ORIGINAL ARTICLE

Therapeutic Effectiveness of Electric Stimulation of the Upper-Limb Poststroke Using Implanted Microstimulators

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ABSTRACT. Turk R, Burridge JH, Davis R, Cosendai G, Sparrow O, Roberts HC, Hughes A-M, Schulman J. Therapeutic effectiveness of electric stimulation of the upper-limb poststroke using implanted microstimulators. Arch Phys Med Rehabil 2008;89:1913-22.

Objective: To investigate the therapeutic effect of functional exercise augmented by programmable implanted microstimulators on arm and hand function.

Design: Before and after study.

Setting: Implantation was performed in a neurosurgery unit, systems were programmed, and tests were conducted in a university laboratory and subjects exercised at home.

Participants: Hemiparetic subjects (N=7) with reduced upper-limb function who were at least 12 months poststroke were recruited from the community. No subjects withdrew.

Intervention: Microstimulators were implanted into the arms and forearms to activate elbow, wrist, and finger extension, and thumb abduction. After training and programming of the system, subjects underwent 12 weeks of functional home-based exercise with stimulation.

Main Outcome Measures: The primary functional measure was the Action Research Arm Test (ARAT). Impairment measures included upper-limb Fugl-Meyer Assessment (FMA) and tests of motor control (tracking index), spasticity (electromyography stretch index) strength, and active range of motion (AROM). The assessor was not blinded, but scores were validated by an independent blinded observer.

Results: All subjects were able to perform functional activities at home by using the system. Compliance was excellent, and there were no serious adverse events. Statistically significant improvements were measured ($P<.05$) in the tracking index ($57.3^{\circ 2}\pm48.65^{\circ 2}$), FMA score ($6.3\pm3.59$), wrist-extensor strength (5.5 ± 4.37N), and wrist AROM ($19.3^{\circ}\pm18.96^{\circ}$). The mean improvement in ARAT score $\pm$ SD of 4.9 ± 7.89 was not statistically significant.

Conclusions: This study has shown the feasibility of a programmable implanted microstimulator system used at home to perform functional exercises and a reduction in impairment after 12 weeks.

Key Words: Electric stimulation; Exercise; Hemiparesis; Rehabilitation; Stroke.

A COMMON FUNCTIONAL PROBLEM after stroke is the inability to open the hand when reaching for or releasing an object because of weakness of the finger extensor muscles and spasticity and stiffness of the finger and wrist flexor muscles. Grip can be limited not only because of an inability to activate finger flexors but also because of weakness of the wrist extensors (ECRL, ECU). To produce an effective power grip or even to manipulate objects requires the wrist to be held in a functional position of slight extension maintained by activity in the wrist extensors. Reaching away from the body to position the hand to grasp and manipulate objects can also be difficult, often because of weakness of the deltoid and triceps and spasticity of the biceps brachii. The aim of therapy is to promote functional recovery through the facilitation of motor control and skill acquisition. There is no conclusive evidence supporting the effectiveness of conventional therapy for upper-limb paresis after stroke, although literature suggests that intensity of treatment,[1] repetition, and task-specific strategies[2-5] using real-life objects[6,7] are most likely to be effective.

FES is one way in which the intensity of treatment can be increased without concomitant increase in therapy contact time. Cyclic electric stimulation with surface-applied electrodes to upper-limb muscles used to repetitively activate paretic muscles has been shown to have a therapeutic effect mainly on impairment measures of motor recovery.[8-10] A recent small controlled study has shown some improvement in function as measured by the ARAT,[11] and other studies[12,13] using a neuroprosthesis suggest improved function especially when in combination with voluntary functional exercise. A recent review[14] concluded that when stimulation was associated with voluntary effort the therapeutic effect was enhanced.[14] FES systems that assist patients to perform specific functions or activ-

List of Abbreviations

ARAT	Action Research Arm Test
AROM	active range of motion
CI	confidence interval
ECRL	extensor carpi radialis longus
ECU	extensor carpi ulnaris
FES	functional electric stimulation
FMA	Fugl-Meyer Assessment
MAS	Modified Ashworth Scale
PIN	posterior interosseus nerve
RCT	randomized controlled trial

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ities of daily living are known as neuroprostheses. Such an example is the Ness H200[a] (formerly, the Handmaster). An exploratory, uncontrolled trial of 18 chronic hemiplegic subjects showed a significant improvement in the FMA after 10 weeks use of the Handmaster, and post hoc analysis showed that there was a greater improvement in the higher functioning group.[15] However, in another study, no therapeutic effect was shown after a period of 3 weeks of regular use at home (eg, subjects' functional ability when the Handmaster was not worn did not improve).[16]

Surface FES systems have the disadvantage of requiring donning and doffing and thus inevitable variation in positioning of the electrodes on the skin. Electrode positions are critical for controlling ulnar and radial deviation of the wrist and selective activation of extensor pollicis longus and abductor pollicis for functional hand opening. Attaching electrodes on the upper arm for stimulation of the triceps brachii muscle is a particular problem for poststroke hemiplegic patients who have impaired sensorimotor control of the shoulder and trunk. Preferential activation of muscles close to the surface means that it is difficult to selectively activate finger extension without wrist extension with surface systems, and, in some cases, it is difficult to pinpoint extensor pollicis longus and abductor pollicis. Targeting the PIN may provide more precise activation of functional finger and thumb extension and thumb abduction, which, together with selective and controlled wrist extension via both ECRL and ECU, may enable more natural wrist and hand movement. In our clinical experience, discomfort is sometimes a reason for noncompliance, particularly when electrode-skin contact is impaired, and in some FES studies, skin irritation has been reported to be a problem.[17] Some of these problems have been addressed by the Ness H200 in which the wrist is held in a functional position of slight extension by a rigid splint and electrodes are attached to the splint so that, as long as the splint is worn in the same position relative to the underlying structures, muscle activation should remain consistent. The disadvantage of this system, however, is that because of lack of selectivity of wrist and finger extension, it does not elicit normative muscle activation patterns, even though the constraint of the splint provides functional movement. In addition, the Ness H200 does not extend to the upper arm for elbow extension, limiting the use for activities of daily living to those subjects who have good elbow extension.

Because of the problems currently experienced with surface systems, this case series investigated a novel system of multiple implanted microstimulators. Electric stimulation through implanted electrodes provides greater specificity of muscle contraction, which allows for more precise activation and control of multiple, small adjacent muscles. In addition, stimulation through implanted electrodes is associated with less discomfort, reduces the daily burden of correctly donning and doffing multiple surface electrodes, and, if necessary, allows for redosing to maintain therapeutic benefit. The purpose of this phase 1 feasibility study was to evaluate the initial safety, reliability, and efficacy of a multiple implanted microstimulator system in facilitating upper-limb motor recovery for persons with chronic hemiplegia.

METHODS

Participants

A convenience sample of subjects was recruited from the community through advertisements in stroke clubs and newsletters. The criteria for inclusion were adults over 18 years who were more than 6 months poststroke, with a hemiparesis resulting in weakness of wrist and elbow extension, but with perceivable voluntary wrist extension up to 75% of passive range. All subjects had sufficient volitional finger flexion to grip, elbow flexion to bring the hand to the mouth, and shoulder flexion to lift the arm away from the body against gravity to an angle of approximately 45°. Subjects with severe spasticity (MAS score >3) were excluded because it has been found previously that stimulation to open a spastic paretic hand during volitional movement can be problematic.[18] Subjects were screened medically, and those with any active device implant (eg, pacemaker), uncontrolled epilepsy, or history of endocarditis, prosthetic valve, or murmur were excluded. Because this study was investigational and demanding on subjects' time, psychologic status (Hospital Anxiety and Depression Scale), cognitive status through the Mini-Mental State Examination,[19] and their attitudes and beliefs toward their condition and rehabilitation through the Multidimensional Health Locus of Control Scales[20] were assessed. Ethics committee approval (no. 04/12/021) and Medicines and Healthcare products Regulatory Agency (no. CI/2004/0027) approval was granted. Subjects gave written informed consent, and the study was performed according to institutional guidelines for good clinical practice in research.

Radiofrequency Microstimulator System

Radiofrequency microstimulators (fig 1) are miniature, single-channel, implantable stimulators that produce capacitively coupled, charge-balanced, asymmetric, biphasic, constant-current pulses. Radiofrequency microstimulators receive power supply and control signals from an external control unit through an inductance coil that, in this application, was worn as 2 cuffs around the arm and forearm (fig 2). A choice of 5 sizes of both arm and forearm cuffs were available and ensured a snug fit and ease in donning and doffing, which all subjects could do without help. Each device was individually addressed, allowing control over timing, ramp rise and fall times, current amplitude, and pulse width. These stimulation parameters were programmed through a personal computer−based fitting system and downloaded to each person's control unit. The control unit measured 35×75×140mm and weighed 400g. While performing their exercise regimen, subjects placed it either on a table in front of them or on another surface nearby.

Implantation Procedure

By using a minimally invasive day-case procedure,[21] implantation was performed by using custom-designed implantation tools in a sterile operating room under local anesthesia. Postoperative paracetamol was prescribed for pain management. One week before implantation, optimal electrode positions had been identified by using needle electromyography electrodes. Coordinates were documented and insertion sites marked on the skin. Using these as a guide, for each device a

Fig 1. The radiofrequency microstimulator (actual size, 17×2.4mm) showing the eyelet used for attachment on the suture.

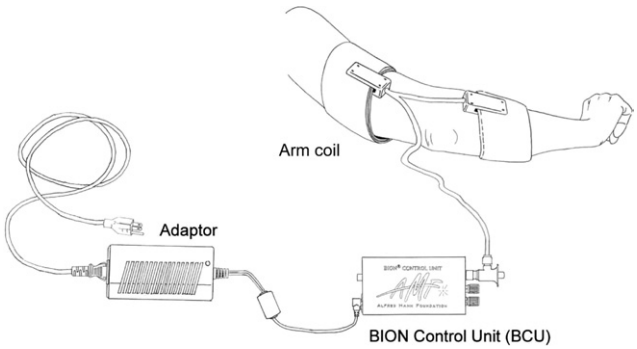

Fig 2. The external components of the radiofrequency microstimulator system.

5-mm skin incision was made. A stimulation probe was used to confirm that the proposed implantation site elicited the desired functional movement, and a dilator with sheath was then introduced over the probe. The probe was then removed; the radiofrequency microstimulator device was inserted through the sheath and ejected into the tissues by using an ejection tool. At each stage of the process, implantation site and thus desired movement was confirmed by using either the stimulation probe (preinsertion of the device) or an external coil to activate the radiofrequency microstimulator device. If the activation of the device did not elicit the desired movement, it was removed by using a suture attached to an eyelet on the device and reinserted. For each subject, 2 radiofrequency microstimulator devices were implanted close to the radial nerve branches to the medial and lateral heads of the triceps to activate elbow extension. To extend the fingers and extend and abduct the thumb for hand opening, either 1 or 2 devices were positioned close to the PIN. Wrist extension was activated by either 2 or 3 devices close to the motor points of ECU and ECRL.

Programming and Home-Exercise Regimen

Design and programming of stimulation sequences for the home-exercise regimen was undertaken by a research physical therapist and began at 2 weeks postimplantation. At the initial fitting session, both the threshold and upper limit, defined as the level above which stimulation became (1) uncomfortable, (2) response reached a plateau, or (3) there was overflow to other muscles, were set for each microstimulator. An algorithm for controlling stimulation output provided stepwise increases in both pulse width and current amplitude so that the charge was minimized. Levels were checked and adjusted if necessary at weekly intervals during the first 4 weeks and at 4 weekly intervals thereafter. Thresholds remained stable.

Specific functional activities were identified for each subject relating to their goals and ability level. Activity programs were designed for each functional activity and were defined by output and timing of stimulation, including rise and fall times, for each microstimulator singly and, when the functional activity required 2 or more devices to be active in synergy, for the combined output so that the movement pattern was optimized. Activity sequences were programmed by using an intuitive, drag-and-drop graphics interface on a personal computer, which allowed rapid adjustment of stimulation parameters. Up to 3 different activity programs were then downloaded and stored in the control unit. The choice of program and level of stimulation (proportional increase on all channels on the selected program) were controlled by the subject by using easy-to-grasp knobs on the control unit.

Subjects attended the laboratory twice weekly during the first 1 to 3 weeks for programs to be designed and to learn how to use the system. As soon as subjects were able to use the system independently and perform the chosen functional activities, they entered the 12-week home-use period. During this period, they continued to attend the laboratory either weekly or on alternate weeks for approximately 1-hour sessions so that adjustments could be made by the research therapist to the stimulation programs and activities progressed in terms of speed at which they were performed and from simple to more complex tasks. Lower-functioning subjects and those with high levels of spasticity were initially set up with simple cyclic stretching exercises alone or before simple functional tasks, but emphasis was on using stimulation to augment voluntary task-based movement. Examples of tasks were opening the hand to grasp a can with the arm supported on a table (coordinated finger and wrist extension but without elbow extension) or polishing a table (elbow extension without hand opening) and, when function was limited by weakness, strengthening exercises such as extending the elbow against a resistance using Therabands.[b] Subjects who already had, or progressed to having, sufficient voluntary activity without excessive finger spasticity used stimulation programs to practice more complex functional reach-and-grasp tasks (fig 3). These involved coordinating multiple joint movements such as reaching (activation of elbow extensors), opening of the hand (adding wrist and finger extension), and, by switching off stimulation to the PIN and thus releasing finger extension, voluntary grasping of a variety of everyday objects while the grip was enhanced by maintained activation of the wrist extensors. Switching off elbow extensors enabled the object to be brought toward the body so that it could be used (eg, drinking from a cup, using a knife to cut vegetables, brushing hair). After use, the activation of elbow extension and then the PIN allowed the object to be replaced and released. During the 12-week home-exercise period, subjects were asked to practice at home using everyday objects for at least 1 hour a day 5 days a week. Subjects were encouraged to practice tasks without using stimulation especially immediately after an exercise session. An automated activity log in each subject's control unit provided a record of use of the stimulator.

Outcome Measures

Outcome measures were applied by the same assessor: 4 weeks and 1 day before implantation (baseline 1 and 2) and at

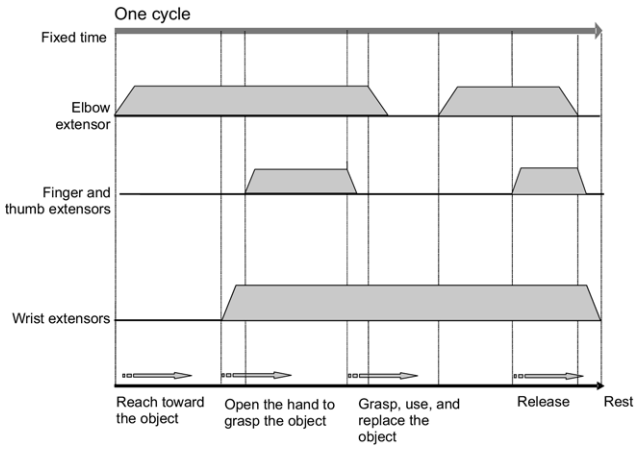

Fig 3. An example of an activity sequence to support reaching, grasping, and releasing an object.

the end of the 12-week home-exercise period, which was between 14 and 17 weeks postimplantation. The first baseline assessment familiarized subjects with the testing procedures and was not used in the analysis. The primary outcome measure for upper-limb function was the ARAT,[22,23] and the primary impairment measure was the ability to perform a tracking test (motor control). The ARAT is a standardized measurement tool that evaluates 4 domains of upper-limb function at an activity level: grasp, grip, pinch, and gross motor function. The total score is the sum of the subscores from the 4 domains, ranging between 0 and 57, with higher scores indicating better function. This measure is widely used in electrical stimulation and other upper-limb rehabilitation studies.[11,24,25] Reliability and validity[26-28] have been established, with a 5.7-point change in score suggested as being clinically important.[29] The ARAT was recorded on video for repeat scoring by a moderator who was blinded to which stage of the trial the video assessment related.

An instrumented wrist rig[30] was used to quantify the following impairments: motor control by accuracy during a tracking task (tracking index), spasticity by the surface electromyographic response to passive stretch of wrist flexors at 1.5Hz termed stretch index, AROM, and isometric force (flexion, extension). Before the study, the wrist rig had been tested for reliability and validity with a group of patients with stroke,[31-34] and ranges of values for an unimpaired age-matched population were identified. Test-retest reliability was shown to be excellent, with intraclass correlation coefficient values ranging from .86 to .98.[34] Repeatability for each measurement using the wrist rig was defined by the repeatability coefficient,[34] which is the size of change required to be reasonably certain (95%) of a real difference not caused by measurement error. By using this range value for each measurement, we were able to detect real change in each subject's performance.

For all wrist rig measures, the subject sat in a specially designed chair with the arm to be tested secured to a molded splint lined with an inflatable pouch that held the hand in midposition (pronation, supination) with the thumb uppermost and the fingers and thumb in comfortable extension. The arm and forearm were secured by 3 self-adhesive (Velcro) straps. The arm support was adjusted so that the shoulders were neither depressed nor elevated, with the elbow at 90° of flexion and the fulcrum aligned with the wrist joint. The rig allowed virtually friction-free movement of the wrist in the horizontal plane.

The raw analog angle and force data were recorded in real time at a sample rate of 1KHz and stored for offline processing by using LabView.[c] Data analysis to generate metrics and indices was performed by using software developed in the Matlab[d] environment. Surface electromyographic signals were recorded by using standardized electrode positions and skin preparation.[35] Electromyographic signals were recorded by using BEAC Biomedical preamplifiers[e] connected to self-adhesive electrodes.[f] Signals were amplified and antialias filtered by using a low-pass filter (cutoff frequency, 250Hz).

For the tracking test, a screen (computer monitor) in front of the subject displayed an elliptical target (target signal) moving sinusoidally horizontally across the screen at a frequency of 0.5Hz through 40° (20° either side of midpoint). The angular position of the wrist (tracking signal) was displayed as a cross, allowing the subject to visually track the target by flexing and extending the wrist trying to keep the cross within the ellipse. Subjects practiced the test several times until they believed they had achieved their best performance. They then rested for 3 to 5 minutes before performing the test for 60 seconds, during which position and electromyographic data were acquired.

Table 1: Subject Demographic Characteristics

Subject ID	Age (y)	Sex	Time From Stroke (y)	Stroke Type	Side of Hemiparesis
1	45	Female	10.5	Ischemic	Left
2	48	Male	1.4	Ischemic	Right
3	49	Male	1.1	Ischemic	Left
4	58	Male	2.3	Ischemic	Right
5	32	Female	7.1	Ischemic	Right
6	44	Male	1.7	Ischemic	Right
7	67	Female	3.2	Ischemic	Left

Accuracy in performance of the tracking task (motor control) was defined as the cross-correlation between the target and tracking signals (tracking index).[32] To measure the stretch index, the same target signal was displayed but at a frequency of 1.5Hz. The subject was asked to relax and avoid any contribution, either assistive or resistive to the procedure, while the assessor moved the wrist through 60° about the midpoint maintaining phase and displacement with the target signal for 40 seconds. Position and electromyographic data were acquired. The electromyographic response to rapid passive wrist extension was quantified by the stretch index, which is calculated from the root mean square electromyographic activity that exceeds baseline resting values during the period between 0° (midpoint) and peak extension and is expressed as millivolts. AROM (in degrees) and peak isometric force (in newtons) were also measured in the rig. For the isometric force test, the wrist was positioned at midpoint and immobilized. The subject was instructed and encouraged verbally to exert maximum force first into extension and then flexion. Force was maintained for 5 seconds, and the maximum value was used in the analysis.

The movement, coordination, and sensation of the upper limb were measured by using FMA upper limb, a valid and reliable measure of poststroke impairments.[27] The resistance to passive movement was measured by the MAS.[36] The order in which tests were conducted was the same for each subject and at each assessment. Wrist rig measures were conducted in the order as follows: AROM, stretch index test, tracking test, and isometric force.

Statistical Analysis

Statistical analysis was performed by using SPSS.[g] Means ± SDs of all outcome measures at baseline 2 and 12 weeks are presented. Mean changes ± SD are reported and statistically significant differences between baseline 2 and 12 weeks have been estimated by using the Wilcoxon signed-rank test. We derived the 95% CI from the standard error of the mean change generated by a paired *t* test. Individual changes in all outcome measures are presented and we have identified where the size of change in ARAT and FMA was clinically important, as suggested in a recent study,[26] and for wrist rig measurements where the effect size was considered a real change as opposed to measurement error based on the previously shown repeatability coefficients. A change of 1 point on the MAS is accepted as clinically important.

RESULTS

Seven subjects were recruited, and their demographic characteristics are shown in table 1. Subjects' ages ranged from 32 to 67 years (mean, 45y); 4 were men, and 3 were women. All subjects had suffered an ischemic stroke ranging from 1.1 to 10.5 years (mean, 3.9y) before recruitment to the study; 3 had

Table 2: Normative Score and Sample Mean Score at Baseline 2 and 12 Weeks for the Main Outcome Measures (N=7)

Outcome Measure (normative score ± SD)	Baseline 2 ± SD	12 Weeks ± SD	Change ± SD, *P** (95% CI)
Function			
ARAT score (57±0)	23.0±12.65	27.9±12.36	4.9±7.89, *P*=.249 (12.322 to –2.607)
Impairments: active tests			
FMA motor score (66±0)	34.60±7.14	40.90±7.97	6.30±3.59, *P*=.027 (−9.608 to −2.693)
Tracking index at 0.5Hz (192.6±10.9)	82.00±49.22	139.30±40.24	57.30±48.65, *P*=.028 (−102.280 to −12.291)
AROM (deg) (139°±9.2°)	75.20±27.53	94.40±18.72	19.30±18.96, *P*=.028 (−36.826 to −1.758)
Isometric force: flexion (N) (125.00±44.68N)	41.00±18.68	45.00±15.73	4.00±11.52, *P*=.499 (−15.049 to 6.261)
Isometric force: extension (N) (56.00±17.33N)	8.00±8.37	13.00±6.12	5.00±4.37, *P*=.028 (−9.510 to −1.424)
Impairment: passive tests			
MAS score for wrist flexors (0±0)	1.70±0.95	1.40±1.27	−0.30±0.76, *P*=.317 (−0.413 to 0.985)
Stretch index at 1.5Hz (0.36±0.36)	5.00±3.68	4.10±3.97	−0.90±3.68, *P*=.866 (−2.514 to 4.291)

NOTE. Values are mean ± SD or mean change ± SD (during the 12-week exercise period) with 95% CI.
*Wilcoxon signed-rank test.

a hemiparesis of the left side and 4 of the right. All subjects were successfully implanted under local anesthetic with between 5 and 7 microstimulators. Two weeks after implantation, activity programs were begun with all subjects. Compliance was good, and the use of the system recorded in the activity log showed an average ± SD of 1.1±.29 hours a day spread over an average of 62±24.5 days.

A mean improvement between baseline and 12 weeks was identified in all outcome measures. The mean ± SD, level of statistical significance, and 95% CI are shown in table 2.

The difference between baseline 2 and the 12-week assessment for each subject is shown in table 3. Individual results of the main outcome measures are shown in figure 4A (ARAT), B (FMA), and C (tracking index).

Moderation of the ARAT scores by a blinded assessor identified 2 instances in which the score varied by 1 point. In both cases, the video recording did not give a completely clear image of the performance of the test. Therefore, the original assessor's scores have been used in the analysis.

Personalized Activity Programs

Activity programs in which voluntary movement was augmented by appropriate stimulation were designed to assist each subject in achieving his/her specific goals and tasks. Goals were only considered to have been achieved when the subject could perform the task without stimulation. Subject 1, who was 10.5 years poststroke, had a baseline ARAT score of 39, limited forward reach, and inability to release objects. The goals were to grasp and release objects away from the body and catch a ball with both hands. To achieve these goals, activity programs progressed from elbow-extension activities, to hand opening with the arm supported, and then to unsupported elbow extension and hand opening to grasp, use, and replace an object such as a glass of drink with the affected hand or a ball using both hands. Initially, she could open her fingers to grasp and release objects more effectively and with a more normalized movement pattern with stimulation. At the end of the 12-week period, both goals were achieved with a satisfactory but slow movement pattern, although she still could not achieve full elbow extension.

Subject 2, who was 16 months poststroke, had a baseline ARAT score of 8, was unable to open his hand, and had limited forward reach, all of which were associated with spasticity. His main goal was to be able to grasp and hold an object such as a can of drink so that it could be opened with the nonaffected hand. Activity programs progressed from single-joint extension at the elbow, wrist, and fingers, to elbow extension while weight bearing through the hand, and finally to reaching and grasping with the arm supported on a table to allow effective hand opening. At the start of the study, even with stimulation, he was unable to perform functional tasks, but, by the end of the 12-week period, he was able to grasp and release small objects close to his body without simulation. With stimulation, he was able to grasp and release larger objects further away from his body. The goal was achieved, and spasticity was reduced. Functional improvement was sufficient to enable him to swing a golf club and hit a ball, which he had not done since his stroke.

Subject 3, who was 13 months poststroke, had a baseline ARAT score of 16 and particular difficulty in opening the hand when the elbow was extended. His goals were to grasp a door handle and open a door, to perform bilateral reach and grasp tasks, and to eat with a knife and fork. Exercises augmented by stimulation progressed from single-joint extension activities to reaching to touch objects, bilateral reaching to grasp a bowl, elbow extension against a resistance, and finally to use the system to reach and grasp a jug and pour water from it. At the end of the 12-week period, he was able to grasp a door handle and eat with a knife and fork. Both tasks could be performed equally well with or without stimulation. Movement pattern was good but slightly slower and less well controlled than normal.

Subject 4, who was 2 years and 3 months poststroke, had a baseline ARAT score of 28, a weak grasp, and a poor release, especially of larger objects. Tremor on effort, which interfered with function, was identified as a specific problem. Specific goals were to be able to wash his body with the affected hand and to reach, grasp, and release without tremor. This subject put considerable effort into activities that progressed from supported to unsupported arm, wrist, and finger extension, and bilateral and unilateral activities reaching to different positions, some above the horizontal. During the first 6 weeks of the exercise program, the strength of contraction elicited by the devices in the triceps (medial heads of triceps, lateral heads of triceps) failed to generate a sufficiently strong contraction to provide functional elbow extension. After the 12-week assessment, 2 further devices were implanted that have worked satisfactorily. Because of poor elbow extension, especially against gravity, this subject had difficulty practicing activities involving high reaching, which may have explained why, although he had an above average improvement on the tracking task (102.8), which measured motor control at the wrist, he had

Table 3: Test Scores at Baseline 2 (B2) and at 12 Weeks (12) and Difference Between Scores (12−B2) for Each Subject

Variable	Subject 1			Subject 2			Subject 3			Subject 4			Subject 5			Subject 6			Subject 7		
Use of the device*																					
Total days		56			59			45			73			53			36			76	
Average h/d		0.99			1.03			1.27			0.83			1.33			0.48			1.26	
Outcome measure																					
CIC/RC	B2	12	12−B2	B2	12	12−B2	B2	12	12−B2	B2	12	12−B2	B2	12	12−B2	B2	12	12−B2	B2	12	12−B2
Function																					
ARAT score																					
5.7	39	40	1	8	17	**9**	16	35	**19**	28	25	−3	33	31	−2	30	40	**10**	7	7	0
Active tests																					
FMA motor																					
6.6	35	41	6	29	37	**8**	36	42	6	39	39	0	44	51	**7**	37	49	**12**	22	27	5
Tracking index																					
60.0	128.9	113.3	−15.7	61.5	146.3	**84.8**	64.7	144.4	**79.7**	89.2	192.0	**102.8**	54.4	74.2	19.8	161.0	180.9	19.9	14.4	124.1	**109.7**
Total ROM																					
42.5	95	104	9	100	99	−1	114	120	6	64	86	22	63	77	14	50	108	**58**	40	82	42
Isometric force: flexion																					
21.7	70	54	−16	35	34	−1	37	53	16	50	50	0	19	25	6	54	70	16	20	31	11
Isometric force: extension																					
7.6	2	5	3	6	10	4	14	17	3	23	22	−1	0	9	**9**	10	19	**9**	1	12	**11**
Passive tests†																					
MAS score																					
−1	1	1	0	3	1	**−1**	1	0	**−1**	2	3	1	1	0	**−1**	1	1	0	3	3	0
Stretch index																					
−2.28	6.3	4.38	−1.92	9.01	0.37	**−8.64**	0.18	0.4	.22	3.28	2.59	−.69	4.82	6.13	1.31	1.45	3.1	1.66	9.97	11.81	1.84

NOTE. Boldface denotes where the change was considered to be clinically important change or a real change greater than the repeatability coefficient.

Abbreviations: CIC, clinically important change; RC, repeatability coefficient; ROM, range of motion.

*The total number of days and average time/day that the stimulation system was used by each subject during the 12-week period (as recorded by the stimulator log function).

†For passive tests, negative scores show improvement.

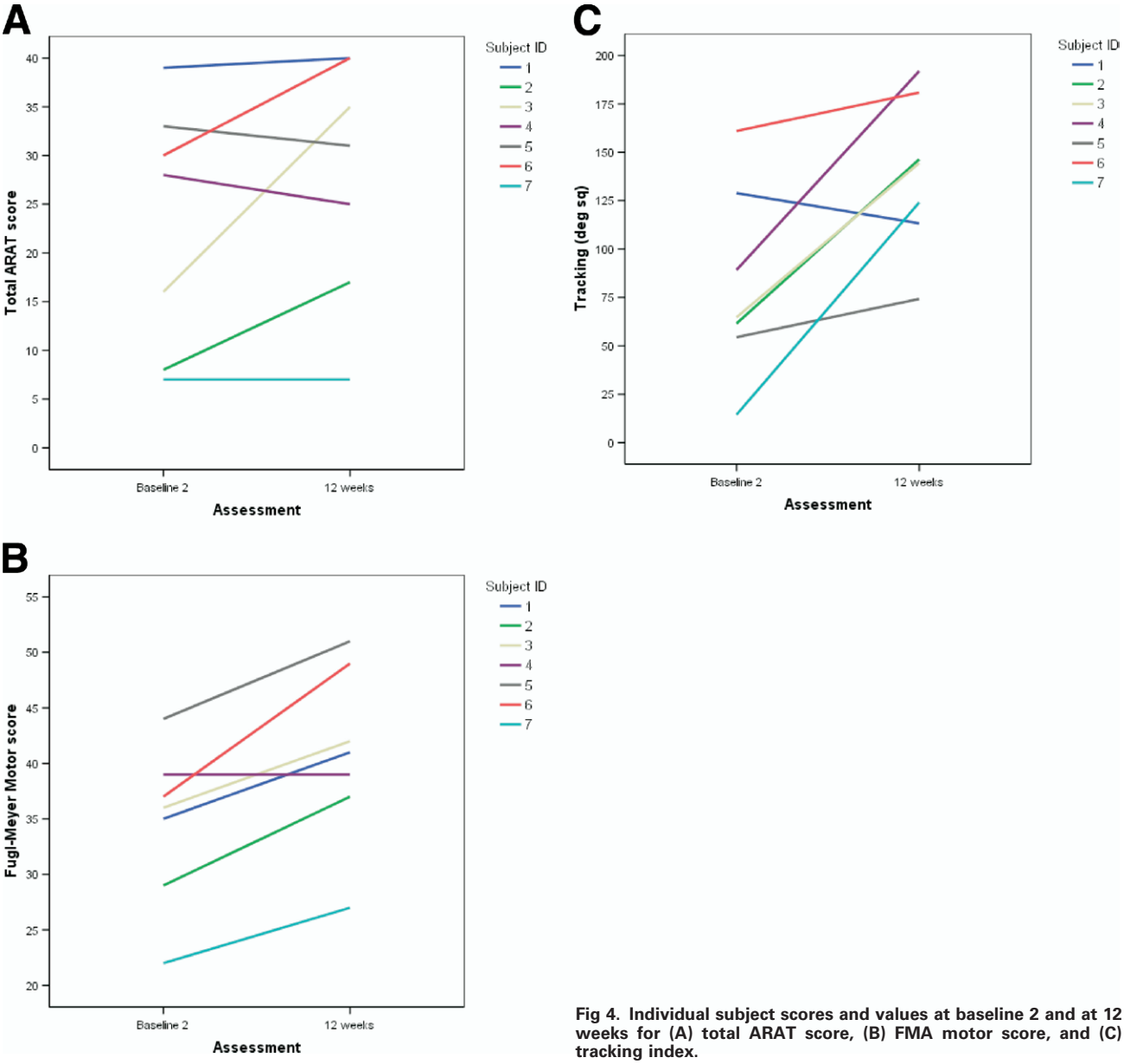

Fig 4. Individual subject scores and values at baseline 2 and at 12 weeks for (A) total ARAT score, (B) FMA motor score, and (C) tracking index.

no improvement in function (ARAT score decrease, 3 points). Tremor remained a problem; however, he was able to wash his body and hair by using both hands. Throughout the period, quality of movement was better with stimulation, and he may therefore have benefited from using the system as a neuroprosthesis.

Subject 5, who was just over 7 years poststroke, had a baseline ARAT score of 33 and some ability to grasp and release small- and medium-sized objects placed close to the body, although this deteriorated quickly with repetition. Her specific goals were to be able to grasp the handlebar brake when riding a bicycle, reach objects out of cupboards, and use a vacuum cleaner. Activities progressed from single-joint activities of the elbow, wrist, and fingers to reaching for a variety of objects at different heights and reaching, grasping, drinking, and replacing a drinking mug. The ability to use a vacuum cleaner with the affected hand was achieved, but she continued to have difficulty releasing objects when combined with the effort of reaching away from the body. Immediately after a period of cyclic stimulation that elicited the movement pattern required for a functional task (hand opening), she was able to perform the task more effectively and with a more normative movement pattern. Performance was always better with stimulation, even at the end of the 12-week period.

Subject 6, who was 19 months poststroke, had a baseline ARAT score of 30, was able to grasp small objects with reasonable dexterity, but was unable to release them; shoulder and elbow control was good. His goals were to pick up and carry moderately heavy large objects and to reach for objects in high cupboards. It was possible to design activities in which these could be practiced and performance of these tasks improved so that by the end of the 12 weeks he was able to release objects placed at high levels, although slowly and with greater than normative effort. Because of unrelated health problems, this subject only used the system for 36 days.

Subject 7, who was 3.2 years poststroke, had the lowest baseline ARAT score of 7 and had only a flicker of activity in the finger and wrist extensors, weak grasp, and inability to release objects. Goals were to hold objects such as a fork in the affected hand and carry a tray with both hands. Activity programs were designed for table polishing, elbow extension with the forearm supported, and this was progressed to grasp-and-release activities but still with elbow support. At the end of the study, this subject managed to carry a tray with both hands, but there was no further improvement in reach and grasp.

In summary, personalized functional exercise with programmed radiofrequency microstimulation resulted in a mean improvement in all outcome measures. Functional improvement (ARAT) was measured in 4 of the 7 subjects, 3 of whom made clinically important changes. Of those who improved functionally, 2 subjects (subjects 2, 3) also had a clinically important change in motor control, and improvement for subject 6 was to within the normative range. One subject (subject 2) who had the highest baseline spasticity score had a meaningful reduction in spasticity measured by the stretch index and a clinically important reduction in resistance to passive movement measured by the MAS. All subjects except subject 2, who ranked second highest on this measure at baseline, had an increase in AROM. Isometric extensor muscle force improved in 6 of 7 cases, and improvement was clinically important in subjects 5, 6, and 7. The 2 subjects who did not change functionally did improve in motor control (subject 4) and extensor muscle isometric force (subject 5).

DISCUSSION

The results of this study have shown that for subjects more than 1 year poststroke improvement in function and reduction of impairment can be achieved through a 12-week program of functional exercise by using implanted microstimulators (radiofrequency microstimulators). No studies have previously reported the effect of fully implanted systems on upper-limb recovery in chronic poststroke subjects, and a recent Cochrane review[37] concluded that there was insufficient robust data to inform clinical use of FES in retraining. Despite this, some studies with subjects less than 12 months poststroke have reported significant benefits when using surface systems that are comparable with our study with subjects who are more than 12 months poststroke, when less improvement would normally be expected. Chae et al[38] in an RCT of 46 acute stroke subjects identified a difference between treatment and control groups after 15 one-hour sessions of 6.6 points on the FMA, comparable to 6.3 in this study. Mann et al[11] in an RCT of 24 subacute stroke subjects found a between-group difference on the ARAT of 2 points at 12 weeks and 4 points at 24 weeks, both of which were statistically significant, compared with 4.9 in this study. Popovic et al[12] investigated functional electric therapy by using surface electrodes; this approach is similar to ours in that stimulation was associated with functional activities. Direct comparison of results cannot be made because they used the Upper Extremity Function Test, which measures speed and number of repetitions of performance of a series of tasks, but they too found a statistically significant improvement that was probably comparable clinically.

Our results also seem to indicate that improvement in function may be associated with an improvement in a range of different impairments. As might be expected, impairments that improved tended to be those on which subjects scored poorly at baseline. Improvement in impairment measures, such as the FMA, AROM, and motor control, was greater than in functional measures, and this may be because impairment measures are more sensitive to change. However, impairment measures may be useful in providing insight into the mechanisms associated with change in function and mechanisms of the effect of electric stimulation. Treatment in this study involved both the arm and forearm and although the ARAT evaluated complex multijoint functional movement of the whole upper extremity, the wrist rig assessment focused only on movement at the wrist; improved motor control at the elbow and shoulder would therefore not be detected. An elbow rig with the capability of measuring the same impairments as the wrist rig is therefore currently under development and will be used in future studies.

Despite narrowly defined selection criteria, subjects presented with different functional problems and different personal goals. The microstimulator system enabled personalized activity programs to be designed that enabled a range of functional activities to be performed by subjects in their own homes and addressed individual goals; this we believe was a reason why motivation was high and compliance generally good. Subject 6 was the least compliant; he only received 19 hours of stimulation over 36 days, and this was because of a period of unrelated ill health during the intervention period.

Improvement in function varied across the sample from a maximum of 19 points on the ARAT to a decrease of 3. Response did not appear to be dependent on baseline level of function (eg, in the ARAT, subject 2's score improved from 8 to 17, whereas subject 7, whose baseline score was 7, made no improvement at all). Subjects 7 and 2 had higher levels of spasticity, but subject 7 had considerable weakness, whereas subject 2 had underlying activity; this scenario seemed to respond positively to the functional exercises using the stimulation. This is contrary to Chae and Hart's study[18] performed by using percutaneous electrodes in which those with higher levels of spasticity did not respond well to the stimulation. Those subjects who improved most in terms of function were less than 2 years poststroke, and there was no relationship between total stimulation time and improvement in any outcome measures. The implications for this are that future studies should recruit subjects sooner after stroke and that lower functioning subjects should not be excluded.

Future Work

Previous studies suggest that voluntary activation of stimulation is important in recovery. De Kroon et al[14] in a systematic review that identified a positive effect of stimulation in 13 of 22 patient groups reported that positive results were more common when stimulation was triggered by voluntary movement. At the end of this first phase of the study, all subjects elected to take part in a second phase in which external touch and angle sensors will be used to trigger activities and provide temporal control over stimulation of different muscle groups. This approach, supported by De Kroon's finding, will enable activities to be performed in response to voluntary command and at the subject's preferred speed. On completion of the second phase, subjects will be able to continue to use the system for a further 5 years; this will enable us to examine the feasibility and acceptability of prolonged use of an implanted system. The longest duration of stimulation found in the literature was 3 months, reported by Sonde et al.[39] Clinically, however, stimulation is often continued for considerably longer but with less good compliance.

Study Limitations

One disadvantage of the current system is that because the devices do not have their own power supply an inductance coil needs to be worn around the arm (see fig 2), which anecdotally subjects reported being an encumbrance. In the future, battery-

powered devices may become available and thus remove the need for the coil except for recharging.

CONCLUSIONS

The feasibility of using implanted microstimulators to augment functional upper-limb movement and the use of the system at home has been shown. Seven subjects with established hemiparesis were successfully implanted with between 5 and 7 radiofrequency microstimulators. After a 12-week period of functional exercise using personalized activity programs supported by electric stimulation, a mean improvement was detected in all outcome measures. Three subjects who made clinically important changes in terms of function had an average increase in score on ARAT of 12.7±5.5. Two further subjects who did not improve functionally did improve in motor control and extensor muscle strength. In 3 cases, stimulation reduced resistance to passive movement (MAS), and in 1 case a meaningful reduction in spasticity (stretch index) was detected. The 3 participants who made the largest overall gains were less than 2 years poststroke.

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