)^	+ (p=0.05)	0.55
Sonde [c;18,21]	FM	2.6 (2.7)^	-0.2 (2.8)^	+ (p<0.05)	0.72
Francisco[17]	FM	27.0 (4.5)^	10.4 (10.4)^	+ (p=0.05)	1.46
Bowman[10]	isom strength ext (Nm)	1.25^	0.15^	+ (p<0.025)	
Cauraugh[20]	FM			0	
functional abilities					
Powell[19]	ARA	0 (0;29)#	2 (0;14)#	0	
Cauraugh[20]	box&block	9.3^	1.5^	+ (p<0.05)	

[a] effect as reported by the author, [b] effect size = difference in gain between both treatment groups divided by the pooled standard deviation, [c] effect size calculated with data presented in second publication[21]
median (interquartile range), ^ mean (standard deviation)
ARA: Action Research Arm test; FM: Fugl Meyer Motor Assessment; isom strength ext: isometric strength wrist extensors.

Table 4. Relationship between reported effect on motor control and five study characteristics

	Reported effect[a]	Stage after stroke	Method of TES	Contrast in therapy intensity[b]	Quality score	Blinded assessment[c]
Chae, 1998[16]	+	acute	NMES	-	13	+
Sonde, 1998[18,21]	+	chronic	TENS	+	8	-
Francisco, 1998[17]	+	acute	EMG-stim	+	8	+
Bowman, 1979[10]	+	sub-acute	PFST	+	7	+
Powell, 1999[19]	0	acute	NMES	+	16	+
Cauraugh, 2000[20]	0	chronic	EMG-stim	-	7	-

[a] effect reported in original publication on outcome measure selected as primary by the reviewers.
[b] + means 'yes', - means 'no'.
[c] + means 'yes', - means 'no or do not know'.

decided to refrain from performing a pooled analysis in this review.[22] Moreover, since a pooled analysis would only include three out of the six studies, the summary effect size would probably be biased.

Several forms of bias could have influenced the results of the various trials, indicating that the results should be interpreted with caution. Firstly, a contrast in the intensity of therapy is known to bias the results in favour of the group receiving the more intensive therapy.[23-25] There was contrast in the intensity of therapy in four of the trials, three of which reported a positive effect (see Tables 2 and 3). This positive effect is attributed to electrical stimulation, but it might also be the result of more intensive therapy. Secondly, some trials reported considerable drop-out rates (see Table 2). Intention-to-treat analysis, a method used to minimize bias of the results due to drop-out, was not applied in any of the studies. Thirdly, the results might be biased due to imbalance of the baseline characteristics. In only one study both groups were considered to be similar with regard to the most important prognostic indicators.[19]

An explanatory trial is required to assess the specific effect or efficacy of an intervention. In an explanatory trial the intervention under study is compared with a placebo, i.e. a placebo-controlled trial. However, placebo electrical stimulation is difficult to achieve, because a prerequisite for a placebo is that patients believe that they actually receive treatment. Technically it is possible to apply sham-stimulation, but due to the absence of any sensory or motor reaction, patients may realize that they have been allocated to the placebo group. The risk of unblinding is considerable and the results will be biased. This problem can be minimized if special measures are taken with regard to the study design.[26] It is recommended that the equipment, instructions, frequency of visits and treatment schedules are identical for both groups. Patients with previous TES experience should not be included, and a cross-over design should be avoided.
The studies included in the present review are all pragmatic studies, comparing two therapeutic strategies. None of the studies used placebo treatment for the control group, but sensory stimulation was used in one trial.[16] However, according to some authors, a possible therapeutic effect of sensory stimulation can not be excluded and therefore it is not a true placebo.[27,28] This implies that no conclusions can be drawn as to whether the reported effects result from a specific effect of TES or from aspecific effects such as contrast in the intensity of therapy, as mentioned above. It is not possible to determine the efficacy of TES or any specific mechanism of action of electrical stimulation.[3,16,19]

With regard to the second research question, no firm relationship could be identified between the effect of electrical stimulation and patient characteristics, method of

stimulation or methodological score. In this context, however, post-hoc subgroup-analyses performed in two studies should be discussed.[18,19] In both studies, the heterogeneous sample was divided in more severely and less severely affected patients, resulting in more homogeneous sub-groups. One of the studies revealed a significant effect of TES on motor control (Fugl-Meyer Assessment) in less severely affected patients, but no effect in the more severely affected patients.[18] The other study showed a significant effect on functional abilities (Action Research Arm-test) in the sub-group with residual voluntary wrist extension, whereas no effect could be shown in the total patient population.[19] These sub-group analyses indicate that less severely affected patients might benefit more from electrical stimulation. This is in accordance with a sub-group analysis performed in an exploratory trial investigating electrical stimulation.[29] However, post-hoc sub-group analyses should be interpreted with caution, and more research is needed to test this hypothesis.

In general, the explicit methods used in systematic reviews limit bias of the results.[12] It can be argued that in this systematic review bias was introduced by focusing on the primary outcome measures selected by the reviewers. However, the particular choices were made with the research question in mind. For each trial the most relevant outcome measures for motor control and functional abilities were selected. Grip strength measurement, the Fugl-Meyer Motor Assessment and dynamometry are all advised for the assessment of motor control.[13] For one study, grip strength was considered to be more relevant than isometric strength of the wrist extensors, and for another the Fugl-Meyer Motor Assessment was selected instead of isometric strength, because in the opinion of the researchers these outcome measures more accurately reflect the concept of motor control. Motor control is more than just powerful wrist extension.
If muscle strength of the wrist extensors had been chosen as primary outcome measure, more studies would have been found to yield positive results. So, indeed, a different selection of primary outcome measures would have resulted in a different distribution of positive and inconclusive trials. However, it would also have answered a different research question, namely a question addressing the effect of TES on muscle strength rather than on motor control.

In conclusion, the present review does suggest a positive effect of electrical stimulation on motor control of the affected upper extremity after stroke. However, at this stage it is not known whether this improvement is clinically relevant or whether functional improvement can be achieved by electrical stimulation.
It is not yet possible to formulate explicit recommendations for the application of electrical stimulation to improve motor control and functional abilities. The positive

results thus far indicate the need for further research to clarify ambiguities with regard to the optimal method of stimulation and to identify the characteristics of patients who will benefit most from electrical stimulation. Explanatory trials are required to determine the efficacy and to elucidate the specific mechanism of action of electrical stimulation. Future studies should also assess the effect of electrical stimulation on functional abilities, since functional improvement in particular is an important goal in the treatment of stroke patients.

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Appendix 1. Search strategy for Medline

#1	electric stimulation therapy or electric stimulation
#2	cerebrovascular disorder or hemiplegia or hemiparesis
#3	arm or upper extremity
#4	rehabilitation
#5	#1 and #2 and #3 and #4
#6	#5 and randomized controlled trial (pt)

Appendix 2. Criteria list for assessment of methodological quality.

Patient selection		
a.	Were the eligibility criteria specified?	Yes / No / Don't know
b.	Treatment allocation	
	1) Was a method of randomization performed?	Yes / No / Don't know
	2) Was the treatment allocation concealed?	Yes / No / Don't know
c.	Were the groups similar at baseline regarding the most important prognostic indicators?	Yes / No / Don't know
Interventions		
d.	Were the index and control interventions explicitly described?	Yes / No / Don't know
e.	Was the care provider blinded to the intervention?	Yes / No / Don't know
f.	Were co-interventions avoided or comparable?	Yes / No / Don't know
g.	Was the compliance acceptable in all groups?	Yes / No / Don't know
h.	Was the patient blinded to the intervention?	Yes / No / Don't know
Outcome measurement		
i.	Was the outcome assessor blinded to the intervention?	Yes / No / Don't know
j.	Were the outcome measures relevant?	Yes / No / Don't know
k.	Were adverse effects described?	Yes / No / Don't know
l.	Was the withdrawal/drop-out rate described and acceptable?	Yes / No / Don't know
m.	Timing follow-up measurements	
	1) Was a short-term follow-up measurement performed?	Yes / No / Don't know
	2) Was a long-term follow-up measurement performed?	Yes / No / Don't know
n.	Was the timing of the outcome assessment in both groups comparable?	Yes / No / Don't know
Statistics		
o.	Was the sample size for each group described?	Yes / No / Don't know
p.	Did the analysis include an intention-to-treat analysis?	Yes / No / Don't know
q.	Were point estimates and measures of variability presented for the primary outcome measures?	Yes / No / Don't know

3

Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke

JR de Kroon
MJ IJzerman
J Chae
GJ Lankhorst
G Zilvold

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Abstract

Objective: Electrical stimulation of the hemiparetic upper extremity following stroke can be applied in a variety of ways. The aim of this review is to explore the relationship between characteristics of stimulation and the effect of electrical stimulation on the recovery of upper limb motor control following stroke.

Methods: A systematic literature search was performed to identify clinical trials evaluating the effect of electrical stimulation on motor control. The reported outcomes were examined to identify a possible relationship between the reported effect and the following characteristics: duration of stimulation, method of stimulation, setting of stimulation parameters, target muscles and stage after stroke.

Results: Nineteen clinical trials were included, and the results of 22 patient groups were evaluated. A positive effect of electrical stimulation was reported for 13 patient groups. Positive results were more common when electrical stimulation was triggered by voluntary movement rather than non-triggered electrical stimulation. There was no relation between the effect of electrical stimulation and the other characteristics examined.

Conclusion: Triggered electrical stimulation may be more effective than non-triggered electrical stimulation in facilitating upper extremity motor recovery following stroke. It appears that the specific stimulus parameters may not be crucial in the effect of electrical stimulation.

Introduction

Upper extremity hemiparesis is a prominent impairment following stroke and has significant impact on activities of daily living (ADLs) and quality of life. Recovery of upper extremity function is most rapid during the first months after stroke.[1,2] However, even 3 months after stroke only 20% of the stroke survivors have normal upper extremity function.[1] Accordingly, the majority of stroke survivors report that impaired upper extremity function is a major problem,[3] and this is associated with a low level of subjective well-being.[4]

There is growing evidence that electrical stimulation (ES) has a positive effect on upper extremity motor recovery following stroke.[5,6,7] Therefore ES might be a useful therapy in the rehabilitation of patients with stroke. However, published reports demonstrate a wide variety of stimulation paradigms with respect to stimulation parameters, method of stimulation and duration of the treatment. This raises the question of how ES should be applied in daily practice.

Various devices are available for the application of ES, which provide different possibilities for adjustment of stimulation parameters including amplitude, pulse duration and pulse frequency. These parameters determine the nature of the evoked response and have impact on patient comfort and safety. ES at low current intensity will evoke a sensory reaction without muscle contraction (i.e. sensory stimulation). In motor stimulation current intensity is high enough to exceed motor threshold and evoke muscle contractions. Increasing current intensity increases the force of muscle contraction,[8] but also the risk of pain and skin irritation.

Basic animal[9] and neurophysiological studies[10] as well as clinical trials[11] suggest that afferent input associated with repetitive movements facilitates improvement of motor function. For this reason it is hypothesised that motor stimulation is more effective in improving motor control than sensory stimulation. Although there is no direct evidence, this is likely since ES that provokes motor activation is associated with cutaneous, muscle and joint proprioceptive afferent feedback, while sensory ES is associated with only cutaneous afferents. Therefore this review focused on motor stimulation.

With regard to motor stimulation, several methods of application have been reported.[7] In NeuroMuscular Electrical Stimulation (NMES), the stimulation is applied according to a pre-programmed scheme, resulting in repetitive muscle contractions without active involvement of the patient.[6] In EMG-triggered electrical stimulation (EMG-stim), ES is provided when volitionally generated EMG signals exceed a preset threshold.[6] In Positional Feedback Stimulation Training (PFST), ES is provided when voluntary muscle contraction produces joint translation beyond a preset threshold.[12] Both of these latter approaches reinforce voluntary muscle contraction. It is suggested that in EMG-stim and PFST the

effect of ES is maximised by adding a cognitive component.[6,12] Transcutaneous Electrical Nerve Stimulation (TENS) is well known for the treatment of pain by evoking a sensory reaction without muscle contraction. By adjusting the stimulation parameters, muscle contractions can be evoked by TENS which is then effectively motor stimulation.
When studies investigating ES differ with respect to stimulation parameters, method of stimulation and duration of the treatment, the question is whether these differences have any effect on therapeutic benefit. Therefore, the aim of the present descriptive literature review is to explore the relationship between several stimulation and clinical characteristics and the effect of ES on motor control of the hemiparetic arm. The characteristics under study are method of stimulation, duration of stimulation, stimulation frequency, amplitude and pulse duration, target muscles and stage after stroke. Motor control is defined as the ability to perform voluntary movements.[13]

Methods

Literature search
A systematic literature search from January 1966 to December 2003 was performed in Medline, Embase and the database of the Cochrane Field 'Rehabilitation and Related Therapies' in order to identify clinical trials in which electrical stimulation was applied to improve motor control of the upper extremity in stroke. The following key words were used: cerebrovascular disorders, hemiplegia, hemiparesis, arm, upper extremity, electric stimulation therapy, electric stimulation, neuromuscular electrical nerve stimulation and transcutaneous electrical nerve stimulation. References of literature were checked for relevant publications.

Selection criteria
Studies meeting the following criteria were included for the review:
1. ES applied to the affected upper extremity in patients with stroke; 2. ES provoking muscle contraction; 3. application of ES with surface electrodes; 4. clinical setting, i.e. case series, case-control or randomised controlled trial; 5. relevant outcome measures for motor control; 6. separate results presented for the upper extremity; 7. full-length publication in English, German, French or Dutch.
The application of these criteria resulted in the exclusion of studies that focused on invasive techniques, such as electro-acupuncture or implanted electrodes. Studies in which ES was applied to the shoulder only were excluded as well.

Data-extraction

For each selected study, stimulation as well as study characteristics were extracted from the publication. Stimulation characteristics were: 1. device applied; 2. method of stimulation; 3. target muscles; 4. duration of stimulation in hours per week and total hours; 5. specific setting for frequency, amplitude and pulse width. Investigators' rationales for their particular setting were noted. The study characteristics were: 1. study design; 2. number of patients; 3. age and stage of the patients; 4. outcome measures. In the present review, the outcome measure considered most relevant for motor control was selected for each trial. For this 'primary' outcome measure, the effect of ES, as reported by the author in the original article, was assessed as positive ($p \leq 0.05$), or negative/no difference ($p > 0.05$). In this context outcome of between-group analysis was assessed for studies with an acute or subacute population to account for spontaneous recovery. However, for chronic patients the within-group analysis was evaluated since spontaneous recovery was not expected.

Statistics

The results were examined to identify a possible relationship between the reported effect and the following characteristics: duration of stimulation (analysed for hours per week and total hours), stimulation method, frequency, amplitude, pulse width, target muscles and stage after stroke. To test a possible relationship between effect and these characteristics, univariate logistic regression analysis was applied for continuous variables and the Chi-square test for categorial variables (SPSS 11.5 for Windows). For the analysis, method of stimulation was dichotomised into triggered (EMG-stim and PFST) or non-triggered (NMES, TENS and electroacupuncture) stimulation. Studies in which all patients received triggered as well as non-triggered ES were excluded for the analysis of method of stimulation. In the analysis of stimulation frequency, studies with a broad frequency range were excluded and in studies with a narrow range the mean of the limits was entered in the analysis. Since the choice of the primary outcome measures by the reviewers might bias the conclusion, an additional analysis was performed with the results reported for grip strength or wrist extensor strength.

Results

Selection of literature

The literature search in the different databases yielded 156 articles altogether. Twenty publications, describing 19 trials, fulfilled all selection criteria and were included in the present review,[12,14-32] see Table 1).

Table 1. Clinical charateristics of included trials

Author	Intervention	n	Age in years mean(sd or range)	Stage	Time post stroke	Outcome measures
Randomised controlled trials						
Bowman[12]	E PFST C no add. therapy	E 15 C 15	no data	subacute	3 wk-4 mo	isometric wrist extension - in 30° flexion - in 30° extension aROM of wrist - in patterned motion - in selective motion
Cauraugh[14]	E EMG-stim C voluntary wrist ext	E 7 C 4	61.64 (9.57)	chronic	3.49 yrs (2.56)	reaction time sustained contr. wrist ext FM, MAS box&block
Cauraugh[15]	E1 EMG-stim/bilat E2 EMG-stim C voluntary wrist/finger ext	E1 10 E2 10 C 5	63.7	chronic	39.1 months	box&block reaction time sustained contr. wrist ext
Cauraugh[16]	EMG-stim/bilat E1 on time 10 sec E2 on time 5 sec C on time 0 sec	E1 10 E2 10 C 6	66.4 (9.7)	chronic	2.8 yrs (1.9)	box&block reaction time sustained contr. wrist ext
Cauraugh[17]	E1 EMG-stim/block E2 EMG-stim/random C voluntary movements	E1 14 E2 14 C 6	E1 65.1 E2 67.3 C 65.8	chronic	E1 3.2 yrs E2 3.3 yrs C 3.1 yrs	box&block reaction time sustained contr. wrist ext

Chae[18]	E NMES C placebo stimulation	E 14 C 14	E 59.4 (11.1) C 60.0 (15.1)	acute	E 13.6 days (7.1) C 17.8 days (5.9)	FM self-care FIM
Francisco[19]	E EMG-stim C additional therapy	E 4 C 5	E 60.3(15.6) C 69.6(16.2)	acute	E 17.5 days(2.4) C 18.2 days (2.3)	FM self-care FIM
Kimberley[20]	E EMG-stim+NMES C sham stimulation	E 8 C 8	E 58.4 (14.5) C 62.8 (13.8)	chronic	E 28.4 mo (18.7) C 38.5 mo (30.7)	isometric strength dig II Motor Activity Log box&block Jebson Taylor finger tracking functional MRI
De Kroon[21]	E1 NMES flex-ext E2 NMES ext only	E1 13 E2 15	E1 58 (17.3) E2 61.7 (9.7)	chronic	E1 14.7 mo (11.8) E2 21.4 mo (16.1)	Ashworth aROM grip strength Motricity Index Action Research Arm test
Sonde[23,24]	E TENS C no add. therapy	E 26 C 18	E 71 (6.0) C 73 (3.5)	chronic	E 9.1 mo (2.2) C 8.3 mo (2.1)	modified Ashworth VAS spasticity VAS shoulder pain pROM, aROM sensation FM Barthel
Wong[25]	E electroacupuncture C no add. therapy	E 59 C 59	E 60.4 (11.1) C 60.6 (10.8)	acute	10-14 days	Brunnstromstage - upper limb - lower limb Chinese FIM

Author	Intervention	n	Age in years mean(sd or range)	Stage	Time post stroke	Outcome measures
Controlled trials						
Kraft[26]	E1 EMG-stim E2 NMES+act E3 PNF C no add. therapy	E1 6 E2 4 E3 3 C 5	E1 59.5 (6.2) E2 64.8 (11.6) E3 67.0 (3.6) C 63.2 (12.3)	chronic	E1 26 mo (23.4) E2 36.8 mo(19.8) E3 14.3 mo (2.5) C 24.2 mo (6.0)	FM grip strength Jebsen-Taylor finger tapping
Mokrusch[27]	E1 EMG-stim E2 NMES C no add. therapy	E1 22 E2 12 C 10	59.8 (8.3)	mixed	6wk (1wk-9wk) 3 chronic patients	modified Ashworth pendulumtest hand extension (myometer) Barthel, FIM well being
Multiple baseline design						
Hummelsheim[28]	baseline - EMG-stim - repetitive movements	20	59 (32-91)	mixed	mean 16.5wk (4wk-24mo)	grip strength isometric hand extension isotonic hand extension RMA (arm section) modified Ashworth
Hummelsheim[29]	baseline - NMES - repetitive movements	12	59.5 (41-80)	subacute	mean 7.6wk (3wk-4mo)	grip strength isometric hand extension isotonic hand extension RMA (arm section) modified Ashworth

Case series						
Alon[30]	NMES	29	61 (13.2)	chronic	4.0 yrs (sd 3.5; range 0.75-13)	grip strength FM (subtest spherical grasp) distance handpalm-finger VAS pain upper limb 3 ADL tasks grasp and hold weight
Baker[31]	NMES	16	range 36-78	mixed	9 subacute: <4mo 7 chronic:> 4mo	sensation spasticity (4point scale) pROM isometric wrist extension
Hendricks[32]	NMES	15	52.8 (20-70)	chronic	4.9 yrs (0.75-18 yrs)	modified Ashworth FM

add: additional; aROM: active range of motion; C: control group; contr: contraction; dig: digiti; E: experimental group; EMG-stim: EMG-triggered electrical stimulation; EMG-stim/bilat: treatment in which subjects received EMG-stim and assistance from unimpaired hand as wrist/finger extension was executed on both limbs; ext: extensor muscles; EMG-stim/block: 10 consecutive movement trials for each muscle group; EMG-stim/random: random order of movement trials; FIM: Functional Independence Measure; FM: Fugl Meyer motor assessment; MAS: motor assessment scale; mo: months; n: number of subjects that completed treatment protocol; NMES: NeuroMuscular Electrical Stimulation; PFST: Positional Feedback Stimulation Therapy; pROM: passive range of motion; RMA: Rivermead Motor Assessment; self-care FIM: self-care components of Functional Independence Measure; TENS: Transcutaneous Electrical Nerve Stimulation; VAS: visual analog scale; yrs: years.

In 6 trials two different methods of ES were applied.[15-17,21,26,27] In 3 of these both ES treatment groups were reviewed separately.[21,26,27] In the other 3, separate analysis of the different treatment groups was not reported, and the overall result of the trial was included for the review.[15-17] In all, the results of 22 patient groups were evaluated.
Of the 19 trials, 12 were randomised controlled trials,[12,14-25] 2 were non-randomised controlled trials,[26,27] 2 trials used a multiple baseline design[28,29] and 3 trials were case series.[30-32]

Subjects
The review included a total of 578 stroke survivors with 392 receiving ES in one form or another. Four studies included patients in the acute stage after stroke (i.e. within one month post-stroke),[18,19,22,25] 2 studies included subacute subjects (between 1 and 6 months post-stroke),[12,29] 10 studies included chronic subjects (> 6 months post-stroke) [14-17,20,21,23,26,30,32] and 3 studies included a mixed population with respect to time since stroke.[27,28,31]
With respect to stroke severity, seven studies restricted inclusion to patients with residual wrist extension (at least 5 to 20 degrees).[12,14-17,19,21] It can be assumed that the same is true for the study described by Hummelsheim et al.,[28] since EMG-stim was applied, which by definition requires residual volitional wrist extensor activity to trigger the stimulation. Inclusion criteria with respect to stroke severity were not specified in 3 studies[25-27] and various criteria were applied in the other studies. All studies were rather heterogeneous with respect to stroke severity.

Characteristics of stimulation
Table 2 presents the stimulation characteristics retrieved from the publications.
Method of stimulation: The method of stimulation varied between the studies, and included NMES (n receiving NMES = 157, n control = 51),[18,21,22,26,27,29,30-32] EMG-stim, (n receiving EMG-stim = 127, n control = 35),[14-17,19,26-28] PFST (n receiving PFST = 15, n control = 15)[12], and TENS (n receiving TENS = 26, n control = 18).[23,24] The study by Wong et al[25] described the effects of electroacupuncture. However, since the acupuncture was applied with surface electrodes, and not with needles, this study was included in the review (n receiving acupuncture = 59, n control = 59). In one study, patients received EMG-stim for half of the treatment time and NMES for the other half.[20]
Frequency: Most authors used fixed frequency ranging from 20 Hz[22] to 50 Hz.[14-17,20] Some authors used a range of frequency[18,19,25-29] and 2 of these adjusted frequency to patient comfort.[18,19] Sonde et al.[23,24] applied low-frequency TENS with a stimulus frequency of 1.7 Hz in pulse trains of 8 pulses with an interval of 14 ms.
Amplitude: Most authors reported a range for the amplitude. However, it was not

always clear whether the range represented the overall range of the device or the range of amplitudes actually used. Reported range varied from as wide as 0-100 mA[31] to as narrow as 30-45 mA.[12]

Pulse duration: Most studies used fixed pulse duration of 200 or 300 μs. In two studies pulse duration was adjusted for optimal contraction and patient comfort.[21,32] In two other studies pulse duration was 500 μs.[28,29]

Rationale for the particular setting applied: All but one study[27] reported that amplitude was adjusted for optimal response, which was 'muscle contraction', 'wrist and finger movements' or 'full joint movement'. In four studies[18,21,31,32] amplitude was adjusted for patient comfort. None of the authors provided rationale for the specific pulse duration or frequency, although several reported that pulse duration[21,32] and/or frequency[18,19] were adjusted for patient comfort. Apart from muscle response and patient comfort no fundamental arguments were presented for the specific setting of stimulation parameters.

Target muscles: A variety of muscles were stimulated. Fourteen studies stimulated the wrist and/or finger extensor muscles.[12,14-23,26,27,31] One of these also stimulated elbow extensors[27], while another also included elbow extensors and shoulder abductors.[17] In 2 trials some patients received additional stimulation of elbow extensors and/or shoulder muscles.[23,26] Five studies stimulated both wrist/finger extensors and flexors.[21,28-30,32] In two trials, both arm and leg muscles were stimulated, either simultaneously[25] or consecutively.[27]

Duration of stimulation: Table 2 shows that there was a wide range in duration of ES treatment: from 30 minutes once a day[25] to 3 times one hour per day,[21,32] for a period of 2 weeks[14-17,25] to 3 months[23]. None of the authors substantiated their specific duration of stimulation treatment.

Table 2. Stimulation characteristics of included trials

Author	Device	Method	Frequency (Hz)	Amplitude (mA)	Pulse duration	Target muscles	Duration of stimulation
Randomised controlled trials							
Bowman [12]		PFST	35	30-45	200 µs	wrist ext	2dd30m, 5d pwk, 4 wk
Cauraugh [14]	Automove 800	EMG-stim	50	14-29		ext dig comm. ext car uln	2dd30m, 3d pwk, 2 wk
Cauraugh [15]	Automove 800	EMG-stim	50	16-29	200 µs	ext dig comm. ext car uln	3dd30m, 4d in 2 wk
Cauraugh [16]	Automove 800	EMG-stim	50	17-28	200 µs	ext dig comm. ext car uln	90 m pd, 4d in 2 wk
Cauraugh [17]	Automove	EMG-stim	50	13-28	200 µs	ext dig comm. ext car uln triceps, ant + mid delt	90 m pd, 2d pwk, 2 wk
Chae [18]	FOCUS, EMPI Inc.	NMES	25-50	0-60	300µs	ext dig comm. ext car rad	1dd60m, 15 sessions
Francisco [19]	Automove AM 706	EMG-stim	20-100	0-60	200 µs	ext car rad	2dd30m, 5d pwk, length of stay
Kimberley [20]	Automove 706	EMG-stim and NMES	50		200 µs	forearm ext	6h pd, 10 d in 3 wk
De Kroon [21]	NESS Handmaster	NMES	36	0-60	50-500 µs	finger ext + flex finger ext only	3dd60m, 7d pwk, 6 wk
Powell [22]		NMES	20		300 µs	ext dig comm. ext car uln + rad	3dd30m, 8 wk
Sonde [23, 24]	Cefar Dual Unit	TENS	trainfreq 1.7 in train 70			wrist ext in 21 subjects also elbow ext or shoulder abductor	1dd60m, 5d pwk, 3 months

Wong [25]	HANS	electro acupuncture	20-25	10-20 mv		4 acupuncture points in arm and 4 in leg	1dd30m, 5d pwk, 2 wk
Controlled trials							
Kraft [26]	Automove	EMG-stim	30-90	20-60 µV	200 µs	wrist ext + additional arm muscles according to subjects ability	1dd60m, 3d pwk, 12 wk
	Respond II	NMES + act	30-90		300 µs	wrist ext	1dd30m, 5d pwk, 3 months
Mokrusch [27]	PeR-Y Rehabilitator	EMG-stim NMES	30-50		300 µs	finger,hand, elbow ext knee flex, feet,toe ext	1-2dd30m, 12.2 wk (4-16)
Multiple baseline design							
Hummelsheim [28]	Bentrofit	EMG-stim	75-80	10-80	500 µs	ext car rad flex car rad	2dd20m, 5d pwk, 2 wk
Hummelsheim [29]	Bentrofit	NMES	75-80	10-80	500 µs	ext car rad flex car rad	2dd20m, 5d pwk, 2 wk
Case series							
Alon [30]	NESS Handmaster	NMES				ext dig comm, ext poll br, flex dig sup, flex poll longus, thenar m.	2dd45m, 3 wk.
Baker [31]	Rancho Los Amigos	NMES	33	0-100	200 µs	ext dig comm. ext car uln + rad	3dd30m, 7d pwk, 4 wk
Hendricks [32]	NESS Handmaster	NMES	36		100-500 µs	ext dig comm, ext poll br, flex dig sup, flex poll longus, thenar m	3dd60m, 7d pwk, 10 wk

Ant+mid delt: anterior and middle deltoid muscle; d: day; dd: times a day; EMG-stim: EMG-triggered electrical stimulation; ext: extensor muscle; ext car rad: extensor carpi radialis; ext car uln: extensor carpi ulnaris; ext dig comm: extensor digitorum communis; ext poll br: extensor pollicis brevis; flex: flexor muscle; flex car rad: flexor carpi radialis; flex dig sup: flexor digitorum superficialis; flex poll longus: flexor pollicis longus; h: hours; m: minutes; NMES: NeuroMuscular Electrical Stimulation; pd: per day; PFST: Positional Feedback Stimulation Therapy; pwk: per week; TENS: Transcutaneous Electrical Nerve Stimulation; thenar m: thenar nuscles; wk: week.

Relationship between treatment effect, and stimulation and study characteristics

Table 3 shows the relationship between reported treatment effect, and stimulation and study characteristics. There was a relationship between treatment effect and method of stimulation. Eight out of the nine patient groups in which triggered stimulation was applied yielded a positive result (88.9%), whereas only four out of 12 groups using non-triggered stimulation yielded positive results (33.3%). The ratio of these success rates is 2.7. The difference in treatment effect with respect to method of stimulation was significant (Chi-square test, p=0.024).

With respect to hours of stimulation per week, total hours of stimulation and frequency of stimulation, univariate logistic regression analysis did not reveal a difference between studies with and without a positive effect. Stage after stroke did not affect the effect of electrical stimulation (Chi-square test).

The data in Table 3 might suggest increased likelihood of a positive effect if elbow and/or shoulder muscles were stimulated in addition to wrist and/or finger extensors. However, in two studies[23,26] it was not known how many subjects received additional stimulation and in which muscles. If these studies are excluded, there is insufficient number of studies that included elbow and shoulder stimulation for analysis.

With respect to amplitude of stimulation, authors reported wide ranges within each study and across studies (Table 2). Nearly all studies reported that amplitude was individually adjusted to achieve muscle contraction or joint movement. This strategy would undoubtedly lead to significant heterogeneity within each study. However, as noted earlier, the actual amplitudes used by subjects were not reported. In view of heterogeneity within the studies and the uncertainty of what was actually used, stimulation amplitude was not further analysed.

The majority of studies reporting on pulse duration used 200 or 300 μs. In view of lack of heterogeneity across studies, pulse duration was not further analysed.

Table 3. Relationship between reported effect on motor control and five characteristics of stimulation and subjects

Author	Results as reported by author[a]	Selected primary outcome measure	Duration of stimulation[b] hours per week	Duration of stimulation[b] total hours	Method of stimulation	Frequency in Hz	Target muscles[c] extensors f	extensors w	extensors e	extensors s	flex f	flex w	Stage after stroke[d]
Bowman [12]	+	isom wrist ext	5	20	PFST	35		+					subacute
Cauraugh [15]	+	sustained contr	3	6	EMG-stim	50	+	+					chronic
Cauraugh [16]	+	sustained contr	3	6	EMG-stim	50	+	+					chronic
Cauraugh [17]	+	sustained contr	3	6	EMG-stim	50	+	+	+	+			chronic
Chae [18]	+	FM	5	15	NMES	25-50	+	+					acute
Francisco [19]	+	FM	5	25	EMG-stim	20-100		+					acute
Hendricks [32]	+	FM	21	196	NMES	36	+				+		chronic
Hummelsheim [28]	+	RMA arm section	3.3	6.7	EMG-stim	75-80		+				+	mixed
Kimberley [20]	+	isom finger ext	20	60	EMG-stim+NMES	50	+	+					chronic
Kraft [26]	+	FM	3	36	EMG-stim	30-90	x	+	x	x			chronic
Mokrusch [27]	+	strength wrist ext	4	48.8	EMG-stim	30-50	+	+	+				mixed
Sonde [23, 24]	+	FM	5	65	TENS	1.7		+	x	x			chronic
Wong [25]	+	Brunnstrom stage	2.5	5	electroacupuncture	20-25		acupuncture points					acute
Alon [30]	0	grip strength	10.5	27.4	NMES	n.s.	+				+		chronic
Baker [31]	0	isom wrist ext	10.5	42	NMES	33	+	+					mixed
Cauraugh [14]	0	FM	3	6	EMG-stim	50	+	+					chronic
Hummelsheim [29]	0	RMA arm section	3.3	6.7	NMES	75-80		+				+	subacute
Kraft [26]	0	FM	2.5	32.5	NMES	30-90		+					chronic
de Kroon [21] flex-ext	0	MI	21	112	NMES	36	+				+		chronic
de Kroon [2] ext only	0	MI	21	112	NMES	36	+						chronic
Mokrusch [27]	0	strength wrist ext	4	48.8	NMES	30-50	+	+	+				mixed
Powell [22]	0	grip strength	10.5	84	NMES	20	+	+					acute

[a] '+' = positive ($p<0.05$), '0' = negative or no difference; results from within-group analyses,[20,21,26,30-32] between-group analyses,[12,18,19,22,25,27] ANOVA[14-17] or comparison of gain in baseline period with gain in ES period.[28,29]

[b] hours per week and total hours calculated with data in the original publication.

[c] f=finger; w=wrist; e=elbow; s=shoulder; flex=flexors; x=not all muscles were stimulated in all subjects; acupunct points = 4 acupuncture points in the arm.

[d] stage after stroke: acute is < 1 month, subacute between 1 and 6 months, chronic > 6 months.

EMG-stim: electromyogram triggered stimulation; FM: Fugl Meyer Motor Assesment; isom wrist ext: isometric strength wrist extensors; isom finger ext: isometric strength finger extensor; MI: Motricity Index; NMES: neuromuscular electrical stimulation; ns: not stated; PFST: position feedback stimulation therapy; RMA: Rivermead Motor Assessment; strength wrist ext: strength wrist extensors; sustained contr: sustained contraction of wrist/finger extensor muscles; TENS: transcutaneous electrical nerve stimulation.

Discussion

Numerous studies have investigated the clinical effects of ES for recovery of motor control after stroke. These studies reported a variety of stimulation parameters, duration of stimulation, subject characteristics and methods of stimulation. The present review of these studies indicates that no relationship between the specific setting of stimulation parameters, duration of stimulation, subject characteristics, and clinical outcome could be detected. However, it appears that triggered stimulation was more likely to yield improvements in motor control than non-triggered stimulation.

Specific stimulation parameters reviewed included frequency, amplitude, and pulse duration. There was no relationship between stimulation frequency and clinical outcome. Regarding stimulus amplitude and pulse duration, no conclusions could be drawn. However, in basic neurophysiologic research the setting of parameters does make a difference with respect to reaction evoked by ES. Textbooks have indicated that careful selection of parameters makes it possible to selectively activate large diameter afferent fibres or motoneurons, at least in the laboratory setting with isolated nerve preparation.[8,33] In addition, different combinations of parameters (pulse duration of 50 µs versus 200 µs, stimulation frequency of 4 Hz versus 110 Hz) have been reported to yield different peripheral neurophysiological effects in the human superficial radial nerve.[34] And it has also been reported that low frequency stimulation (3 Hz) induces prolonged depression of cortical excitability, while high frequency (30 Hz) induces prolonged facilitation.[35] Given the aforementioned implications of parameter setting for neurophysiologic reaction, one might expect that different neurophysiologic reactions were evoked in the studies included for this review. However, there were no indications that different neurophysiologic reactions were associated with differences in clinical outcome. The common end point in all studies was muscle contraction, despite the differences in parameter setting. From this it is hypothesised that muscle contraction is crucial in the effect of ES, rather than stimulus parameters.

Muscle contraction also seemed to be the primary intent of most investigators of the studies in this review, as amplitude was adjusted to obtain an optimal motor response. Although not explicitly stated by all authors, their goal appeared to be the maximising of muscle and joint afferent feedback via ES mediated repetitive movement therapy to facilitate motor recovery. This is consistent with the hypothesis of Asanuma & Keller,[10] that afferent feedback associated with repetitive movements induces LTP in the motor cortex, which then modifies the excitability of specific motor neurons and facilitates motor learning.

Another common consideration for selection of specific stimulation parameters was

subject comfort. Studies relating comfort and pulse duration reveal a preference for pulses of 300 μs over 50 or 1000 μs.[36,37] Most studies reporting on pulse duration used 200 or 300 μs. Increasing amplitude beyond motor threshold not only excites motor neurons, but also small diameter unmyelinated C fibers that elicit painful sensations when stimulated. High amplitude stimulation will therefore be uncomfortable for the patient.[8] Most studies adjusted amplitude to produce muscle contraction or joint translation without subject discomfort. For motor stimulation textbooks advise a tetanized contraction, which is usually achieved at a stimulation frequency of 30-35 Hz.[8,38] Frequencies markedly higher than this can cause rapid muscle fatigue and also affect patient comfort.[8,38,39] However, none of the studies included in this review assessed patient comfort. Therefore it was not possible to draw conclusions with regard to a possible relation between stimulation parameters and subject comfort, or to formulate more specific recommendations for stimulation parameters to minimise discomfort.

There was no relationship between duration of stimulation and effect. Stimulation as little as 2.5 hours per week was enough to obtain a positive effect in 1 study,[25] but stimulation as much as 21 hours per week was not enough to guarantee an effect in another.[21] In contrast to expectations,[40,41] the likelihood of a positive effect did not increase with increasing intensity (hours per week) or total dose (total hours) of stimulation. This may be an artefact of our methodology. The treatment outcome in this review was dichotomised to either 'positive' or 'no effect'. Due to heterogeneity of studies, the extent of improvement was not taken into consideration. Thus, it is possible that among studies with a 'positive' effect, a dose-response relationship exists.

This review did not detect a relationship between subject characteristics and outcome of ES. Positive results were obtained in studies that exclusively evaluated acute, subacute and chronic subjects. Thus, positive results were reported regardless of acuity. Previous subgroup analyses suggested better outcomes among those with less severe hemiparesis.[22,23,32] However, due to heterogeneity of severity of hemiparesis, the present review could not elucidate a relation between stroke severity and outcome. Among the studies there was heterogeneity of target muscles. There might be an indication that stimulation of elbow and shoulder muscles in addition to finger and wrist extensor muscles promotes a positive effect of stimulation, but the subgroups were considered too small to draw reliable conclusions on this aspect of ES.

The one positive relation that emerged from the review is that triggered stimulation may be more effective than non-triggered stimulation in producing improvements in motor control. Although both methods of ES provide muscle and joint proprioceptive

feedback, triggered stimulation adds a cognitive component. Thus, afferent feedback associated with ES mediated muscle contraction and joint translation is time locked to subject cognitive intent. Animal studies have demonstrated that specific types of behavioural experiences that induce long-term plasticity on motor maps appear to be limited to those that entail the development of new motor skills.[42] When monkeys were trained to retrieve food pellets from a small well[9,43,44] or rats were trained to retrieve food from a rotating well[45] there was evidence of task-specific cortical reorganization. However, repetitive movement tasks that did not require skill acquisition (i.e. automatic) were not associated with any significant changes in motor cortex.[44,45] From a clinical perspective, the behavioural experiences that induce long-term plasticity in humans are likely to be those activities that are important and meaningful, and require cognitive investment and effort. Given this perspective, repetitive movement therapy where the subject is cognitively involved in generating the movement (i.e. triggered ES) is more likely to be important and meaningful than therapy where the subject is not cognitively involved (i.e. non-triggered ES). However, since none of the studies directly compared methods in a randomised controlled trial, there is no evidence that triggered ES is indeed more effective than non-triggered ES.

This review was not able to detect a relationship between stimulation parameters, duration of stimulation and subject characteristics, and clinical outcome. However, the inability to detect a relationship does not mean that a clinically relevant relationship does not exist. The significant heterogeneity of subjects, both within and across groups likely contributed numerous confounding variables and possibly diluted relationships that might otherwise be apparent. Due to the heterogeneity of the studies, clinical outcome was dichotomised, as noted above, and this further reduced the amount of information available for analysis and the likelihood that a relationship could be detected. The review results might also be biased by the choice of the primary outcome measures. Since the focus was motor control, measures that assess movement broadly, such as Fugl-Meyer Motor Assessment, Rivermead Mobility Assessment and Motricity Index were preferred over isometric wrist extensor strength and grip strength. Nevertheless, post-hoc analysis focussing on grip strength and wrist extensor strength yielded similar results, thereby making the conclusion that triggered ES might be more effective than non-triggered ES more robust.

The questions posed in this review can only be addressed fully by directly testing them in clinical trials. Future trials should compare EMG-stim and non-triggered ES. It should be investigated whether it is beneficial or not to apply ES to elbow and shoulder muscles in addition to wrist and finger extensors. Dose response trials should determine

the optimal dose for ES. With respect to stimulation frequency, amplitude and pulse duration, a theoretical framework as to how these parameters might influence clinical outcome should be formulated prior to testing in clinical trials. The more important factor might be muscle activation and joint translation rather than stimulus parameters; the elucidation of the mechanism of action of ES should be subject of future studies. The determination of optimal clinical characteristics for ES treatment is challenging and important, but difficult due to multiple confounding variables. Finally, future studies should further document clinical relevance and should preferably use a common core set of outcome measures. The present review focussed on motor control. Improvements in motor control should translate to improvements in activities of daily living, and this aspect of ES should be evaluated in future trials.

In conclusion, it appears that triggered or volitionally activated ES is more likely to yield improvements in motor control than non-triggered ES. In this review, no relationship between stimulus parameters, duration of treatment, subject characteristics, and clinical outcome could be detected. Future clinical trials should determine the most appropriate method of stimulation, optimal prescriptive parameters, clinical indications and effect of ES at the level of activities of daily living.

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4

Electrical stimulation of the upper extremity in stroke: stimulation of the extensors of the hand versus alternate stimulation of flexors and extensors

JR de Kroon
MJ IJzerman
GJ Lankhorst
G Zilvold

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Abstract

Objective: To investigate whether there is a difference in functional improvement in the affected arm of chronic stroke patients when comparing two methods of electrical stimulation (ES).

Design: Explanatory trial in which 30 chronic stroke patients with impaired arm function were randomly allocated to either alternating ES of the extensor and flexor muscles of the hand (group A) or ES of the extensors only (group B). Primary outcome measure was the Action Research Arm test (ARA) to assess arm function. Grip strength, Motricity Index, Ashworth Scale and range of motion of the wrist were secondary outcome measures.

Results: Improvement on the ARA was 1.0 point in group A and 3.3 points in group B; the difference in functional gain was 2.3 points (95% CI: -1.06 to 5.60). The success rate (i.e. percentage of patients with a clinically relevant improvement of > 5.7 points on the ARA) was 27% in group B (4 patients) and 8% in group A (1 patient). The differences in functional gain and success rate were not statistically significant, neither were the differences between the two groups on the secondary outcome measures.

Conclusion: The difference between the two stimulation strategies was not statistically significant.

Introduction

Most stroke patients suffer from impairments of the affected arm. As a consequence, functional use of the arm is limited, thereby affecting the activities of daily living. The majority of stroke patients consider impaired arm function to be a major problem[1] and arm motor impairments are associated with a low level of subjective well-being.[2]

Electrical stimulation (ES) is one of the therapeutic strategies that are applied to improve impaired arm function. ES has been claimed to have a positive effect on spasticity,[3,4] range of motion[5,6] and muscle strength.[5,7] More recently, studies have mainly focused on the effect of ES on motor control[8,9] and arm function.[10,11] Although these studies suggest a positive effect of ES on motor impairment of the affected upper extremity, the evidence is not conclusive[12,13] and many questions remain with regard to efficacy and optimal stimulation strategy.

One aspect of stimulation strategy concerns the target muscles. In the literature, publications can be found of ES applied to the flexor muscles of wrist and fingers,[4] the extensor muscles[3,6,8-10] or both flexors and extensors alternately,[14-16] and in all cases a positive effect of ES was found on one or more outcome measures.

ES of the spastic wrist flexor muscles was compared with passive stretch of the wrist flexors by King,[4] who reported a significantly greater effect of ES on flexor spasticity. However, Alfieri[3] stated that 'no direct stimulus must be allowed to reach spastic muscles' and he reported a reduction in flexor spasticity after ES of the extensor muscles. Other studies, in which ES was applied to the extensor muscles, reported improvement in range of motion of the wrist[6], wrist extensor strength[10] and motor impairment.[8,9]

A combination of extensor and flexor stimulation is applied in studies using the NESS Handmaster[14,15] and the MESH-glove.[16] These uncontrolled studies report a positive effect on muscle tone,[14,15] passive and active wrist extension,[14,16] motor impairment,[15,16] and arm function.[14]

The exact mechanism underlying the action of ES has not yet been elucidated, but neurophysiologic models produce arguments in favor of each strategy. Improvement in extensor muscle strength, through ES of the extensors, might provide sufficient power to overcome flexor spasticity. On the other hand, ES of the flexors might cause fatigue in the spastic muscles, and thereby reduce spasticity. At spinal level, ES evokes reflexes,[3,4] reciprocal and recurrent inhibition might explain the reducing effect on flexor spasticity that is achieved by stimulation of the extensors and flexors, respectively. The repetitive movements evoked by ES may facilitate motor recovery by repetitive afferent feedback due to neural plasticity.[8,17] This concept might be valid for the stimulation of both flexors and extensors.

It can be argued that stimulation of the extensors is to be preferred, because it is

moving the hand opposite the synergistic pattern, as is advocated in neurodevelopment treatment.[18] On the other hand, in functional movements both flexors and extensors contribute in a balanced way, and this might be regained best by stimulation of both muscle groups.
It is not known which argument is the most convincing, and because of the mutual relationship between the mechanisms, the overall benefit is not clear. No clinical study has yet been carried out to compare these strategies.
Therefore, the present phase II trial was designed to investigate whether there is a difference in functional improvement in the affected arm of patients with chronic stroke, measured with the Action Research Arm test, when comparing alternating ES of the extensor and flexor muscles of the hand with ES of the extensor muscles only.
In theory, stimulation of the extensors versus stimulation of the flexors would be most obvious because this comparison would provide the greatest contrast. However, stimulation of the flexor muscles only is contradictory to the implicit beliefs of clinicians that to focus on the flexor pattern might be potentially harmful to the patient. It was therefore decided to compare the two strategies that are most frequently applied in daily practice and reported in clinical studies: ES of the extensor muscles versus alternating ES of the extensor and flexor muscles.

Methods

Subject selection
Subjects were recruited from the outpatient clinics of two rehabilitation centers in the Netherlands. The local Ethics Committee approved the study protocol, and all subjects who were included gave written informed consent.
Subjects were included if they met the following inclusion criteria: an interval of more than 6 months since unilateral stroke (infarction or hemorrhage) in the territory of the middle cerebral artery; between 18 and 80 years of age; impaired function of the upper extremity due to spastic paresis (spasticity was defined as a synergistic movement pattern or an Ashworth Score of 1 or more; paresis was defined as wrist extensor strength grade 4/5 or less (Medical Research Council); voluntary extension of wrist (at least 10 degrees from resting position) and fingers; stable general health status.
Subjects were excluded if they had: a cardiac pacemaker (on demand); an epileptic fit less than 6 months before the start of stimulation; metal implants in the affected arm; pre-existent functional limitations of the affected upper extremity; serious contractures of shoulder, elbow or wrist (clinical assessment); severe cognitive impairments or severe aphasia resulting in inability to understand the trial; wrist circumference too large for

appropriate fitting of the stimulation apparatus; no reaction to test stimulus; intensive ES treatment prior to this trial.

Baseline characteristics

At baseline the following data were collected: age, gender, diagnosis (infarction or hemorrhage), hemisphere of stroke, time since stroke, dominant arm pre-stroke, cognitive function (Mini Mental State Examination), neglect (letter-cancellation test[19]) and sensory function (alternating and simultaneous touching of both hands, with eyes closed; thumb-finding test[20]). Neglect was defined as a difference of two or more between the affected and the unaffected side in the letter-cancellation test. Sensory disorders were considered to be present if a subject's score deviated from normal on one or both sensory function tests.

Intervention

All included subjects received ES. They were randomized to group A (alternating ES of the flexors and extensors of wrist and fingers) or group B (ES of the extensors only). A computer-generated randomization list was used to perform randomization and to guarantee equal group sizes.

The NESS Handmaster was used to apply the ES. The Handmaster is a splint containing five surface electrodes, with an external control box connected to the splint with a cable. On the control box, different stimulation modes can be selected. In this trial only the exercise mode (alternating extension and flexion) and exercise/open mode (extension only) were used.

The stimulating frequency was 36 Hz. Pulse width and amplitude were individually adjusted to obtain an optimal motor reaction without any side effects such as pain or skin irritation. The duty cycle of the Handmaster was set at 40%, and kept constant during the treatment period.

For each subject a splint was prepared, in which the electrode position was individually adjusted in order to evoke optimal finger movements according to randomization. This fitting of the Handmaster was carried out by a trained physiotherapist or occupational therapist. After fitting, the treatment protocol commenced. The subjects in group A received alternating stimulation of the extensor and flexor muscles for 6 weeks, and subjects in group B received stimulation of the extensor muscles only for the same period of time.

The subjects were asked to exercise 3 times a day, starting with 20 minutes per session. During the first 10 days, the stimulation time was gradually increased to the maximum of 1 hour per session. The therapist checked the stimulation each week for the first 2 weeks, and subsequently every 2 weeks. During these control visits the therapist

scored the subject's opinion with regard to the effect of stimulation on muscle tone and arm function on a 3-point scale: worse, no change, better. The stimulus intensity was adjusted if necessary, and any adverse effects were recorded. Co-interventions were also recorded.

Outcome measures

A therapist who was blinded for the treatment allocation made three assessments: immediately before the start of the treatment (t0), at the end of the 6-week treatment period (t1), and after a follow-up period of 6 weeks (t2).

Primary outcome measure: The Action Research Arm test (ARA) was used to assess manual dexterity of the affected arm.[21] In the ARA, which consists of 19 items, the subject is asked to grasp, move and release objects of different size and shape and to perform 3 gross movements. Each item is scored on a 4-point scale, ranging from 0 (no part of the action can be performed) to 3 (the action is performed completely and within the time limits).[22] The reliability and validity of the ARA have been confirmed[21,22] and it has been found to be responsive to improvement in upper extremity function in chronic stroke subjects.[23]

Secondary outcome measures: Grip strength was assessed with a Baseline® hydraulic hand dynamometer (Fabrication Enterprises Incorporated, New York) with a maximum of 90 kg. The adjustable handle was set in the second position for all subjects. Maximum grip strength of the affected and the unaffected hand were measured in turn, three times each. Grip strength is a sensitive measure of recovery that can span the whole range of recovery.[24] The reliability of grip strength in chronic stroke is good if it is analyzed as the hand ratio, i.e. the ratio of the mean value of the affected hand to the mean value of the unaffected hand.[25] Therefore, hand ratio was used for the analysis and presentation of the results of the grip strength measurements.

The arm section of the Motricity Index (MI) was applied for the assessment of motor impairment.[26] In the MI, pinch grip, elbow flexion and shoulder abduction are tested; the scoring system is similar to the Medical Research Council (MRC) grades. The reliability and validity of the MI have been confirmed, and the test has been found to be sensitive to change.[26] Resistance to passive movement was assessed according to the Ashworth Scale,[27] and a goniometer was used to measure the active range of motion of the wrist joint.

Data-analysis

Baseline characteristics of the two treatment groups were compared to evaluate the success of randomization.

Mean and standard deviations were calculated to summarize scores on the ARA test,

hand ratio, MI and active range of motion. For the Ashworth Scale, median and range were calculated.
Non-parametric tests were applied to analyze the main effects. Between-group analyses were performed for the time-periods t0-t1 and t0-t2 (Mann-Whitney U-test). If there was a baseline difference in an important prognostic factor for a specific outcome measure, an additional analysis was performed, with this factor as covariable (ANCOVA).
For the primary outcome measure (ARA test), the percentage of subjects who showed clinically relevant improvement was determined for both groups (the percentage of success with a 95% confidence interval). The minimal clinically important improvement was set at 10%, i.e. 5.7 points on the ARA.[22] Chi-square tests were applied to evaluate the difference in success rate and the difference between the opinions of the subjects. The statistical analyses were performed with SPSS 11.5 for Windows. The significance level was set at 0.05.
The objective of the present trial was to investigate whether there is a difference between two stimulation strategies. Therefore, an on-treatment analysis was performed, and not an intention-to-treat analysis, which would have been necessary if investigating the effectiveness of ES.[28]

Results

Included subjects

Thirty subjects were included, and 28 completed the treatment program. The characteristics of these subjects are summarized in Table 1. The two groups were comparable with regard to age, time since stroke, percentage with non-hemorrhagic stroke, gender, neglect, cognitive function and sensory disorders. However, notwithstanding randomization, there were more subjects in group B with right hemiparesis, and thus more subjects with an impaired dominant arm. Grip strength of the affected hand and the hand ratio were also higher in group B. There was no clinically significant difference between the two groups with regard to initial scores for the other outcome measures.

Intervention

One subject dropped out of the treatment program a few days before the final date. Because she only missed a few ES sessions and had completed all assessments, it was decided to include this subject in the analysis. However, two other subjects dropped out much earlier. One dropped out after 1 week because she experienced an increase in involuntary movements of the arm between the stimulation sessions. In our opinion, this was a result of the way in which she coped with the therapy rather than an effect

Table I. Patient characteristics and initial values

	Group A (flexors and extensors)	Group B (extensors only)
N	13	15
Age in years mean (sd)	58 (17.3)	61.7 (9.7)
Months post stroke mean (sd)	14.7 (11.8)	21.4 (16.1)
Right hemiparesis (%)	3 (23)	8 (53.3)
Dominant arm affected (%)	4 (30.8)	7 (46.7)
Non-hemorrhagic stroke (%)	11 (84.6)	14 (93.3)
Female (%)	4 (30.8)	4 (26.7)
MMSE[a] median (range)	28 (26-30)	27 (16-30)
Neglect present (%)	3 (23.1)	3 (20)
Sensory disorder present (%)	8 (61.5)	7 (46.7)
Co-interventions Low intensity/higher intensity	6 3/3	6 4/2
ARA test[b] mean (sd)	28.6 (15.3)	28.9 (13.1)
Grip strength mean (sd)	11.2 (9.1)	14.8 (7.0)
Hand ratio mean (sd)	0.25 (0.17)	0.37 (0.15)
Motricity Index mean (sd)	64.3 (18.1)	60.7 (13.9)
Ashworth Scale median (range)	1 (0-3)	1 (1-2)
Barthel Index median (range)	20 (17-20)	20 (16-20)

[a] MMSE = Mini Mental State Examination, [b] ARA test = Action Research Arm test

of the stimulation itself, and the situation normalized as soon as she stopped having ES. The other subject dropped out after 2 weeks because the 1-hour treatment program 3 times a day occupied her too much. For these two subjects, the reason why they dropped out early in the treatment period was not related to the specific stimulation method to which they had been assigned. They were both excluded from the analysis (on-treatment analysis).

Twelve subjects received other therapy during the ES treatment. This varied from fitness training once a week to more intensive outpatient treatment in the rehabilitation center. Subjects who received co-interventions were equally distributed over groups A and B, and there was a similar distribution of low and higher intensity co-interventions (see Table 1).

Approximately half of the subjects had some redness of the skin, but only at the beginning of the treatment period. This was either under the electrodes or where there was pressure from the splint on the wrist. In all cases the redness disappeared soon after the initial stimulation sessions and did not result in any burns or pressure sores. Four subjects felt pain during the stimulation, but this disappeared as the intensity of the stimulation was decreased. Apart from this temporary redness and pain, no adverse effects were reported.

Outcome in both groups

Table 2 shows the results of the assessments for both groups on all outcome measures, and the changes from baseline to end of treatment and end of follow-up.

Table 2. Results of the assessments at t0, t1 and t2, and changes in the assessments.

		t0 start of treatment	t1 end of treatment	change t0-t1	t2 end of follow-up	change t0-t2
Action Research Arm test [a] (0-57, 0 = no arm function)						
A: flexors and extensors	n=13	28.6 (15.3)	29.6 (16.5)	1.0 (3.3)	29.6 (17.1)	1.0 (5.3)
B: extensors only	n=15	28.9 (13.1)	32.1 (12.7)	3.3 (5.0)	32.2 (13.5)	3.3 (4.5)
Hand ratio [a]						
A: flexors and extensors	n=13	0.25 (0.17)	0.31 (0.15)	0.06 (0.07)	0.28 (0.16)	0.02 (0.07)
B: extensors only	n=15	0.37 (0.15)	0.41 (0.18)	0.04 (0.09)	0.40 (0.17)	0.03 (0.09)
Motricity Index [a] (0-100, 0 = no voluntary movement)						
A: flexors and extensors	n=13	64.3 (18.1)	65 (16.6)	0.7 (1.5)	61.9 (15.3)	-2.3 (7.7)
B: extensors only	n=15	60.7 (13.9)	62.7 (12.9)	1.9 (7.6)	62.6 (13.8)	1.9 (9.4)
Ashworth Scale [b] (0-4, 0 = normal muscle tone)						
A: flexors and extensors	n=13	1 (0;3)	2 (0;3)	0 (-1;1)	1 (0;2)	0 (-1;1)
B: extensors only	n=15	1 (1;2)	1 (1;2)	0 (-1;0)	1 (0;2)	0 (-1;1)
Active ROM [c] of the wrist [a] (in degrees)						
A: flexors and extensors	n=13	88.2 (27.6)	87.6 (34.9)	-0.5 (19.1)	95.8 (33.6)	7.6 (19.1)
B: extensors only	n=15	94.4 (26.3)	95.1 (24.9)	0.6 (16.4)	103.9 (18.9)	9.5 (15.5)

[a] mean (sd)
[b] median (range)
[c] ROM = range of motion

Primary outcome measure: Action Research Arm test

Figure 1 shows the mean ARA scores for both groups. During the treatment period the mean ARA score in group B improved by 3.3 points (95% confidence interval: 0.51 to 6.02), whereas the mean score in group A improved only slightly (1.0 point, 95% confidence interval: -0.97 to 2.97). In both groups there was no deterioration during follow-up. The difference in functional gain between group A and B was not statistically significant (Mann-Whitney U-test: t0-t1 p=0.25; t0-t2 p=0.39; 95%CI t0-t1: –1.06 to 5.60; 95%CI t0-t2: –1.47 to 6.14). The baseline difference in hand ratio might bias the outcome on the ARA test. An additional analysis, with the initial hand ratio as co-variable, also showed no significant difference between the two groups (ANCOVA: p=0.10).

Four of 15 subjects in group B improved more than the clinically relevant difference of 5.7 points (range 7-12 points), and the percentage of success in group B was 27% (95% confidence interval: 8 to 55%). In group A, 1 of 13 subjects improved more than 5.7 points (7 points), resulting in a success percentage of 8% (95% confidence interval: 0-36%). This difference in success is not significant (Chi-square test, p=0.33). The ratio of the success rates in group B and group A is 3.4, indicating that the chance of success in group B was 3.4 times higher than in group A (95% confidence interval: 0.44 to 27.24)

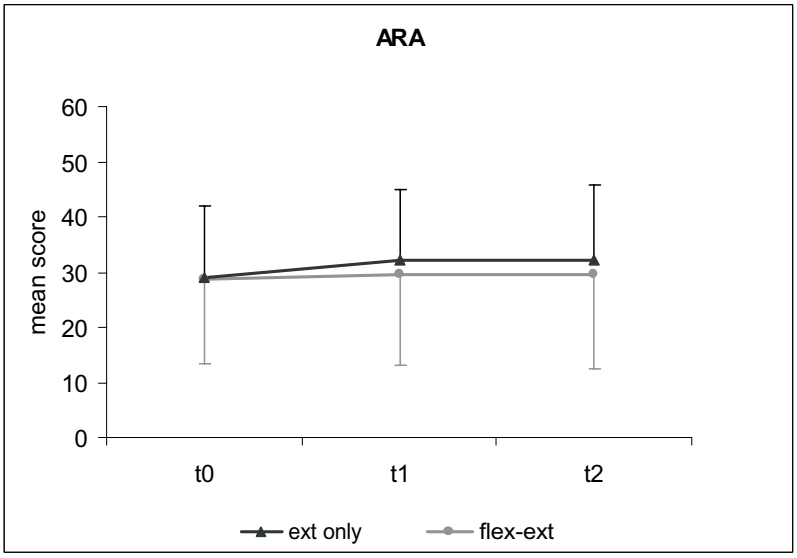


Figure 1. Mean scores and standard deviations on the Action Research Arm test (ARA) for group A (alternating flexion and extension) and group B (extension only). ES treatment was applied between t0 and t1.

Secondary outcome measures:

Hand ratio: Table 2 and Figure 2 show that the hand ratio of both groups improved during treatment, but there was some decline during follow-up. The improvement in the flexor-extensor group (group A: 0.06; 95% confidence interval: 0.01 to 0.10), was somewhat greater than in the extensor only group (group B: 0.04; 95% confidence interval: -0.01 to 0.09), but the difference in gain was not statistically significant (Mann-Whitney U-test: t0-t1 p=0.27; t0-t2 p=0.69). An additional analysis, with correction for the baseline difference in initial hand ratio, also showed no difference between the groups (ANCOVA, p=0.59).

Motricity Index: This index for motor impairment showed no treatment effect for either group (Table 2 and Figure 2), and also no difference between the two groups (Mann-Whitney U-test: t0-t1 p=0.44: t0-t2 p=0.12).

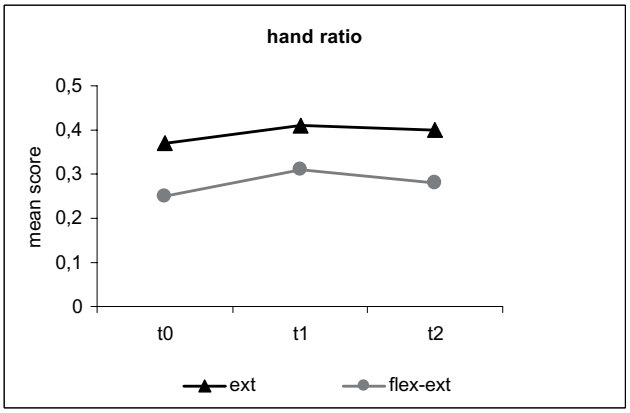
Ashworth Scale: The median change in Ashworth Scale during treatment and at follow-up was zero for both groups (Table 2). Statistical analysis showed no difference between the groups (Mann-Whitney U-test: t0-t1 p=0.62; t0-t2 p=0.82).

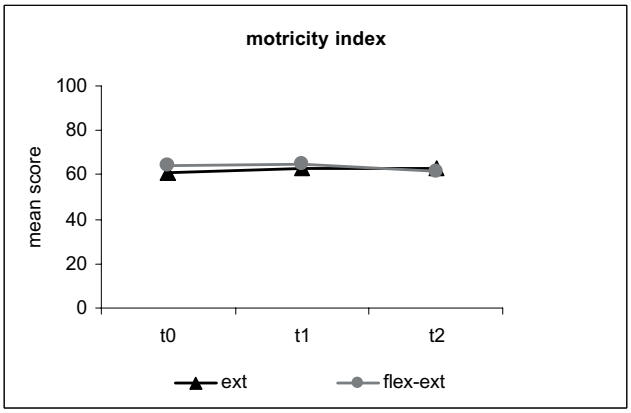
Active range of motion of the wrist: Table 2 and Figure 2 show that the active range of motion (aROM) of the wrist did not change during the treatment period in either group. However, the aROM improved in both groups during follow-up, probably as a result of increased active extension (Figure 2). No difference was found between the two groups (Mann-Whitney U-test: t0-t1 p=0.79; t0-t2 p=0.79).

Subjects' opinion about the treatment

Functional improvement was reported by 8 subjects in group A (62%) and 13 subjects in group B (87%). Five subjects in group A and 2 subjects in group B reported no change in function of the affected arm (38% and 13%, respectively). The subjects mainly described functional improvement as better ability to grasp and release small objects and more functional use of the affected arm in the activities of daily living. In group A, 9 of 13 subjects reported a decrease in muscle tone (69%) and 4 reported no change (31%). A decrease in muscle tone was reported by 11 of 15 subjects in group B (73%), whereas 2 subjects reported no change (13%) and 2 reported an increase in muscle tone (13%). There was no significant difference between the two groups with regard to the subjective score for function and muscle tone (Chi-square test). These subjective opinions did not correspond with the outcomes on the Ashworth Scale and the ARA test.

Donning and doffing of the splint was no problem for most of the subjects. Three subjects needed help; two only initially and one throughout the entire trial.





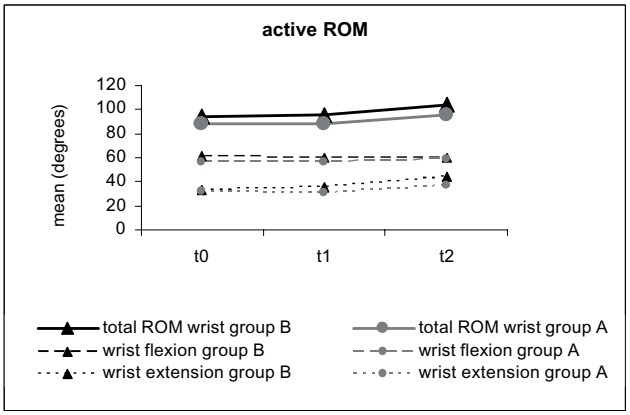


Figure 2. Mean scores for the secondary outcome measures hand ratio, motricity index and active ROM for group A (alterning flexion and extension) and group B (extension-only). ES treatment was applied between t0 and t1.

Discussion

This trial investigated whether there was a difference in functional improvement of the affected arm in chronic stroke patients when comparing two strategies of electrical stimulation. ES of the extensor muscles yielded a non-significant improvement in arm function, compared to alternating ES of flexors and extensors. Therefore, the main conclusion of this trial is that there is no significant difference between the two methods of stimulation with regard to functional improvement, as assessed by means of the Action Research Arm test.

The fact that the difference between the two groups was not statistically significant is probably due to a power problem, i.e. a type II error. Because this trial was the first to compare these two stimulation strategies, it was not possible to perform a reliable power calculation beforehand. However, the 95% confidence interval for the difference in functional gain (-1.06 to 5.60) does suggest that it is reasonable to assume that a significant effect would have been found if the study had had more power.[28]

Apart from statistical significance, clinical relevance is also important for therapeutic interventions. Neither the difference between the groups, nor the improvement in the group that received ES of the extensor muscles only, exceeded the minimal clinically important difference (MCID) of 10%, i.e. 5.7 points on the ARA test[22]. In the present trial, the MCID was also used to calculate success rates with regard to functional improvement in both groups. The percentage of success was 27% in the group receiving ES of the extensors (4 of 15 subjects) and 8% in the other group (1 of 13 subjects). This difference in success rate was not significant either.

The clinician who applies ES to improve arm function might be tempted to choose ES of the extensors only, based on more functional gain, a higher success rate and more subjects reporting functional improvement, compared to the results of alternating ES of flexors and extensors found in the present trial. However, the lack of a statistically significant difference between the two methods in this respect indicates that this choice would not be based on scientific evidence.

Maximal grip strength, expressed as the ratio between the affected and the non-affected side, is a valuable marker of hand and arm function in chronic stroke.[25] In the present trial, the hand ratio improved in both groups during the treatment. The improvement in hand ratio was more pronounced in the flexor-extensor group, and this was probably due to the fact that the flexor muscles of the hand were trained in this group, but not in the extensor-only group. Although the hand ratio improved in both groups, and the gain was greater in the flexor-extensor group, gain in hand ratio was only associated with functional improvement in the group receiving ES of the extensors only.

Apparently gain in grip strength does not guarantee functional improvement.
After the treatment, the hand ratio decreased in both groups, but the decrease was less in the extensor only group. An explanation might be that the gain in grip strength was maintained by the improvement in function in this group.
This study does not confirm the tone-reducing effect of ES of the extensor muscles, as claimed by Alfieri,[3] but it appears that the result of flexor and extensor stimulation is not merely a sum of the positive effects of reciprocal and recurrent inhibition.
Assessment of the active range of motion of the wrist resulted in the unexpected finding that in both groups improvement in range of motion occurred only in the follow-up period. The meaning and explanation of this finding in relation to the effect of ES are puzzling. However, the improvement found in active extension at follow-up can not be considered as a measurement error. Measurement errors are random in direction, and are not likely to occur only at follow–up.

When the results of the present trial are compared with those of previous trials in chronic stroke patients, it is striking that the previous studies reported improvement in passive range of motion,[14,16] active range of motion,[14,16] muscle tone[3,14,15] and motor control,[15] whereas in the present trial no effect of the treatment was found on range of motion, muscle tone or motor control in either of the two groups. One explanation is that this might be due to subject characteristics. Comparison of baseline characteristics with those in previous trials revealed that the subjects in previous trials were, in general, more severely affected than the subjects included in the present trial. It is possible that more severely affected subjects benefit more from ES with regard to muscle tone and range of motion. The present trial specifically focused on less severely affected subjects, i.e. subjects with active voluntary wrist extension. This was based on previous sub-group analyses suggesting that less severely affected subjects might benefit more from ES with regard to motor control and function.[9,15] Based on these sub-group analyses, improvement in motor control was expected to be found in the present study population.
The aforementioned studies were mainly non-randomized trials, and their positive results might therefore be biased. Pocock states that only randomized controlled trials can provide a reliably unbiased estimate of treatment effect.[29] To date, three RCTs focusing on ES in chronic stroke patients have been published.[9,11,30] Sonde et al. reported an improvement in motor control without any reduction of muscle tone; functional abilities and strength were not assessed in this trial.[9] The lack of improvement in motor control that was found in the present trial is not in accordance with the results of the trial carried out by Sonde et al.

Cauraugh et al.[11] focused on less severely affected subjects, like those in the present trial. Spasticity and range of motion were not assessed, but they reported improvement in sustained contraction of the wrist extensor muscles and function (box and block test), but no effect on motor control.[11] From the publication it is not clear whether there was no gain in motor control, or no difference in gain. In a later trial, functional improvement was confirmed,[30] but the clinical relevance of this improvement was not discussed. From the present trial it appears that functional improvement can be clinically relevant for some subjects.
The results of the present trial and previous RCTs on ES are therefore inconclusive with regard to motor control, but functional improvement can be achieved by ES in chronic stroke patients, at least in those with residual voluntary wrist extension.

The exact mechanism underlying this functional improvement is still unclear. However, the results of the present study and the study carried out by Cauraugh et al[11] suggest that improvement in motor control is not a prerequisite for functional gain. It can be hypothesized that functional gain is achieved by improvement in movement strategies or enhanced movement efficiency. The clinical opinion is that improvement in movement strategy is associated with reduction in muscle tone,[18] but that is not in accordance with the findings of the present trial. It is more likely that muscle strength is a crucial factor in movement efficiency. Grip strength is shown to be a good marker of hand function, but the results of the flexor-extensor group in the present trial show that an increase in grip strength alone is not enough to achieve functional improvement. Strength of wrist and finger extension might be more important. The stabilizing effect of extension power to the wrist is a component of grip strength, and extension power itself is important for use of the fingers in most functional hand activities.[11] In the studies carried out by Cauraugh,[11,30] functional improvement is associated with increased sustained contraction of the stimulated wrist extensors. We hypothesize that this is also true in the present trial. Although muscle strength of the finger extensors was not assessed, it can be assumed that extensor muscle strength increased most in the extensor-only group, because these muscles were trained most in this group, and it was this group in which most functional improvement was found.
It might therefore be argued that the difference between the extensor-only group and the flexor-extensor group with regard to functional improvement is merely a result of the difference in intensity i.e. duration of extensor stimulation between the two groups. In our opinion, this argument is only valid if ES of the flexors is believed to be completely neutral. However, the theories described in the Introduction indicate that flexor stimulation is bound to have some influence on the impaired arm. Therefore, the present trial is not just a dose-effect study of extensor stimulation, but a comparison of

two different stimulation strategies. The exact influence of flexor stimulation is still not known, but the trial showed that the addition of flexor to extensor stimulation had no additional value.

In conclusion, there was no statistically significant difference between ES of the extensor muscles of the hand and alternate ES of flexor and extensor muscles. Functional improvement in chronic stroke patients can be achieved by ES, but at group level the functional gain did not exceed the minimal clinically relevant difference. Future studies should focus on patient characteristics, in order to identify patients who might benefit in a clinically relevant way. Given the importance of arm function improvement, more research is needed to elucidate the determinants of functional recovery and the specific mechanisms underlying the action of electrical stimulation.

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5

Electrical stimulation of the upper extremity in stroke: cyclic versus EMG-triggered stimulation

JR de Kroon
MJ IJzerman

Submitted for publication

Abstract

Background and Purpose: EMG-triggered electrical stimulation is thought to be more effective in improving motor function than cyclic electrical stimulation because of active involvement of the subject. However, a comparative trial has not yet been published. The present trial was designed to compare the effect of cyclic and EMG-triggered electrical stimulation on motor impairment and function of the affected upper extremity in chronic stroke.

Methods: Twenty-two subjects were randomly assigned to either cyclic or EMG-triggered electrical stimulation of the wrist and finger extensor muscles. In both groups stimulation was applied at home for a 6-week period, three 30-minute sessions per day. Primary outcome measure was the Action Research Arm test (ARA, 0-57 points) to assess arm function. Grip strength, Fugl-Meyer Motor Assessment (FM) and Motricity Index (MI) were secondary outcome measures. Assessments were made at the start of the treatment and after 4, 6 and 12 weeks.

Results: Cyclic as well as EMG-triggered stimulation resulted in an increase of the ARA-score after the treatment period of 2.3 and 4.2 points respectively. The difference in functional gain was not statistically significant. Grip strength, FM and MI showed improvement in both groups as well, the differences between the groups were not significant either.

Conclusion: The present study did not detect a significant difference between EMG-triggered and cyclic electrical stimulation with respect to improvement of motor function of the affected arm in chronic stroke.

Introduction

There is growing evidence that electrical stimulation (ES) has a positive effect on motor recovery of the affected arm after stroke.[1,2] ES might therefore be useful in the rehabilitation of patients with stroke. However, several methods of application have been reported and this raises the question which method should be applied in daily practice.

In cyclic ES, the stimulation is applied according to a pre-programmed scheme, resulting in repetitive muscle contractions without active involvement of the subject. Examples of cyclic ES are Neuromuscular Electrical Stimulation (NMES) and Transcutaneous Electrical Nerve Stimulation (TENS).[2,3] In EMG-triggered electrical stimulation (EMG-stim), ES is provided when volitionally generated EMG signals exceed a preset threshold.[4] In the latter approach the subject is actively involved, and voluntary muscle contraction is reinforced by volitionally triggered ES.

From a systematic review of clinical trials it was concluded that volitionally triggered ES may be more effective than cyclic ES.[5] This conclusion was derived from the finding that the likelihood of a positive outcome was higher in studies which applied volitionally triggered ES as compared to cyclic ES. This finding is in line with animal studies that have demonstrated that only exercises aimed at the development of new motor skills induce long-term plasticity on motor maps.[6] Automatic repetitive movement tasks were not associated with any significant changes in motor cortex.[7] From a clinical perspective, the activities that induce long-term plasticity in humans are likely to be those activities that are meaningful and require cognitive investment, rather than automatic activities. From this it is hypothesized that repetitive movement therapy where the subject is cognitively involved in generating the movement (i.e. volitionally triggered ES) is likely to be more effective than therapy where the subject is not cognitively involved (i.e. cyclic ES). However, thus far no randomized controlled trial in which volitionally triggered ES was directly compared to cyclic ES has been published, so there is no direct evidence that one method is indeed more effective than the other.

The present trial investigates whether there is a difference in motor recovery and functional improvement in the affected arm of chronic stroke patients when comparing volitionally triggered ES (EMG-stim) of the wrist extensors with cyclic ES.

Methods

Subject selection

Subjects were recruited from the outpatient clinics of a rehabilitation centre, the surrounding general hospitals and the patients' association. The local Ethics Committee approved the study protocol.

Subjects were included if they met the following inclusion criteria: 1. an interval of more than 6 months since unilateral supratentorial stroke (infarction or hemorrhage); 2. between 18 and 80 years of age; 3. impaired function of the upper extremity due to spastic paresis (spasticity was defined as a synergistic movement pattern or an Ashworth Score of 1 or more; paresis was defined as wrist extensor strength grade 4 or less {Medical Research Council}); 4. voluntary extension of the wrist (at least 10° from resting position); 5. stable general health status. 6. written informed consent.

Subjects were excluded if they had: 1. a cardiac pacemaker (on demand); 2. an epileptic seizure less than 6 months before the start of stimulation; 3. metal implants in the affected arm; 4. pre-existent functional limitations of the affected upper extremity; 5. serious contractures of shoulder, elbow or wrist (clinical assessment); 6. severe cognitive impairments or severe aphasia resulting in inability to understand the trial; 7. skin problems underneath the electrodes; 8. inadequate motor response to test stimulus; 9. not enough voluntary muscle contraction of wrist extensors to trigger stimulation; 10. no tolerance for surface stimulation. Criteria 8, 9 and 10 were assessed during a single test session with both modes of stimulation before inclusion and randomization.

Baseline characteristics

At baseline the following data were collected: age, gender, diagnosis (infarction or hemorrhage), hemisphere of stroke, time since stroke, dominant arm pre-stroke, cognitive function (Mini Mental State Examination), neglect (letter-cancellation test[8]) and sensory function (alternating and simultaneous touching of both hands with eyes closed; thumb-finding test[9]). Neglect was defined as a difference of two or more between the affected and the unaffected side in the letter-cancellation test. Sensory disorders were considered to be present if a subjects' score deviated from normal on one or both sensory function tests.

Intervention

All subjects received ES of the wrist and finger extensor muscles of the affected arm. They were randomized to either cyclic ES or EMG-stim by means of a computer-generated randomization list.

The Automove AM800 (Danmeter a/s, Odense, Denmark) was used to apply ES in both

groups. Surface electrodes were attached to the dorsal side of the forearm to evoke balanced extension of wrist and fingers. The position of the electrodes was marked with a permanent marker for the duration of the treatment, to guarantee the electrodes were placed consistently across stimulation sessions. The electrodes used could serve for stimulation as well as EMG detection The Automove can provide stimulation in different modes; in this trial the cyclic- and the auto-mode were used. In the cyclic-mode the stimulation was applied automatically, without active involvement of the subject (cyclic ES). In the auto-mode stimulation was triggered by voluntary EMG activity of the subject, only if the threshold was reached (EMG-stim). Initially the threshold was 50 μV. If the subject successfully reached the threshold it automatically increased slightly. If the threshold was not met, the AM800 decreased the threshold to a level closer to the EMG-activity the subject could produce. In either mode biphasic pulses with a frequency of 35 Hz and pulse duration of 300 μs were administered for 6 seconds with 1-s ramp-up, 1-s ramp-down and 9-s stimulus off. The setting of the aforementioned stimulation parameters and mode of stimulation was locked in order to avoid accidental changes. Amplitude was individually adjusted to obtain an optimal motor response without any side effects such as pain or skin-irritation.
The subjects received directions in the use of the Automove according to randomization. They applied the stimulation at home, and were instructed to exercise three 30-minute sessions a day for a period of 6 weeks. Each subject started with a stimulation time of 15 minutes, which was gradually increased to 30 minutes per session during the first week. The time subjects actually spent with training was recorded by the Automove. The therapist checked the stimulation each week for the first 2 weeks, and subsequently every 2 weeks. During these control visits the therapist scored the subjects' opinion with regard to the effect of stimulation on arm function on a 3-point scale: worse, no change, better. The stimulus intensity was adjusted if necessary, and any adverse effects were recorded. Co-interventions were also recorded.

Outcome measures
A therapist blinded for treatment allocation made four assessments: immediately before the start of the treatment (t0), after 4 weeks of treatment (t1); at the end of the 6-week treatment period (t2), and after a follow-up period of 6 weeks (t3).
Primary outcome measure: The Action Research Arm test (ARA) was used to assess manual dexterity of the affected arm.[10] In the ARA, which consists of 19 items, the subject is asked to grasp, move and release objects of different size and shape and to perform 3 gross movements. Each item is scored on a 4-point scale, ranging from 0 (no part of the action can be performed) to 3 (the action is performed completely and within the time limits),[10] the maximum score is 57. The reliability of the ARA has been

confirmed and it is able to detect clinically relevant improvement in chronic stroke.[10]
Secondary outcome measures: Grip strength was assessed with a Baseline hydraulic hand dynamometer (Fabrication Enterprises Incorporated, New York) with a maximum of 90 kgs; the adjustable handle was set in the second position for all subjects. Maximum grip strength of the affected and the unaffected hand were measured in turn, three times each. The hand ratio was used for analysis of the grip strength measurements. The hand ratio is the ratio of the mean value of the affected hand to the mean value of the unaffected hand and its reliability is good.[11]
The arm sections of the Motricity Index (MI)[12] and the Fugl-Meyer Motor Assessment (FM)[13] were applied for the assessment of motor impairment. In the MI, pinch grip, elbow flexion and shoulder abduction are tested; the scoring system is similar to the Medical Research Council grades and the maximum score is 100. The FM was applied to assess the ability to move the affected arm out of the synergistic pattern; the maximum score is 66. The reliability and validity of both tests have been confirmed.[12,14]

Data analysis
Baseline characteristics of the two treatment groups were compared to evaluate the success of randomization. Mean and standard deviations were calculated to summarize scores on the ARA, hand ratio, MI and FM. Separate linear mixed model analyses were conducted to evaluate main effects for each outcome measure over the complete trial period, i.e. treatment and follow-up. Group (cyclic ES and EMG-stim) and time (outcome assessments) were entered in the model. In addition, the baseline value and time post-stroke were entered as co-variables to correct for the baseline difference.The percentage of subjects who showed clinically relevant improvement on the primary outcome measure (ARA) was determined in each group. Clinically relevant improvement was defined as 10%, i.e. 5.7 points on the ARA.[10] Chi-square tests were applied to evaluate the difference in success rate and the difference between the opinions of the subjects. All statistical analyses were performed with SPSS 11.5 for Windows. The significance level was set at 0.05.

Results

Subjects
Twenty-two subjects were included and 21 completed treatment and follow up. The characteristics of the 21 subjects are summarized in Table 1.
Notwithstanding randomization, the mean intake scores on the clinical measures were higher in the EMG-stim group, indicating that the subjects in the cyclic ES group were

more severely affected. Mean time post stroke was longer in the EMG-stim group.

Table 1. Baseline characteristics and initial values.

	Cyclic ES	EMG-triggered ES
N	10	11
Age in years*	60.6 (10.9)	57.4 (8.0)
Months post stroke†	16.5 (6-48)	27 (7-115)
Right hemiparesis (%)	3 (30)	3 (27.3)
Dominant arm affected (%)	3 (30)	6 (54.5)
Non-hemorrhagic stroke (%)	8 (80)	10 (90.9)
Male (%)	8 (80)	8 (72.7)
Mini Mental State Examination†	28 (22-30)	28.5 (23-29)
Neglect present (%)	0 (0)	3 (27.3)
Sensory disorder present (%)	4 (40)	6 (54.5)
Action Research Arm test*	14.8 (10.3)	22.8 (11.8)
Hand ratio*	0.28 (0.10)	0.42 (0.14)
Fugl-Meyer Motor Assessment*	29.0 (10.6)	38.4 (7.7)
Motricity Index*	52.3 (15.1)	66.1 (13.4)

*mean (sd)
†median (range)

Intervention

One subject in the cyclic ES group dropped out after 2 weeks. She experienced complaints of overuse such as swelling and stiffness in her affected hand. She was advised to stop with ES, after which the complaints disappeared. One subject in the EMG-stim group experienced similar complaints, to a lesser extent and only after stimulating for more than 15-20 minutes. It was decided to reduce the treatment protocol to 15-20 minutes 3 times a day, only for this particular patient. From then on he could tolerate the treatment well; he fulfilled the 6 weeks training program.

Due to technical problems, the time subjects actually spent with the treatment could not be retrieved in 6 subjects. The data for the other 15 subjects showed no difference between the groups. Mean treatment time was 48.12 hours (sd 14.3) in the cyclic group (n=7) and 48.25 hours (sd 9.7) in the EMG-stim group (n=8). Five subjects received other therapies during the ES treatment, 3 subjects in cyclic ES group and 2 in the EMG-stim group. This additional therapy was mainly aimed at walking.

Only in the first days of the treatment period, a few subjects experienced some temporary redness of the skin under the electrodes or pain during stimulation, both related to stimulation amplitude; others had shoulder complaints related to the position of shoulder and arm during stimulation or some muscular pain after stimulation. Apart from these temporary complaints, no adverse effects were reported. All but one subject were completely independent in application of the treatment, although two needed assistance when changing the batteries.

Clinical outcome measures

Table 2 shows the results of the assessments for both groups on all outcome measures, and the change from baseline to end of treatment and end of follow up.

Action Research Arm test: Both groups showed improvement of arm function as assessed with the ARA, immediately after treatment as well as at follow up (figure 1). The overall difference in effect between the groups was not significant (p=0.731).

At group level the improvement during treatment was clinically significant for neither of the groups. In the cyclic group, 2 out of 10 subjects improved more than the clinically relevant difference of 5.7 points (both improved 7 points), yielding a percentage of success of 20%. In the EMG-stim group the percentage of success was 36%, with 4 out of 11 subjects improving more than 5.7 points (6, 6, 9 and 17 points). These percentages were the same for t2 and t3. Differences in success were not significant (Chi square test p=0.635).

Hand ratio: The mean ratio of both groups improved over the entire trial period, the change was only small in the EMG-stim group. The mixed model analysis revealed no significant difference between the groups (p=0.322).

Fugl Meyer Motor Assessment: Both groups improved on the FM. The gain was most pronounced for the cyclic ES group, but the overall difference in gain was not significant (p=0.974).

Motricity Index: There was no significant difference between the groups with respect to the scores on the Motricity Index (p=0.390).

Subjective scores

The majority of subjects were positive about the effects of their ES-treatment with respect to arm function. In the cyclic ES group 9 subjects reported improvement (90%) and 1 reported no change (10%); in the EMG-stim group the numbers were 7 (64%) and 4 (36%) respectively. Functional improvement was mainly described as better ability to grasp objects with the affected hand. There was no significant difference between the 2 groups with regard to the subjective scores (Chi square test, p=0.31).

Table 2. Means and standard deviations of all outcome measures.

	t0 0 wks	t1 4 wks	t2 6 wks	change t0-t2	t3 12 wks	change t0-t3
Action Research Arm test (0-57, 0 = no arm function)						
cyclic ES (n=10)	14.8 (10.3)	15.7 (11.5)	17.1 (11.4)	2.3 (2.9)	18.4 (12.1)	3.6 (4.3)
EMG-triggered ES (n=11)	22.8 (11.8)	26.4 (13.5)	27.0 (13.2)	4.2 (6.7)	25.0 (12.7)	2.2 (6.4)
Hand ratio						
cyclic ES (n=10)	0.28 (0.10)	0.33 (0.16)	0.33 (0.17)	0.05 (0.11)	0.32 (0.15)	0.04 (0.07)
EMG-triggered ES (n=11)	0.42 (0.14)	0.45 (0.16)	0.43 (0.14)	0.01 (0.07)	0.44 (0.15)	0.03 (0.05)
Fugl-Meyer Motor Assessment (0-66, 0 = no voluntary movement)						
cyclic ES (n=10)	29.0 (10.6)	34.2 (11.9)	35.2 (11.8)	6.2 (5.8)	34.0 (12.4)	5.0 (5.9)
EMG-triggered ES (n=11)	38.4 (7.7)	40.6 (6.5)	41.9 (6.7)	3.5 (5.2)	41.2 (8.0)	2.8 (6.0)
Motricity Index (0-100, 0 = no voluntary movement)						
cyclic ES (n=10)	52.3 (15.1)	58.5 (12.7)	54.9 (13.6)	2.6 (9.2)	58.1 (17.9)	5.8 (10.0)
EMG-triggered ES(n=11)	66.1 (13.4)	70.7 (11.7)	71.5 (8.6)	5.4 (13.2)	66.5 (13.0)	0.5 (4.2)

Treatment was applied between t0 and t2.

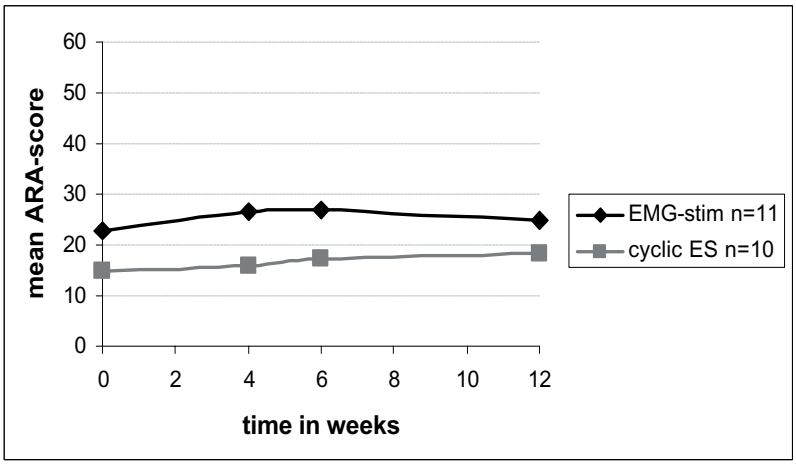

Figure 1. Mean ARA-scores for both stimulation groups. Treatment was applied between week 0 (t0) and week 6 (t2).

Discussion

The present trial compared cyclic and EMG-triggered electrical stimulation of the affected arm in chronic stroke, and showed no statistical differences in measures of motor recovery between both methods of stimulation.
Beforehand it was hypothesized that EMG-triggered ES may be more effective, based on a literature review[5] and animal studies[6,7,15] which revealed that repetitive movement training in which the animal was cognitively involved (like in EMG-stim) did result in long-term plasticity of motor maps of the cortex,[7,15] whereas automatic repetitive movements (like in cyclic ES) did not. The exercises reported to result in cortical changes were aimed at the development of new motor skills such as retrieving food pellets from a small well.[15] In EMG-triggered ES, cognitive effort is required to provide the initial EMG-signal. But once the threshold is reached no further active involvement is needed. The increasing threshold with increased voluntary EMG provides a training aspect, but EMG-triggered ES does not involve skill training. Therefore, the contrast in the present study was not as large as the contrast between the animal studies. This may be an explanation for the lack of difference between both stimulation groups, contrary to the expectations.

A recent trial reported cortical changes after a combination of cyclic ES and EMG-stim.[16] Since the subjects spent half of the daily treatment time with cyclic ES and the other half with EMG-stim it is not known if only one or both methods of ES provoked the cortical

changes. The cortical changes reported concerned a significant increase in intensity of activation of the ipsilateral somatosensory cortex as assessed by fMRI, without changes in the motor cortex. However, the affected arm of the subjects did improve on functional outcome measures. Since this functional improvement was not associated with a change in motor cortex activation, it may be hypothesized that changes in motor cortex activation are not necessary for motor improvement.
Thus far, three other randomized controlled trials compared aspects of ES stimulation strategies.[17-19] These trials showed improvement on motor impairment and/or functional abilities of the affected arm in chronic stroke, but none of these trials revealed a significant difference between the stimulation groups either. From this it may be hypothesized that ES can be beneficial in chronic stroke, regardless of the specific method of application of ES. The different ES strategies applied all evoke repetitive movements, which are probably more crucial in the effect of ES than the specific stimulation parameters evoking the muscle contractions[5] or the duration of the stimulus on-time.[18] However, the strategies compared considerably differed by some specific other aspects, which at least theoretically have different mechanisms of action.[17,19] For example, one trial compared ES of the wrist extensors with alternate ES of wrist flexors and extensors.[19] Extensor stimulation is thought to exert its action by recurrent inhibition at spinal level and by increasing extensor muscle strength, resulting in more power to overcome flexor spasticity. Flexor stimulation on the other hand, is described to work by reciprocal inhibition and causing fatigue of the spastic flexor muscles. The theoretical differences in mechanism of action did not result in differences in outcome after 6 weeks of ES of extensors only versus alternate ES of flexors and extensors. Possibly the differential effects studied thus far counterbalance each other, resulting in the same net effect.
In all, the aforementioned emphasizes the importance of further research to elucidate the mechanism of action explaining the effect of ES. The intriguing question is whether cortical mechanisms do explain the effect of ES (in part), or not.

The present study does confirm that functional gain can be obtained in the chronic stage after stroke.[20] This is important, since the impaired arm function is associated with a low level of well-being[21] and improvement can decrease the burden of stroke. At group level the gain accomplished by ES is not clinically relevant, but for some individual subjects it is. The question is which subject factors determine whether or not a subject will benefit. At this stage there is hardly any evidence on this issue. Post-hoc subgroup-analyses suggest that less impaired subjects will benefit more from ES.[2] In the present study however, the subjects in the EMG-stim group were on average less affected but they did not improve more (Table 2). It remains to be solved whether or not the severity of stroke affects the effect of ES.

In conclusion, the present study did not detect a significant difference between volitionally triggered ES and cyclic ES. Future research should further elucidate the mechanism of action of ES and define optimal subject characteristics, in order to optimize the treatment.

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6

Evaluation of central changes in cyclic and EMG-triggered stimulation of the upper extremity in chronic stroke

JR de Kroon
MJ IJzerman

Submitted for publication

Abstract

Background: Central mechanisms are thought to play a role in the mechanism of action of electrical stimulation (ES) to improve upper extremity function in stroke. The aim of the present trial was to evaluate if ES of the affected upper extremity in stroke evokes central changes as assessed by motor activation parameters, and whether there is a difference in change of these parameters between cyclic and EMG-triggered stimulation.

Methods: Twenty-two subjects were randomly assigned to either cyclic or EMG-triggered ES of the wrist and finger extensor muscles. In both groups stimulation was applied at home for a 6-week period, 3 times 30 minutes per day. Clinical outcome was assessed with the Fugl Meyer Motor Assessment and the Action Research Arm test. EMG measurements were performed to evaluate changes in motor activation parameters. Delay in initiation, delay in termination and co-contraction between extensor carpi radialis and flexor carpi radialis were determined for isometric voluntary wrist extension and flexion. Assessments were made at the start of the treatment and after 4 and 6 weeks.

Results: Cyclic as well as EMG-triggered stimulation resulted in improvement on the clinical outcome measures. Neither of the methods of stimulation resulted in a significant change for any of the motor activation parameters, and there was no difference between cyclic and EMG-triggered ES with respect to the EMG-parameters.

Conclusion: The present study did not detect evidence for cyclic or EMG-triggered ES to provoke central changes as assessed with motor activation parameters.

Introduction

Electrical stimulation (ES) is one of the therapies applied to the affected arm in subjects with stroke. There is growing evidence that ES in general has a positive effect on motor impairment of the affected arm.[1,2] However, ES can be applied in a wide variety of ways, and there are still many questions with regard to optimal method of stimulation[3] and the underlying mechanism of action. Most likely the mechanism of action of ES is multi-factorial, with peripheral and central factors contributing to the effect.

Peripheral factors accounting for local reconditioning are well established. The repetitive muscle contractions and movements evoked by ES are claimed to result in reduction of edema[4] and improvement of peripheral blood circulation[5] and range of motion.[6,7] In addition, ES does result in improvement of muscle strength,[8-11] significant gain is already reported after training periods as short as 2 weeks.[8,9] This cannot be explained by local muscle hypertrophy, since a 2-week period is too short for significant muscle hypertrophy to occur.[12,13] Central neural mechanisms such as increasing number of motor units activated and synchronization of activation are thought to be responsible for an early gain in strength.[12] In addition, ES may facilitate motor relearning, which is thought to result from central mechanisms as well.[1,14]

Studies in healthy subjects support the existence of a central effect of ES,[15,16] by demonstrating activation of the sensorimotor cortex,[15] and changes in the excitability of the cortical projection to hand muscles[16] by peripheral stimulation. And recently, an intensive ES treatment period in chronic stroke was reported to result in significant cortical changes as assessed by fMRI,[10] indicating a cortical component to ES in subjects with stroke. However, fMRI is a rather indirect measure of motor function and the findings of functional neuroimaging studies in motor recovery after stroke are equivocal.[17] Moreover, in addition to the cerebral cortex, the basal ganglia, thalamus and spinal cord play a role in motor function and recovery, and reorganization in these structures cannot be assessed by fMRI.[17]

Parameters like co-contraction[18,19] and delay in initiation and termination of muscle contraction[20,21] more directly reflect the final common pathway of central (i.e. cerebral and spinal) factors in motor activation, and are an alternative way to assess ES mediated central changes. ES has been reported to decrease co-contraction in chronic stroke,[22,23] supporting the existence of a central effect of ES in stroke. The extent to which ES provokes central changes might depend on the method of ES applied. Based on animal studies it can be hypothesized that EMG-triggered ES is more likely to result in central changes than cyclic ES because of the volitional component in EMG-triggered ES.[24,25] Exploration of this hypothesis is important in order to gain more insight in the mechanism of action of ES.

The aim of the present explorative trial is twofold. First, in order to extend previous trials, we evaluated if ES of the affected upper extremity in stroke evokes changes in central motor activation parameters. The second aim was to investigate whether there is a difference in change of these parameters between cyclic and EMG-triggered stimulation of the affected upper extremity in stroke.

Methods

Subject selection

Subjects were recruited from the outpatient clinics of a rehabilitation centre, the surrounding general hospitals and the patients' association. The local Ethics Committee approved the study protocol.

Subjects were included if they met the following inclusion criteria: 1. an interval of more than 6 months since unilateral supratentorial stroke (infarction or haemorrhage); 2. between 18 and 80 years of age; 3. impaired function of the upper extremity due to spastic paresis; spasticity was defined as a synergistic movement pattern or an Ashworth Score of 1 or more; paresis was defined as wrist extensor strength grade 4 or less (Medical Research Council); 4. voluntary extension of the wrist (at least 10° from resting position); 5. stable general health status; 6. written informed consent.

Subjects were excluded if they had: 1. a cardiac pacemaker (on demand); 2. an epileptic seizure less than 6 months before the start of stimulation; 3. metal implants in the affected arm; 4. pre-existent functional limitations of the affected upper extremity; 5. serious contractures of shoulder, elbow or wrist (clinical assessment); 6. severe cognitive impairments or severe aphasia resulting in inability to understand the trial; 7. skin problems underneath the electrodes; 8. inadequate motor response to test stimulus; 9. not enough voluntary muscle contraction of wrist extensors to trigger stimulation; 10. no tolerance for surface stimulation. Criteria 8, 9 and 10 were assessed during a single test session with both modes of stimulation before inclusion and randomization.

Baseline characteristics

At baseline the following data were collected: age, gender, diagnosis (infarction or haemorrhage), hemisphere of stroke, time since stroke, dominant arm pre-stroke, cognitive function (Mini Mental State Examination), neglect (letter-cancellation test[26]) and sensory function (alternating and simultaneous touching of both hands with eyes closed; thumb-finding test[27]). Neglect was defined as a difference of two or more between the affected and the unaffected side in the letter-cancellation test. Sensory disorders were considered to be present if a subjects' score deviated from normal on

one or both sensory function tests.

Application of electrical stimulation

All subjects received ES of the wrist and finger extensor muscles of the affected arm. They were randomized to either cyclic ES or EMG-triggered stimulation (EMG-stim) by means of a computer-generated randomization list.

The Automove AM800 (Danmeter a/s, Odense, Denmark) was used to apply ES in both groups. Surface electrodes were attached to the dorsal side of the forearm to evoke balanced extension of wrist and fingers. The position of the electrodes was marked with a permanent marker for the duration of the treatment, to guarantee the electrodes were placed consistently across stimulation sessions. The electrodes used could serve for stimulation as well as EMG detection. The Automove can provide stimulation in different modes; in this trial the cyclic- and the auto-mode were used. In the cyclic-mode the stimulation was applied automatically, without active involvement of the subject (cyclic ES). In the auto-mode stimulation was triggered by voluntary EMG activity of the subject, only if the threshold was reached (EMG-stim). Initially the threshold was 50 μV. Every time the subject successfully reached the threshold it automatically increased slightly, to a maximum of 2000 μV. If the threshold was not met, the apparatus decreased the threshold to a level closer to the EMG-activity the subject could produce. In either mode biphasic pulses with a frequency of 35 Hz and pulse duration of 300 μs were administered for 6 seconds with 1-s ramp-up, 1-s ramp-down and 9-s stimulus off. The setting of the aforementioned stimulation parameters and mode of stimulation was locked in order to avoid accidental changes. Amplitude was individually adjusted to obtain an optimal motor response without any side effects such as pain or skin-irritation.

The subjects received directions in the use of the Automove according to randomization. They applied the stimulation at home, and were instructed to exercise 3 times 30 minutes a day for a period of 6 weeks. Each subject started with a stimulation time of 15 minutes, which was gradually increased to 30 minutes per session during the first week. The therapist checked the application of the stimulation each week for the first 2 weeks, and subsequently every 2 weeks. The stimulus intensity was adjusted if necessary, and any adverse effects were recorded.

Outcome measures

A therapist who was blinded for the treatment allocation made three assessments: immediately before the start of the treatment (t0), after 4 weeks of treatment (t1) and the end of the 6-week treatment period (t2).

Clinical outcome measures: The arm section of the Fugl Meyer Motor Assessment

(FM, 0-66 points)[28] was applied for the assessment of motor impairment. The FM scale measures synergy patterns, voluntary movement and coordination of shoulder, elbow, wrist and hand. Reliability and validity have been confirmed.[29]
The Action Research Arm test (ARA, 0-57 points)[30] was used to assess manual dexterity of the affected arm. In the ARA, which consists of 19 items, the subject is asked to grasp, move and release objects of different size and shape and to perform 3 gross movements. Each item is scored on a 4-point scale, ranging from 0 (no part of the action can be performed) to 3 (the action is performed completely and within the time limits)[31]. The reliability of the ARA has been confirmed and it is able to detect clinically relevant improvement in chronic stroke.[31]
Laboratory assessment of motor activation parameters: EMG measurements were performed in order to determine the delay in initiation and termination as well as the co-contraction index of isometric voluntary muscle contraction according to the method described by Chae.[18,20] Conductive solid gel electrocardiogram electrodes with foam were used to record EMG activity (ARBO®, 4.2 * 2.4 cm, Tyco/Healthcare, Neustadt/Donau, Germany). Five electrodes were placed on the affected as well as the non-affected arm of the subject; two were placed over the extensor carpi radialis (ECR), two over the flexor carpi radialis (FCR) and one ground electrode over the olecranon. Each measurement started with the non-affected arm, so the subject could familiarize with the procedure. The arm was placed in an apparatus to stabilize the forearm, wrist and hand in neutral position for isometric contractions. The elbow was positioned in approximately 135 degrees flexion, and the shoulder in 30 degrees abduction. Subjects were instructed to contract the wrist extensor muscles as quickly and forcefully as possible against the apparatus as soon as they heard a beep, and to stop the contraction immediately as the beep stopped. Six extension trials were recorded, 3 trials with a 3-second beep and 3 with a 5-second beep conform the procedure described by Chae.[18,20] To prevent subject's anticipation to start and end of the beep, the beeps were presented in random order and started at a random delay between 1000 and 3500 milliseconds after the trigger button was pushed. The procedure was repeated for wrist flexion of the unaffected hand, and extension and flexion of the affected hand respectively. The complete assessment resulted in four sets (extension non-affected, flexion non-affected, extension affected and flexion affected) of six trials (three with a 3-sec beep and three with a 5-sec beep). Previous work did not reveal a difference between 3- and 5-sec trials,[18,20] indicating subject's anticipation was successfully prevented. In the present trial data presentation and analysis was limited to the 3-sec trials. EMG was measured with a Porti5-16/ASD EMG system (TMSi, Enschede, the Netherlands). The EMG signals were bipolarly amplified 20 times, analogue band-pass filtered from 5 to 500 Hz, sampled at 2048 Hz and 22-bit A/D converted.

Data analysis

Delay in initiation was defined as the time between the start of the beep and the start of the EMG-burst, delay in termination as the time interval between the end of the beep and the end of the EMG-burst (figure 1a). For determination of delays a custom made interactive software program was used, which performed an automatic and objective analysis of the EMG-bursts based on approximated generalized likelihood ratios.[32,33] The software provided a number of possible options for start and end of the EMG-burst, from which the researcher selected those options which visually matched the start and end of the EMG-burst best.

The same software was used to calculate the co-contraction index. For each contraction the root mean square (RMS) of the extensor and flexor muscle was calculated over the last 2 seconds of the beep to avoid the non-stationary effects at the start of the contraction. The co-contraction-index was defined as the ratio between the RMS of the antagonist and the RMS of the agonist (figure 1b).

For each experimental condition the mean value of the second and third 3-sec trial was calculated for each subject. The first 3-sec trial was considered to be a test and therefore excluded from the analysis. To summarize data, mean and standard deviation of the EMG-parameters were calculated for both treatment groups.

To analyze the within-group difference a paired sample t-test was applied if data were normally distributed, and the Wilcoxon signed rank test if not. For between-group analysis either the independent sample t-test or the Mann- Whitney U test was used. If necessary, a univariate analysis of variance was applied with the baseline value entered as co-variable to correct for inequality at baseline. All statistical analyses were performed with SPSS 11.5 for Windows; statistical significance was set at $p \leq 0.05$ for the clinical outcome measures. Because of the multiple tests for the EMG parameters the level of significance was adjusted to ≤ 0.01.

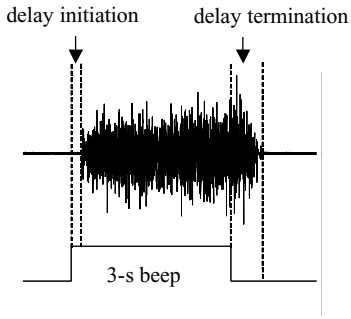

Figure 1a. Delay in initiation is the interval between start of the beep and start of the EMG signal. Delay in termination is the interval between end of beep and end of EMG signal.

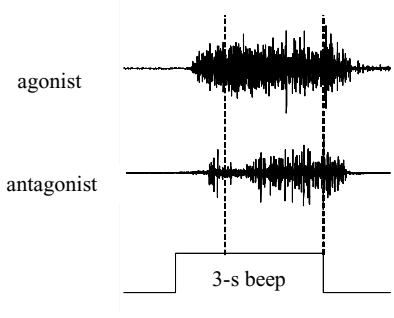

Figure 1b. Co-contraction index is RMS antagonist divided by RMS agonist. RMS is calculated over the 2-s window between the dashed lines.

Results

Twenty-two subjects were included and 21 fulfilled the complete protocol including follow-up. Subject characteristics are summarized in table 1.

Table 1. Baseline characteristics.

	Cyclic ES	EMG-triggered ES
N	10	11
Age in years*	60.6 (10.9)	57.4 (8.0)
Months post stroke†	16.5 (6-48)	27 (7-115)
Right hemiparesis (%)	3 (30)	3 (27.3)
Dominant arm affected (%)	3 (30)	6 (54.5)
Non-hemorrhagic stroke (%)	8 (80)	10 (90.9)
Male (%)	8 (80)	8 (72.7)
Mini Mental State Examination†	28 (22-30)	28.5 (23-29)
Neglect present (%)	0 (0)	3 (27.3)
Sensory disorder present (%)	4 (40)	6 (54.5)

*mean (sd)
†median (range)

Baseline assessments

In table 2 the scores on the motor activation parameters for the affected and the non-affected arm are presented. The scores for the affected arm show longer delay times, increased co-contraction index and decreased RMS-values. The difference between both arms was significant for co-contraction index and RMS ECR on both experimental conditions, for the other parameters only on flexion task. The reduction of agonist RMS in the affected arm is far more pronounced than the reduction of antagonist RMS. Apparently the increased co-activation index is predominantly an effect of decreased agonist activation.

Clinical outcome measures

The scores for the FM and ARA are presented in table 3. Both groups show improvement over time, which was nearly significant for the ARA in the EMG-stim group and significant for ARA in the cyclic groups and for the FM in both groups. The between group differences were not significant.

Table 2. Baseline values of the EMG-parameters for the affected and non-affected arm.

	Affected arm mean (sd)		Non-affected arm mean (sd)		Difference between both arms
Delay initiation					
wrist extension	0.300	(0.074)	0.275	(0.076)	p=0.281
wrist flexion	0.304	(0.085)	0.258	(0.048)	p=0.042
Delay termination					
wrist extension	1.012	(0.478)	0.913	(0.586)	p=0.558
wrist flexion	2.165	(1.381)	0.759	(0.450)	p=0.000
Co-contraction index					
wrist extension (FCR/ECR)	0.296	(0.190)	0.111	(0.051)	p=0.001
wrist flexion (ECR/FCR)	0.268	(0.193)	0.147	(0.066)	p=0.013
RMS ECR					
wrist extension (agonist)	60.810	(24.892)	273.866	(125.457)	p=0.000
wrist flexion (antagonist)	20.675	(14.940)	53.647	(34.037)	p=0.000
RMS FCR					
wrist extension (antagonist)	19.547	(16.546)	24.106	(9.522)	p=0.302
wrist flexion (agonist)	99.389	(68.990)	358.887	(191.490)	p=0.000

ECR: extensor carpi radials; FCR: flexor carpi radials

Table 3. Means and standard deviations of the clinical assessments and p-values for within and between group analyses for the change between t0-t2.

	t0 0 wks	t1 4 wks	t2 6 wks	change t0-t2	within group*	between group^
ARA 0-57, 0 = no arm function						
cyclic ES	14.8 (10.3)	15.7 (11.5)	17.1 (11.4)	2.3 (2.9)	p=0.034	p=0.492
EMG-stim	22.8 (11.8)	26.4 (13.5)	27.0 (13.2)	4.2 (6.7)	p=0.066	
FM 0-66, 0 = no voluntary movement						
cyclic ES	29.0 (10.6)	34.2 (11.9)	35.2 (11.8)	6.2 (5.8)	p=0.008	p=0.654
EMG-stim	38.4 (7.7)	40.6 (6.5)	41.9 (6.7)	3.5 (5.2)	p=0.048	

ARA: Action Research Arm test; FM: Fugl Meyer Motor Assessment
* paired sample t-test
^ univariate analysis of variance

EMG-parameters

Table 4 and figure 2 show the mean and standard deviation for the EMG-parameters at the assessments for both treatment groups. Differences between t0 and t2 are presented in table 4, as well as p-values for the within and between groups analysis. Inspection of the individual data revealed some very extreme values, which could not be explained by physiological variation or treatment effect. These extreme values were therefore excluded from further analysis.

Delay in initiation and termination: Compared to delay in initiation, delay in termination was much longer for both groups and the large standard deviations indicate more variety between subjects. Within-group analysis did not reveal any significant changes in delay in initiation and delay in termination in the two groups, nor for wrist extension, neither for wrist flexion. There were no significant differences between both methods of stimulation either.

Co-contraction index: Also for the co-contraction index there were no significant within or between-group differences.

RMS: In the EMG-stim group the RMS-values show a trend to increase over time, not only for the extension task, but also for flexion. The within and between group differences were not significant.

Table 4. Means and standard deviations of the EMG-parameters at t0, t1 and t2 and the change between t0-t2.

	t0 0 wks	t1 4 wks	t2 6 wks	change t0-t2	within group	between group
Delay initiation						
wrist extension cyclic ES n=9	0.304 (0.077)	0.312 (0.045)	0.337 (0.097)	0.034 (0.122)	p=0.429*	p=0.576*
wrist extension EMG-stim n=11	0.288 (0.073)	0.254 (0.087)	0.296 (0.104)	0.009 (0.075)	p=0.714*	
wrist flexion cyclic ES n=9	0.340 (0.040)	0.353 (0.133)	0.339 (0.085)	-0.001 (0.102)	p=0.980*	p=0.330#
wrist flexion EMG-stim n=11	0.252 (0.051)	0.244 (0.061)	0.289 (0.095)	0.037 (0.106)	p=0.280*	
Delay termination						
wrist extension cyclic ES n=10	1.111 (0.481)	1.173 (0.733)	1.227 (0.509)	0.116 (0.448)	p=0.435*	p=0.667*
wrist extension EMG-stim n=10	0.913 (0.478)	1.134 (0.713)	0.944 (0.558)	0.031 (0.415)	p=0.817*	
wrist flexion cyclic ES n=10	2.414 (1.545)	1.516 (1.260)	1.827 (1.142)	-0.587 (2.172)	p=0.415*	p=0.520#
wrist flexion EMG-stim n=10	1.658 (0.874)	1.510 (0.879)	1.643 (0.887)	-0.016 (1.275)	p=0.969*	
Co-contraction index						
wrist extension cyclic ES n=9	0.309 (0.218)	0.355 (0.217)	0.322 (0.220)	0.013 (0.236)	p=0.859^	p=0.808*
wrist extension EMG-stim n=10	0.283 (0.172)	0.290 (0.232)	0.275 (0.170)	-0.008 (0.134)	p=0.799^	
wrist flexion cyclic ES n=9	0.210 (0.098)	0.251 (0.153)	0.220 (0.105)	0.010 (0.092)	p=0.953^	p=0.914#
wrist flexion EMG-stim n=11	0.316 (0.240)	0.333 (0.200)	0.246 (0.181)	-0.069 (0.241)	p=0.477^	
RMS extensor carpi radialis						
wrist extension cyclic ES n=10	61.60 (28.19)	57.53 (24.30)	71.64 (33.56)	10.04 (31.25)	p=0.336*	p=0.456*
wrist extension EMG-stim n=10	60.02 (22.63)	83.45 (35.95)	84.20 (35.73)	24.18 (49.66)	p=0.158*	
wrist flexion cyclic ES n=10	20.25 (19.04)	21.33 (17.12)	18.01 (10.02)	-2.24 (10.73)	p=0.799^	p=0.247^
wrist flexion EMG-stim n=10	21.10 (10.41)	33.29 (23.03)	26.80 (17.71)	5.70 (13.47)	p=0.139^	
RMS flexor carpi radialis						
wrist extension cyclic ES n=9	15.93 (15.77)	17.47 (12.88)	16.95 (7.04)	1.02 (11.01)	p=0.260^	p=0.370^
wrist extension EMG-stim n=11	22.50 (17.32)	27.24 (19.31)	29.94 (22.91)	7.43 (10.54)	p=0.050^	
wrist flexion cyclic ES n=10	90.63 (81.58)	102.35 (83.35)	88.97 (64.47)	-1.66 (29.15)	p=0.959^	p=0.324#
wrist flexion EMG-stim n=10	112.93 (58.12)	112.10 (61.79)	123.84 (71.10)	10.91 (43.76)	p=0.386^	

* parametric test; ^ non-parametric test; # univariate analysis of variance.

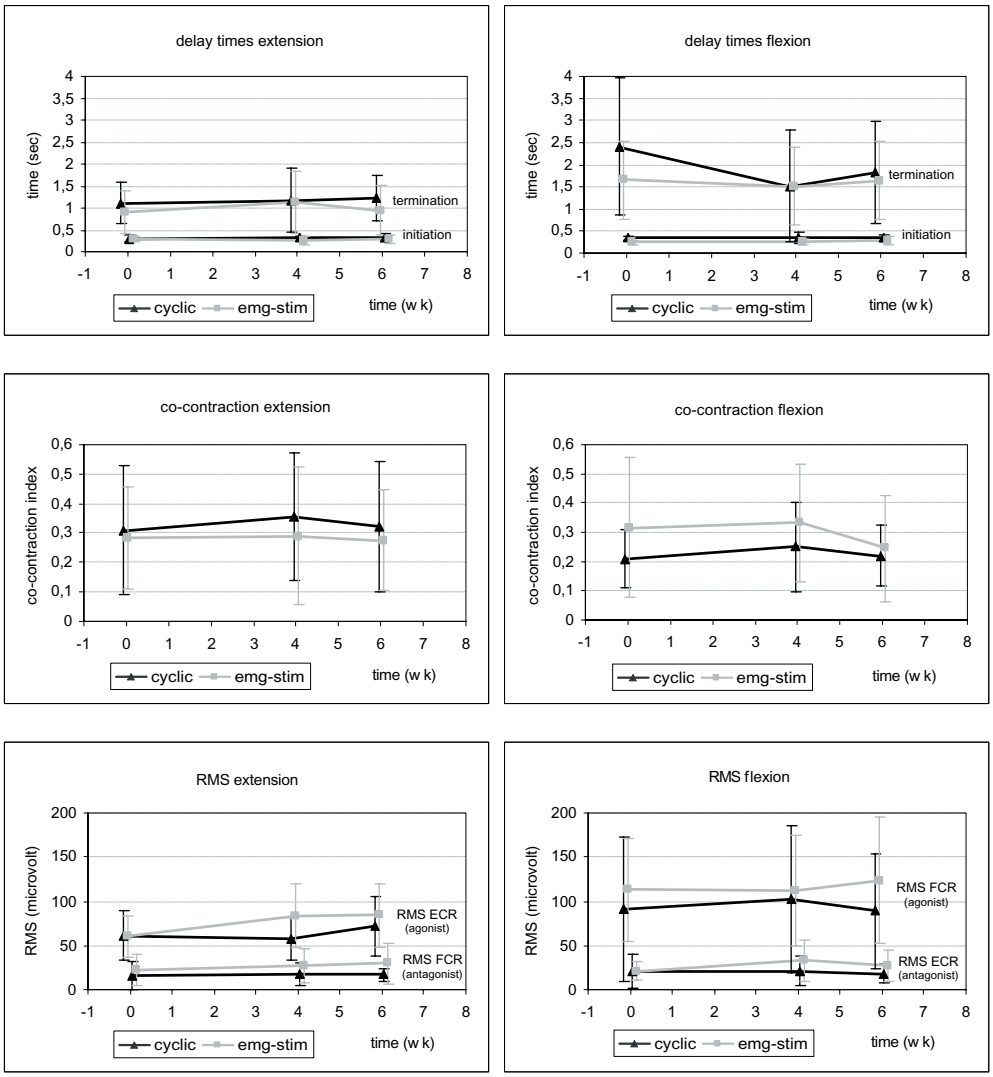

Figure 2. Mean and standard deviation for the five EMG parameters at week 0 (t0), week 4 (t1) and week 6 (t2). Delay times, co-contraction index and RMS values for the extension task are on the left, for the flexion task on the right.

Discussion

The present trial explored whether a 6-week period of either cyclic or EMG-triggered stimulation could provoke changes in central motor activation parameters. Although the clinical outcome measures did show functional improvement in both stimulation groups, neither of the stimulation methods resulted in changes in the EMG-parameters.
Beforehand the expectation was that if ES evoked changes in the central motor activation parameters, these would be more pronounced in the EMG-stim group. However, the results of this study did not reveal any difference between both methods of stimulation with respect to central changes. The expectation was based on a literature review[3] and animal studies[24,25] which revealed that repetitive movement training in which the animal was cognitively involved (like in EMG-stim) did result in long-term plasticity of motor maps of the cortex,[24] whereas automatic repetitive movements (like in cyclic ES) did not.[25] The exercises reported to result in cortical changes were aimed at the development of new motor skills such as retrieving food pellets from a rotating table.[24] In EMG-triggered ES, cognitive effort is required to provide the initial EMG-signal. But once the threshold is reached no further active involvement is needed. The increasing threshold with increased voluntary EMG provides a training aspect, but EMG-triggered ES does not involve skill training. Therefore, the contrast in the present study was not as large as the contrast between the animal studies. This may be an explanation for the lack of difference in change of motor activation parameters between both stimulation groups. More than that, the motor activation parameters did not change at all. At least 2 arguments can be posed to explain these findings: 1. the parameters applied are not responsive enough to detect changes evoked by ES; 2. ES does not evoke changes in the central motor activation parameters.

First, the EMG-parameters applied were modified after Chae.[18,20] Our baseline assessment confirmed the findings of Chae: in the affected arm the delays were longer and co-contraction increased as compared to the non-affected arm. However, the differences in our population were not as large as in Chae's, especially with respect to delay times.[18,20] We believe this to result from a difference in study population with regard to FM scores with a mean of 43 (sd 17, range 4-65) in the Chae study and a mean of 33.9 (sd 10.0, range 10-50) in the present study. The more severely affected subjects in Chae's study had long delay times in particular.
The method used to assess the motor activation parameters was an automatic burst detection algorithm, as applied in gait analysis.[33] The analysis of delay in initiation was very straightforward, with the start of the burst being very distinct. Unlike in gait however, the end of the burst was far less clear, especially in the affected arm. The

bursts inclined to end stepwise or, in extreme cases, fade out rather than end. Therefore, analysis of delay in termination often provided several possible end times from which the researcher had to select the one which visually matched the end of the burst best, based on preset criteria. In our opinion, not only the increased delay in termination but also the jolting termination of a voluntary contraction is an example of impaired motor control as a consequence of stroke. Therefore we expect the latter phenomenon to have been present in previous studies as well,[20,21] although it has not been documented before.
The large standard deviations at the assessments indicate large between-subject variations, especially for delay of termination, the co-contraction index and RMS-values. Moreover, the large standard deviations of the difference in score between the assessments indicate a large variation in change during treatment. Whereas in some subjects delay times and/or the co-contraction index actually do decrease, the scores increase in others. Therefore there are no significant changes at group level. Other sources of variation in the t0-t2 difference may be physiological day-to-day variation, inaccuracy of the method or a combination of both. Most likely the physiological day-to-day variation is the principal component of variation, but it would be a research project itself to determine the cause of the variation exactly, which is beyond the scope of the present article. However, given this variation, changes due to treatment can only be detected if they are really substantial, which was not the case in the present study.

Second, the present results may also indicate that cyclic ES and EMG-stim do not evoke changes in the central motor activation patterns. This would be in contrast with previous studies,[22,23] who reported a significant[23] or nearly significant[22] decrease in co-activation after a period of ES. Clinical outcome measures were not assessed in these studies, so it is not known if the changes in co-activation were associated with clinical improvement. In contrast to our study, these two publications reported results of ES of flexors and extensors and co-activation was assessed during movement and defined in a different way. This variety in definitions and methods to assess co-activation may underlie the difference in conclusions.
Change in delay of termination during ES has not been assessed before, but Cauraugh[8] did assess change in delay of initiation, defined as total reaction time, pre-motor time and motor time.[8] EMG-triggered ES of the affected hand did not change the reaction times, like in our study. In all, it remains to be solved whether or not ES evokes changes in motor activation parameters such as delay times and co-contraction.

Looking at motor activation parameters in a broader context than exploration of changes after a period of ES reveals that no longitudinal studies on these parameters have been

published for the upper extremity. It is not known whether or not the motor activation parameters improve with motor recovery of the arm after stroke. However, other therapies than ES do result in changes of motor activation parameters.[34,35] Robot therapy is reported to improve muscle activation patterns in chronic stroke.[35] And movement training out of the constraining pattern reduced abnormal co-activation significantly.[34] It appears that particularly the studies determining motor activation parameters during movement report improvement of the parameters after treatment.[22,23,34] We therefore suggest that especially dynamic assessment of motor activation parameters might be an important tool in further unravelling the mechanisms behind functional recovery. The first step should be to determine the relation between changes in motor activation patterns and functional recovery.

In conclusion, the present study did not find evidence for ES to evoke central changes as assessed with motor activation parameters. However, both cyclic and EMG-triggered ES resulted in improvement of clinical outcome measures. The mechanism behind this improvement is not yet clear and more research is advocated to further explore the mechanism of action of electrical stimulation.

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7

General discussion

General discussion

The research described in this thesis was performed to progress towards evidence based application of electrical stimulation (ES) to improve upper extremity function after stroke. The findings will be discussed here, together with some specific issues with respect to ES treatment and implications for daily clinical practice and further research.

What is the evidence for ES?

Thus far a great many trials have been studying the effect of ES on upper extremity motor recovery after stroke and most authors conclude positive with respect to the effect of ES. In the majority of studies more than one outcome measure was applied. It seems that if some outcome measures resulted in a positive outcome and some not, the positive results tend to be emphasized to reach a positive conclusion, which is thereby biased.

Systematic reviews of literature are performed to summarize the results of individual trials and reach an overall conclusion. The explicit methods used in systematic reviews are considered to limit bias and increase accuracy of conclusions.[1] In recent years, several systematic reviews investigating the effect of ES on arm motor function after stroke were published.[2-6] In the 2 systematic reviews described in chapter 2 and 3 of this thesis,[3,4] we focused on the outcome measure we considered most relevant for motor impairment. In respectively 4 out of 6 RCTs[3] and 13 out of 22 subject groups[4] the effect of ES was positive, leaving about 1/3 of the studies without a positive effect. The latter review was not primarily aimed at the effectiveness of ES and no overall conclusion with respect to the effect of ES was presented. The review of RCTs concluded that the available RCTs suggest a positive effect of ES on motor impairment.[3] A pooled analysis was not performed because of heterogeneity with regard to patient characteristics and method of stimulation. Barreca[2] however did perform a meta-analysis in which EMG-triggered ES (1 RCT and 2 cohort studies) and cyclic neuromuscular stimulation (2 RCTs) were analyzed separately. For both methods of stimulation a significant treatment effect in favor of ES over the control group was found (level I evidence according to the criteria of Sackett[7]). Another meta-analysis[6] of 5 studies with EMG-triggered stimulation revealed a significant overall mean effect size of 0.82.

The conclusions of a third meta-analysis were less positive.[5] Van Peppen reached conclusions by either pooling or applying the best evidence hypothesis if pooling was not possible. The best evidence hypothesis consists of 5 levels of evidence based on number and methodological quality of the studies: strong evidence, moderate evidence,

limited evidence, indicative findings and no or insufficient evidence.[8] For neuromuscular stimulation (cyclic ES) the best evidence hypothesis showed limited evidence for muscle strength (2 RCTs) and dexterity (1 RCT). With respect to EMG-triggered ES, pooling showed a non-significant homogeneous summary effect size for synergism (2 RCTs) and best evidence hypothesis yielded insufficient evidence for muscle strength (1 RCT and 1 controlled trial) and dexterity (2 RCTs).
It appears that even though systematic reviews and meta-analyses are performed on a systematic and explicit way based on objective criteria, this does not necessarily mean that the same conclusions are reached. Thus, there is not yet an unambiguous answer to the question "what is the evidence for ES?".

There are several reasons for the ambiguity, the common denominator being heterogeneity. The criteria for systematic reviews may be explicit, but they were not the same in the aforementioned reviews. Due to dissimilarity in search strategy the reviews did not include the same publications. The number of studies in each pooled analysis or best evidence hypothesis was very small, ranging from only one (item dexterity)[5] to five.[6] In addition, in one review studies with different outcome measures were pooled together,[2] whereas they were reviewed separately in another.[5] And different methods were applied in the quantitative analysis, i.e. the Z-statistic[2,9] or pooling individual effect sizes (Hedges' g) into a weighted summary effect size.[5,10] These dissimilarities probably all contributed to the variety in conclusions, ranging from a significant treatment effect[2,6] and limited evidence[5] to insufficient evidence and a non-significant effect.[5] It appears that the review using the most stringent criteria yielded the most reserved conclusion.[5]

There is also marked heterogeneity between and within the individual studies investigating the effect of ES (chapter 2 and 3).[3,4] Between studies there is a variety in acuity, outcome measures and methods of stimulation applied. Within study heterogeneity with respect to stroke type and severity may attenuate the effect and together with the small numbers of subjects included it decreases statistical power to reveal significant effects.

Subject population
Heterogeneity of the subject population may reduce treatment effect. However, little is known about the relation between subject characteristics and effect obtained from ES treatment. The (possible) impact of three characteristics will be discussed here.
Stage after stroke: Motor recovery after stroke is most prominent is the first weeks after stroke,[11,12] and rehabilitation may then accelerate functional recovery.[12] An early start

of treatment is therefore advocated.[13] This does not necessarily imply that therapy in chronic stroke is not effective. The review described in chapter 3 of this thesis did not detect a relation between effect of ES and acuity; positive results were reported for acute, sub-acute and chronic subjects.[4] ES may be more effective in acute subjects, but since the study outcomes were dichotomized it was not possible to draw conclusions on this aspect of ES treatment.
Severity: Subgroup-analyses suggest that less severely affected subjects might benefit more from ES with respect to motor recovery.[14-16] For example, ES resulted in significant gain in dexterity only in subjects with residual wrist extensor strength.[15]
Lesion location: The site of the lesion might play a role in predicting the effect of ES.[17] Subjects with cortical lesions were less prone to benefit from ES as compared to those with an intact cortex, but especially the absence of lesions in the periventricular white matter increased the possibility for improved motor capacity after stimulation.[17] However, these findings might be biased since the MRI data to localize the lesions were obtained three years after the ES trial in only 14 out of the 44 subjects initially randomized; subjects with recurrent stroke were excluded. Therefore these findings should be tested in a larger prospective study.

Based on the sub-group analyses described above, inclusion in the trials described in this thesis was limited to subjects with voluntary wrist extension (chapter 4, 5 and 6).[18-20] Nevertheless heterogeneous subject populations were included, with a mean ARA score of 28.8 (sd 13.9; range 8-52) for all subjects in chapter 4 and 19.0 (sd 11.6; range 4-37) for chapter 5 and 6. The treatment effect was heterogeneous as well. In the trial described in chapter 5, overall mean improvement was 3.3 points on the ARA. Two subjects deteriorated, four remained stable and 15 improved on the ARA. Of those subjects improving (range 1-17 points), the improvement was considered to be clinically relevant in six. In our studies the patient numbers were regarded to be too small to perform reliable subgroup-analyses. However, it is important to know the characteristics of the subjects improving in order to distinguish responders from non-responders and be able to focus the treatment on those who are most likely to benefit in a clinically relevant way. Future studies should explore this issue.

Measuring arm function
In all publications describing results of a trial on ES, the conclusions are based on statistical significance. This is obvious, since only statistically significant results count as scientific evidence for effect. However, the clinical relevance of the improvements gained usually remains underexposed and not much is known about the minimal clinically relevant

difference of the outcome measures commonly applied in stroke rehabilitation research. A literature search in PubMED with the terms Action Research Arm Test AND clinically relevant difference yielded only 3 publications. One was the explanatory trial described in chapter 4, in which we determined the percentage of subjects with clinically relevant gain on the ARA.[18] The other 2 were publications by van der Lee[21,22] from which we adopted the definition of 10% of the total score, i.e. 5.7 points for the ARA, to be clinically relevant. The question is whether 10% is relevant indeed. The impact of a 10% gain on the way subjects perform their daily activities is not known. More over, with a maximum score of 57, an improvement from 10 to 16 points is bound to have other consequences than from 30 to 36. However, the 10%-rule seems a good starting point, the more so because 5.7 points on the ARA has been demonstrated to be more than the measurement error.[22] Since most therapeutic strategies aim for improvement of motor function it seems peculiar that not more attention is being paid to the clinical relevance of improvements gained.

The Action Research Arm test was the primary outcome measure in our clinical trials (chapter 4 and 5). The ARA is a performance test with good clinimetric properties.[22] The ARA is classified as a test measuring changes in arm function[23] and to assess specific arm abilities (i.e. focal disability).[24] However, of the 19 test items in the ARA, only the item in which the subject has to pour water from one glass to another is a functional activity indeed. The other items are merely laboratory tasks.
Adding a test like the Arm Motor Ability Test[25] might be useful. In this test the subject actually performs 17 tasks like cutting meat, using the telephone and putting on a sweater; unilateral tasks have to be performed with the affected arm. The tasks are rated on 2 domains, i.e. functional ability and quality of use. But also the AMAT does not provide information about how subjects actually perform their functional activities at home.

Mechanisms behind the effect of ES

A placebo-controlled trial is required to assess the specific effect of an intervention, but true placebo ES is difficult to achieve (chapter 2). However, it seems unlikely that there is a specific effect to the current applied in ES. The review described in chapter 3 did not detect a relation between the specific setting of stimulation parameters and reported effect.[4] Although the setting of parameters does make a difference with respect to reaction evoked by ES in basic neurophysiological research, there were no indications that different neurophysiological reactions were associated with differences in clinical outcome. The common end point in all studies was muscle contraction, despite

differences in parameter setting. And therefore muscle contraction seems to be crucial in the effect of ES rather than stimulus parameters.[4]
The same review did conclude that voluntary triggered ES, like EMG-triggered stimulation, may be more effective in facilitating arm motor recovery than ES applied automatically without effort of the subject, such as cyclic ES (chapter 3).[4] This hypothesis could not be confirmed in a direct comparison of EMG-triggered and cyclic ES, which did not reveal a difference in clinical outcome (chapter 5).[19] Another trial comparing the effect of ES of the wrist extensor muscles with alternate stimulation of wrist extensors and flexors did not detect a significant difference either (chapter 4).[18] As yet there is no evidence that one method of ES is better than another, regardless of theoretical differences between them (chapter 4 and 5). This strengthens the view that a specific effect is unlikely. ES may be merely an aid to perform repetitive movement training.

Brain plasticity is one of the mechanisms contributing to functional recovery and therapy may enhance neuroplasticity.[12] It is posed that the effect of ES on motor recovery is also explained by cortical neuroplasticity, induced by the afferent input associated with repetitive movements.[26-28] There is evolving evidence that ES evokes cortical changes indeed, not only in healthy subjects, but also in subjects suffering from stroke.[29] ES was reported to result in functional improvement associated with significant increase in cortical intensity in the somatosensory cortex, but not in the motor cortex as assessed with functional magnetic resonance imaging (fMRI). This underlines that the relation between neuroplasticity, fMRI changes and functional recovery is equivocal and not yet fully understood.[30,31]
In addition to plasticity behavioral compensation is thought to play a role in functional recovery.[12] For example, locking the elbow in a synergistic pattern enables the subject to compensate for the paretic elbow muscles. It has also been reported that ES can reduce co-contraction around the elbow.[32,33] In light of the aforementioned the question is whether this will result in functional gain. Dynamic EMG might be a valuable tool for further exploration of this issue, in combination with kinematics and functional outcome measures.

Towards more effective ES treatment

Based on current knowledge about motor relearning and recovery after stroke, training should comprise the following key elements: repetitive, intensive, attention demanding, task-oriented, and feedback.[12,34-36]
ES includes the repetitive element by evoking repetitive muscle contractions. And especially when subjects are instructed for home-based training, ES can be applied

at high intensity. Additionally, EMG-triggered stimulation requires active involvement of the subject (attention demanding) and offers feedback, i.e. stimulation, if the voluntary EMG-activity reaches the threshold value. However, the active involvement is only required to trigger the stimulation; once the threshold is reached and stimulation evoked no further cognitive effort is necessary until the next muscle contraction is called for. ES treatment may be more effective if more attention is asked from the subject. For example, considerably more cognitive effort is necessary if voluntary EMG is not only used to trigger stimulation, but also to control stimulation duration or amplitude proportionally to the EMG-signal.[28,37]

ES is predominantly applied to the wrist and finger extensor muscles, to evoke repetitive wrist extension (chapter 3). Obviously this cannot be considered task-oriented functional training. ES may be more effective if combined with functional training.[38] Functional electrical therapy was reported to result in more gain as compared to training of the same daily activities without stimulation.[39] The authors speculate that a longer treatment period and stimulation of more proximal muscles in addition to wrist/finger extensors and flexors could make the affected arm useful for daily activities.[39]

There are also indications that the combination of two treatment paradigms is more effective.[36] For example, the combination of EMG-stim and simultaneous contralateral voluntary wrist extension improved motor functions more than just EMG-stim.[40] Interesting opportunities might be obtained by combining ES with strategies facilitating motor relearning by their action directly in the brain. For example, neuropharmalogical drugs such as amphetamine, levodopa or fluoxetine are reported to optimize activity-dependent relearning of skills after stroke,[34] although the results are ambiguous because the effect of medication can be modified by several factors, e.g. subject characteristics.[41] Also non-invasive cortical stimulation[42] may have a beneficial effect on arm motor recovery. And dual stimulation, i.e. peripheral stimulation combined with repetitive transcranial magnetic stimulation (TMS) has been reported to improve functional measures.[43]

Obviously the true merits of the strategies proposed to enhance the effect of ES need to be investigated thoroughly.

Implications for clinical practice and further research

At this stage it can be concluded that the scientific evidence for ES to improve motor function of the upper extremity in stroke is not complete. It is not known which method of ES is most effective, for which subjects and by which mechanism. These questions dilute the overall effectiveness and should be elucidated in order to obtain unambiguous evidence. In spite of the remaining questions, individual subjects do benefit from ES and

it seems justified to apply ES in clinical practice. Even more so because is it not ethical to hold back a treatment which might be beneficial, given the impact of impaired arm function on well-being, and the fact that ES is a safe treatment modality.
ES treatment aiming at motor recovery should be applied to subjects with residual wrist extension, and can be administered in the acute, sub-acute and chronic stage after stroke. Based on the theories about motor relearning, the clinician might be inclined to apply EMG-triggered stimulation, but there is no direct evidence yet that one method of ES is better than the other. Application of ES in rehabilitation treatment is in line with clinical guidelines.[44,45] ES should preferably be applied in clinical trials, so that the experience gained can be used to further enlarge the scientific basis of ES treatment.
Explanatory trials are recommended to complete the evidence. These trials should incorporate extrinsic clinical outcome measures to define the most effective ES modality and intrinsic measurements like functional Magnetic Resonance Imaging, Transcranial Magnetic Stimulation, Positron Emission Tomography and ElectroMyoGraphy to further elucidate the mechanism of arm function recovery by ES. Future studies should also explore patient characteristics to identify subjects who might benefit in a clinically relevant way and determine the effect of ES on activities of daily living. The ultimate goal is to decrease the burden of impaired arm function for those who suffer from stroke.

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8

Summary

Impaired arm function is a prominent consequence of stroke and has substantial impact on activities of daily living and quality of life. One of the therapies applied to improve upper extremity function is electrical stimulation (ES). Many positive effects of ES are reported, but there are questions about the scientific evidence. Moreover, there is a wide variety in stimulation paradigms and setting of stimulation parameters. It is not known if one strategy is better than the other and this is connected to indistinctness with respect to the specific mechanism of action of ES.
The aim of this thesis was to progress towards evidence based application of ES. In order to reach this goal it was necessary to evaluate the available evidence on the effectiveness of ES, to explore the relative value of the different methods of stimulation and parameter settings and gain more insight in the underlying mechanisms of action of ES.

The first step was to assess the available evidence on the effect of ES with respect to upper extremity recovery. The results of a systematic review of randomized clinical trials (RCT) that have studied the effect of ES on motor control and functional abilities are described in **chapter 2**. Six RCTs were identified by a systematic literature search. The methodological score of these RCTs ranged from 7 to 16 on a scale from 0 to 19. In the six trials, four different methods of ES were applied to subjects in the acute, sub-acute or chronic stage after stroke. Four out of the six trials reported a significant treatment effect for motor control. Because of the heterogeneity with respect to method of ES and subject characteristics a pooled analysis was not performed. There was no relation between the reported effect and subject characteristics, method of stimulation or methodological quality. In all, the findings of the systematic review suggest a positive effect of ES on motor control. No conclusions could be drawn with respect to functional abilities since these were only assessed in two trials; one reported a positive effect, the result of the other was indifferent.

The heterogeneity with respect to stimulation paradigms raised the question if there is a relation between the characteristics of the specific stimulation applied and the therapeutic benefit gained. This issue was investigated in a second systematic review which is described in **chapter 3**. Characteristics under study were method of stimulation, specific setting for stimulation frequency, amplitude and pulse duration, duration of ES treatment, stage after stroke and target muscles. For this review not only RCTs, but also controlled trials and case series were included. The literature search yielded

19 trials. Since in some trials 2 subject groups received a different method of ES, the results of 22 subject groups were evaluated. A positive effect of ES on motor control was reported in 13 out of the 22 subject groups. Eight out of the nine patient groups in which volitionally triggered stimulation was applied yielded a positive result (88.9%), whereas only four out of 12 groups using non-triggered stimulation yielded positive results (33.3%). The difference in treatment effect with respect to method of stimulation was significant (Chi-square test, p=0.024). Therefore volitionally triggered ES may be more effective than non-volitionally triggered ES in facilitating upper extremity motor recovery following stroke. There was no relation between the effect of ES and the other characteristics examined. The variety in setting of stimulation parameters between the studies was bound to have evoked different neurophysiological reactions, but these were not associated with differences in clinical outcome. Stimulation parameters may therefore not be crucial in determining the effect of ES.

One of the varieties in stimulation strategies concerns target muscles. Stimulation of wrist and finger extensor muscles and alternate stimulation of extensors and flexors of the hand are most commonly applied. Neurophysiological models provide arguments in favor of each strategy, but it is not known if both strategies are equally effective or that one is better than the other. Therefore an explanatory trial was designed to investigate whether there is a difference in motor recovery and functional improvement in the affected arm of chronic stroke patients when comparing ES of the extensor muscles of the hand with alternating stimulation of extensors and flexors (**chapter 4**). Thirty subjects were included and randomized over the two stimulation paradigms. ES was applied with the NESS Handmaster, three 60-minute sessions a day for a period of 6 weeks. The primary outcome measure was the Action Research Arm test (ARA) with a maximum score of 57. Grip strength, Motricity Index (MI), Ashworth Scale and active range of motion (ROM) were the secondary measures. Improvement on the ARA was 1.0 point (95% CI: -0.97 to 2.97) in the flexor/extensor group and 3.3 points (95% CI: 0.51 to 6.02) in the extensor only group. The success rate (i.e. percentage of patients with a clinically relevant improvement of > 5.7 points on the ARA) was 27% in the extensor group (4 patients) and 8% in the flexor/extensor group (1 patient). The between-group differences in functional gain and success rate were not statistically significant, neither were the differences between the two groups on the secondary outcome measures. At this stage there is no evidence that one of the two stimulation paradigms explored is better than the other.

The review described in chapter 3 concluded that volitionally triggered ES may be more effective than non-volitionally triggered ES. To test this hypothesis another explanatory

trial was designed to compare these two stimulation paradigms (**chapter 5**). Twenty-two chronic stroke patients were randomized over either EMG-triggered stimulation (= volitionally triggered ES) or cyclic ES (= non-volitionally triggered ES), 21 fulfilled the study protocol. Stimulation was applied with the Automove AM800, three 30-minute sessions a day for a period of 6 weeks. The Action research Arm test (ARA) was the primary outcome measure, secondary outcome measures were grip strength and the arm sections of the Motricity Index (MI) and the Fugl-Meyer Motor Assessment (FM). Cyclic as well as EMG-triggered ES resulted in an increase of the ARA-score after the treatment period of 2.3 (95% CI: 0.22 to 4.38) and 4.2 points (95% CI: -0.34 to 8.71) respectively. The difference in functional gain was not statistically significant. A clinically relevant difference of more than 5.7 points on the ARA was achieved by 2 out of 10 subjects in the cyclic group and 4 out of 11 in the EMG-triggered group. Grip strength, FM and MI showed improvement in both groups as well, the differences between the groups were not significant either. In this trial the findings of the review could not be confirmed, there is no direct evidence that volitionally triggered ES is more effective than non-volitionally triggered ES.

There are still many questions with regard to the mechanism of action underlying the effect of ES. Central mechanisms are thought to play a role. The trial described in **chapter 6** was designed to evaluate if ES of the affected upper extremity in stroke evokes central changes as assessed by motor activation parameters, and whether there is a difference in change of these parameters between cyclic and EMG-triggered stimulation. Twenty-two subjects with chronic stroke were randomly assigned to one of the two stimulation strategies. ES was applied to the wrist and finger extensor muscles, 3 times 30 minutes per day for a period of 6 weeks. Clinical outcome was assessed with the Fugl Meyer Motor Assessment and the Action Research Arm test. EMG measurements were performed to evaluate changes in motor activation parameters: delay in initiation, delay in termination and co-contraction between extensor carpi radialis and flexor carpi radialis were determined for isometric voluntary wrist extension and flexion. Baseline comparison between the affected and non-affected arm confirmed impairment of the affected arm on these parameters. After ES-treatment both groups improved on the clinical outcome measures. However, neither of the motor activation parameters did change significantly in any of the two stimulation groups and there was no difference between cyclic and EMG-triggered ES with respect to the EMG-parameters. Therefore the trial did not detect evidence for cyclic or EMG-triggered ES to provoke central changes as assessed with motor activation parameters.

In the general discussion in **chapter 7** the evidence for ES and implications for clinical

practice and further research are discussed. Since our review of RCTs (chapter 1) three more systematic reviews were published. These reviews reached different conclusions and this illustrates that there is not yet unambiguous evidence for the effect of ES. The reason for this equivocality is heterogeneity, not only with respect to criteria applied by the reviews but also between studies (method of ES and stage after stroke) and within studies (subjects characteristics such as severity and stroke type). At this stage it is not known which method of ES is most effective, for which subjects and by which mechanism of action. These issues need to be elucidated in order to obtain unambiguous evidence. In this context ES should be optimized according to the current knowledge about motor relearning and recovery after stroke. Explanatory trials are recommended to answer the specific questions with respect to most effective ES modality and the characteristics of subjects who might benefit in a clinically relevant way. These trials should incorporate extrinsic assessment of effect of ES on activities of daily living and intrinsic assessments such as functional Magnetic Resonance Imaging, Transcranial Magnetic Stimulation and ElectroMyoGraphy to further elucidate the mechanism of arm function recovery by ES.

Samenvatting

In Nederland worden elke dag 80 mensen getroffen door een beroerte. Een beroerte is ook wel bekend onder de term CVA (cerebrovasculair accident ofwel een ongeval met de bloedvaten in de hersenen). Een CVA kan veroorzaakt worden door een bloedpropje wat de bloedvoorziening van een deel van de hersenen verstopt (bij 80% van de CVA-patiënten), of een bloeding die de bloedvoorziening belemmert (bij 20%). Het meest zichtbare gevolg van een CVA is een halfzijdige verlamming, maar een CVA kan ook lijden tot spraakstoornissen, geheugenproblemen of karakterveranderingen. Gelukkig is er vaak sprake van natuurlijk herstel, vooral in de eerste 3 maanden na een CVA. Maar ondanks dat heeft na 3 maanden slechts 20% van de CVA-patiënten een volledig herstelde functie van de aangedane arm en hand. Dat betekent dat een grote meerderheid van de CVA-patiënten de aangedane arm beperkt of helemaal niet in kan schakelen. En velen ervaren dat als een groot probleem omdat het hen belemmert bij dagelijkse activiteiten zoals wassen, aankleden, eten en drinken, maar ook bij hobbies en werk. Juist die beperkte armhandfunctie heeft een negatieve invloed op het algemene gevoel van welbevinden. Therapie gericht op verdere verbetering van de armhandfunctie is dan ook van groot belang, en electrostimulatie (ES) is een van de behandelingen die in de dagelijkse praktijk kan worden toegepast.

Bij ES worden door plakkers op de arm kleine stroomstootjes toegediend waardoor de spieren van de arm samentrekken. In de literatuur worden vele positieve effecten van ES beschreven met betrekking tot de armhandfunctie na een CVA, maar het wetenschappelijke bewijs dat ES een positief effect heeft is nog beperkt. Studies die het effect van ES onderzoeken gebruiken verschillende manieren van ES, en de instelling van stimulatie parameters zoals frequentie, stroomsterkte en duur van de stroomstootjes is in elke studie anders. Het is niet bekend of de ene manier van stimuleren beter is dan de andere, en welke instelling van stimulatie parameters optimaal is; dat komt ook omdat het nog onduidelijk is hoe ES precies werkt. Om ES in de praktijk goed toe te kunnen passen is het wel van belang dat het effect wetenschappelijk aangetoond is, en dat bekend is welke manier van toediening het meeste effect heeft en hoe het werkt. Het onderzoek dat beschreven is in dit proefschrift is dan ook uitgevoerd om de wetenschappelijke basis van ES te evalueren, om de relatieve waarde van de verschillende ES methoden en parameterinstellingen te onderzoeken en om meer inzicht te krijgen in het werkingsmechanisme van ES met betrekking tot verbetering van de armhandfunctie na een CVA.

De eerste stap was een systematisch literatuur onderzoek van gerandomiseerde studies (randomised controlled trial; RCT). In een RCT worden de patiënten 'at random' ofwel door loting verdeeld (gerandomiseerd) over de onderzoeksgroepen, en een RCT geldt als de meest zuivere manier om het effect van een behandeling te onderzoeken. De resultaten van het literatuuronderzoek staan beschreven in **hoofdstuk 2**. In totaal werden 6 RCTs gevonden waarin het effect van ES op de aangedane arm na een CVA onderzocht werd. De methodologische kwaliteit van de studies werd bepaald aan de hand van vooraf opgestelde criteria, en varieerde van 7 tot 16 op een schaal van 0 tot maximaal 19. Alle 6 RCTs bepaalden het effect van ES op de willekeurige motoriek van de aangedane arm en 4 van de 6 rapporteerden een positief effect. Slechts 2 studies evalueerden het effect op functionele vaardigheden van de arm; 1 rapporteerde een positief effect. De bevindingen van dit literatuuronderzoek suggereren een positief effect van ES op de willekeurige motoriek van de aangedane arm na een CVA. Hardere uitspraken kunnen gedaan worden door de effecten van verschillende RCTs bij elkaar op te tellen en te middelen. Dat is bij dit onderzoek niet gedaan in verband met verschillen tussen de RCTs (heterogeniteit) met betrekking tot patiëntkenmerken en stimulatiemethode.

De heterogeniteit van de studies roept de vraag op of er een relatie is tussen de manier waarop de stimulatie toegepast wordt en het effect dat behaald wordt. Deze vraag werd onderzocht in een tweede systematisch literatuuronderzoek (**hoofdstuk 3**). Factoren die bestudeerd werden waren de methode van stimuleren, de instelling van stimulatieparameters (frequentie, stroomsterkte en pulsduur), de totale behandelduur, het stadium na het CVA waarin de patiënten verkeerden (acuut is binnen 1 maand, subacuut is tussen 1 en 6 maanden en chronisch is meer dan 6 maanden na het CVA) en de spiergroepen die behandeld werden. Voor dit onderzoek werden 19 klinische studies geïncludeerd waarin het effect van ES op de motoriek onderzocht werd. Omdat in een aantal studies 2 verschillende patiënt groepen elk een andere manier van ES toegediend kregen konden de resultaten van 22 patiënt groepen geëvalueerd worden. Een positief effect van ES op de motoriek werd gerapporteerd voor 13 van de 22 patiënt groepen. Vooral de stimulatiemethode waarbij de patiënt actief betrokken is resulteerde in een positief effect. Bij deze methode moet de patiënt eerst zelf de spieren aanspannen en pas als een drempelwaarde overschreden wordt volgt de stimulatie (actieve ES). Dit in tegenstelling tot de methode waarbij de stimulatie volgens een cyclisch programma wordt toegediend en de patiënt zelf in het geheel niet actief hoeft te zijn (cyclische ES). Bij 8 van de 9 patiënt groepen waarbij actieve ES werd toegediend werd een positief effect gerapporteerd (88.9%), terwijl slechts 4 van de 12 groepen met cyclische ES een positief effect behaalden (33.3%). Het verschil tussen beide manieren van stimuleren

was statistisch significant. Actieve ES lijkt dus effectiever in het verbeteren van de willekeurige motoriek dan cyclische ES, hoewel een echte conclusie pas getrokken kan worden na een directe vergelijking van beide methoden.
Er was geen enkele relatie tussen het effect van ES en de andere factoren die onderzocht werden. Het is bekend dat de verschillende instellingen van de stimulatieparameters verschillende reacties oproepen in de zenuwen, maar het verschil in neurofysiologische reacties had geen invloed op het effect van de stimulatie. Blijkbaar is de instelling van de stimulatieparameters niet van belang voor het effect van ES.

Een van de variaties tussen de verschillende manieren van stimuleren betreft de spiergroepen die gestimuleerd worden. ES van de strekspieren van de pols en afwisselende ES van de strek- en buigspieren worden het meest toegepast. Sommige neurofysiologische argumenten pleiten voor ES van de strekspieren, terwijl andere juist pleiten voor afwisselende ES van strek- en buigspieren. Omdat niet bekend is welke argumenten het zwaarst wegen is niet bekend of beide manieren even effectief zijn, of dat de ene beter is dan de andere. Daarom werd een exploratief onderzoek opgezet om het effect van beide methoden op de armhandfunctie van CVA-patiënten in de praktijk te vergelijken (**hoofdstuk 4**). Aan dit onderzoek deden 30 patiënten in het chronische stadium na een CVA mee. Zij werden door loting verdeeld over de 2 behandelgroepen; beide groepen pasten de stimulatie gedurende 6 weken 3 keer per dag 1 uur toe. Voor en na de behandelperiode werden metingen gedaan om het effect van ES in kaart te brengen. Het betrof de volgende metingen: de Action Research Arm test voor het meten van de handvaardigheid (ARA; maximum score is 57); het armdeel van de Motricity Index om de willekeurige motoriek te scoren (MI; maximum is 100); de knijpkracht uitgedrukt als ratio van de aangedane hand ten op zichte van de niet-aangedane hand; de Ashworth schaal voor het meten van de spierspanning en de maximale actieve bewegingsuitslag over de pols. De ARA was de primaire uitkomstmaat. Na 6 weken stimuleren was de groep die ES van de polsstrekkers toepaste gemiddeld 3.3 punten vooruitgegaan op de ARA, de groep met ES van de strekkers en buigers 1.0 punt. Het verschil tussen beide groepen op de ARA was niet statistisch significant, evenmin als het verschil op de andere meetinstrumenten. Vooraf werd bepaald dat een verbetering van 5.7 punten of meer op de ARA van klinisch belang is. Geen van beide stimulatiemethoden haalde op groepsniveau een klinisch relevante verbetering. In de groep met ES van de polsstrekkers gingen 4 patiënten meer dan 5.7 punten vooruit (succespercentage 27%), in de andere groep slechts 1 (succespercentage 8%). Het verschil in succespercentage was niet statistisch significant. Op dit moment is er dan ook geen bewijs dat een van de 2 onderzochte manieren van stimuleren beter is dan de andere.

Uit het literatuuronderzoek beschreven in hoofdstuk 3 volgde de veronderstelling dat actieve ES effectiever is dan cyclische ES. Deze hypothese werd getoetst in een exploratief onderzoek dat beschreven is in **hoofdstuk 5**. Aan dit onderzoek deden 22 chronische CVA-patiënten mee. Zij werden door loting verdeeld over actieve en cyclische stimulatie van de polsstrekkers. In beide groepen pasten de patiënten de ES gedurende 6 weken 3 keer per dag 30 minuten toe. Voor en na de behandeling werden metingen gedaan om het effect van de stimulatie te bepalen. De Action Research Arm test (ARA) werd afgenomen voor het meten van handvaardigheid, de armdelen van de Motricity Index (MI) en de Fugl Meyer Motor Assessment (FM) voor het scoren van de willekeurige motoriek en ook de knijpkracht werd gemeten. Ook nu was de ARA de primaire uitkomstmaat. Na 6 weken was er in beide groepen een verbetering op alle uitkomstmaten. Op de ARA ging de actieve groep 4.2 punten vooruit en de cyclische groep 2.3 punten. In de actieve groep was de verbetering bij 4 van de 11 mensen klinisch relevant (succespercentage 36%), zij gingen namelijk meer dan 5.7 punten vooruit. Het succespercentage in de cyclische groep was 20% omdat 2 van de 10 mensen een klinisch relevante vooruitgang boekten. Het verschil tussen beide groepen wat betreft verbetering op de ARA en succespercentage was niet statistisch significant. Ook voor de andere uitkomstmaten was er geen significant verschil tussen beide groepen. Deze studie kon dus de hypothese dat actieve ES effectiever zou zijn dan cyclische ES niet bevestigen.

Veranderingen op hersenniveau lijken een rol te spelen bij het werkingsmechanisme van ES, deze veranderingen worden ook wel omschreven als centrale veranderingen of hersenplasticiteit. In het onderzoek beschreven in **hoofdstuk 6** werd bekeken of ES leidde tot centrale veranderingen gemeten met spier aansturingsparameters, en of er een verschil was in de mate van centrale veranderingen tussen actieve en cyclische ES. De spier aansturingsparameters zijn parameters die iets zeggen over de manier waarop spieren aangestuurd worden door de hersenen. Het gaat om parameters zoals de snelheid waarmee spieractiviteit start of stopt als reactie op een signaal van buiten, en de mate waarin spieren selectief aangespannen kunnen worden. Bij CVA-patiënten zijn de reacties vaak vertraagd en is er sprake van toegenomen co-contractie, dwz dat spieren minder goed afzonderlijk aangespannen kunnen worden. De spier aansturingsparameters kunnen worden gemeten met electromyografie (EMG).
Voor dit onderzoek werden 22 patiënten in het chronische stadium na een CVA door loting verdeeld over actieve en cyclische ES van de polsstrekkers. Beide groepen pasten de stimulatie 3 keer daags 30 minuten toe gedurende 6 weken. Behalve de spier aansturingsparameters werden ook klinische uitkomstmaten gemeten om het effect van ES te bepalen (Action Research Arm test en Fugl Meyer Motor Assessment).

Na de behandelperiode waren beide groepen vooruit gegaan op de ARA en de FM. Maar de spier aansturingsparameters waren in geen van beide groepen significant veranderd en er was geen verschil tussen actieve en cyclische ES met betrekking tot de spier aansturingsparameters. Het kan zijn dat de klinische vooruitgang samen ging met centrale veranderingen, maar deze konden niet aangetoond worden met de spier aansturingsparameters.

In de algemene discussie in **hoofdstuk 7** wordt het wetenschappelijk bewijs voor het effect van electrostimulatie besproken, samen met implicaties voor de praktijk en aanbevelingen voor verder onderzoek. Sinds het literatuuronderzoek van RCTs beschreven in hoofdstuk 1 zijn er nog 3 systematische literatuuronderzoeken gepubliceerd en daarin worden verschillende conclusies getrokken. Dit betekent dat er nog geen eenduidige wetenschappelijk bewijs is voor het effect van ES. Een belangrijke reden hiervoor is heterogeniteit, niet alleen wat betreft de criteria die in de verschillende literatuuronderzoeken toegepast werden, maar ook heterogeniteit tussen de studies (methode van stimuleren en stadium na CVA) en in de studies (ernst en type van het CVA). De heterogeniteit verdunt het effect van ES. Het is op dit moment nog niet duidelijk welke methode van stimuleren het meest effectief is bij welke CVA-patiënt en volgens welk werkingsmechanisme. Deze kwesties moeten opgehelderd worden om een eenduidig bewijs met betrekking tot het effect van ES te kunnen krijgen. In dit kader is het ook van belang ES te optimaliseren. Er zijn aanwijzingen dat ES beter werkt als met behulp van de stimulatie praktische activiteiten getraind worden zoals bijvoorbeeld een glas oppakken om te drinken. Exploratief onderzoek wordt aanbevolen om er achter te komen wat de meest effectieve methode van stimuleren is en wat de kenmerken zijn van de patiënten die na een behandeling met ES hun aangedane arm beter in kunnen schakelen bij hun dagelijkse activiteiten. Uiteindelijk kan dan de behandeling met ES gericht worden op de mensen met die kenmerken, met als doel dat zij minder beperkt worden in hun dagelijks handelen.

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Over de auteur

Joke de Kroon werd geboren op 27 december 1968 in de stad Groningen als dochter van Friezen om útens. In 1982 verhuisde het gezin terug naar Friesland en ging zij in Leeuwarden naar de Rijks Scholen Gemeenschap, waar zij in 1987 het VWO-diploma behaalde. Daarna ging ze Geneeskunde studeren in Groningen. Met het keuzeproject 'Houding en beweging' begon haar interesse in de revalidatiegeneeskunde. De wetenschappelijke stage was haar eerste kennismaking met de wetenschap. Met een Erasmusbeurs vertrok ze voor 3 maanden naar Newcastle upon Tyne (UK) om een onderzoeksproject uit te voeren bij de afdeling 'Clinical Neuroscience' van de universiteit aldaar. Na keuzecoschappen neurologie en revalidatiegeneeskunde behaalde ze op 29 september 1994 het artsexamen.
Haar eerste baan was de functie van AGNIO (assistent geneeskundige niet in opleiding) op de afdeling neurologie van het Medisch Spectrum Twente in Enschede. Daarna volgde een AGNIO functie in revalidatiecentrum Beatrixoord te Haren.
Verzekerd van een opleidingsplaats ging ze in de herfst van 1996 op reis. Het hoogste punt van een prachtige trekking door de Himalya in Nepal was bijna 5200m. Dankzij deze hoogtestage keerde ze in topvorm terug. Kort daarop volgde op 5 januari 1997 het hoogtepunt op haar sportieve CV: een dag na de officiële tocht schaatste zij de Friese 11-stedentocht.
Op 1 januari 1997 startte zij als AGIO (assistent geneeskundige in opleiding) met de opleiding tot revalidatiearts bij revalidatiecentrum 'Het Roessingh' in Enschede. Het AGIO-contract werd na 2 jaar omgezet in een AGIKO-aanstelling (assistent geneeskundige in opleiding tot klinisch onderzoeker), waarna de opleiding tot revalidatiearts gecombineerd werd met het uitvoeren van een promotieonderzoek. Voor dit onderzoek kreeg zij een AGIKO-stipendium van ZonMW. De opleiding tot revalidatiearts werd afgerond per 31 december 2001 en met de promotie is ook het wetenschappelijke deel van het AGIKO-schap afgerond.
Sinds 1 april 2004 is zij in dienst van revalidatiecentrum Heliomare in Wijk aan Zee en werkt zij als revalidatiearts in het Spaarneziekenhuis Hoofddorp/Heemstede.