Neuromuscular Electric Stimulation in Addition to Exercise Therapy in Patients with Lower Extremity Paresis Due to Acute Ischemic Stroke. A proof-of-concept randomised controlled trial

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Neuromuscular electric stimulation in addition to exercise therapy in patients with lower extremity paresis due to acute ischemic stroke.

A proof-of-concept randomised controlled trial.

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Abstract

Introduction Exercise therapy and neuromuscular electrical stimulation (NMES) during the initial 14 days after stroke may benefit recovery of gait. We aimed to determine whether poststroke NMES of vastus medial and tibial muscles during exercise therapy is more effective than exercise therapy alone.

Method In this proof-of-concept randomised trial patients with first-ever acute ischemic stroke and a leg paresis (40–85 years of age) were randomised (1:1) to 10 minutes of daily NMES + exercise therapy or exercise therapy alone. Primary outcome was the between-group difference in change in 6 Minute Walk Test (6MWT) at 90 days post stroke estimated with a mixed regression model. Secondary outcomes included 10 Meter Walk Test, Fugl-Meyer Motor Assessment, Guralnik Timed Standing Balance, Sit to Stand, Timed Up and Go, EQ-5D-5L, Montreal Cognitive Assessment and Becks Depression Inventory.

Results 50 stroke survivors (25 in each group) with a mean age of 67 years (range 43-83) were included. An insignificant between-group difference in change of 28.3 meters (95%CI -16.0 to 72.6, p= 0.23, adjusted for baseline) in 6MWT at 90-days follow-up was found, in favour of the NMES group. All secondary outcomes showed no statistically significant between-group difference. The conclusion was that adding NMES to exercise therapy had no effect on poststroke walking distance measured by the 6MWT or any of the secondary outcomes.

Trial registration (ClinicalTrials.gov): NCT03653312

Keywords: Acute stroke, Neuromuscular electrical stimulation, exercise therapy, leg paresis, rehabilitation, 6 Minutes Walking Test.

Introduction

Stroke is a leading cause of death and disability and is prevalent in the Western world.(1, 2) Further, stroke incidence is expected to increase due to population ageing worldwide.(3)

Some of the most frequent post stroke impairments include hemiparesis and disabled motor function.(4) The greatest improvement in leg functioning occurs in the first month post-stroke.(5) Early intensive rehabilitation, including exercise and functional motor ability, starting in the acute phase (1-7 days post stroke (6)) or sub-acute phase (1 week to 6 months post stroke (6)) is associated with recovery of activities, enhanced neural plasticity (7, 8) and greater improvement in motor function and functionality.(9-13) Early intensive rehabilitation improves the level of self-reliance in walking, dressing, eating and bathing.(14-17) However, despite intensive rehabilitation, functional outcome of patients with severe hemiparesis is poor.(18, 19)

NMES activates the sensory-motor system via electrical pulses to the nerve and muscles (20, 21) and facilitates voluntary movement and strengthening of muscles.(22, 23) Neuromuscular electrical stimulation (NMES) of the lower limb is safe and inexpensive and has the potential to facilitate recovery in terms of muscle strength standing balance (23), improved gait speed (24) and everyday activity. (25) Additionally, electrical stimulation can increase the excitability of corticospinal neural pathways to paretic muscles and induce neuroplasticity.(26, 27)

NMES has shown to be an effective complementary technique in the rehabilitation of patients in the chronic phase post stroke (22-24), but little is known about effects of NMES combined exercise therapy early post stroke.(24) If effective, adding NMES to exercise therapy might improve functional outcomes in patients with hemiparesis. Regaining the ability to walk is a crucial goal for stroke survivors (28), and the 6MWT have been used extensively in measuring walking capacity in stroke patients.(25, 29, 30)

Therefore, the aim of this parallel group, proof-of-concept randomised controlled trial (RCT) was to determine if early NMES during exercise therapy is superior to exercise therapy alone in improving walking distance measured by the 6 minute walk test (6MWT) in patients with acute ischemic stroke with paresis in the lower extremities 90 days post stroke. Secondary endpoints included measurements of speed, functions and activities of daily living and quality of life.

We hypothesised that 14 days of NMES of the affected leg during exercise therapy would improve walking distance, measured by the 6MWT, at 90 days post stroke compared to exercise therapy alone.

Methods

Trial design

This trial was a parallel group RCT (1:1 treatment allocation) with 90 days follow-up adhering to the CONSORT statements for reporting RCTs. The trial was pre-registered at ClinicalTrials.gov (NCT03653312).(31)

Randomisation and allocation concealment

A study nurse, not otherwise involved in the study, randomly distributed the 50 patients one after the other to exercise therapy with NMES or exercise therapy alone. The allocation number was stored in opaque sealed envelopes, only accessible by the central study coordinator. The central study coordinator only opened the sealed envelopes after informed consent and baseline measures had been obtained. Patient and physiotherapist were not blinded to group allocation due to the electrically induced muscle contraction.

Participants

Patients were recruited at the Neurovascular Center, Department of Neurology at Zealand University Hospital, Region Zealand, Denmark between November 2018 and March 2020. Information, verbal and written consent, inclusion, baseline measurements and randomisation were conducted at the acute stroke unit during hospitalisation.

Patients were eligible for inclusion if they had: first-time acute ischemic hemispheric stroke verified by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) or were diagnosed by a stroke physician based on clinical symptoms within 2 days after stroke onset; were 40 to 85 years of age; had leg paresis (manual muscle testing 2-4 (32)); were independent in their global ADLs following the modified Rankin Scale (mRS) ≤1 (33)); and deemed cognitively relevant for participation by a speech therapist, physiotherapist or nurse.

Patients were excluded if they were unable to understand verbal or written information in Danish; had a pacemaker, current or previous arm / leg blood clot, no sensation in the affected leg, were pregnant, suffered from insufficiently medically treated depression and/or drug/alcohol abuse, untreated hypertension (BT> 150/90) at

inclusion, epilepsy or dementia.

The study was approved by the Research Ethics Committee of Region Zealand, Denmark (SJ-444), and by the Danish Data Protection Agency (REG-80-2015). All patients gave written, informed consent in accordance with the Declaration of Helsinki prior to inclusion in the study.

Intervention

Exercise therapy with or without NMES of the medial vastus and the anterior tibial muscles was an addition to regular rehabilitation. The anterior tibial muscle appears to receive a significant monosynaptic corticospinal drive that plays an important role during the swing phase of human walking, and the vastus medialis is an important prime mover in ADL.(34) The interventions were initiated within 48 hours after ischaemic stroke onset and administered daily for 14 days by a trained physiotherapist with experience in stroke rehabilitation (see Figure 1). After two to three days at the acute stroke unit, patients were transferred to either in-hospital rehabilitation or home, depending on their continued need of hospitalisation. Exercise therapy was conducted at either the acute stroke unit, the rehabilitation centre or the patients' residence.

Exercise Therapy

Both groups received 10 minutes daily exercise five days a week for two weeks. The exercise consisted of daily life activities, altering between rising from and sitting down on a chair and walking every other day, respectively. The rising from and sitting down on a chair followed the programmed stimulation loops with 7 seconds of muscle contraction during activity (rising from and sitting down a chair) and 7

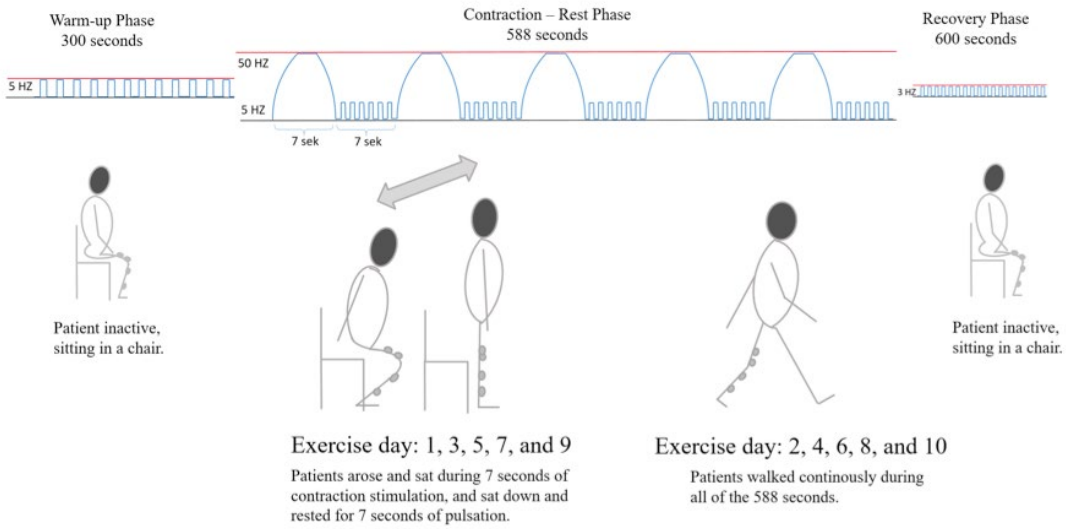
seconds of pulsation-pause, while the patient rested while sitting on the chair. The physiotherapist used a stopwatch for the patients without NMES to mediate when to be active and when to rest. On walking days, the activity was continuous during the 10 minutes active stimulation period, without pauses unless the patient needed it. All kinds of walking aids were allowed if needed. Additional activity and regular rehabilitation was not recorded, but patients were encouraged to do as much activity as possible.

Neuromuscular electrical stimulation

In the NMES-group a physiotherapist started the intervention by placing two sets of external electrodes at the paretic leg at the medial vastus and the anterior tibial muscles.(35) The reference electrode was placed 1/3 down from the top of the muscle. The placement of the active electrode was found using a motor point pen to search for the motor spot where the motoric nerve innervates the muscle. The spot is about 2/3 down the muscle, and elicits a visually clear and significant muscle contraction.(35)

For the electrical stimulation a Chattanooga Wireless Professional NMES - 4 Channels fixed programme called “Resistance 1” was used. The programme consisted of tree phases: a warm-up phase, contraction/active rest-phase and a final recovery phase.

Figure 1 Exercise and Stimulation Parameters.



The warm-up period of 300 seconds of 5Hz pulse-trains 1.5 seconds passive/0.5 seconds active. Then 588 seconds (9.8 minutes) of stimulation loops with 1.5 second of increasing amplitude (ramping up) where muscle contraction is building up; then isometric contraction for 4.75 seconds at 50 Hz; then a short ramp down phase for 0.75 seconds to 0 Hz; followed by 7 seconds with pulses of 5 Hz every second. Then the final recovery phase of 600 seconds (10 minutes) with 3Hz pulses every 0.5 second.

Patients were not moving in the warm-up and the final recovery phase. The stimulation level was determined individually for each patient at the beginning of each session. Due to adaptation of the NMES the stimulation level was adjusted to visual contraction without exceeding the patients' pain threshold, every second minute throughout the 10 minutes active stimulation phase. The definition of the stimulation amplitude of the given stimulation was defined as the highest possible amplitude that elicits visible muscle contraction without any discomfort, pain or muscle cramps.

Outcomes

Table 1 shows the timing of clinical assessments. The primary outcome measure was the between-group difference in change in the 6MWT (36) at 90 days post stroke in a repeated measurement design. The 6MWT measures the distance an individual can walk over a total of six minutes on a hard, flat surface. The individual should walk as far as possible at comfortable walking speed in six minutes. The 6MWT at comfortable walking speed has been used extensively in measuring walking capacity in stroke patients (25, 29, 30) and is an often-used validated test for community walking in stroke rehabilitative trials.(36-38)

The secondary outcome measures outlined in Table 1 include a) 10 Meter Walk Test (10MWT), a timed 10 meter walk test at comfortable walking speed, not starting from standing still position. The test was repeated 3 times and the fastest attempt recorded (39); b) Fugl-Meyer Assessment-Lower extremity part (both motoric part E+F and total score E+F+I+J), a quantitative, measurement evaluating sensorimotor stroke recovery (40); c) the Timed Up and Go-test (41), which measures the time in seconds it takes to rise from a chair and walk 3.1 meters (10 ft), return and sit down again; d) 30 seconds Chair-Stand test, which measures lower body strength and endurance (42); e) Guralnik, a quick timed standing balance test from three different positions (the feet together, semi-tandem position and tandem position). Each position must be held for a maximum of 10 seconds. One second equals one point. The total score is made up of the sum of the seconds that are completed (0-30 points).(43)

The following outcomes were only obtained at the end of intervention (14 days post stroke) and at follow-up (day 90 post stroke): a) EQ-5L-5D – which is a 5 dimensions, self-reported questionnaire including both the score on the descriptive index (ranging from 0-5, low scores indicating high quality of life) and the score on a

visual-analogue scale (ranging from 0-100, where high score indicates high quality of life) (44), b) Montreal Cognitive Assessment, a test to identify mild cognitive impairment on a 0-30 point score where 30 indicate no impairment (45), and c) Becks Depression Inventory is a 21 item multiple-choice self-report questionnaire for measuring the severity of depression ((0-63 possible point scores 1-10 is considered normal/no depression, 40 points or more indicates extreme depression).(46)

Age, sex, stroke risk factors (smoking, alcohol consumption, Body Mass Index (BMI), comorbidities, stroke severity (Scandinavian Stroke Scale) (47) and modified Rankin Scale (33) were collected from patients' medical records.

Adverse events were identified either in the hospital records or at follow-up. Minor adverse events included minor serious pain, rash, itching, cramps associated with stimulation power and/or exercise therapy. Serious adverse events were identified according to the definition established by the US food and Drug Administration.(48)

All outcome measures were assessed by a trained unblinded assessor (HB) at baseline, about an hour prior to intervention start, at end of intervention 14 days after inclusion and at follow-up 90 days post stroke. The between-group difference for the 6MWT (36) at 90 days was used to assess lasting effects of physical therapy with NMES.

All baseline, assessments were performed at the acute stroke unit. End-scores and follow-up assessments were performed at the patients' residences at the specific point in time (stroke unit, patient's home, inpatient rehabilitation centres, nursing home). All assessments were done by one unblinded physiotherapist (HB).

Table 1 Outcome Measures

	Baseline	**14 days**	**90 days**
Physical performance tests			
6 Minute Walk Test (6MWT)	X	X	X
10 Meter Walk Test (10 MWT)	X	X	X
Sit to stand	X	X	X
Timed up and go	X	X	X
Guralnik timed standing balance	X	X	X
Fugl-Meyer motor part, under extremity	X	X	X
Fugl-Meyer total score, under extremity	X	X	X
Montreal Cognitive Assessment		X	X
Becks Depression Inventory		X	X
EQ-5D-5L = EuroQol Group 5-Dimension Self-Report Questionnaire		X	X
Adverse events			
Patient reported at follow-up		X	X
Medical record review			X

Blinding

Blinding of the patients was not possible since the NMES elicits visible involuntary muscle contractions. Assessor blinding was not possible because the first author included, assessed, and started intervention. Group allocation was concealed for statistical analysis and a blinded interpretation of the study results was conducted and published before unblinding the data to reduce interpretation bias (49, 50) (See Appendix 1).

Sample size

A 34.4-meter difference in change between groups in 6MWT is considered clinically relevant.(51) Therefore the study was powered to detect a between group difference in 6MWT of 34.4 meters or more from baseline to 90 days post stroke. We assumed a common SD of 6MWT of 38.7 (51), required a power of 80% and an alpha level of 0.05. To detect a clinically relevant difference without dropouts, 21 patients in each of the intervention groups were needed. We planned to recruit a total of 50 patients to account for loss to follow-up (20%).

Statistical Methods

A detailed statistical analysis plan was made publicly available before conducting blinded statistical analysis of the results (52) (Appendix 2):

Baseline characteristics for each group were reported as medians with boundaries of interquartile range (Q1-Q3) and counts with proportions for continuous and categorical data respectively.

The primary endpoint analysis was an intention to treat analysis (ITT) of between-group difference in 6MWT change from baseline to 90 days post stroke, and included all randomised patients. The ITT analysis was a mixed model repeated measurement. Patient id was included as random factor and treatment group and time (assessments at baseline, 14 and 90 days) as fixed factors. Additionally, adjustment for baseline differences were included in modelling. As defined in the statistical analysis plan (Appendix 2), a confidence interval not including 34.4 meters or more in the 6MWT would be interpreted as a lack of a clinically relevant difference. A secondary per protocol (PP) (crude) analysis excluded all individuals, who had been lost to follow up, and individuals not adhering (participating in less than 80% of the exercise days) to the treatment (i.e. participating in less than 8 of the 10 exercise sessions). Between

group differences were determined with an unpaired t-test. Between group differences were reported as mean with a 95% confidence interval (95% CI) for the ITT and PP analysis (adjusted and crude). Within-group changes in 6MWT from baseline to 90 days post stroke were assessed with a paired t-test and reported as mean and 95%CI for each group.

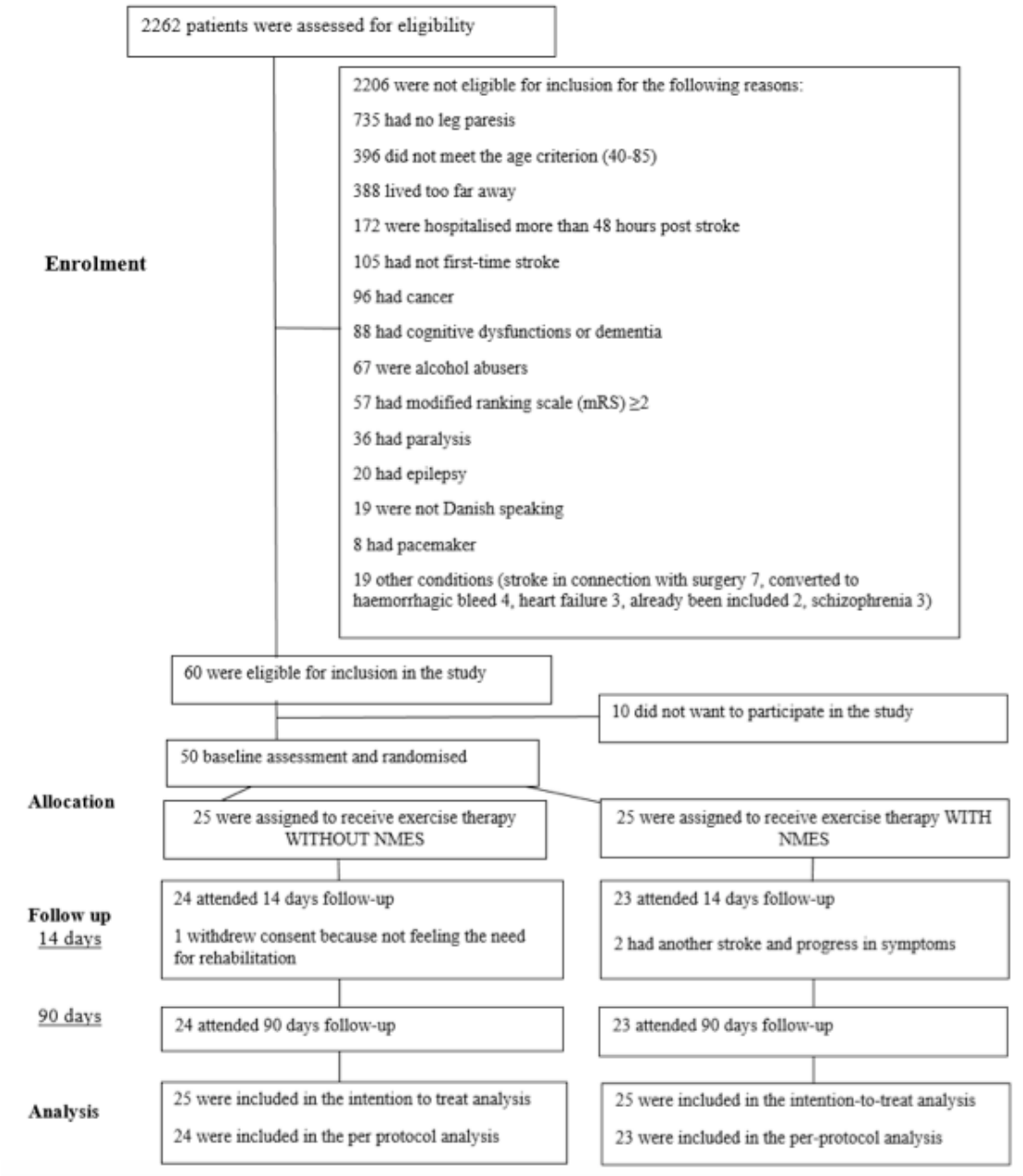
The secondary outcomes 10 MWT and Fugl-Meyer motoric part were analysed as described for 6MWT. Since the assumption of normality were violated in the remaining secondary outcomes changes from baseline to 90 days post stroke were assessed with a paired Wilcoxon signed rank test and reported as a pseudomedian with 95% CI. Between group differences were determined with the exact two sample Wilcoxon-Mann-Whitney test and reported as a pseudomedian with 95% CI. Bootstrapping was used to compute confidence intervals with the mixed regression model. A p-value of less than 0.05 was considered statistically significant. Analyses were performed with RStudio version 1.1.447 and all statistical procedures were discussed and agreed upon with two experienced biostatisticians.

Results

In total 50 patients were randomised to one of the two groups, 25 patients in each. 23 patients (92%) in the exercise therapy with NMES group and 24 (96%) in the exercise therapy only group completed the primary 90 days follow-up. All randomised patients (n=50) were included in the ITT analysis. Figure 2 details the inclusion and participation flow.

Two patients in the exercise therapy with NMES group were hospitalised with a recurrent stroke within the first week of intervention and thus excluded from further participation. One patient in the exercise therapy only group withdrew consent. All remaining patients participated in all 10 exercise sessions. This resulted in a per protocol analysis set of 23 in the exercise therapy with NMES group and 24 in the exercise therapy group (see flowchart fig 2).

Figure 2 Flowchart of patients through the trial.



NMES =Neuromuscular electrical stimulation

Baseline characteristics were similar in the two study groups (*Table 2)*.

Table 2 Baseline characteristics.

	Exercise therapy	Exercise therapy with NMES
Age, median (Q1-Q3)	72 (58-76)	68 (62-72)
Female, n (%)	10 (40)	10 (40)
BMI, median (Q1-Q3)	26.4 (24.8-27.7)	27.2 (24.5-29.4)
Height, median (Q1-Q3)	1.7 (1.7-1.8)	1.8 (1.7-1.8)
Smoking, n (%)		
None	8 (32)	7 (28)
Previous	7 (28)	5 (20)
Current	10 (40)	13 (52)
Alcohol misuse (> 7/14 items per week)	1 (4)	1 (4)
Comorbidities, n (%)	4 (16)	5 (20)
Received thrombolysis, n (%)	5 (20)	4 (16)
Infarction in the right hemisphere, n (%)	14 (56)	13 (52)
SSS score, median (Q1-Q3)	52 (51-54)	51 (45-55)
Current use of walking aids, n (%)	2 (8)	1 (4)
Outcomes		
6 MWT (meters), median (Q1-Q3)	260 (189-318)	213 (160-327)
10 MWT (meters/sec), median (Q1-Q3)	0.9 (0.7-1.1)	0.7 (0.5-1)
Fugl-Meyer Motor Part, under extremity, median (Q1-Q3)	30 (26-31)	28 (25-30)
Fugl-Meyer Total score, under extremity median (Q1-Q3)	79 (78-83)	80 (76-82)
Guralnik, median (Q1-Q3)	17 (13-23)	20 (11-28)
Sit to stand, median (Q1-Q3)	7 (6-10)	8 (5-10)
Timed up and go (sec), median (Q1-Q3)	14.4 (10.5-19.4)	19.5 (10.5-27.1)

SSS-Score = Scandinavian Stroke Scale (46). Scale from 0-58 point, 58 is no symptoms

6MWT = 6 Minute Walk Test, 10MWT = 10 Meter Walk Test, BMI = Body Mass Index, NMES =Neuromuscular electrical stimulation.

Outcomes

Primary outcome

There was no statistically significant between-group difference (mean difference of 39.2 meters (95% CI -26.4 to 104.8) (crude) and 28.3 meters (95%CI -16.0 to 72.6) (adjusted)) in the mean change of the 6MWT from baseline to the 90 days follow-up (see Table 3 and Figure 3).

Similarly, there was no statistically significant between-group difference in the mean change of the 6MWT from baseline to end of intervention (14 days after inclusion and

baseline test); mean difference of 19.3 meters (95%CI -28.4 to 67.1) (crude) and 8.4 meters (95%CI -35.9 to 52.7) (adjusted)).

Both groups improved in 6MWT from baseline to the 90 days follow-up. The Exercise therapy group improved 144.2 (95%CI 94.8 to 193.6) meters while exercise therapy with NMES improved 183.4 (95%CI 137.7 to 229.2) meters (Table 3). Improvements in both groups exceeded the threshold for minimally important difference (MID) of 35 meters.(51).

Secondary outcomes

None of the secondary outcomes demonstrated a statistically significant between-group difference (Table 2 and Table 3).

Except for two cases of recurrent stroke within the first week, no adverse events or serious adverse events were reported in either group.

Table 3 Outcomes at 90 days.

	Total No. Of assessments		**Improvement in outcome from baseline to 90 days (95% CI)**		**Between two Groups Difference in Mean**	
Primary outcome	Exercise therapy	Exercise therapy with NMES	Exercise therapy	Exercise therapy with NMES	Crude	Adjusted
6 MWT meters	73	71	144.2 (94.8 to 193.6) [a]	183.4 (137.7 to 229.2) [a]	39.2 (- 26.4 to 104.8) [b]	28.3 (- 16.0 to 72.6) [e]
Secondary outcomes						
10 MWT m/sec	73	71	0.44 (0.27 to 0.61) [a]	0.57 (0.43 to 0.72) [a]	0.14 (-0.08 to 0.36) [b]	0.08 (-0.09 to 0.24) [e]
Fugl-Meyer motor-scale	73	71	3.5 (2.1 to 5.0) [a]	4.0 (2.4 to 5.6) [a]	0.46 (-1.6 to 2.5) [b]	-0.50 (-2.0 to 1.0) [e]
Fugl-Meyer total lower extremity scale	73	71	4.5 (3.0 to 6.5) [c]	6.0 (3.0 to 11.5) [c]	1 (-2 to 4) [d]	0.4 (-0.92 to 0.91) [f]
Guralnik balance	73	71	6.5 (2 to 12) [c]	11 (6.5 to 15.0) [c]	3 (-3 to 7) [d]	4.0 (-2.1 to 2.0) [f]
Timed sit to stand	73	71	3.5 (2.0 to 6.0) [c]	6.0 (4.5 to 7.5) [c]	2 (0 to 5) [d]	1.8 (-2.8 to 2.7) [f]
Timed up and go	73	71	- 6.9 (-11.3 -3.6) [c]	- 10.0 (-15.0 to -5.7) [c]	-2.0 (-6.7 to 1.6) [d]	-0.6 (-0.94 to 0.97) [f]
			Improvement in outcome from 14 to 90 days (95% CI)		**Between to Groups Difference in Mean**	
	Exercise therapy	Exercise therapy with NMES	Exercise therapy	Exercise therapy with NMES	Crude	Adjusted
EQ-5D-5L	48	46	-2 (-3 to 0.0) [c]	-1.5 (-3.5 to 0) [c]	0 (-1 to 2) [d]	-0.14 (-2.14 to 2.17) [f]
EQ-5D-5L Visuel Aanalog Scale	48	46	3.5 (-7.0 to 13.5) [c]	4.5 (-5.5 to 13.5) [c]	2 (-11 to 15) [d]	3.8 (-1.9 to 1.9) [f]
Montreal Cognitive Assessment score	48	46	1.84 (0 to 3.5) [c]	2.0 (0 to 4.5) [c]	0 (-2 to 2) [d]	1.3 (-1.96 to 1.96) [f]
Beck Depressions Inventory	48	46	-1.5 (-3.5 to 1.0) [c]	-1.5 (-4.0 to 0) [c]	-1 (-3 to 2) [d]	-0.8 (-2.0 to 2.0) [f]

6MWT = 6 Minute Walk Test, 10MWT = 10 Meter Walk Test, EQ-5D-5L = EuroQol Group 5-Dimension Self-Report Questionnaire, NMES =Neuromuscular electrical stimulation

Total number of assessments (n=75)

a Paired t-test

b Unpaired two sample t-test, pseudo median with 95% CI

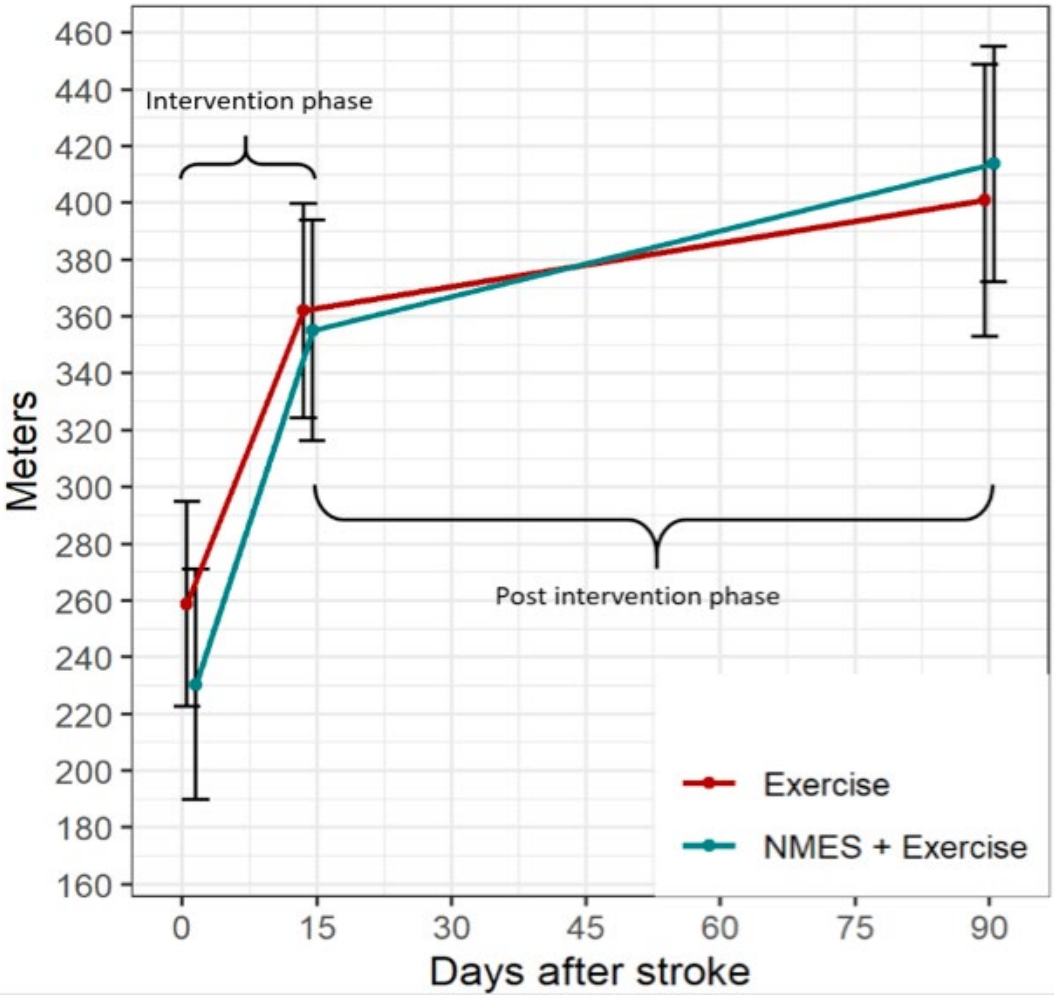
c Paired Wilcoxon signed rank test with continuity correction, pseudo median with 95% CI

d Exact two sample Wilcoxon-Mann-Whitney Test, pseudo median with 95% CI

e Mixed regression (repeated measurements, adjusted for baseline differences and random effect of individuals), mean and 95% CI

f Bootstrapping, mean and 95% CI

Figure 3 Primary outcome (6MWT) at baseline, 14 days and 90 days for the two groups (mean and 95% CI).



NMES =Neuromuscular electrical stimulation

Discussion

In this proof-of-concept RCT of acute stroke patients, we demonstrated that adding NMES to exercise therapy was not superior to exercise therapy alone in improving walking distance (primary outcome), walking speed, motor functions, balance, self-reported quality of life, cognition or depression.

This is the first trial to investigate the effect of NMES in addition to exercise therapy compared to exercise therapy alone in acute stroke patients with paresis of the lower

extremities. Both groups experienced statistically significant improvements in all outcomes and a clinically relevant improvement (exceeding 34.4 meters (51)) in the primary outcome (6MWT). As the confidence interval in the adjusted between-group analysis of 6WMT included the predefined minimal clinically relevant difference of 34.4 meters (51), the true difference in change between the two treatment strategies could potentially be clinically relevant in favour of the exercise therapy with NMES-group. Furthermore, most of the outcomes showed a statistically insignificant tendency to greater improvement in the group receiving exercise therapy with NMES than exercise therapy alone. However, as it is more likely that the true effect lies closer to the mean difference in change between groups (53), our results do not support an additional clinically relevant effect from NMES in addition to exercise therapy.

Not finding a between-group difference is a phenomenon seen before (54). Winters et al highlight, that regaining function after stroke is primarily due to time and spontaneous recovery.(55) Van der Vliet et al (56) pointed out, in a more recent article, that about 70%-90 % of patients show proportional recovery from 30 % to over 90 % within the first 3 months post stoke but about 10 % to 30% of patients fail to show significant spontaneous neurological recovery. These patients are classified as "non-recoverers". Winters et al therefore propose stratification of patients into subgroups with comparable patterns of spontaneous recovery in the future (55). If this stratification was possible in our study, it might have given the opportunity to show an effect of the intervention including NMES as the recovery of patients would possibly be more homogeneous. A suggestion for considerations in future studies would therefore be to find and include non-recoverers for a more effective personalised therapeutic intervention.

Considerations for dose and length

When interpreting our findings, the dose and length of intervention (10 minutes per day for 10 out of 14 days) are important to consider. They might be insufficient to exceed the effect of spontaneous recovery and exercise therapy. Studies carried out in the late subacute to chronic phase (3-6< months post stroke)(6), used doses and lengths of intervention of 2-12 weeks, 20-60 min per session, and 1-5 sessions per week, but stimulation parameters were very sparsely described.(24) In other studies, showing effect of NMES intervention, patients received electrical stimulation while seated or lying (57-59) or were more than 6 months post onset of stroke.(23, 24, 35) None of these studies are directly comparable to our study because of patients being in the post stroke phase and without activity during stimulation.

Acute stroke patients experience physical and mental distress during hospitalisation. (60) A intervention period with higher frequency and dose was not prioritised due to considerations concerning the patients' well-being and their stressful situation, (60) combined with financial and logistical limitations. It is possible that "more is better", like Lohse et al found in 2014 (61), and we cannot rule out that a longer intervention period with a greater daily dose might have altered the results.

However, in this trial we wanted to add an intervention, that would potentially be feasible to implement in clinical practice in the acute and sub-acute phase post stroke onset, and therefore we prioritised not to extend the duration of the neuromuscular electrical stimulation further. We found that the intervention was feasible, safe and tolerated because of the low dropout and high participation in the intervention both with and without NMES.

Recommendations for future studies

Even though spontaneous recovery over time is expected to be a major contributor to regain motor function (55), we do not know the relative contribution of rehabilitation, NMES and other interventions the patients may have received. Compare the findings in this trial with a group which did not receive daily exercises or no exercise at all would be interesting. However, it would not be ethically appropriate to require no activity or mobilisation at all, since recommendations and standard treatment of stroke survivors are mobilisation and active rehabilitation (62). Likewise, whether NMES is more or less effective targeting different muscle groups, a different electrode placement, dose and length of intervention and/or stimulation parameters require further investigation. Another recommendation for future studies could also be to investigate the effect of NMES and exercise therapy on muscle strength and mass in patients with acute stroke, although challenged by safety issues and a potential lack of ability among the patients to perform the tests.

Limitations:

The power calculation was based on data from patients in the chronic phase post stroke (6, 51), as no data from acute stroke patients existed. It is highly possible that patients in the chronic phase are more aligned in their biological diversity and neurological recovery compared to acute stroke patients since patients in the chronic phase have plateaued in their spontaneous recovery.(6) The power calculation could, thus, have underestimated the needed sample size, increasing the risk of type II error.

The dose and content of rehabilitative interventions offered for stroke patients differs according to the patient's individual need and the rehabilitation unit responsible for the rehabilitation. We had no knowledge of or influence on what intervention dose, length or frequency the patients were offered and received during hospitalisation or

municipal rehabilitation. We therefor do not know if the patients in one group were more active than the other and if the outcomes were because of the intervention or a result of other rehabilitative efforts.

Lastly, with this electrical stimulation setup it was impossible to assess and standardize the daily dose of stimulation parameters. The stimulation-effect was decided by the muscle contraction and patients pain threshold, which varied from day to day. Even with daily registration of stimulation parameters, we could not be sure that the given dose of electrical stimulation was sufficient to elicit muscle contraction during the whole exercise period.

Conclusion

In this proof-of-concept RCT, we demonstrated that NMES in addition to exercise therapy during the first 14 days after onset of ischemic stroke did not improve walking distance or any of the secondary outcomes.

Future studies with a longer trial period, stratifying patients into subgroups with comparable patterns of expected spontaneous recovery – if possible within 48 hours post stroke, and greater sample size, than in this study are suggestions of how rehabilitation research could go on exploring the potential for NMES as an amplifier in stroke recovery.

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Author Contributions

Conceptualization: HB, CA, STS, TW. Data curation: HB, LL. Statistical Analysis Plan: HB, LL, STS, NA, TW. Formal analysis: HB, LL. Funding acquisition: HB. Investigation: HB. Methodology: HB, STS, GK, NA, TW. Project administration: HB. Visualisation: HB. Writing – original draft: HB. Writing review and editing: HB, STS, LL, GK, NA, and TW.

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