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Transcutaneous Auricular Vagus nerve Stimulation with Concurrent Upper Limb Repetitive Task Practice for Post Stroke Motor Recovery: A pilot study

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Abstract

Goal

Invasive vagus nerve stimulation (VNS) has the potential to enhance the effects of physiotherapy for upper limb motor recovery post stroke. Noninvasive, trans-auricular branch VNS (taVNS) may have similar benefits but this has not been evaluated in stroke recovery. We sought to determine the feasibility of transcutaneous auricular VNS (taVNS) delivered alongside upper limb repetitive task-specific practice post stroke and its effects on a range of outcome measures evaluating limb function.

Materials and Methods

Thirteen participants >3 months post ischemic stroke with residual upper limb dysfunction were recruited from the community of Sheffield, UK (October - December 2016). Participants underwent 18 x 1-hour sessions over 6 weeks in which they made 30-50 repetitions of 8-10 arm movements concurrently with taVNS (NEMOS®, Cerbomed, 25 Hz, 0.1 ms pulse width) at maximum tolerated intensity (mA). An electrocardiogram and rehabilitation outcome scores were obtained at each visit. Qualitative interviews determined the acceptability of taVNS to participants.

Results

Median time post-stroke was 1.16 years and baseline median/IQR Upper limb fugl-meyer (UFM) was 63 (54.5-99.5). Participants attended 92% of the planned treatment sessions. Three participants reported side effects, mainly fatigue, but all performed mean of >300 arm repetitions per session with no serious adverse events. There was a significant change in the UFM with a mean increase per participant of 17.1 points (SD 7.8).

Conclusion

taVNS is feasible and well tolerated alongside upper limb repetitive movements in post stroke rehabilitation. The motor improvements observed justify a Phase 2 trial in patients with residual arm weakness.

Introduction

Approximately half of stroke survivors have persisting arm weakness, which significantly impedes activities of daily living. Upper limb interventions to enhance neuroplasticity post stroke usually involve "repetitive task-specific practice" (RTP) in which the patient makes repeated movements of the arm directed towards a functional goal.

Mounting evidence from animal and human studies suggest that stimulation of the vagus nerve (VNS) enhances the effects of RTP by boosting neuroplasticity. In rats with ischaemic stroke, delivery of VNS *concurrently with* "pulls" of a lever to obtain food led to more rapid recovery of the stroke-affected forelimb. [12] These improvements were associated with an enlargement of the associated motor cortex.[3] Delivery of VNS *concurrently* with a stimulus can also treat tinnitus (a condition caused by maladaptive plasticity), where the pairing of VNS with different auditory tones can reduce the person's perception of the unwanted sound[4].

Several mechanisms may explain the beneficial effects of VNS on plasticity. [5] For example, VNS increases levels of brain-derived neurotrophic factor (BDNF), and IL-B (both key regulators of neuroplasticity).[56] VNS also stimulates the release of acetylcholine (ACh) and noradrenaline.[7] One study in mice post stroke found that selective obliteration of the cholinergic cortical projections from the Nucleus Basilis completely offset the effects of VNS on limb movement [8] suggesting a key role for ACh in mediating plasticity from VNS.

VNS is already a licensed treatment in humans for epilepsy and depression. In these cases, stimulators are implanted directly onto the vagus nerve. This "invasive" VNS was also used in a recent pilot trial of VNS in 20 human stroke survivors with arm weakness.[9] In that trial, participants were randomised in a cross-over trial to either 6 weeks of intensive repetitive

task practice (RTP) paired with VNS or RTP alone. In the per-protocol analysis, the VNS group improved their Upper Extremity Fugl-Meyer (UFM) score by 9.6 points compared to only 3.0 in the RTP-only group (between-group difference 6.5 points, 95% CI 0.4-12.6; P =0.04).[10] Whilst such results are encouraging, recruitment into such studies can be challenging for many stroke survivors are unfit for, or are reluctant to undergo surgery.

Recently, devices that can stimulate the vagus nerve non-invasively have become available. One device, called NEMOS^{R} (Cerbomed, Germany) when placed in the horizontal depression of the outer ear (the "concha") (Figure 1) stimulates the "auricular branch" of the vagus nerve. Functional magnetic resonance brain imaging (fMRI) studies have demonstrated that transcutaneous auricular VNS (taVNS) activates the same areas within the brain as surgically implanted VNS (i.e. the Nucleus Tractus Solitarius, the Locus Coeruleus and the Nucleus Accumbens)[11] suggesting equivalent mechanisms of action.

Transcutaneous auricular VNS devices are also well tolerated by patients with diseases such as migraine and epilepsy, with no serious adverse reactions having been reported in clinical trials to date. However, taVNS has not yet been tested in the context of stroke recovery.

We aimed to determine the feasibility, tolerability, acceptability and safety of taVNS alongside RTP in stroke survivors with arm weakness following a stroke. We also determined the responsiveness-to-change of a range of rehabilitation outcome measures. Our findings will be used to inform the design of a future randomized trial of taVNS in stroke recovery.

Materials and Methods

This was a single-group pre-post intervention study. The protocol was approved by Sheffield Research Ethics Committee (ref 15/YH/0397). The study design conformed to the CONSORT-statement extension for pilot and feasibility studies (http://consort-statement.org). The study was registered at ClinicalTrials.gov (reference NCT03170791). All participants gave written informed consent for the study.

Participants

Eligible participants were screened, approached and recruited by weekly liaison with Community Stroke Service in Sheffield, UK between October -December 2016. All study treatments took place at the Clinical Research Facility at the Northern General Hospital, Sheffield. Participants were eligible if they (1) were over 18 years of age, (2) had an anterior circulation ischaemic stroke at least 3 months previously, (3) had active shoulder abduction and finger flexion. No strict cut-offs were required for baseline upper limb function as long as the participant could engage with the therapist and perform the limb movements. Participants were not eligible if they: (1) had impairments of upper limb function other than those caused by stroke, (2) were participating in any other research trial (3) had aphasia or cognitive difficulties severe enough to interfere with the informed consent process, task specific practice or communication of adverse events, (4) were pregnant or trying to get pregnant, (5) had a pacemaker or other implanted electrical device or (6) had severe spasticity (a Modified Ashworth Score[12] $\geq$3).

Sample size

We aimed to recruit a minimum of 12 participants as this is the minimum number required for a pilot/feasibility study[13].

Outcome Measures

At the initial study visit, demographics, time since stroke, medication and vascular risk factors were obtained from participants. Hospital records and imaging results were viewed to record the size, location and precise date of the stroke. Two measures of upper limb movement and functional independence were assessed by the study physiotherapists: Upper Limb Fugl-Meyer (UFM) [14] and Action Recovery Arm Test (ARAT)[15,16]. The participants also completed the following self-report measures: Modified Rankin Score (mRS),[17] Barthel Index,[18] Stroke Impact Scale (SIS),[19] Motor Activity Log (to measure use of the impaired limb in a variety of activities of daily living such as putting on shoes, drying hands, wiping a kitchen counter, using a television remote-control),[20] Patient-health Questionnaire (PHQ9)[21], Generalised Anxiety Disorder 7 (GAD7)[22] and the Fatigue Assessment Scale[23]. The upper limb assessment scales was chosen because they capture the three domains of the International Classification of Functioning framework (impairment, function and participation) and incorporate objective as well as patient-reported outcome measures. Mood and anxiety were assessed as depression is a common complication of stroke and can impede rehabilitation as well as being potentially moderated by VNS.[24] All outcomes were measured again at the final treatment visit.

An electrocardiogram (ECG) was performed at baseline and at the end of each treatment session and the pulse (beats/min) rate, PR interval (ms), QRS duration (ms) and the corrected QT interval (ms) were recorded by the ECG machine. These were reviewed by JR and compared to baseline values. At each treatment visit, details of any side effects or difficulties experienced by participants during or after the intervention were recorded.

Intervention

The taVNS ear piece was fitted to the participants left ear such that the electrodes made contact with the concha (Figure 1). The intensity (mA) of stimulation was increased slowly by increments of 0.1 mA until the participant's reported maximum tolerable level and this intensity used for the rest of the session. The manufacturers (Cerbomed, Germany) reprogrammed the stimulator to avoid the usual "ramp-up" (increase in mA) each time it was switched on. The pulse width was 0.1 ms and frequency 25 Hz.

Exercise programmes were tailored to the participant's impairments and goals. Each session began with large- range arm movements, frequently involving bilateral activities, either reciprocal or symmetrical and using equipment e.g. pedals, a pole or ball to assist independent movement. This was followed by repetitive task-specific movements e.g. turning cards, manipulating or lifting objects, opening and closing bottles (Table 1).

Approximately 7 - 10 tasks with 30 to 50 repetitions were attempted (aiming for > 300 repetitions in total) per session. [25] The physiotherapist turned the stimulation "on" by pressing a button on the stimulator unit when the participant began to move the arm and "off" when the movement ceased. The frequency of sessions (3 times a week for 6 weeks) matched that used in the trial of invasive VNS[12] which reported improvements in function post stroke.

The number of arm movements per session were recorded.

Qualitative interviews

After the final treatment session, a semi-structured interview was conducted. The topic guide incorporated open-ended questions regarding the acceptability of the electrical stimulation. The interviews allowed participants to share experiences that the researchers had not anticipated.[26] Interviews lasted 30-45 minutes and were recorded and transcribed verbatim.

Data analysis

Analyses were mainly descriptive, as the study was not powered for inferential analysis. We calculated the proportion of participants who completed the 6- week intervention, the mean number of arm movements per hour for each participant, and the proportion of invited therapy sessions attended. Details of any adverse events were recorded at each visit and were coded according to NHS Research Authority definitions (where serious adverse event is defined as any event resulting in hospitalization, significant disability or death, is life-threatening, a congenital defect or requiring intervention)[27]. The proportion of participants reporting minor side effects or adverse reactions to taVNS was determined from the interview responses. Where there existed a proposed Minimal Clinically Important Difference (MCID) for a scale, we calculated the number of participants who achieved this change (e.g. for the Upper-limb fugl-meyer, MCID = 10 points)[28], and for ARAT (5.7 points))[29].

We calculated effect sizes (Cohen's d) for each measure using the following formula: (mean post-intervention minus mean at-baseline) divided by the standard deviation at baseline.

We regarded a meaningful change in the ECG parameters to be a) a change of 20% in resting heart rate and/or b) a 10% change from baseline PR/QRS or QTc or c) a deviation outside the normal reference range for any of these values or d) the development of a non-sinus rhythm

Qualitative data were analysed with a thematic framework approach[30]. Transcripts were first coded according to themes decided *a priori* that were focused on the specific aims of the study, such as experience of the stimulation, experience of the physiotherapy and wider experiences of the study. Data relating to each theme was placed into a matrix enabling data for each participant and each theme to be carefully compared. Transcripts were then checked

to ensure there were no elements were overlooked by the pre-existing themes. The themes arising and the analytical process were examined by a second reviewer to ensure rigour.

Criteria for Proceeding to a definitive trial

Pre-specified success criteria included the following: 1) More than 2/3 planned treatment sessions attended 2) All participants achieving mean task repetitions per session >300 3) <1/3 participants experiencing side effects from intervention 4) absence of serious adverse events.

Results

Twenty interested participants were contacted. After telephone screening, 18 were invited for further assessment. Of these, 13 met inclusion criteria (Figure 2). Reasons for exclusion included spasticity (n=2), aphasia (n=1) and absence of active arm movement (n=2).

The 13 participants [(10 males, mean (SD) age 64.5 (6.9), median (IQR) years since stroke 1.16 (IQR 0.7-3.6), median (IQR) baseline total UFM 63 (54.5-99.5)] underwent a combined total of 215 therapy sessions. This equated to 92% of the total expected sessions. One participant withdrew after her 5th visit because the sessions were too constraining on her time. Another participant missed 6 sessions part way through due to a bereavement but returned to complete the remaining sessions so her data were included in the final analysis. The other 11 participants completed the entire treatment course of 18 sessions (Figure 3).

The median (range) intensity of taVNS delivered was 1.4 (1-3.2) mA. The mean (SD) number of arm movements per 1-hour session was 464 (70) with all 12 participants achieving at least 300 arm movements per hour. Table 1 shows the type and number of arm repetitions performed by one participant as they progressed through the programme.

Only three participants reported side effects. These included light-headedness in one participant and general tiredness and fatigue in two. Only the former was considered by the researchers to be possibly attributed to the taVNS. No associated ECG changes were seen.

Table 2 shows the outcome measurements at Visit 18 compared to baseline. Four measures showed improvement. The mean (SD) improvement in UFM from baseline to Visit 18 was 17.1 (SD 7.8) with 10 participants (83%) achieving an increase of >10 points (the minimum clinically important difference) and an overall effect size of 0.68. The mean (SD) ARAT increased by 2.5 (3.6) points (effect size 0.10), the mean MAL by 3.4 (11) points (effect size

0.04) and the mean SIS by 5.6 points (14.1) (effect size 0.17). The reported MCID for ARAT (5.7) was achieved by 3 (25%) participants. The other outcome measures changed very little or not at all (Table 2). There were no significant changes in ECG recordings for rate, PR/QRS or QTc interval.

Qualitative Interviews

Two key themes were the experience of the intervention, (the perceived advantages of the intervention.

The experience of the intervention.

Most participants felt that the electrical stimulation was comfortable. Only one participant felt that the sensation stung when it was turned up too high.

Most participants were happy with the frequency and duration of visits. Some participants commented that the exercises were tiring.

The participant complaining of light-headedness was uncertain if this was related to the taVNS. He and two others reported tiredness and some muscle stiffness but all three believed this was related to the intensity of the exercise programme rather than the taVNS.

Perceptions of effectiveness

Eleven out of the twelve participants felt that they had improved upper limb function, mentioning e.g. improved dexterity, strength and/or flexibility with tasks such as putting a coat on, brushing hair and gripping objects in the kitchen.

"You know it all used to be really terribly heavy; it was an effort to lift it because it was heavy and now I can, I can do it"

Discussion

We recruited 13 participants who between them attended 215 treatment sessions in which transcutaneous auricular VNS (taVNS) was delivered concurrently with repetitive task practice (RTP). Only one participant withdrew from the study. Despite the added treatment with taVNS, all 12 remaining participants were able to perform >300 arm movements per hour - the threshold which triggers plasticity in animal models. [25] The treatment was generally well tolerated and almost all felt that their arm function improved during the study.

Of the 9 outcome measures we assessed, the UFM was the most sensitive to change (Table 2), increasing by a mean (SD) of 17 (7.8) points. The UFM scale measures the "impairment" domain of the International Classification of Functioning and is designed specifically for use in post-stroke hemiplegia, measuring actual recovery rather than compensatory movement.[31] UFM was also the outcome which improved significantly in the trial of invasive VNS in stroke motor recovery [9] and has been recently deemed a core outcome in stroke recovery.[32]

Transcutaneous VNS has the advantage over invasive VNS in that it does not require surgery. Furthermore, whilst invasive VNS can cause cough, hoarseness, voice alteration and parenthesis[33], to our knowledge there have been no reports of serious adverse reactions to taVNS in the literature to date. Our high retention rate and the positive feedback from participants further suggest that a future trial of taVNS in stroke recovery is feasible.

There were, however some potential limitations to this study. First, it would have been preferable to conduct the qualitative interviews with a researcher not directly involved in the therapy. However, the participants were open in describing suboptimal aspects of the programme and felt immediately at ease being interviewed by a familiar researcher. Second, at this stage we can only speculate about the size of any beneficial effect of the taVNS

combined with RTP alone. However, a recent Cochrane review (11 trials, 749 participants) found that RTP alone produced surprisingly modest improvements in arm function post stroke regardless of time interval since stroke.[34] In that review, the standardized mean difference (i.e. the mean effect size taking into consideration differences in motor outcome scales between studies) for RTP versus usual care/placebo was 0.25 (95% confidence interval (CI) 0.01 to 0.49).[34] In contrast, we observed an effect size for UFM of 0.68 with 10/12 participants achieving an increase of at least 10 points in UFM score. Our findings are thus in keeping with a potentially powerful effect of taVNS but this needs to be further tested in a controlled trial setting. Such a trial could deploy "sham" taVNS by inverting the electrodes in the ear[35] which does not activate central vagal connections.[35]

A further limitation is that the intensity of RTP was greater than that given in clinical practice by physiotherapists in the UK. However, taVNS may in future be self-administered by patients allowing frequent sessions at low cost. Furthermore, the advantage of treating participants in a clinical research facility as done here, was to ensure adherence to the treatment protocol.

taVNS appears to be a safe, feasible, and acceptable treatment for stroke survivors undergoing RTP for the upper limb. The improvements in arm function were greater than expected based on of RTP-alone. A Phase 2 clinical trial is warranted to establish the efficacy of taVNS for recovery of the upper limb post stroke.

Declarations

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None

Conflicts of Interest/Disclosure(s)

None

Author contributions

JR designed the study, oversaw the progress of the study and wrote the manuscript. NS supervised the physiotherapists (LM, KF, TO, ME) who delivered the intervention and interviewed the participants. AA assisted with participant recruitment. AM conceived and helped to design the study, provided methodological expertise and assisted with data analysis and interpretation and helped to write the manuscript. All authors contributed significantly to the preparation and subsequent revisions of the manuscript.

All authors have read and approved the final version of the manuscript.

References

1. Khodaparast N, Hays SA, Sloan M, et al. Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke. *Neurobiol Dis*. 2013;60:80-88.

2. Hays SA, Khodaparast N, Ruiz A, et al. The timing and amount of vagus nerve stimulation during rehabilitative training affect poststroke recovery of forelimb strength. *Neuroreport*. 2014;25(9):676-682.

3. Porter B, Khodaparast N, Fayyaz T, et al. Repeatedly pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. *Cereb Cortex*. 2012;22(10):2365-2374.

4. Kreuzer PM, Landgrebe M, Frank E, Langguth B et al. Repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus after traumatic brain injury: a case study. *J Head Trauma Rehabil*. 2013;28(5):386-389.

5. Hays S A, Rennaker RL, Kilgard MP. *Targeting Plasticity with Vagus Nerve Stimulation to Treat Neurological Disease*.; 2013.

6. Follesa P, Biggio F, Gorini G, et al. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Res*. 2007;1179(1):28-34.

7. Bear MF, Singer W. Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature*. 1986;320(6058):172-176.

8. Hulsey DR, Hays SA, Khodaparast N, et al. Reorganization of Motor Cortex by Vagus Nerve Stimulation Requires Cholinergic Innervation. *Brain Stimul*. 2016;9(2):174-181.

9. Dawson J, Pierce D, Dixit A, et al. Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Ischemic Stroke. *Stroke*. 2016;47(1):143-150.

10. http://www.rehabmeasures.org/lists/rehabmeasures/dispform.aspx?ID=908.

11. Frangos E, Ellrich J, Komisaruk BR. Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans. *Brain Stimul*. 2014;8(3):624-636.

12. Ansari NN, Naghdi S, Younesian P, Shayeghan M. Inter- and intrarater reliability of the Modified Modified Ashworth Scale in patients with knee extensor poststroke spasticity. *Physiother Theory Pract*. 2008;24(3):205-213.

13. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005;4(4):287-291.

14. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med*.

1975;7(1):13-31.

15. McDonnell M. Action research arm test. *Aust J Physiother*. 2008;54(3):220.

16. Hsieh CL, Hsueh IP, Chiang FM, Lin PH. Inter-rater reliability and validity of the Action Research arm test in stroke patients. *Age Ageing*. 1998;27(2):107-114.

17. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: Implications for stroke clinical trials - A literature review and synthesis. *Stroke*. 2007;38(3):1091-1096.

18. Mahoney F BD. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J*. 1965;14:61-65.

19. Duncan PW, Lai SM, Bode RK, Perera S, DeRosa J. *Stroke Impact Scale-16: A Brief Assessment of Physical Function.*; 2003.

20. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity motor activity log-14 for measuring real-world arm use. *Stroke*. 2005;36(11):2493-2496.

21. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med*. 2010;8(4):348-353.

22. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.

23. Mead G, Lynch J, Greig C, Young A, Lewis S, Sharpe M. Evaluation of fatigue scales in stroke patients. *Stroke*. 2007;38(7):2090-2095.

24. O'Reardon JP, Cristancho P, Peshek AD. Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond. *Psychiatry (Edgmont)*. 2006;3:54-63.

25. Birkenmeier RL, Prager EM, Lang CE. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair*. 2010;24(7):620-635.

26. Pope C, Mays N. *Qualitative Research in Health Care*.; 2006.

27. NHS Health Research Authority website. http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/.

28. Arya KN, Verma R, Garg RK. Estimating the minimal clinically important difference of an upper extremity recovery measure in subacute stroke patients. *Top Stroke Rehabil*. 2011;18 Suppl 1:599-610.

29. Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. 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*. 2001;82(1):14-19.

30. Ritchie J, Lewis J, Nicholls CM, Ormston R. The Foundation of Qualitative Research.

Qual Res Pract A Guid Soc Sci Students Res. 2013:0-25.

31. Singer B, Garcia-Vega J. The Fugl-Meyer Upper Extremity Scale. *J Physiother*. 2017;63(1):53.

32. Kwakkel G. Standardised measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR). *Int J Stroke*. 2017 (5):451-461.

33. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *J Clin Neurophysiol*. 2001;18(5):415-418.

34. French B, Thomas LH, Coupe J, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev*. 2016;2016(11).

35. Kraus T, Kiess O, Hosl K, Terekhin P, Kornhuber J, Forster C. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - A pilot study. *Brain Stimul*. 2013;6(5):798-804.

Table 1 Practice programme for Participant 005 showing number of repetitions of each arm movement.

	Visit number																	
Activity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**Total**
Gleniohumeral joint (GHJ) flexion	80	60	60									30	30						260
Elbow extension	80	60	60									30	30					30	320
Forearm supination / pronation	80	80	60	60	60	40	40	40	40	40	60	40	40	40	40	40	40	30	870
Wrist extension	80	80	60		40	40	40	40	40	40	30	40	40	30	30	30	30	30	720
Arm cycle forwards		40	40	50	50	80	100	100	100	100	100	100	100	120	120	150	150	150	1650
Arm cycle backwards		20	20	30	30	40	50	50	60	80	100	100	100	100	120	120	120	150	1290
Walking pole-direction			40	60	60	60	60	60		40	40			40	40	40	40		580
Sliding towel				60	60	60	80	80	100	60	60	60	60	60	60	80	80	80	1040
Pushing gym ball bilaterally				60	40	40			40	40					40				260
GHJ external / internal rotations				20	40	40	40	40	50	50	50	60	60	40		40	40	30	600
Total movements	320	340	340	340	380	400	410	410	430	450	440	460	460	430	480	500	500	500	7590

Table 2 showing baseline and Visit 18 scores for outcome assessments and mean (SD) change (across all 12 participants)

	Baseline visit	**Final intervention visit (end of week 6)**		
Outcome measure*	**Mean (SD)**	**Mean (SD)**	**Mean (SD) Change in score†**	**Effect size**
UFM	71.2 (25.3)	88.3 (23.1)	17.1 (7.8)	0.68
ARAT	21.3 (25.2)	23.8 (26.9)	2.5 (3.6)	0.10
MAL	68.6 (89.6)	72 (86.2)	3.4 (11.0)	0.04
SIS	207.4 (33.6)	213 (33.2)	5.6 (14.1)	0.17
FAS	23.2 (4.6)	21.4 (4.8)	1.8 (5.1)	0.41
PHQ9	5.5 (7.1)	4.2 (1.5)	1.3 (2.9)	0.18
GAD7	3 (4.2)	2.5 (3.6)	0.5 (1.2)	0.12
mRS	2.67 (0.65)	2.67 (0.65)	0	0
BI	17.3 (2.8)	17.3 (2.8)	0	0

*UFM= Upper Limb Fugl-Meyer score, ARAT= Action Recovery Arm Test, mRS= Modified Rankin Score[17] BI= Barthel Index [18], SIS=Stroke Impact Scale,[19] MAL= Motor Activity Log,[20] PHQ9= Patient-health Questionnaire-9[21], GAD7= Generalised Anxiety Disorder 7[22] and FAS= Fatigue Assessment Scale[23]. † change shown in direction of improvement in function/mood etc