Higher doses of intensive upper limb rehabilitation for moderate to severe impairment in acute, subacute stroke: Phase I dose escalation study

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Abstract

Background: Optimizing moderate to severe upper limb recovery is likely to require a higher dose of rehabilitation training than is currently delivered, but the feasibility and acceptability of higher dose regimes is unclear in the early-stage post stroke.

Objective: To determine the maximum time on task of upper limb rehabilitation in people with moderate to severe impairment in acute and early sub-acute stage of stroke, in a phase 1 dose-escalation study.

Methods: Participants were recruited using a 3+3 study design from two stroke units and rehabilitation centers in Belgium. Patients received standard care plus escalating doses of upper limb motor training at four levels: 1 (40 minutes), 2 (67 minutes), 3 (100 minutes) and 4 (133 minutes). Treatment was provided for three daily sessions, starting with three participants at level 1 and if dose was completed based on dose-limiting criteria, it was escalated to the next level with three new participants.

Results: Eighteen participants were recruited (median days post-stroke: 7.5 [Q1:5; Q3: 23.25]) with a mean Fugl Meyer Assessment Upper Extremity score of 29.4 (SD: 11.2). The maximum tolerated time on task of upper limb rehabilitation was, 100 minutes per day, with an additional 35 minutes of routine upper limb therapy provided as part of standard care. Level of fatigue and rate of perceived exertion were highest at dose level 4, resulting in participants not completing the dose of 133 minutes.

Conclusions: Confirmative with existing literature using a different intervention, individuals with moderate to severe impairment in the early stages of stroke can tolerate higher doses of upper limb rehabilitation than those typically administered in

standard care. These findings support future investigation into phase I/IIa dose-finding clinical trials exploring long-duration, high-intensity upper limb rehabilitation programs in the early post-stroke period.

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Keywords: dosage, session length, arm and hand movement, time spent on upper limb rehabilitation, FES, cerebrovascular accident

Introduction

Immediately after stroke, reduced function of the upper limb is reported in 35–69% of patients [1,2]. Recovery of moderately or severely affected upper limbs is lower than those that are only mildly affected [3]. One reason for poorer outcomes is that they receive less upper limb rehabilitation in acute and early subacute stages of stroke [4,5].

Clinical rehabilitation guidelines currently recommend a total of 3 hours per day of targeted motor therapy, including upper limb rehabilitation training, 5 days a week[6-8]. Generally, low rehabilitation doses are provided in the early post-stroke stage, indicating that these targets are not being met[9]. Increased session lengths of upper limb rehabilitation, focusing on quality of movement, have been found to be feasible for improving motor impairment. Specifically, up to 6 hours in chronic stroke (in a clinical service design) and an additional hour per day with a weekly hour of robot therapy in subacute stroke (in a pilot Phase IIa randomized controlled trial) have been shown to be feasible.[10,11]. In people with moderate to severe impairment in the chronic stage, a 12-week program involving five daily hours of upper limb training combined with Functional Electrical Stimulation (FES) was feasible and led to clinically significant improvement[12]. However, neither of these studies were powered phase III clinical trials which would underpin a definite claim of benefit.

There is a lack of consensus and evidence for the recommendation of higher doses of upper limb rehabilitation very early after stroke.[13] In preclinical research involving rats with acute and very early sub-acute stroke, intensive and enriched rehabilitation paradigms facilitate neurological recovery, specifically in the context of severe stroke, by promoting the restoration of forelimb motor function[14-17]. In humans, there is minimal evidence for feasibility and demonstration of high dose (>60 minutes

session length), multimodal upper limb rehabilitation programs (>60 minutes) in the acute and subacute stage especially for moderate to severe upper limb impairment [18,19]. A recent large systematic review has shown that generally low dose upper limb rehabilitation programs are currently being considered in the first six months post stroke, resulting in lack of clinical meaningful effects[20]. Patients in the early stage post stroke generally present with increased fatigue, depression or cognitive impairment [21,22]. The assumption that early-stage patients cannot adhere to high-intensity programs without prior assessment of impairments like fatigue and appropriate dose parameters is not supported by evidence. In the study by Dromerick et al., 2019, a two-hour modified constraint induced movement programme was delivered and was found to be feasible early after stroke[18]. However, the latter study lacked information about the distribution of the dose practice protocol (e.g., session length and time-on-task), and did not report on safety parameters such as fatigue, pain, or rehabilitation intensity.

Current stroke rehabilitation guidelines also recommend incorporating mental task practice into other rehabilitation interventions to enhance upper limb recovery in the early stages, particularly for individuals with moderate to severe impairments [23]. To support this, a recent network meta-analysis has also shown that interventions such as mental imagery is one of most effective interventions for treating upper limb impairment.[24] It is now time to take a step back and conduct Phase I research before Phase II to determine the toxicity and tolerated doses of potential treatments, such as a high-dose multimodal program aligned with clinical guidelines, focused on improving quality of movement in the early stage of stroke.

The Stroke Recovery and Rehabilitation Roundtable's consensus papers call for a more rigorous approach to developing interventions for stroke recovery[25,26]. Dose-finding studies offer a way to provide clear justification for the dose of stroke recovery interventions [27,28] Phase I dose-escalation studies, which originated in pharmacological research, are now a promising new approach in neurological rehabilitation. These studies begin with a low dose and gradually increase it. he goal is to determine the maximum tolerated dose (MTD)—the highest dose at which unacceptable side effects do not occur—in a small number of patients. Using a Phase I, single-ascending dose clinical trial, this research sought to answer the question: What is the maximal time on task for upper limb rehabilitation that can be performed by people with moderate to severe impairments in the early stage of stroke, while also exploring the safety and feasibility of this higher dose after acute and early sub-acute stroke? The main objective addressed was to explore the safety and feasibility of a higher dose of upper limb rehabilitation after acute and early sub-acute stroke in a phase 1, single-ascending dose clinical trial. Based on research conducted using similar rehabilitation approaches in the sub-acute phase of stroke, t was hypothesized that participants could tolerate approximately one hour of additional upper limb rehabilitation beyond standard care [11].

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical Approval was sought from Medical Ethics Committee of Ziekenhuis Oost-Limburg (ref: Z-2021046) and protocol was registered on clinical trials.gov (Identifier: NCT04973553). Potential participants from the Stroke or Geriatric Units at Campus Sint-Jan, Genk or at the rehabilitation centres at Sint-Barbara, Lanaken, Ziekenhuis Oost-Limburg and Cliniques universitaires Saint Luc Brussels, Belgium, were

screened as per criteria and approached with a participant information sheet by medical or health care professional staff. If the candidate agreed to take part, they were asked to complete an informed consent form.

Patients needed to have: (a) a first-ever unilateral, diagnosed stroke by a neurologist as defined by the World Health Organisation [29], (b) been admitted to the acute hospital or rehabilitation center, (c) upper limb hemiparesis or hemiplegia with a trace of muscle contraction:≥grade 1 at shoulder (abductors or elevators) or wrist/finger extensors measured by the Medical Research Council Scale and a score of <61 on the Motricity Index [30], (d) the age of > 18 years and (e) the ability to provide informed consent. Patients with stroke were excluded if they had: (a) other neurological impairments and (b) unable to respond to commands (score of >1 on the command item of the National Institutes of Health Stroke Scale)[31].

Descriptive measures were collected for all recruited participants, including age, gender, handedness, stroke lesion (side, type, and location, e.g., cortical or sub-cortical), and total score of the National Institutes of Health Stroke Scale.

Study Design

A single-ascending dose clinical trial was conducted to determine the MTD. Up to six participants were enrolled in each successive cohort following a 3+3 design (Figure 1) [32,33]. The MTD was defined as the highest dose allowing participants to complete a fixed maximum level of upper limb therapy for three days without experiencing dose-limiting toxicity (DLT) [32,34]. The MTD was considered reached when at least two participants in a cohort experienced DLT during the three-day rehabilitation program (Figure 1). If only one participant experienced DLT, a new

cohort of three participants was treated at the same dose level. A maximum of 24 participants (six per dose level) were required for this study design.

Dose levels

The dose of the prescribed upper limb rehabilitation program was increased gradually according to a Modified Fibonacci Increment method (MFI). Four dose levels, based on time on task, were thereby determined[32,35] Four dose levels, based on time on task, were thereby determined: (A) Familiarization starting dose: 20-minutes session (MFI); (B) Dose level 1: 40 minutes (MFI x 2.00); (C) Dose level 2: 67-minutes (MFI x 1.67); (D) Dose level 3: 100 minutes (MFI x 1.50) and (C) Dose level 4: 133-minutes (MFI x 1.33)[35].

The number of dose levels was determined in consultation with healthcare professionals and medical teams from different acute care and rehabilitation centers in Belgium, through conference calls and face-to-face meetings. Consensus was reached during the meetings on the maximal number of levels based on the remaining time left on the timetables of the patients in rehabilitation settings, for additional therapy in top of the patients' daily standard care. After inclusion, all participants completed a 20-minute familiarization starting dose session. The starting dose of 20 minutes was selected based on current approximate duration focused on arm activity training during acute and subacute rehabilitation post stroke[36,37]. Subsequently, they underwent a three-day rehabilitation program at their assigned dose level. Our initial decision to implement a 3-day rehabilitation program was based on the established principles of dose escalation in classic drug intervention design[38], as well as earlier preclinical studies that demonstrated the feasibility of 3-day exercise training programs at early stages of stroke[39,40]. Specifically, these studies showed that early exercise training after ischemic stroke in rats improves functional outcomes by enhancing

cerebral hemodynamics and promoting angiogenesis at cortical level. Secondly, a 3-day program allowed timely inclusion of participants and start-up of the study in one week.

Content of Upper limb rehabilitation program

Physiotherapists and occupational therapists from every site documented the time spent and content of upper limb rehabilitation as part of standard care. Additional multimodal upper limb rehabilitation program was conducted by main author (LTT) and co-authors (SC, NB, LT). Sections of the dose dimension tool was explained to five staff members involved in the study. Every episode time on task length of the upper limb rehabilitation program were recorded from the dose dimension tool by the researchers [41]. Episode on-task behaviour was logged in the tool defined as any activity that directly contributed to the completion of the assigned rehabilitation program. The process of logging in the information on the tool was monitored by the main author of this paper.

The planned program consisted of three components:

A) Upper limb motor training protocol

The hierarchy began with training isolated active/passive joint movement of the scapula, shoulder, elbow, forearm, wrist, fingers, and thumb, as was utilized by Daly et al., 2019. Body position such as supine, side-lying or sitting was considered to ensure good quality of movement, increased awareness of any abnormal movements with a focus on variable speed control, accuracy and repetition. As a person attained enhanced coordination of individual and/or multiple joints, these motions became integrated into the functional elements of tasks and later whole task practice such as piling cones or reaching for a bottle. When the therapist observed

compensation from the trunk, the participant was either given a break or else the movement/task was adapted.

B) Functional Electrical Stimulation (FES) protocol

If participants did not have contraindications (pacemaker or a severe skin conditions), FES (NeuroTrac Sports XL-CE marked) was applied with two to four electrodes that were set synchronous or in alternation. Either the proximal muscles (e.g. anterior deltoid or triceps) or distal muscles (e.g. extensor digitorum or extensor pollicis longus) were stimulated with two to four electrodes encouraging active movement during augmented functional training (e.g. reaching for a glass). Short muscle contractions were delivered at a frequency 35Hz, pulse width 250μs, contraction time 8 sec, relaxation time 5sec, ramp up/down 2 sec.

C) Mental task practice or mirror therapy

For mental task practice, participants were asked to mentally simulate an action such as reaching a bottle from a table lasting 5 seconds for each action. The latter was also sometimes combined with the FES program during the relaxation phase [42]. For mirror therapy, the participants' affected upper limb was behind the mirror and moved the unaffected upper limb by executing of arm, hand and finger postures, viewing its mirror image as if it were the affected one.

For dose levels 1 and 2, upper limb training occupied 50% or 67% of session time, while FES comprised 50% or 33% respectively. For dose levels 3 and 4, both morning and afternoon sessions allocated 70% to upper limb training and 30% to FES. However, FES was reduced to 20% in the afternoon, with 10% dedicated to

mirror therapy. Participants received one optional 5-minute break per session, excluded from total session time.

Safety assessment monitoring

Safety assessment monitoring was conducted by a medical doctor (co-author PH). DLT thresholds were defined as: failure to complete more than 80% of prescribed three-day rehabilitation dose [e.g. in dose level 40minutes x 3=120 minutes), medical complications or high levels of fatigue, pain or rate of perceived exertion. These measures were assessed by calculating mean scores at the beginning, middle, and end of each session. In stroke, high levels of fatigue and pain negatively impact on sensorimotor performance and behavior[43] leading to prolonged reaction times, increased muscle activation, decreased motor unit firing frequency and reduced position sense[44,45]. These factors influence the planned upper rehabilitation programme. The intensity of training is now widely recognized as a fundamental and necessary element of exercise prescription in rehabilitation[46]. Intensity is also commonly monitored using the rate of perceived exertion scale[47].

These were scored using specific rating scales:

Fatigue by the Visual Analogue Scale-Fatigue [48]- Participants rated their fatigue on item 4 on a 0-10 scale (0 = not at all fatigued, 10 = extremely tired). A mean score ≥8 indicated severe fatigue was considered a sign of DLT [49].

Pain by the Numeric Rating Scale [50]- Participants rated their level of pain 0-10 scale, with 10 being the most intense level of pain and 0 being no pain. A mean score ≥ 8 indicated too painful, was considered a sign of DLT [50].

Borg Rating of perceived exertion (BRPE) [51]- This is a simple, reliable method of monitoring exercise intensity, which is crucial for any exercise program[52]. Participants were asked: “what was the highest perceived intensity of effort during those tasks on a scale of 6–20, 6 relating to no effort and 20 relating to maximal intensity of effort?”. Therefore, a mean score of ≥ 17 indicated the training was too hard or extremely hard, was considered a sign of DLT [47,53].

Upper limb behavioral assessment monitoring

Clinical outcome measures were collected at baseline (day 1) and at post-intervention (days 4-7) by the author of the paper (LTT) and co-author (SC). The authors of this paper (LTT and SC) trained together in performing and scoring the assessments in a standardised protocols [54,55]. To ensure high intra-rater reliability, the first two participants were scored jointly by the two assessors. The Fugl-Meyer Assessment Upper Extremity (FMA-UE), assessed motor impairment and coordination of the impaired upper limb with a maximum motor score of 66 [56]. The Motricity Index assessed upper limb strength (shoulder abduction, elbow flexion and pinch grip), with a maximum score of 99 [57]. The Action Research Arm Test assessed disability by testing the ability to grasp, move, and release objects and also gross upper limb movements with a maximum score of 57 [58]. These are recommended outcome measures of upper limb impairment and disability [59].

Data Analyses

After testing for normality, descriptive analyses included calculation of median (interquartile range [IQR]) for demographics and mean (standard deviation) for safety and clinical measures in JMP®, Version 17. SAS Institute Inc., Cary, NC, 1989–2023. Figures representing the mean (SD) scores (for all the three sessions) for safety

measures per dose level were plotted on MATLAB (R2022b). Exploratory analysis on the effect of intervention based on clinical measures (FMA-UE, Action Research Arm Test and Motricity Index) were conducted.

Results

Demographics

Eighteen participants (33% Female and 67% Male) consented and took part in the research (Table 1). They had median age of 67 years (Q1:57; Q3:72.25) and were at a median time post stroke of 7.5 days (Q1:5; Q3: 23.25). The mean FMA-UE score at baseline was 29.4 (SD: 11.2) (Table 2). Participant enrolment began on October 8, 2021, and concluded on December 16, 2023.

Standard care

In both acute and rehabilitation units, standard care (time with the therapist) consisted of 30-minute occupational therapy sessions focused on upper limb bimanual movement and unimanual functional tasks and one hour of lower limb training. Due to a different practice at one rehabilitation center, standard care for three of six participants at dose level 4 included a higher dose of upper limb therapy: 70 minutes per day, plus 15 minutes of mobilization techniques to promote normal active range of movement prior to the program. The first three participants in the fourth dose level received a lower standard care dose, and one experienced DLT. The subsequent three participants in the same dose level received the higher standard care dose (70 minutes of upper limb therapy plus 15 minutes of mobilization), and one also experienced a DLT.

Maximum tolerated upper limb rehabilitation dose

The MTD of upper limb rehabilitation was determined to be 100 minutes time on task (dose level 3) in addition to standard care for three consecutive days. Two participants withdrew early: one due to a second stroke (dose level 2) and another due to extreme fatigue (dose level 4). A third participant at dose level 4 could not complete 80% of the required time due to fatigue. While four of the six participants at dose level 4 completed 115-133 minutes time on task, those at lower doses generally followed the planned program. One participant unresponsive to FES received additional upper limb training instead. Mirror therapy was applied to three participants with severe impairments at levels 3 and 4.

Safety and clinical measures per dose level

The mean change of end-from-baseline scores of reported fatigue and BRPE, were highest at dose level 4 (*Level 1*: Fatigue -0.8, BRPE +0.1; *Level 2*: Fatigue +1.7, BRPE +1.5; *Level 3*: Fatigue +2.1; BRPE +3.3; *Level 4*: Fatigue +3.7; BRPE +5.0). Neck and back pain were reported in three participants in dose level 2, shoulder pain in five participants in dose levels 3 and 4 and a headache in participants in dose level 4, There was no change on level of pain at dose level 1 but small increase in level of pain in dose levels 2 (+ 2.0), 3 (+0.3) and 4 (+0.2) (Figure 3).

Largest mean change in FMA-UE from baseline was identified in dose level 3 (Level 1: + 1.67 [SD: 11.24]; Level 2: 11.8 [SD:6.58]; Level 3: 15.67 [SD: 12.66]; Level 4: 9.75 [SD: 17.35] (Table 3). One must note that due to the presented phase 1 research design, changes in clinical measures cannot be used to claim efficacy or effectiveness.

Discussion

The findings from this dose-escalation study are consistent with the existing literature using a different intervention, showing that people with moderate to severe impairment in early stage of stroke can tolerate higher doses of upper limb rehabilitation than typically administered in standard care. This research presents results from the first phase 1 dose escalation study aiming to explore the safety and maximal session length of upper limb rehabilitation for moderate to severe upper limb impairments in acute and early subacute stage of stroke. The maximum tolerated daily dose of rehabilitation, 100 minutes of time on task in addition to the standard 30 to 60 minutes of upper limb training, was higher than hypothesized. Changes in clinical measures were also presented; however, the intent of a phase 1 study is not efficacy, and therefore the changes observed should not be interpreted as any indication of efficacy.

High dose rehabilitation programs in the early phase of rehabilitation for people with stroke are currently underutilized in clinical practice [5]. In this study, we found that participants 50 minutes time on task of upper limb rehabilitation in the morning and 50 minutes time on task in the afternoon, on top of their standard care. This aligns with the SMARTS2 study where people with sub-acute stroke tolerated 120 minutes time on task of neuroanimation therapy, when divided into one-hour morning and afternoon sessions[60]. Similar to the aforementioned study, we also demonstrated the feasibility of upper limb motor training, focusing on quality of movement in addition with FES in the early stage of stroke for individuals with moderate to severe impairment. Other early stroke studies have also found higher-dose rehabilitation programs with different content to be feasible such as task-specific training in Phase

II Critical Period After Stroke Study (20 extra hours) [19] or Constraint Inducted Movement Therapy (2-3 hours session length) in the VECTORS study [18]. However, while the ARAT was our chosen primary outcome measure, it only assesses whether a task can be completed, not how well it is performed.[13] Furthermore, the primary focus of some interventions may prioritize compensatory strategies over quality of movement, while the latter is a priority in the early stage of stroke[61].

Treating moderate to severe upper limb motor impairment is complex and multifaceted. This complexity arises from underlying neural mechanisms including severity of white matter hyperintensities, lesion location and corticospinal tract impairment, [62,63] as well as the level of spasticity [64]. Beyond motor impairment severity, comorbidities such as cardiovascular health, cognitive impairment, fatigue and pain can hinder the implementation of high-dose rehabilitation in some patients [22,65]. Despite these challenges, the presented research suggests that high-dose upper limb rehabilitation may be feasible for people with moderate to severe impairment in the early post stroke stage. From dose level 2 onward, participants rarely reported high levels of fatigue and BRPE, and pain did not appear to be a major issue. While participants seem to be consistent in performing the planned time on task in the first two dose levels, consistency decreased at levels 3 and 4. Recent preclinical work in rats has shown feasibility of 5-day high-dose upper limb rehabilitation programs[14,15,66]. Future research should investigate the comparative efficacy of 3-day and 5-day protocols, particularly in the context of acute upper limb rehabilitation research and could phase larger doses over five days, as three days may be insufficient for adapting to higher doses. This study's small sample size limits the generalizability of these results to the broader stroke population. Furthermore, the specific type of training used may not be generalizable to other upper limb

training modalities. However, considerations of optimal training conditions—fatigue, alertness, and pain—may apply to other upper limb rehabilitation studies. Future Phase I/II dose-finding research should explore the feasibility of longer duration programs in larger samples.

A 3+3 research design allows for a systematic evaluation of tolerability and efficacy. However, as 3+3 phase 1 designs originate in pharmacological trials, the DLT criteria chosen for this research– such as fatigue and pain are not directly comparable to drug toxicity. While fatigue, perceived exertion, and pain may not be as immediately life-threatening, they can significantly impact a patient's quality of life, functional ability, and overall recovery. The chosen safety measures are crucial for assessing effective neurorehabilitation strategies, particularly given the active participation in the training. Elevated levels of fatigue and pain can lead to secondary complications and hinder rehabilitation efforts. For example mental fatigue can be considered a proxy for exercise tolerance, reflecting how well patients can think or plan or execute (neural activation) movements of the impaired upper limb[67]. Shoulder pain, prevalent in 30 and 65% of patients poses an increased risk in the very early stage of stroke.[68] We acknowledge patient heterogeneity (e.g. impairment severity, cognitive function or age) the importance of individualized treatment. Our approach is based on the principle of starting with a conservative dose and gradually increasing it as tolerated, allowing for personalized adjustments, based on individual patient factors. Close symptom monitoring enables early idenfication, allowing for dose adjustments. Future research could then analyze patient subgroups (e.g., based on age, cognitive status) to better understand how the intervention affects different populations.

Phase I upper limb rehabilitation research in the acute and early subacute stage of could significantly enhance understanding and improve outcomes for patients and our research is confirmative to the previous findings demonstrating the feasibility of high dosing of UL training[10,18,60]. However, certain limitations need to be also considered. The maximum dose levels were determined in consultation with clinical staff for reasons of feasibility in one's health care context where also other medical examinations or rehabilitation sessions (i.e. physical therapy for balance or walking) took place. This could be perceived as a hypothetical limitation to the chosen study design approach. However, the maximal dose for upper limb rehabilitation already reflected that patients with early state of stroke can manage a higher upper rehabilitation dose compared to usual standard care. Our research involved a 3-day rehabilitation program, and we acknowledge that further research is needed to explore the feasibility of the maximal dose for a longer duration (e.g. 5 days per week) and assess if safety remains assured for people in the early stage of stroke. Safety measures were self-reported, and rehabilitation practices varied across centers. Participant (P18) had already a high level of fatigue at the start of the study. However, including participants with lower levels of fatigue was not added as a criterion to the study. Safety assessment monitoring was conducted by researchers and health care professionals' part of the team. We acknowledge they were not independent from the trial, causing some potential bias in the monitoring process. Also, recruiting people with stroke who have been admitted to rehabilitation implies they have capacity to participate in therapy, causing potential selection bias. However, it is noted that, in Belgium, rehabilitation programs are offered to almost every patient with stroke when needed, without any formal selection processes. Other dimensions relating to dose from the Dose articulation framework[41] such as

episode level dimensions, episode episode difficulty, episode time off task behaviour or number of repetitions were not recorded. However, we did indeed measure exercise session intensity using the Borg Rating of perceived exertion, which is a recommended measure of such construct. Additionally, assessor blinding was absent, affecting outcome interpretation.

Conclusion

Using a dose escalation methodology, it was identified that the maximum dose of 100 minutes of time on task upper limb rehabilitation (in addition to standard care) for individuals with moderate to severe impairment within 14 days post stroke. This phase I study focused on safety, not efficacy, with respect to upper limb impairment. The small sample size warrants caution in generalizing these findings to other patient populations. Future phase I/II research should investigate larger sample sizes, assess test-retest reliability of the protocol, explore various rehabilitation programs, and examine program lengths beyond the three-day model for individuals in the early post stroke stage.

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Dissemination

The results of this trial were presented at the European Stroke Organisation Conference (ESOC) in Basel in May 2024 and the World Congress of Neurorehabilitation in Vancouver in May 2024.

Declaration of Conflicting interests

The Authors declare that there are no conflicts of interest.

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Tables

Table 1: Demographics and clinical profiles of participants recruited into the study

Participant code	Dose Level	Days post-stroke	Type of stroke	Age Range	Ethnicity	Hand dominance	Side of stroke	Location of stroke	NIHSS[1] Score	Baseline MI[2] Score
P01	1	3	I	36-40	Caucasian	R	L	Middle Cerebral Artery	11	11
P02	1	6	I	61-65	Caucasian	R	L	Parietal/Frontal Cortices	9	55
P03	1	5	I	71-75	Caucasian	R	R	M2 segment	4	39
P04	2	3	I	66-70	Caucasian	R	R	Thalamocapsular	4	47
P05	2	5	I	56-60	Caucasian	R	R	Anterior Medullar Oblongata	1	54
***P06**	2	5	I	81-85	Caucasian	L	L	Lacunar/Pons	3	69
P07	2	18	I	71-75	Caucasian	R	L	Parietal, M3 segment, Anterior cerebral Artery	11	49
P08	2	29	H	71-75	Caucasian	R	L	Internal Capsule	2	60
P09	2	15	I	71-75	Caucasian	L/R	R	Lacunar	4	60
P10	3	30	H	56-60	Caucasian	R	L	Basal Ganglia	9	50
P11	3	9	I	81-85	Caucasian	R	R	Frontal, Parietal, Gyrus precentralis	11	50
P12	3	5	I	56-60	Caucasian	L/R	L	Frontal, Anterior periventricular, high subinsular	4	61
P13	4	6	I	56-60	Caucasian	R	L	Middle Cerebral Artery	1	39
P14	4	4	I	66-70	Caucasian	R	R	Corona Radiata/ Putamen	4	57
***P15**	4	16	I	81-85	Caucasian	R	R	Lacunar/Corona Radiata	6	28
P16	4	30	H	41-45	African	R	L	Internal capsule	6	58
P17	4	24	I	56-60	Caucasian	R	L	Internal Capsule	8	39
***P18**	4	23	I	71-75	Caucasian	R	L	Sylvian Fissure	14	33
Median (Q1:Q3)/%		**7.5 (5:23.25)**	**83% I 17% H**	**67 years (57:72.5)**	**94% Caucasian 6% African**	**83% R 6% L, 11% L/R**	**61% L 39% R**	**50% cortical Stroke 50% Sub-cortical stroke**	**5 (3.75:9.5)**	**50 (39:58.5)**

***Participants who experienced Dose-limiting toxicity are presented in grey; [1] NIHSS= National Institutes of Health Stroke Scale; [2]MI= Motricity Index score out of 100 points**

Table 2: Planned and delivered time on task, number of sessions and episodes per day per included participant

Participant		Day 1			Day 2			Day 3		
	Planned time on task per day (minutes)	Delivered time on task minutes)	Number of sessions	Number episodes	Delivered time on task (minutes)	Number of sessions	Number episodes	Delivered time on task (minutes)	Number of sessions	Number episodes
P01	40	40	1	2	40	1	2	40	1	2
P02	40	40	1	2	40	1	2	40	1	2
P03	40	40	1	2	40	1	2	40	1	2
P04	67	67	1	2	67	1	2	67	1	2
P05	67	67	1	2	67	1	2	67	1	2
P06	67	67	1	2	Drop out- due to second stroke			Drop out- due to second stroke		
P07	67	60	1	2	50	1	2	55	1	2
P08	67	67	1	2	67	1	2	67	1	2
P09	67	67	1	2	67	1	2	67	1	2
P10	100	100	2	4	100	2	4	100	2	4
P11	100	100	2	4	100	2	5	100	2	5
P12	100	100	2	5	100	2	4	100	2	4
P13	133	125	2	4	113	2	5	112	2	5
P14	133	133	2	4	133	2	5	133	2	4
P15	133	107	2	4	111	2	5	100	2	5
P16	133	118	2	4	111	2	4	122	2	4
P17	133	116	2	4	110	2	4	120	2	4
P18	133	53	2	5	35	1	2	Drop out due to severe fatigue		

Table 3: Change from baseline in Fugl Meyer Assessment – Upper Extremity, Action Research Arm Test and Motricity Index [bottom figure] of all the participants that completed the upper limb rehabilitation three-day program at the four dose levels.

Participant code	Baseline FMA-UE[1] Score	Post FMA-UE[1] Score	Δ from Baseline	Baseline ARAT[2] Score	Post ARAT[2] Score	Δ from Baseline	Baseline MI[3] Score	Post MI[3] Score	Δ from Baseline
Dose level 1									
P01	11	13	2	0	0	0	11	11	0
P02	31	35	4	16	23	7	55	55	0
P03	29	29	0	5	5	0	39	39	0
Dose level 2									
P04	44	54	10	32	42	10	47	83	36
P05	25	45	20	17	49	32	54	64	10
P07	37	42	5	6	10	4	49	70	21
P08	46	55	9	29	33	4	60	73	13
P09	42	55	13	39	50	11	60	77	17
Dose level 3									
P10	22	35	13	7	14	7	50	55	5
P11	31	44	13	9	20	11	50	69	19
P12	39	60	21	38	57	19	61	84	23
Dose level 4									
P13	12	19	7	3	4	1	39	44	5
P14	42	54	12	26	45	19	57	84	27
P16	32	47	15	23	38	15	58	70	12
P17	18	23	5	5	10	5	39	55	16

Figures

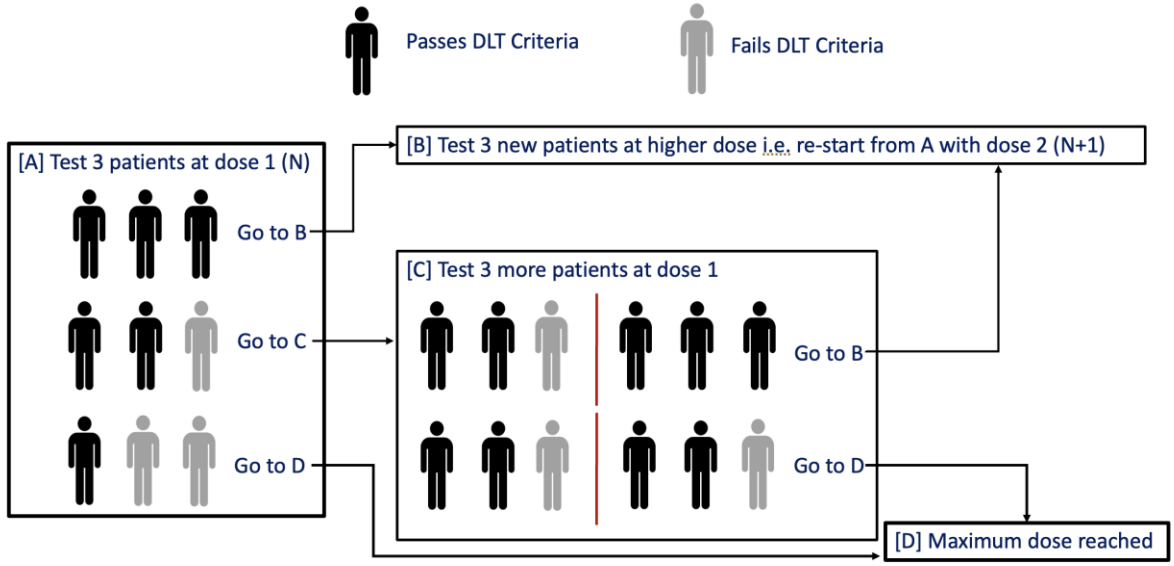

Figure 1: 3+3 Study Design (adapted from Dite et al., 2016)

Three participants are included in dose level 1. If all three complete the dose without experiencing Dose-Limited Toxicity (DLT), the dose is escalated to level 2 with three new participants. If one out of the three initial participants experience a DLT, three new participants are included at the same dose level. If an additional participant in this second group experiences a DLT, the maximum dose is reached. If all three participants in the second group complete the dose, the dose is escalated. If two out of the initial three participants experience DLT, the maximum dose is reached.

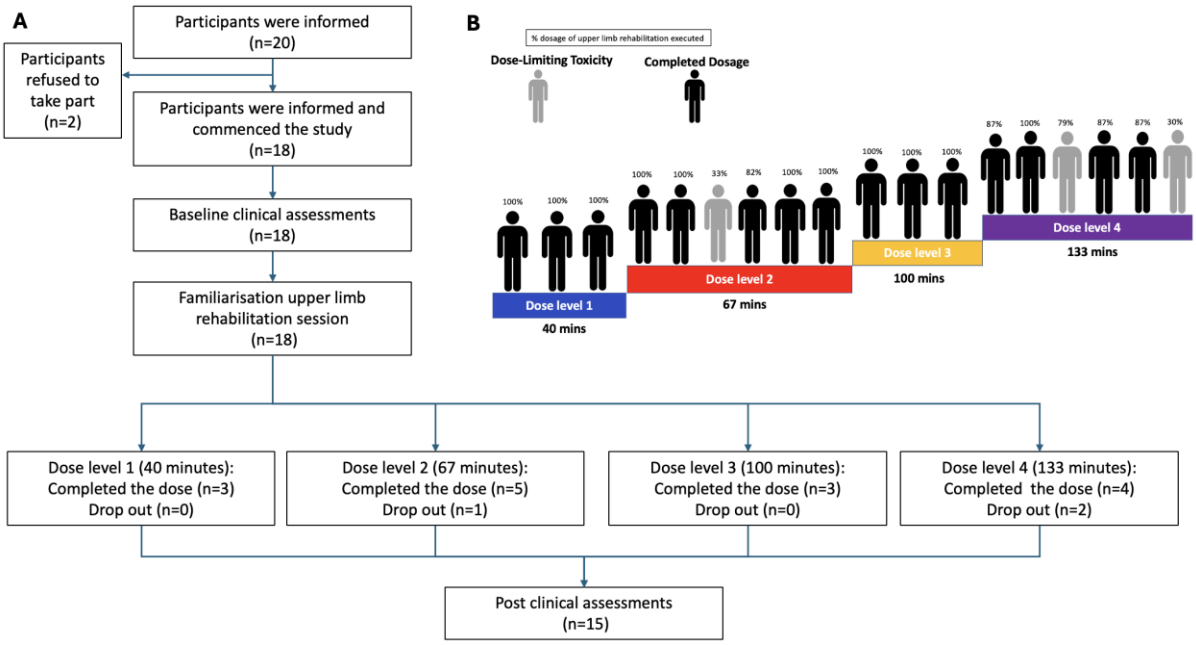

Figure 2: [A] Flow-diagram showing the step-by-step process of recruitment and data collection for the presented study [B] Displaying the participants that took part in the research with the percentage performed time on task of upper limb rehabilitation program displayed on top of each participant. Classified as completing the dose [black] or showing Dose-Limiting Toxin [grey]

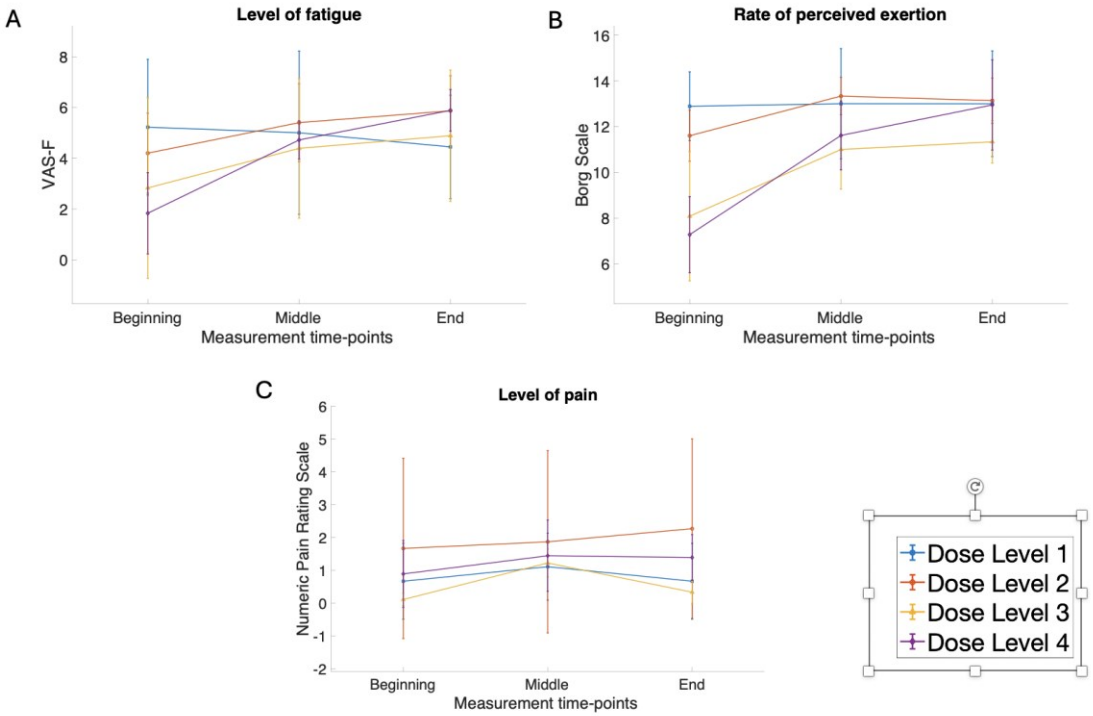

Figure 3: [A]: Mean (SD) scores for level of fatigue measured by Visual Analogue Scale-Fatigue (VAS-F); [B] Mean (SD) scores for Perceived rate of exertion measured by the Borg Scale; [C]: Mean (SD) Scores for level of pain measured by Numeric Pain Rating Scale per dose level at beginning, middle and end of the three upper limb rehabilitation sessions