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Added-value of Early Post-stroke Spasticity Reduction during Arm-hand Rehabilitation in Improving Functional Arm-hand Skill Performance: A Multiple Baseline Single Case Experimental Design Study

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Abstract

Background: Focal spasticity management in patients in the sub-acute phase after a stroke is mainly based on expert opinion. Evidence for the optimal type and intensity of multidisciplinary rehabilitation programs is scarce. This study will investigate the added-value of reduction of early signs of spasticity in the sub-acute phase after stroke on arm-hand rehabilitation outcome involving a well-described rehabilitation intervention. Reduction of early signs of spasticity will be done using abobotulinum toxin A.

Methods/design: This study comprises three methodological approaches, i.e.: i) a (multiple baseline) single case experimental design involving 10 individuals; ii) a meta-analysis of the data of all single cases (single armed group design); iii) non-randomized double armed group design, i.e. a case-matched control design in which each patient receiving early post-stroke spasticity reduction treatment will be matched (according to arm-hand capacity, spasticity level, age, gender, and Utrechtse Arm-hand Test scores) to a case from a prospective cohort study on changes in arm-hand status in 89 stroke patients performed previously. Improvement of arm-hand skill performance will be gauged using: a) the Action Research Arm Test, gauging functional capacity; b) the ABILHAND, gauging perceived level of arm-hand skill proficiency; and c) bilateral arm accelerometry, gauging actual arm-hand skill performance in daily life. Furthermore, arm-hand function will be measured using: a) Fugl-Meyer Motor Assessment; b) hand-held dynamometry (grip strength); c) Motricity Index (functional strength); and d) Modified Ashworth Scale (spasticity levels in the upper extremity).

Statistical analyses include permutation tests involving the time series of each subject separately, Kruskal-Wallis tests and Mann-Whitney U-tests.

Discussion: Results of this study will provide evidence on the added-value of reduction of early signs of spasticity in the upper extremity on functional arm-hand skill performance in sub-acute stroke patients with either a severely or moderately affected arm-hand and moderate to severe grades of spasticity.

Keywords: Sub-acute stroke; Rehabilitation; Spasticity; Upper limb; Functional performance

Abbreviations: 3D=Three Dimensional; AE=Adverse Event; AHF=Arm-Hand Function; AHSP=Arm-Hand Skill Performance; AMUSE=Activity Monitoring of Upper extremity Use in Stroke patients during and after rEhabilitation; ARAT= Action Research Arm Test; CARAS=Concise Arm and hand Rehabilitation Approach in Stroke; CCMO=Centrale Commissie Mensgebonden Onderzoe (Central Committee for patient-related research); ABoNt-A=Abobutulinum toxin type A; FM=Fugl-Meyer Motor Assessment; ICF=International Classification of Function, disability and health; ICMJE=International Committee of Medical Journal Editors; MAS=Modified Ashworth Scale; METC=Medical Ethics Committee; MI=Motricity Index; SAE=Serious Adverse Event; SCED=Single Case Experimental Design; T.=Measurement time point at baseline (Tbl); clinical discharge (Tcd) and 3, 6, 9 and 12 months after clinical discharge (T3m, T6m, T9m, T12m); T6w/T12w=Time point at 6; weeks12weeks; UAT=Utrechtse Arm-hand Test; WMO=Wet Medisch-wetenschappelijk Onderzoek met mensen (Dutch Medical Research Involving Human Subjects Act)

Introduction

In stroke survivors, the presence or absence of voluntary motor activity in the affected arm and hand is the most important predictor of dexterity outcome and the level of performance regarding daily activities. In order to select the potentially most effective treatment, it is advocated to stratify persons with an impaired arm and hand into a limited number of arm-hand function strata [1,2].

A Concise Arm and hand Rehabilitation Approach in Stroke (CARAS) [3] has been developed to structure and implement the treatment of Arm-Hand Function (AHF) and Arm-Hand Skill Performance (AHSP) in stroke survivors. CARAS is based on: A) level of arm-hand impairment, B) detailed training descriptions captured in different training modules, C) principles of self-efficacy [4-6], and D) the swift implementation of innovations. Based on the UAT (Utrecht Arm-hand Test) [7] scores, patients are allocated to one of three training programs, i.e. CARAS program 1, aimed at the severely impaired AHF subgroup (UAT 0-1), CARAS program 2 aimed at the moderately impaired AHF subgroup (UAT 2-3) and CARAS program 3, aimed

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at the mildly impaired AHF subgroup (UAT 4-7). Program 1 is titled "*taking care and prevention*". It is designed for stroke survivors who are not able to use their affected arm and hand for skill performance in daily life situations (non-functional arm-hand). Programs 2 and 3 are high intensity, task-oriented arm-hand performance training programs in which patients learn to integrate their affected arm and hand in daily occupations to optimize their overall functional abilities in daily situations. In this part a distinction is made between persons who have a moderately affected arm and hand, i.e. those who are able to use their affected arm and hand for passive and active stabilization tasks, like fixating bread while making a sandwich; and persons with a mildly affected arm and hand, who are able to use their affected arm and hand instantaneously in daily situations. Currently, CARAS has been implemented in everyday stroke rehabilitation practice in a number of rehabilitation centers throughout the Netherlands.

In order to monitor the development, i.e. either progression or deterioration, of both AHF and AHSP during and after rehabilitation, a single-arm prospective cohort study has been performed, involving 89 patients who participated in CARAS. This study, called AMUSE (Activity Monitoring of Upper extremity use in Stroke patients during and after rehabilitation (CCMO code: NL35681.068.11)), involved data collection at all levels of the ICF (International Classification of Function, disability and health [8]) at the start of rehabilitation (baseline), at clinical discharge and at 3, 6, 9 and 12 months post discharge, thus providing a time series per patient [9].

In a number of stroke patients with a moderate to severely affected arm and hand, moderate to severe grades of spasticity (Modified Ashworth Scale (MAS) scores +1 to 3) may occur already in an early, sub-acute phase post-stroke. This may seriously hinder AHF and AHSP treatment, leading to a slowing down of the patient's functional recovery. The problems caused by spasticity can occur at the level of impairment (e.g. restricted joint range of movement, pain and involuntary movement) and at the level of activity and participation (i.e. inability to perform daily activities, and limitations in taking up societal roles like work, family roles and leisure activities) [10].

There is a myriad of literature on the benefits of reducing spasticity on rehabilitation training effects regarding AHF and AHSP in chronic stroke patients [11-18]. However, thus far little evidence is available on the added-value of early spasticity reduction during rehabilitation training on the improvement of AHF and AHSP in sub-acute stroke patients. In a large study (n>300), Shaw et al. [19] recruited stroke patients in the sub-acute phase, but this study could not demonstrate improved active function. Foley et al. [15] reported small benefits as to improve passive AHF. Baker et al found modest but significant improvements on active AHF, although evidence quality was reported as being low [20]. A number of studies explored the added value of arm-hand rehabilitation immediately after the injection of botulinum toxin. Prazeres et al. [21] and Wolf et al. [22] did not find botulinum toxin plus rehabilitation to be superior to placebo plus rehabilitation with respect to AHF improvement. Takekawa et al. [23] and Devier et al. [24] reported improved AHF in stroke patients with a moderately to mildly impaired arm-hand who received botulinum toxin in combination with a tailored arm-hand rehabilitation program. Reducing the influence of the spastic component demands a holistic multidisciplinary approach to combine spasticity management and rehabilitation to optimize the likelihood of positive treatment effects [12,25-30]. In most cases, a delay between spasticity reduction and improvement of AHF exists, suggesting that motor relearning continues as muscle tone is returning to baseline. The optimal types (modalities, therapy approaches, settings) and intensities of therapy for improving activity (active and passive function) in adults with post-stroke spasticity, in the short and longer term, however, are still unclear [31].

To date, evidence for the optimal type and intensity of multidisciplinary rehabilitation programs following focal spasticity management are based on expert opinion only. The present study will investigate the added-value of reduction of early signs of spasticity in the sub-acute phase after stroke on arm-hand rehabilitation treatment outcome involving a well-described rehabilitation intervention ('treatment-as-usual'), i.e. CARAS. This reduction of early signs of spasticity will be done using abobotulinum toxin A. It is assumed that reduction of spasticity in the upper extremity at an early, sub-acute, stage after stroke may enable the patient to: a) exercise more independently at an earlier stage; and b) exercise in a wider variety of therapy conditions also featuring more exercise challenges.

This, in turn, may lead to better treatment outcome at the ICF (International Classification of Functioning, activity and participation) [8] function level and activity level.

Aim

The aim of the present study is to investigate the added-value of reduction of early signs of spasticity in the upper extremity on improving functional arm-hand skill performance in sub-acute stroke patients with either a severely or moderately affected arm-hand (Utrechtse Arm-hand Test (UAT) [7] scores 1-3) and moderate to severe grades of spasticity, i.e. Modified Ashworth Scale (MAS) [32] score +1 to3. Therapy-as-usual, involving a regular, well-documented, concise arm-hand rehabilitation treatment (called CARAS) [3] will be provided during each patient's rehabilitation program.

The general research question is:

To what extent does reduction of spasticity in the shoulder, arm and hand muscles, adjuvant to a Concise Arm-hand Rehabilitation Approach in Stroke (CARAS), improve functional arm-hand skill performance in sub-acute post-stroke patients with a moderately to severely affected arm-hand (UAT scores 1-3) and moderate to severe grades of spasticity?

This general research question is subdivided in to three specific sub-questions, to be analyzed and answered using 3 design approaches. Each design approach is explained in-depth below.

- Sub-question 1 (necessitating a single case experimental design):

Which relation exists between the time the spasticity reducing treatment was started in the sub-acute phase after stroke in subject X and any changes in the time series' trend regarding each patient's arm-hand function and arm-hand skill performance?

- Sub-question 2 (necessitating a single arm group design):

To what extent does the rate of improvement as to arm-hand function and arm-hand skill performance change after baseline as a result of the spasticity reducing treatment in sub-acute stroke patients?

- Sub-question 3 (necessitating a non-randomized double arm group design):

To what extent do sub-acute stroke patients receiving spasticity-reducing therapy adjunct to CARAS improve more as to their arm hand function and arm-hand skill performance than patients who only received CARAS (i.e. patients from the AMUSE study [9])?

Methods/Design

This study (version: V2, dated June 16th, 2016) has received ethical approval by the Medical Ethics Committee of Maxima Medical Centre in Veldhoven, the Netherlands (METC reference number: W16.027; CCMO code: 56494.015.16). This study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen (WMO) [33]).

Design & duration

The current interventional study gauges the added-value of early post-stroke spasticity reduction in the upper extremity during 'therapy as usual', on AHF and AHSP levels in sub-acute stroke patients using three methodological approaches, i.e.:

i) A (multiple baseline) single case experimental design [34] involving 10 individuals.

ii) A meta-analysis of the data of all single cases (single arm group design).

iii) Non-randomized double arm group design, i.e. a case-matched control design in which each patient receiving early post-stroke spasticity reduction treatment will be matched (according to arm-hand capacity, spasticity level, age, gender, UAT score) to a case from the AMUSE study [9].

After patient's eligibility screening and written informed consent, both primary and secondary outcome measures will be taken at baseline, followed by measurements at 1-wk intervals during the 2 x 6 weeks (total 12 wks, i.e. CARAS training episode 1 and CARAS training, episode 2 CARAS treatment and at 2-wks intervals during the ensuing 3 months follow up, resulting in a time series per patient per outcome measure. (Figure 1). Blinding of participants, therapists or data analysts as to the intervention provided is not possible in this study.

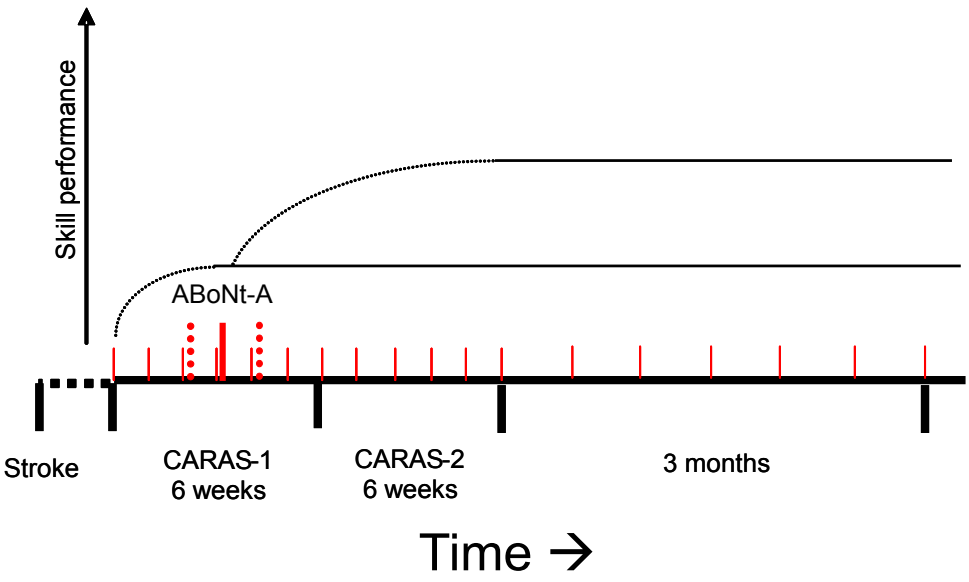
Generic explanation of the study designs used:

i) Multiple baseline single case experimental design:

In single case experimental design studies time series, consisting of many sequential observations (measurements), are recorded for each individual subject. After a baseline period an experimental stimulus or intervention is applied. In the subsequent time phase the effect of this experimental stimulus or intervention on primary and secondary outcome measures relative to baseline values is investigated. The length of the baseline phase may be constant between participants (e.g. measurements may be taken weekly for 5 wks) or may vary between participants (e.g. in subject A baseline measurements may be taken weekly for 4 wks, whereas for subject B baseline measurements may be taken weekly for 5 wks, and for subject C for 6 wks). The latter approach, featuring different starting moments of the experimental stimulus or intervention across participants in a study, is called "*multiple baselines across subjects*".

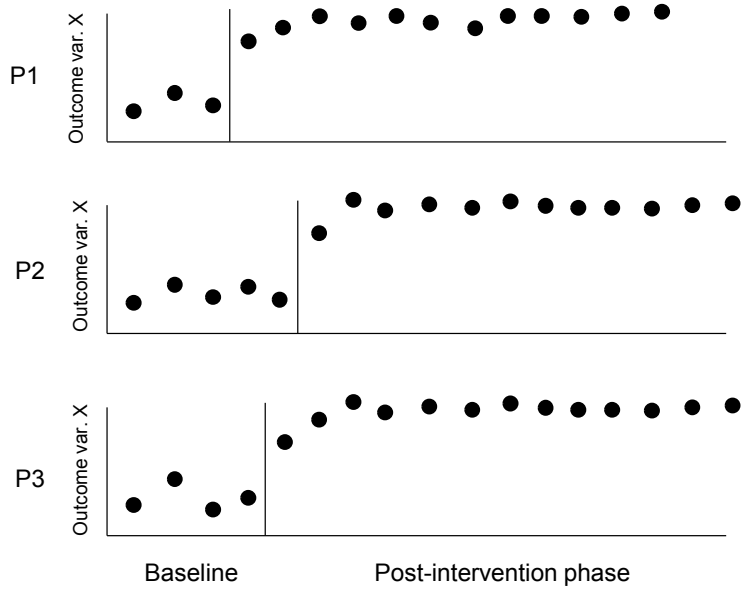
Using a 'multiple baseline' design in single case experimental research, as is done in the present study, strengthens the design [34], because it reduces the chance of any changes in the outcome parameters after the experimental stimulus of intervention being attributable to other factors than the experimental stimulus or intervention applied. In other words: If changes in outcome parameters occur ONLY AFTER the application of the experimental stimulus or intervention, the chance of this change being caused by a chance factor is reduced. We can (statistically) relate the 'position on the time axis' of the occurrence of the intervention to the 'position on the time axis' of the occurrence of any effect (outcome measure time series trend changes). In Figure 2 an example of a multiple baseline design across subjects is depicted.

Since the subjects in the proposed study are patients in the sub-acute phase after stroke, it is likely that their performance will improve due to e.g. spontaneous recovery and the therapy they receive, especially in the early phase post-stroke. On the other hand, the occurrence of spasticity in this sub-acute phase may slow down or



ABoNt-A=application of ABoNt-A. Vertical red solid lines: measurement dates. Vertical dotted lines=delineation of multiple baseline, i.e. the time window in which ABoNt-A is applied. Horizontal lines=level of (postulated/expected) arm-hand skill performance. CARAS-1=CARAS training episode 1. CARAS-2=CARAS training episode 2.

Figure 1: Measurement points in time.



Dotted line: experimental stimulus or intervention. Dark dots: measurements of outcome variable X. P1, X.P2, X.P3: participants

Figure 2: Example of a multiple baseline design across subjects

hamper improvement in voluntary movements. The baseline data (i.e. the baseline time series representing changes in the outcome measures during baseline phase) thus may reflect effects of spontaneous recovery and/or effects of 'therapy as usual' (in our case CARAS). These baseline data may show a trend (e.g. towards gradual improvement of arm-hand parameter outcome over time, or e.g. a non-improvement of arm-hand parameter outcome due to spasticity starting to develop). If, at some point, a spasticity-reducing treatment is applied, the trend of arm-hand parameter outcome observed in the prior phase (baseline phase) may change (the patient may become proficient more rapidly regarding outcome measure X or Y). An example of this concept is given in Figure 3.

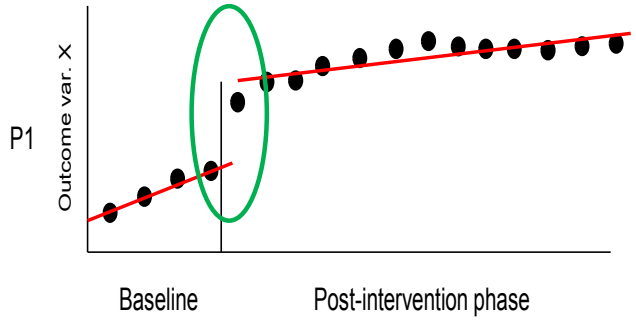
ii) Meta-analysis of the data of all single cases (single arm group design)

First, each time series of each subject will be 'de-trended' for any baseline trends, similar to the approach reported by Franck et al. [35]. This will result in a 'detrended' time series for each subject, data of which are rendered mutually independent by this de-trending technique. The latter is important in view of the ensuing statistics to be used. Next, for each subject, mean values of the residuals from the baseline phase and the post-intervention phase will be calculated. Subsequently, for each of the (two) phases, these data will be pooled across subjects, after which non-parametric statistical analyses will be performed on the pooled dataset.

iii) Case-matched control design (non-randomised double arm group design)

In this design, for each of the participants in the present study, a case-matched control subject from the database of the AMUSE study will be sought. All stroke patients suffering from arm-hand problems, who are admitted to Adelante rehabilitation centre, receive CARAS treatment.

In the (previously performed) AMUSE study 89 sub-acute stroke patients who entered Adelante rehabilitation centre and who suffered



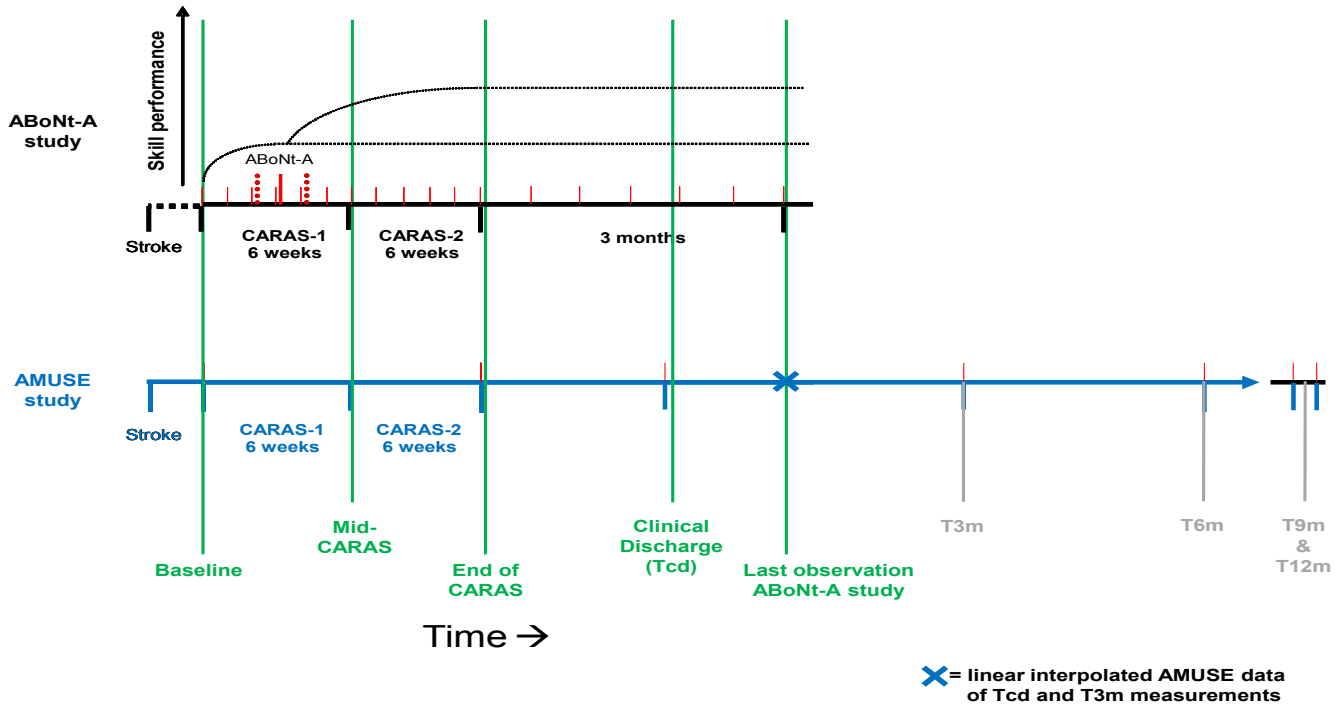
Dotted line: experimental stimulus or intervention. Dark dots: measurements of outcome variable X. P1: participant 1. Solid lines: baseline trend and post-intervention trend. (For simplicity reasons a linear trend line is depicted here. Other, higher order trend lines may be used.)

Figure 3: Example of change in time series trend

from arm-hand problems due to the stroke, were monitored during their rehabilitation phase and up to 12 months post-discharge [9].

As to the frequency of measurements/assessment, in the AMUSE study arm-hand assessments at ICF function level and at activity level were performed at baseline (i.e. before arm-hand treatment started), at 6 wks into the CARAS arm-hand training program, immediately after the CARAS training program (i.e. at 12 wks post-baseline), at clinical discharge, and at 3, 6, 9 and 12 months post-discharge. Measures at ICF participation level were done at baseline, clinical discharge and at 12 months post-discharge. In order to compare data from the AMUSE study and the present study measurement, we will use data of the present study that are collected at the same time points during the AMUSE study. In Figure 4 an overview of the 'synchronous' measurement dates for both the AMUSE study and the present study are depicted (Figure 4).

The AMUSE study and the present single case experimental design study share 5 similar measurement dates.



ABoNt-A=application of ABoNt-A. CARAS-1=CARAS training episode 1. CARAS-2=CARAS training episode 2. T=Measurement moment at 3, 6, 9 and 12 months after clinical discharge.

Figure 4: Measurement dates for both the AMUSE study and the present study.

- AMUSE: baseline (Tbl)

The time at which baseline measurements are performed in the AMUSE study is identical to the time at which the first baseline measurement of the present study is performed (Figure 4).

- AMUSE: mid-CARAS & end-CARAS (T6w & T12w)

Similarly, after the initial 6 weeks of CARAS training an arm-hand assessment has been performed in the AMUSE study (T6w or Tmid-CARAS). This measurement time is identical to one of the present study measurement dates. This also applies to the AMUSE measurement date immediately after CARAS has finished, i.e. after 12 weeks of CARAS training (T12w or T_end-of-CARAS).

- AMUSE: clinical discharge

In the AMUSE study arm-hand assessments are also performed at clinical discharge (Tcd). Again, this measurement time is identical to one of the present study measurement dates. (Figure 4, fourth vertical dotted line.)

- Last measurement date of the present study

In the AMUSE study no exact measurement date as counterpart of the last measurement of the present study is available. However, a good approximation of data from the AMUSE study at a similar time point may be performed by linearly interpolating the AMUSE data using data from Tcd and T3m, taking into account the time difference between Tcd and the time at which the last measurement of the present study was taken. (Figure 4, X-mark.)

Setting

All patients in the present study will be identified among the sub-acute stoke patient population of Adelante rehabilitation centre in Hoensbroek, the Netherlands. The present study will be performed at Adelante in Hoensbroek. All patients who, in the past, have participated in the AMUSE study (anonymous database data of which will be used in the case-matched control design part of the present study) were patients from Adelante rehabilitation centre.

Study population

The present study focusses on adult sub-acute stroke patients with either a severely or moderately affected arm-hand (Utrecht Arm-hand Test (UAT) [7] scores 1-3) and moderate to severe grades of spasticity, i.e. Modified Ashworth Scale (MAS) score +1 to 3. These patients will be recruited from the patient population of the department of brain injury rehabilitation of the Adelante rehabilitation centre in Hoensbroek, The Netherlands. This study will include 10 patients who develop (early signs of) spasticity in the upper extremity during the sub-acute phase after stroke.

Stroke patients who have a severe paretic arm and hand (UAT scores 1-3) at admission to the rehabilitation centre will be asked to participate (by letter from their rehabilitation physician (KR)) as soon as possible after admission to the rehabilitation centre. After giving written informed consent, collected by the researcher (JAF), measurements will start according to the protocol described.

Patients, who develop early signs of spasticity in the arm and/or hand, i.e. within 5 weeks after start of arm-hand treatment (CARAS), will remain in the study. In patients who have a severe paretic arm and hand (UAT scores 1-3) at admission to the rehabilitation centre, but who do not develop early signs of spasticity within 5 wks after start of arm-hand treatment (thereby not being in the target group),

measurements to be used in the study will cease. Their rehabilitation treatment will follow 'therapy-as-usual' as will their regular therapy-related clinimetrics. Any research data of the latter patient group recorded for the sole purpose of the research will be discarded/erased.

Inclusion criteria: In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age>=18 yrs
- Supratentorial stroke, i.e. arteria cerebri media infarction.
- Sub acute phase after stroke, i.e. between 2 wks and 3 months post-stroke.
- Severe paretic arm and hand: UAT scores 1-3.
- Functional disabling spasticity in the upper extremity: Modified Ashworth Scale (MAS) scores +1 to 3 (developing within 5 weeks after the start of CARAS).
- Eligible to participate in CARAS for a period of 12 wks.
- Being able to understand the questionnaires and measurement instructions.

As to functional disabling spasticity in the upper extremity, patients developing spasticity in the early sub-acute phase after stroke (i.e. within 5 wks after the start of CARAS) with a Modified Ashworth Scale (MAS) score of +1 to 3 will continue to participate in the study.

Exclusion criteria: A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Severe non-stroke related co-morbidity that may interfere with arm-hand function.
- Additional complaints that may interfere with the execution of the measurements.
- No informed consent.

Sample size calculation

As to the Single Case Experimental Design (SCED), by definition these studies involve 1 person. Despite this, a sample size calculation is needed given the group-wise analyses of the second and third part of the present study, i.e. the meta-analysis of the data of all single cases (single arm group design) and the case-matched control design (non-randomized double arm group design).

The sample size calculation is based on data from the AMUSE cohort study, i.e. on the improvement on the main outcome measure used in the present study (ARAT) as observed in patients with an UAT scores of 1-3 who did (Group A) or did not (Group B) develop signs of spasticity in the upper extremity within the AMUSE study. In the present study the ARAT is the primary outcome measure. Mean improvement on the ARAT after 12 weeks of CARAS was 17.3 points (sd: 12.2) for Group A and 38.3 points (sd: 19.2) for group B. Given a two-sample method, a double-sided statistical test, a power of 80% and an alpha of 0.05, a loss to follow-up of 10%, 10 participants per group are needed.

It is expected from clinical experience, our experiences with the AMUSE cohort study, and recent influx numbers of patients in Adelante rehabilitation centre that the number of 10 patients meeting the inclusion criteria within a reasonable time span (i.e. 16 months) is well-feasible. The data of 10 case-matched control subjects will be extracted from the AMUSE database. Therefore, in total, data of 20 patients will be used.

Interventions

CARAS: Arm-hand rehabilitation treatment will be provided according to the CARAS approach as described by Franck et al. [3]. In Adelante rehabilitation centre and multiple other rehabilitation centres in the Netherlands, CARAS is 'therapy-as-usual'. After a standard initial clinical assessment, patients will receive arm-hand rehabilitation treatment for 2 x 6 weeks. Based on the UAT scores, patients are allocated to one of three training programs, i.e.:

- CARAS program 1: severely impaired AHF subgroup (UAT=0-1).
- CARAS program 2: moderately impaired AHF subgroup (UAT=2-3).
- CARAS program 3: mildly impaired AHF subgroup (UAT=4-7).

Program 1 is titled "*taking care and prevention*". It is designed for stroke survivors who, due to the severity of the stroke, are not able to use their affected arm and hand for skill performance in daily life situations (non-functional arm-hand). Programs 2 and 3 are high intensity, task-oriented arm-hand performance training programs in which patients learn to integrate their affected arm and hand in daily occupations to optimize their overall functional abilities in daily situations. In this part a distinction is made between persons who have a moderately affected arm and hand, i.e. those who are able to use their affected arm and hand for passive and active stabilisation tasks, like fixating bread while making a sandwich; and persons with a mildly affected arm and hand, who are able to use their affected arm and hand instantaneously in daily situations.

CARAS is the standard therapy (therapy-as-usual) provided by physiotherapists and occupational therapists to all stroke patients with arm-hand problems who are admitted to Adelante rehabilitation centre for treatment. This means that the decision to apply CARAS is taken before inclusion of the patient in the study.

The present study focusses on patients with initial UAT scores of 1-3.

Spasticity-reducing treatment: In order to reduce spasticity, abobotulinum toxin A (ABoNt-A) will be administered once, i.e. directly following the sequence of baseline measurements in each patient who is developing (early signs of) spasticity in the upper extremity.

In the present study abobotulinum toxin A (ABoNt-A) is a non-investigational product. abobotulinum toxin selectively targets cholinergic nerve endings *via* binding to ecto-acceptors to block acetylcholine release at the neuromuscular junction thereby abolishing the motor end-plate potential. This causes prolonged muscle weakness. Original nerve terminals regain function 12 wks after ABoNt-A injection with full recovery of nerve-evoked muscle contraction [36]. In clinical practice reduced muscle tone is seen up to 24 wks in the sub-acute phase in patients with early post-stroke spasticity [37,38].

ABoNt-A will be administered by a senior rehabilitation physician at Adelante rehabilitation centre. Patients will receive ABoNt-A injected according to clinical judgement into the dominant spastic muscles of the arm and/or forearm. The total maximum dose for the upper limb will be 1000U [39]. ABoNt-A dosage for individual muscles will be in line with the dose ranges reported by Dashtipour et al. [40], and Gracies et al. [39]. Muscles will be identified using electro stimulation or echography according to the normal practice of the clinician.

The decision to use ABoNt-A is entirely based on clinical necessity, i.e. when a patient is developing spasticity in the upper limb muscles on

the affected side (MAS score +1 to 3), as established by the rehabilitation physician. After the first finding of this increased MAS score, the decision to apply ABoNt-A will be taken by the rehabilitation physician and the application itself will be done within 1 wk.

Patients in the target group, i.e. those who have a severe paretic arm and hand (UAT scores 1-3) at admission to the rehabilitation centre, will be asked to participate as soon as possible after admission to the rehabilitation centre. After giving informed consent, measurements will start according to the protocol described. Therapy adherence will be monitored, based on regular clinimetric assessment, as part of the regular daily clinical practice.

Data collection & measures used

At the patient's entry into the study, i.e. after the eligibility screening and patient's written informed consent, the following socio-demographic variables will be recorded: age, gender, educational level and the patient's living situation. Furthermore, medical variables, obtained from medical files of the referring consultant in rehabilitation medicine, include: stroke type (haemorrhagic or ischemic), lesion site, time since stroke, paresis level, co-morbidity, hand dominance prior to the stroke, and arm- hand function status (UAT score). During the informed consent procedure, patients will be asked for permission to use this information of their medical file.

Data collection started on October 10th, 2016 when the first patient was included. Currently, patients are being recruited and enrolled.

As to the primary outcome measures, improvement of the patients' functional arm-hand skill performance capacity will be gauged by using the Action Research Arm Test (ARAT) [41-44]. The ARAT is reliable, valid and sensitive to change in patients after stroke [42,44-46]. It consists of four subtests comprising 16 grasp movements and three reaching movements. Items are scored on a 4-point scale, with a max score of 57.

Secondary outcome measures include:

- ABILHAND [47,48], gauging perceived level of arm-hand skill/activity proficiency. The ABILHAND is a semi-structured interview, using a 3-level ordinal rating scale: impossible (0), difficult (1), and easy (2) to perform. The ABILHAND is valid, responsive and clinically useful [47,49].
- Bilateral arm activity monitoring [50,51]: As to actual arm-hand skill performance, bilateral activity monitors (3D accelerometry, AX3, Axivity Ltd) will be worn around both wrists for a period of 4 consecutive days.
- Fugl-Meyer Motor Assessment (FM) [44], gauging arm-hand function level. The upper extremity section of the FM is a reliable and valid test for measuring changes in arm-hand-function in stroke patients [52,53]. Its score ranges from 0 to 66.
- JAMAR strength test [54], gauging muscle strength, expressed in Newton.
- Motricity Index (MI) [55], gauging functional strength measurement during performance of daily tasks.
- Modified Ashworth Scale (MAS) [32] gauging spasticity levels in the upper extremity.

During the first 12 wks measurements involving the ARAT, ABILHAND, FM, JAMAR, MI and MAS will be performed weekly. In the ensuing 3 months these measures will be administered every 2 wks. The accelerometry measurements will be performed once every 3 wks.

Data storage & safety

Data collected will be stored in an electronic trial master file on a secured network drive of the Adelante network. All data will be coded immediately during measurement. Coding will be done using a combination of numeric and alphanumeric characters, which are not related to the participant and cannot be used to trace/identify the participant. Non-coded data (e.g. participant's name) will be recorded separately. HAMS is the person who has sole access to the coding key. The non-coded data will solely be accessible to two persons, i.e. JAF and HAMS. The anonymised data will be accessible to JAF, RJEMS, and HAMS.

Four yrs after the project has finished all identifiable data will be destroyed, preventing any further link between the results and participants. All data will be destroyed and/or deleted after 15 yrs.

Data processing & statistical analysis

General: For graphical data presentation, time series per subject and boxplots (for grouped data) will be used. As to all data, any change over time of 5% or more will be considered a meaningful change.

From the accelerometer data mean 'activity counts' during waking h will be calculated for both hands. A 'count' is an occasion at which the accelerometer signal exceeds a predefined threshold, indicating(arm-hand) activity intensity. An example of identifying waking h (or 'uptime') is given in Figure 5.

For each 'uptime' the amount of time a patient used hands, no hands, his affected hand and his unaffected hand will be calculated. Similarly, the number of 'counts' at occasions where a patient used hands, no hands, his affected hand and his unaffected hand will be calculated. These data will each be averaged across the number of days the accelerometers were worn.

Handling of missing values: When 1 or 2 (temporally adjacent) value(s) are missing, these missing value(s) will be estimated by linear interpolation using the two valid adjacent values in the time series. In case of the final time series observation missing, the 'last-observation-carried-forward' principle will be used. In case of 3 or more consecutive missing values, the whole case (for the measure at hand) will be discarded.

First design procedure: Single case experimental design: Statistics regarding ARAT, ABILHAND, FM, JAMAR and MI will encompass permutation tests involving the time series of each subject separately. The length of the baseline epoch will vary between 4-6 wks between subjects. This procedure will provide an answer to the question whether there is a relation between the time the spasticity reducing treatment was started in subject X and any changes in the time series' trend regarding each patient's arm-hand capacity (ARAT), each patient's arm-hand perceived performance (ABILHAND), as well as arm-hand function (FM), grip strength (JAMAR) and functional arm-hand strength (MI). (Figure 3) Here, data are analyzed for each subject separately. MAS results will be reported descriptively by plotting the time series of each subject.

Second design procedure: Meta-analysis of the data (single arm group design): Regarding ARAT, linear detrending for any baseline trends per subject, using a least squares method, to (partially) compensate for improvements caused by e.g. spontaneous recovery and/or other treatment received, will be calculated. The time series

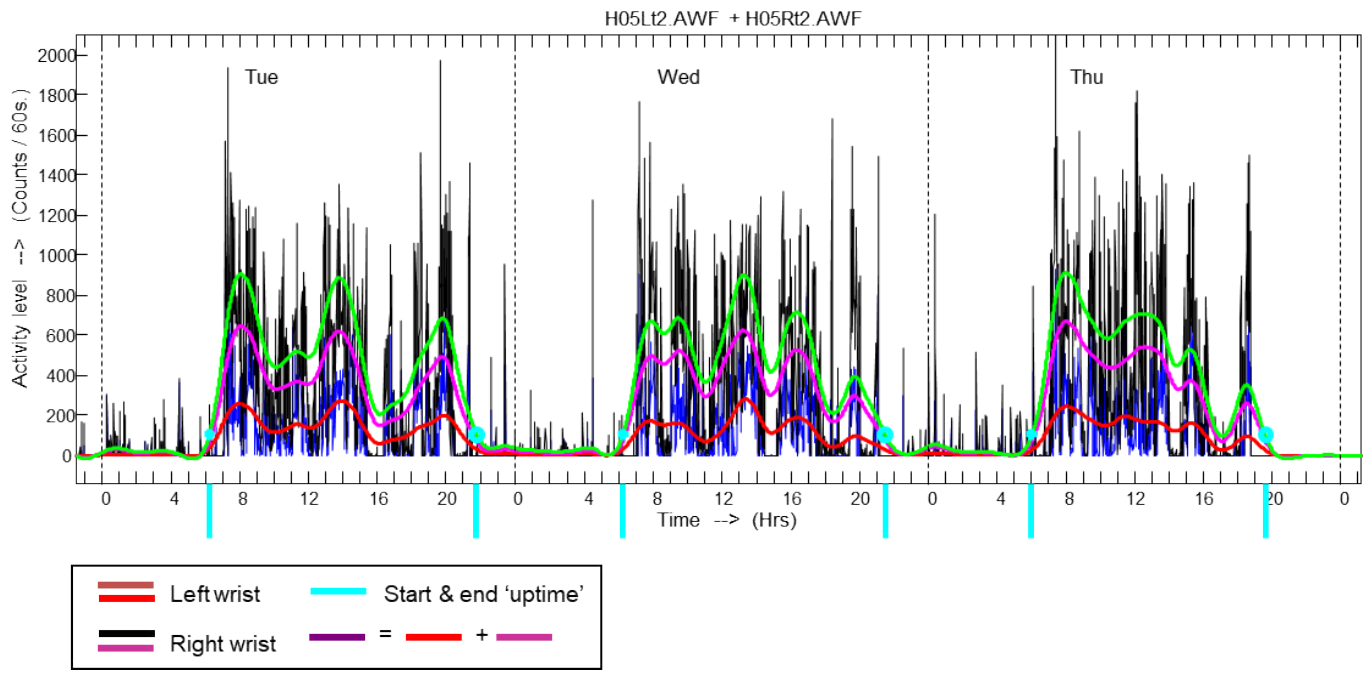


Figure 5: Identifying uptime from accelerometer signals.

of these residuals (data of which thus having been rendered mutually independent) of the whole group, will be further processed and analysed.

Per subject, mean residuals data of ARAT will be calculated for the baseline phase (Phase A), for the treatment phase after application of the spasticity reducing therapy (Phase B), and for the post-treatment up to 3 months post-CARAS (Phase C), thus resulting in 3 mean values per subject per measure.

These mean residuals per phase will be statistically tested using non-parametric Kruskal-Wallis tests in a group design. Next, multiple comparison analysis, involving Mann-Whitney U-tests between phases A & C and phases B & C will be performed using a Bonferroni correction in order to avoid spurious false positive findings. This procedure will provide an answer to the question whether, at a group level, patients improved as to their arm-hand capacity (ARAT) faster after baseline as a result of the spasticity reducing treatment.

Data processing and statistical analysis for the ABILHAND, mean 'activity counts', FM, JAMAR, and MI will be similar to the procedures described for the ARAT. MAS results will be reported descriptively.

Third design procedure: Case-matched control design (non-randomized double arm group design): Finally, per subject, differences between baseline means and follow-up means will be calculated. The latter values will then be contrasted with similar values from a matched group of patients from the AMUSE study (see earlier). In this design, for each of the participants in the present study, a case-matched control subject from the database of the AMUSE study will be sought.

In order to compare data from the AMUSE study and data from the present study measurement dates from the present study that are synchronous to the measurement dates of the AMUSE study will be identified. In Figure 4 an overview of the 'synchronous' measurement dates for both the AMUSE study and the present study are depicted.

Each subject from the SCED study part will be matched with a person from the AMUSE study according to the following procedure: Upon entry in the SCED study (baseline phase) each patient will be assessed (identical to the assessment performed in the AMUSE study subjects) in which his/her UAT score will be identified. Based on this UAT score of the SCED study subject we will search our AMUSE database for persons with an equal UAT score. Next, a match will be sought regarding the age, gender and (baseline) ARAT scores. Matching cases for spasticity level will be done when subjects first show signs of spasticity occurring, i.e. within the first 5 weeks after the start of CARAS. As an indication: About 50% of patients who have suffered an arteria cerebri media infarction and who were admitted to Adelante rehabilitation centre developed a functional limiting form of spasticity within 3-5 wks after the start of the arm-hand training program (CARAS).

Statistical analyses of the primary outcome variable (ARAT) will include Mann-Whitney U-tests. This procedure will yield whether or not patients receiving spasticity-reducing therapy adjunct to CARAS have improved more as to their arm-hand capacity than patients who only received CARAS (i.e. patients form the AMUSE study).

Again, data processing and statistical analysis for the ABILHAND, mean 'activity counts', FM, JAMAR, and MI will be similar to the procedures described for the ARAT. MAS results will be reported descriptively.

Data reporting

The investigators, without restrictions, will report the general, anonymous results of this study in scientific papers, and at international congresses. For all scientific reporting the guidelines

of the International Committee of Medical Journal Editors (ICMJE) [56] will be adhered to.

Auditing and annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited Medical Ethics Committee (METC) once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments. The METC exempted this study from instating a data monitoring committee. Furthermore, the sponsor/investigator adheres to Dutch law concerning any possible independent audit, at any time, by representatives of the competent national authorities.

Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 wks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

Safety reporting

Temporary halt for reasons of subject safety: In accordance to section 10, sub-section 4, of the Dutch Person-related Research Act (WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Adverse events (AEs): Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to CARAS and/or the application of abobotulinum toxin A. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Serious adverse events (SAEs): A serious adverse event is any untoward medical occurrence or affects that:

- Results in death.
- Is life threatening (at the time of the event).
- Requires hospitalisation or prolongation of existing inpatients' hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as a serious adverse event. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs through the web portal Toetsing Online to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Follow-up of adverse events: All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

Result and Discussion

Given the specific research (sub) questions, a number of issues have been taken into account in setting up this study protocol, leading to a combination of three methodological designs.

Firstly, we proposed time series analyses, i.e. a (multiple baseline) single case experimental design, in order to more individually control for spontaneous recovery and effects of therapy as usual in the sub-acute stage after stroke, which may vary considerably between patients. Modeling spontaneous recovery and effects of therapy as usual during baseline measurements has two advantages: a) the time series may be detrended for baseline trends, making any underlying mechanism to be investigated more pronounced, and b) the residuals obtained after the detrending procedure are mutually independent, thus making them eligible for statistical analyses aimed at the possible relation between the time the spasticity reducing treatment was started in the sub-acute phase after stroke in a single subject and any changes in the time series' trend regarding this patient's level of arm-hand function and arm-hand skill performance.

Secondly, pooling the averaged, baseline-detrended data of all subjects enables group-wise data analyses gauging the (average) rate of improvement in arm-hand performance.

Thirdly, in our previous single-armed prospective cohort study, i.e. the AMUSE study [9], we obtained longitudinal data on changes in arm-hand function and arm-hand skill performance in a large group of stroke patients' typically seen in daily clinical practice. By matching patients who have received a spasticity reducing treatment with patients from the aforementioned cohort study, we can assess the added value regarding the rate of improvement in arm-hand performance that may be attributable to the spasticity reducing treatment relative to 'therapy as usual only' in sub-acute stroke patients.

The results of this study will provide evidence on the added-value of reduction of early signs of spasticity in the upper extremity on improving functional arm-hand skill performance in sub-acute stroke patients with either a severely or moderately affected arm-hand and moderate to severe grades of spasticity.

This information may lead to changes in therapy service delivery necessitating therapist to reconsider their currently used training programs. Furthermore, it may lead to further optimization of treatment and systematic treatment monitoring, potentially leading to better outcome of arm-hand treatment in sub-acute stroke patients.

Declarations

Trial sponsor/initiator/contact

The trial sponsor/initiator is Adelante Centre of Expertise in Rehabilitation and Audiology, Zandbergsweg 111, 6432CC, Hoensbroek, the Netherlands (www.adelante-zorggroep.nl). PI and contact person for scientific queries is HAMS, (Address: Zandbergsweg 111, 6432 CC, Hoensbroek, the Netherlands; T: +31455282221; E: h.seelen@adelante-zorggroep.nl) Contact person for public queries is JAF (Address: see above; T: +31.45.528.23.58; E: h.franck@adelante-zorggroep.nl).

This trial was registered in the Dutch Trial Register (code: NTR6027) on August 4th, 2016. The secondary identifying number is: CCMO code: NL56494.015.16.

Ethics approval and consent to participate

This study (version: V2, dated June 16th, 2016) has received ethical approval by the Medical Ethics Committee of Maxima Medical Centre in Veldhoven, the Netherlands (METC reference number: W16.027; CCMO code: 56494.015.16).

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References

1. Langhorne P, Bernhardt J, Kwakkel G (2011) Stroke rehabilitation. Lancet 377: 1693-1702.
2. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G (2010) Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: Early prediction of functional outcome after stroke: The EPOS cohort study. Stroke 41: 745-750.
3. Franck JA, Halfens JAM, Smeets RJEM, Seelen HAM (2015) Concise Arm and hand rehabilitation approach in stroke (CARAS): A practical and evidence-based framework for clinical rehabilitation management. OJOT 3: 10.
4. Bandura A (1994) Self-efficacy. Ramachaudran VS, Editor. Academic press. New York.
5. Bandura A (1997) Self-efficacy: The exercise of control. W.H Freeman and Company. New York.
6. Lorig KR, Ritter P, Stewart AL, Sobel DS, Brown BW, et al. (2001) Chronic disease self-management program: 2-year health status and health care utilization outcomes. Med Care 39: 1217-1223.
7. Kruitwagen-van Reenen ET, Post MW, Mulder-Bouwens K, Visser-Meily JM (2009) A simple bedside test for upper extremity impairment after stroke: Validation of the Utrecht Arm/Hand Test. Disabil Rehabil 31: 1338-1343.
8. World Health Organization (2001) International Classification of Functioning, Disability and Health: ICF. World Health Organization, Geneva.
9. Franck JA, Smeets RJEM, Seelen HAM (2017) Changes in arm-hand function and arm-hand skill performance in patients after stroke during and after rehabilitation. PLoS One 12: e0179453.
10. Demetrios M, Gorelik A, Louie J, Brand C, Baguley IJ, et al. (2014) Outcomes of ambulatory rehabilitation programmes following botulinum toxin for spasticity in adults with stroke. J Rehabil Med 46: 730-737.
11. Bakheit AM, Thilmann AF, Ward AB, Poewe W, Wissel J, et al. (2000) A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke 31: 2402-2406.
12. Bhakta BB (2000) Management of spasticity in stroke. Br Med Bull 56: 476-485.
13. Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, et al. (2002) Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 347: 395-400.
14. Esquenazi A, Albanese A, Chancellor MB, Elovic E, Segal KR, et al. (2013) Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. Toxicon 67: 115-128.
15. Foley N, Pereira S, Salter K, Fernandez MM, Speechley M, et al. (2013) Treatment with botulinum toxin improves upper-extremity function post stroke: A systematic review and meta-analysis. Arch Phys Med Rehabil 94: 977-989.
16. McCrory P, Turner-Stokes L, Baguley IJ, De Graaff S, Katrak P, et al. (2009) Botulinum toxin A for treatment of upper limb spasticity following stroke: A multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes. J Rehabil Med 41: 536-544.
17. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM (2000) Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: A randomised double blind placebo controlled trial. J Neurol Neurosurg Psych 69: 217-221.
18. Cardoso E, Rodrigues B, Lucena R, Oliveira IR, Pedreira G, et al. (2005) Botulinum toxin type A for the treatment of the upper limb spasticity after stroke: A meta-analysis. Arq Neuropsiquiatr 63: 30-33.
19. Shaw LC, Price CI, van Wijck FM, Shackley P, Steen N, et al. (2011) botulinum toxin for the upper limb after stroke (botuls) trial: Effect on impairment, activity limitation and pain. Stroke 42: 1371-1379.
20. Baker J, Pereira G (2016) The efficacy of Botulinum Toxin A for limb spasticity on improving activity restriction and quality of life: A systematic review and meta-analysis using the GRADE approach. Clinical Rehabilitation 30: 549-558.
21. Prazeres A, Lira M, Aguiar P, Monteiro L, Vilasbôas Í, et al. (2018) Efficacy of physical therapy associated with botulinum toxin type A on functional performance in post-stroke spasticity: A randomized, double-blinded, placebo-controlled trial. Neurology International 10: 20-23.
22. Wolf S, Milton B, Reiss A, Easley K, Shenvi N, et al. (2012) Further assessment to determine the additive effect of botulinum toxin type a on an upper extremity exercise program to enhance function among individuals with chronic stroke but extensor capability. Arch Phys Med Rehabil 93: 578-587.
23. Takekawa T, Abo M, Ebihara K, Taguchi K, Sase Y, et al. (2013) Long-term effects of injection of botulinum toxin type A combined with home-based functional training for post-stroke patients with spastic upper limb hemiparesis. Acta Neurol Belg 113: 469-475.
24. Devier D, Harnar J, Lopez L, Brashear A, Graham G (2017) Rehabilitation plus onabotulinumtoxina improves motor function over onabotulinumtoxina alone in post-stroke upper limb spasticity: A single-blind, randomized trial. Toxins 9: 1-9.
25. Esquenazi A, Novak I, Sheean G, Singer BJ, Ward AB (2010) International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments-introduction. Eur J Neurol 17: 1-8.
26. Olver J, Esquenazi A, Fung V, Singer B, Ward A (2010) Botulinum toxin assessment, intervention and aftercare for lower limb disorders of movement and muscle tone in adults: International consensus statement. Eur J Neurol 17: 57-73.
27. Sunnerhagen KS, Olver J, Francisco GE (2013) Assessing and treating functional impairment in poststroke spasticity. Neurol. 80: 35-44.
28. Turner-Stokes L, Baguley IJ, De Graaff S, Katrak P, Davies L, et al. (2010) Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: A secondary analysis from a double-blind placebo-controlled randomized clinical trial. J Rehabil Med 42: 81-89.
29. Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P (2013) Results from the Upper Limb International Spasticity Study-II (ULISII): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management. BMJ Open. 3: e002771.

30. Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P, Zakine B (2013) Upper limb international spasticity study: Rationale and protocol for a large, international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin A in real-life clinical practice. BMJ Open 3: e002230.

31. Demetrios M, Khan F, Turner-Stokes L, Brand C, McSweeney S (1987) Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. Cochrane Database Syst Rev 6: CD009689.

32. Bohannon RW, Smith MB (1987) Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 67: 206-207.

33. http://wetten.overheid.nl/BWBR0009408/2017-03-01.

34. Barlow DH, Nock MK, Hersen M (2008) Single case experimental designs: Strategies for studying behavior change. Pearson Publishing. Cambridge.

35. Franck JA, Timmermans AAA, Seelen HAM (2013) Effect of a dynamic hand orthosis for functional use of the impaired upper limb in sub-acute stroke patients: A multiple single case experimental design study. Technol Disabil 25: 177-1787.

36. Dolly JO, Aoki KR (2006) The structure and mode of action of different botulinum toxins. Eur J Neurol 13: 1-9.

37. Rosales RL, Efendy F, Teleg ES, Delos Santos MM, Rosales MC, et al. (2016) Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: A meta-analysis. J Neurol Sci 1371: 6-14.

38. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, et al. (2012) Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: A randomized controlled trial. Neurorehabil Neural Repair 26: 812-821.

39. Gracies JM, Brashear A, Jech R, McAllister P, Banach M, et al. (2015) Safety and efficacy of abobotulinum toxin A for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: A double-blind randomised controlled trial. Lancet Neurol 14: 992-1001.

40. Dashtipour K, Chen JJ, Walker HW, Lee MY (2015) Systematic Literature Review of abobotulinum toxin A in Clinical Trials for Adult Upper Limb Spasticity. Am J Phys Med Rehabil 94: 229-238.

41. Van der Lee JH, Beckerman H, Lankhorst GJ, Bouter LM (2001) The responsiveness of the action research arm test and the Fugl-Meyer assessment scale in chronic stroke patients. J Rehabil Med 33:110-113.

42. Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, et al. (2001) The intra- and interrater reliability of the action research arm test: A practical test of upper extremity function in patients with stroke. Arch Phys Med Rehabil 82:14-19.

43. Van der Lee JH, Roorda LD, Beckerman H, Lankhorst GJ, Bouter LM (2002) Improving the Action Research Arm test: a unidimensional hierarchical scale. Clin Rehabil 16: 646-653.

44. Weerdt de WHM (1985) Measuring recovery of arm-hand function in stroke patients: A comparison of the brunnstrom-fugl-mayer test and the action research arm test. Physiother Can 37: 65-70.

45. Hsieh CL, Hsueh IP, Chiang FM, Lin PH (1998) Inter-rater reliability and validity of the action research arm test in stroke patients. Age Ageing 27: 107-113.

46. Yozbatiran N, Der-Yeghiaian L, Cramer SC (2008) A standardized approach to performing the action research arm test. Neurorehabil Neur Rep 22:78-90.

47. Penta M, Tesio L, Arnould C, Zancan A, Thonnard JL (2001) The ABILHAND questionnaire as a measure of manual ability in chronic stroke patients: Rasch-based validation and relationship to upper limb impairment. Stroke 32: 1627-1634.

48. Penta M, Thonnard JL, Tesio L (1998) ABILHAND: A Rasch-built measure of manual ability. Arch Phys Med Rehabil 79: 1038-1042.

49. Ashford S, Slade M, Malaprade F, Turner-Stokes L (2008) Evaluation of functional outcome measures for the hemiparetic upper limb: A systematic review. J Rehabil Med 40: 787-795.

50. Lemmens RJ, Timmermans AA, Janssen-Potten YJ, Pulles SA, Geers RP, et al. (2014) Accelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: A randomized controlled trial. PLoS One 9: e96414.

51. Van der Pas SC, Verbunt JA, Breukelaar DE, van Woerden R, Seelen HA (2011) Assessment of arm activity using triaxial accelerometry in patients with a stroke. Arch Phys Med Rehabil 92: 1437-1342.

52. Gladstone DJ, Danells CJ, Black SE (2002) The fugl-meyer assessment of motor recovery after stroke: A critical review of its measurement properties. Neurorehabil Neur 16: 232-240.

53. Salter K, Jutai JW, Teasell R, Foley NC, Bitensky J, et al. (2005) Issues for selection of outcome measures in stroke rehabilitation: ICF Participation. Disabil Rehabil 27: 507-528.

54. Hamilton GF, McDonald C, Chenier T (1994) Meting van de grijpkracht: Waarde en betrouwbaarheid van de bloeddrukmeter en de 'Jamar grijpdynamometer'. Stimulus. 13: 164-165.

55. Wade DT (1989) Measuring arm impairment and disability after stroke. Int Disabil Stud 11: 89-92.

56. http://www.icmje.org/recommendations/archives/2005_urm.pdf