J Rehabil Med 2005; 37: 65–74

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REVIEW ARTICLE

RELATION BETWEEN STIMULATION CHARACTERISTICS AND CLINICAL OUTCOME IN STUDIES USING ELECTRICAL STIMULATION TO IMPROVE MOTOR CONTROL OF THE UPPER EXTREMITY IN STROKE

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Objective: **Electrical stimulation can be applied in a variety of ways to the hemiparetic upper extremity following stroke. 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 when non-triggered electrical stimulation was used. 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 determining the effect of electrical stimulation.**

Key words: electrical stimulation therapy, upper extremity, stroke, rehabilitation, review.

J Rehabil Med 2005; 37: 65–74

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Submitted April 15, 2004; accepted August 30, 2004

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 (5–7). 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 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 hypothesized that motor stimulation is more effective in improving motor control than is 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 only with 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

 ISSN 1650–1977
DOI 10.1080/16501970410024190

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 pre-set threshold (6). In positional feedback stimulation training (PFST), ES is provided when voluntary muscle contraction produces joint translation beyond a pre-set 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 maximized 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 ES 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 in the review:

- ES applied to the affected upper extremity in patients with stroke
- ES provoking muscle contraction
- application of ES with surface electrodes
- clinical setting, i.e. case series, case-control or randomized controlled trial
- relevant outcome measures for motor control
- separate results presented for the upper extremity
- 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 only to the shoulder were excluded as well.

Data-extraction

For each selected study, stimulation as well as study characteristics were extracted from the publication. Stimulation characteristics were:

- device applied
- method of stimulation
- target muscles
- duration of stimulation in hours per week and total hours
- specific setting for frequency, amplitude and pulse width. Investigators' rationales for their particular setting were noted.

The study characteristics were:

- study design
- number of patients
- age and stage of the patients
- 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 dichotomized 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 I). In 6 trials 2 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 randomized controlled trials (12, 14–25), 2 were non-randomized 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 1 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, 7 studies restricted inclusion to patients with residual wrist extension (at least 5–20 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 II 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, 29–32), EMG-stim, (*n* receiving EMG-stim = 127, *n* control = 41) (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 2 studies pulse duration was adjusted for optimal contraction and patient comfort (21, 32). In 2 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 4 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 2 trials, both arm and leg muscles were stimulated, either simultaneously (25) or consecutively (27).

Duration of stimulation. Table II shows that there was a wide range in duration of ES treatment: from 30 minutes once a day (25) to 3 times 1 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.

Relationship between treatment effect, and stimulation and study characteristics

Table III 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 9 patient groups in which triggered stimulation was applied yielded a positive result (88.9%), whereas only 4 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 III might suggest an increased likelihood of a positive effect if elbow and/or shoulder muscles were stimulated in addition to wrist and/or finger extensors. However, in 2 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 II). 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

Table I. *Clinical characteristics of included trials*

Author	Intervention	*n*	Age (years) Mean (SD or range)	Stage	Time post-stroke	Outcome measures
Randomized controlled trials						
Bowman (12)	E PFST C no additional therapy	E 15 C 15	no data	subacute	3 weeks – 4 months	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 years (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 seconds E2 on time 5 seconds C on time 0 seconds	E1 10 E2 10 C 6	66.4 (9.7)	chronic	2.8 years (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 years E2 3.3 years C 3.1 years	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 months (18.7) C 38.5 months (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 months (11.8) E2 21.4 months (16.1)	Ashworth aROM grip strength Motricity Index Action Research Arm test
Powell (22)	E NMES C visits to physiotherapist	E 27 C 28	E 69.0 (10.8) C 66.4 (12.2)	acute	E 23.9 days (7.7) C 22.9 days (5.5)	resting wrist angle pROM, aROM isometric wrist extension at 0°, 15° and 30° modified Ashworth grip strength Action Research Arm test 9-hole peg test VAS discomfort star cancellation test Rankin, Barthel
Sonde (23, 24)	E TENS C no additional therapy	E 26 C 18	E 71 (6.0) C 73 (3.5)	chronic	E 9.1 months (2.2) C 8.3 months (2.1)	modified Ashworth VAS spasticity VAS shoulder pain pROM, aROM sensation FM Barthel
Wong (25)	E electroacupuncture C no additional therapy	E 59 C 59	E 60.4 (11.1) C 60.6 (10.8)	acute	10–14 days	Brunnstrom stage: upper limb lower limb Chinese FIM

Table I. *Continued*

Author	Intervention	*n*	Age (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 additional 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 months (23.4) E2 36.8 months (19.8) E3 14.3 months (2.5) C 24.2 months (6.0)	FM grip strength Jebsen-Taylor finger tapping
Mokrusch (27)	E1 EMG-stim E2 NMES C no additional therapy	E1 22 E2 12 C 10	59.8 (8.3)	mixed	6 weeks (1–9 weeks) 3 chronic patients	modified Ashworth pendulum test hand extension (myometer) Barthel, FIM well being
Multiple baseline design						
Hummelsheim (28)	baseline-EMG-stim-repetitive movements	20	59 (32–91)	mixed	mean 16.5 weeks (4 weeks – 24 months)	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 7.6 weeks (3 weeks – 4 months)	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 years (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 <4 months 7 chronic >4 months	sensation spasticity (4-point scale) pROM isometric wrist extension
Hendricks (32)	NMES	15	52.8 (20–70)	chronic	4.9 years (0.75–18 years)	modified Ashworth FM

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 = extension or 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; flex = flexor muscles; FM = Fugl Meyer motor assessment; MAS = motor assessment scale; *n* = number of subjects that completed treatment protocol; NMES = neuromuscular electrical stimulation; PFST = positional feedback stimulation therapy; PNF = proprioceptive neuromuscular facilitation; 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 analogue scale.

or 300 μs. In view of lack of heterogeneity across studies, pulse duration was not further analysed.

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 neurophysiological 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 motoneurones, at least in the laboratory setting with isolated nerve preparation (8, 33). In addition, different combinations of parameters (pulse duration of 50 μs vs 200 μs, stimulation frequency of 4 Hz vs 110 Hz)

Table II. *Stimulation characteristics of included trials*

Author	Device	Method	Frequency (Hz)	Amplitude (mA)	Pulse duration (μs)	Target muscles	Duration of stimulation
Randomized controlled trials							
Bowman (12)		PFST	35	30–45	200	wrist ext	2 times a day 30 minutes, 5 days per week, 4 weeks
Cauraugh (14)	Automove 800	EMG-stim	50	14–29		ext dig comm, ext car uln	2 times a day 30 minutes, 3 days per week, 2 weeks
Cauraugh (15)	Automove 800	EMG-stim	50	16–29	200	ext dig comm, ext car uln	3 times a day 30 minutes, 4 days in 2 weeks
Cauraugh (16)	Automove 800	EMG-stim	50	17–28	200	ext dig comm, ext car uln	90 minutes per day, 4 days in 2 weeks
Cauraugh (17)	Automove	EMG-stim	50	13–28	200	ext dig comm, ext car uln, triceps, ant + mid delt	90 minutes per day, 2 days per week, 2 weeks
Chae (18)	FOCUS, EMPI Inc.	NMES	25–50	0–60	300	ext dig comm, ext car rad	1 time a day 60 minutes, 15 sessions
Francisco (19)	Automove AM 706	EMG-stim	20–100	0–60	200	ext car rad	2 times a day 30 minutes, 5 days per week, length of stay
Kimberley (20)	Automove 706	EMG-stim and NMES	50		200	forearm ext	6 hour per day, 10 days in 3 weeks
De Kroon (21)	NESS Handmaster	NMES	36	0–60	50–500	finger ext + flex or finger ext only	3 times a day 60 minutes, 7 days per week, 6 weeks
Powell (22)		NMES	20		300	ext dig comm, ext car uln + rad	3 times a day 30 minutes, 8 weeks
Sonde (23, 24)	Cefar Dual Unit	TENS	trainfreq 1.7 in train 70			wrist ext + in 21 subjects also elbow ext or shoulder abductor	1 time a day 60 minutes, 5 days per week, 3 months
Wong (25)	HANS	electro acupuncture	20–25	10–20 mv		4 acupuncture points in arm and 4 in leg	1 time a day 30 minutes, 5 days per week, 2 weeks
Controlled trials							
Kraft (26)	Automove	EMG-stim	30–90	20–60 μV	200	wrist ext + additional arm muscles according to subjects ability	1 time a day 60 minutes, 3 days per week, 12 weeks
	Respond II	NMES + act	30–90		300	wrist ext	1 time a day 30 minutes, 5 days per week, 3 months
Mokrusch (27)	PeR-Y Rehabilitator	EMG-stim or NMES	30–50		300	finger, hand, elbow ext, knee flex, feet, toe ext	1–2 times a day 30 minutes, 12.2 weeks (4–16)
Multiple baseline design							
Hummelsheim (28)	Bentrofit	EMG-stim	75–80	10–80	500	ext car rad, flex car rad	2 times a day 20 minutes, 5 days per week, 2 weeks
Hummelsheim(29)	Bentrofit	NMES	75–80	10–80	500	ext car rad, flex car rad	2 times a day 20 minutes, 5 days per week, 2 weeks
Case series							
Alon (30)	NESS Handmaster	NMES				ext dig comm, ext poll br, flex dig sup, flex poll longus, thenar m.	2 times a day 45 minutes, 3 weeks
Baker (31)	Rancho Los Amigos	NMES	33	0–100	200	ext dig comm, ext car uln + rad	3 times a day 30 minutes, 7 days per week, 4 weeks
Hendricks (32)	NESS Handmaster	NMES	36		100–500	ext dig comm, ext poll br, flex dig sup, flex poll longus, thenar m	3 times a day 60 minutes, 7 days per week, 10 weeks

Ant + mid delt = anterior and middle deltoid muscle; 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; NMES = neuromuscular electrical stimulation; PFST = positional feedback stimulation therapy; TENS = transcutaneous electrical nerve stimulation; thenar m = thenar nuscles.

Table III. *Relationship between reported effect on motor control and 5 characteristics of stimulation and subjects*

Author	Results as reported by author[a]	Selected primary outcome measure	Duration of stimulation[b]		Method of stimulation	Frequency (Hz)	Target muscles[c]						Stage after stroke[d]
							Extensors				Flexors		
			Hours per week	Total hours			f	w	e	s	f	w	
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 (21) 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; 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; n.s. = 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.

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 neurophysiological reaction, one might expect that different neurophysiological reactions were evoked in the studies included for this review. However, 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 the differences in parameter setting. From this it is hypothesized 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 maximizing 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 neurones 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 neurones, but also small diameter unmyelinated C fibres 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 minimize 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 dichotomized 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 correlation 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 randomized 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 dichotomized, 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.

ACKNOWLEDGEMENT

This study was supported by the National Health Research Council of the Netherlands.

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