UC Irvine
UC Irvine Previously Published Works

Title

Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded Everest Trial.

Permalink

https://escholarship.org/uc/item/38h3v0s4

Journal

Neurorehabilitation and neural repair, 30(2)

ISSN

1545-9683

Authors

Levy, Robert M
Harvey, Richard L
Kissela, Brett M
et al.

Publication Date

2016-02-01

DOI

10.1177/1545968315575613

Copyright Information

Peer reviewed

Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded *Everest* Trial

Robert M. Levy, MD, PhD[1], **Richard L. Harvey, MD**[2,3], **Brett M. Kissela, MD**[4], **Carolee J. Winstein, PhD**[5], **Helmi L. Lutsep, MD**[6], **Todd B. Parrish, PhD**[2], **Steven C. Cramer, MD**[7], **and Lalit Venkatesan, PhD**[8]

Abstract

Background. This prospective, single-blinded, multicenter study assessed the safety and efficacy of electrical epidural motor cortex stimulation (EECS) in improving upper limb motor function of ischemic stroke patients with moderate to moderately severe hemiparesis. *Methods.* Patients ≥4 months poststroke were randomized 2:1 to an investigational (n = 104) or control (n = 60) group, respectively. Investigational patients were implanted (n = 94) with an epidural 6-contact lead perpendicular to the primary motor cortex and a pulse generator. Both groups underwent 6 weeks of rehabilitation, but EECS was delivered to investigational patients during rehabilitation. The primary efficacy endpoint (PE) was defined as attaining a minimum improvement of 4.5 points in the upper extremity Fugl-Meyer (UEFM) scale as well as 0.21 points in the Arm Motor Ability Test (AMAT) 4 weeks postrehabilitation. Follow-up assessments were performed 1, 4, 12, and 24 weeks postrehabilitation. Safety was evaluated by monitoring adverse events (AEs) that occurred between enrollment and the end of rehabilitation. *Results.* Primary intent-to-treat analysis showed no group differences at 4 weeks, with PE being met by 32% and 29% of investigational and control patients, respectively (*P* = .36). Repeated-measures secondary analyses revealed no significant treatment group differences in mean UEFM or AMAT scores. However, post hoc comparisons showed that a greater proportion of investigational (39%) than control (15%) patients maintained or achieved PE (*P* = .003) at 24 weeks postrehabilitation. Investigational group mean AMAT scores also improved significantly (*P* < .05) when compared to the control group at 24 weeks postrehabilitation. Post hoc analyses also showed that 69% (n = 9/13) of the investigational patients who elicited movement thresholds during stimulation testing met PE at 4 weeks, and mean UEFM and AMAT scores was also significantly higher (*P* < .05) in this subgroup at the 4-, 12-, and 24-week assessments when compared to the control group. Headache (19%), pain (13%), swelling (7%), and infection (7%) were the most commonly observed implant procedure-related AEs. Overall, there were 11 serious AEs in 9 investigational group patients (7 procedure related, 4 anesthesia related). *Conclusions.* The primary analysis pertaining to efficacy of EECS during upper limb motor rehabilitation in chronic stroke patients was negative at 4 weeks postrehabilitation. A better treatment response was observed in a subset of patients eliciting stimulation induced upper limb movements during motor threshold assessments performed prior to each rehabilitation session. Post hoc comparisons indicated treatment effect differences at 24 weeks, with the control group showing significant decline in the combined primary outcome measure relative to the investigational group. These results have the potential to inform future chronic stroke rehabilitation trial design.

Introduction

Hemiparesis is the most common cause for functional motor limitations poststroke. Approximately 6 months poststroke, 30% to 66% of stroke patients regain partial functional upper limb use,[1-4] and less than 20% completely recover.[2,5] Upper limb motor training is an essential part of a comprehensive poststroke rehabilitation program, but the benefits of training vary among patients. Recent evidence indicates that task-oriented therapies targeting arm and hand function are effective in specific subsets of patients,[6] but a majority

[1]Marcus Neuroscience Institute, Boca Raton, FL, USA
[2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[3]The Rehabilitation Institute of Chicago, Chicago, IL, USA
[4]University of Cincinnati, Cincinnati, OH, USA
[5]University of Southern California, Los Angeles, CA, USA
[6]Oregon Health & Science University, Portland, OR, USA
[7]University of California, Irvine, CA, USA
[8]St. Jude Medical, Plano, TX, USA

Corresponding Author:
Richard L. Harvey, The Rehabilitation Institute of Chicago, 345 East Superior Street, Chicago, IL 60611, USA.
Email: rharvey@ric.org

of patients do not regain adequate motor function with rehabilitation alone.[7,8]

Neuronal plasticity in surviving motor and premotor cortices is presumed to play a major role in motor recovery poststroke.[9-12] Evidence suggests that plasticity can be modulated by various exogenous means: behavioral training, plasticity-enhancing drugs, and electrical stimulation.[13] Results from preclinical studies using cortical stimulation (CS) in experimental animal models with motor deficits induced by focal cortical lesions illustrate the importance of pairing CS with skilled motor training for providing behavioral and neurophysiological benefits.[14-16]

Evidence obtained from noninvasive CS studies using repetitive transcranial magnetic stimulation (rTMS)[17-20] and transcranial direct current stimulation (tDCS)[21,22] substantiate claims for the role of CS in improving motor skill in the hemiparetic hand. Both these noninvasive techniques have practical limitations for use in a clinical setting. The cranial anatomical target for TMS or tDCS must be reestablished at each therapeutic session,[23] and TMS cannot be applied during motor training. In contrast, invasive electrical CS involves epidural or subdural placement of the stimulating electrode at the target, allowing for greater consistency and ease in delivering stimulation throughout the course of task-oriented motor training. TMS and tDCS are relatively safe, but extent of the induced electrical field on the cortical surface is highly dependent on the positioning of the coil or electrode delivering stimulation. Predictive modeling studies have shown that direct electrical CS has the spatial resolution of a few millimeters, whereas the TMS resolution spans several centimeters.[24] The depth of penetration of conventional TMS coils is approximately 2 cm from the scalp and there is a tradeoff between spatial resolution and depth of penetration of the induced field.[25] Computational modeling using an extruded slab of cortical neurons indicates that electrical CS can stimulate neurons deep within the sulci at higher thresholds when compared to the neurons on the crowns or lips of the gyri.[26] But, our knowledge of differences in efficacy between the 2 stimulation techniques is limited as there are no human clinical studies directly comparing the effectiveness and sustainability of these neurostimulation modalities.

Two multicenter clinical feasibility studies[27,28] examined the effectiveness of epidural electrical CS (EECS) delivered during rehabilitation in stroke patients with upper limb hemiparesis. Significant improvements in upper limb motor function were observed in the investigational groups compared to their respective control groups.

In this study, we evaluated the safety and efficacy of a larger, prospective, multicenter, single-blinded, randomized phase-III clinical trial called *Everest*. We hypothesized that the combination of EECS and task-oriented upper limb motor rehabilitation would result in a greater proportion of patients achieving clinically meaningful improvements in motor control, and arm and hand motor function when compared to patients undergoing only rehabilitation. This study also assessed the safety of an EECS system in treating motor deficits in patients with chronic stroke.

Methods

Study Design

This prospective, randomized, single-blind, multicenter study was conducted at 21 sites in the United States, and was approved by the institutional review board at each study site. The trial was conducted under an Investigational Device Exemption from the Food and Drug Administration (FDA). All study participants provided written informed consent prior to entering the study.

The primary objectives of the study were to determine the safety and efficacy of targeted subthreshold EECS delivered during task-oriented rehabilitation in order to enhance motor recovery in chronic stroke patients with upper limb hemiparesis. A detailed description of the study design, patient selection criteria, and methods were previously published.[29] We briefly review the design in the sections below.

Study Participants

Inclusion criteria: Male and female subjects at least 21 years old with moderate to moderately severe upper extremity hemiparesis due to an ischemic infarct that occurred ≥4 months prior to enrollment were considered for this study. Moderate to moderately severe impairment was defined as a score of 28 to 50 (inclusive) on the upper extremity Fugl-Meyer scale (UEFM).[30-35]
Exclusion criteria: Subjects with a primary hemorrhagic stroke, severe sensory deficit, or moderate to severe hemispatial neglect and/or anosognosia; or a history of seizures were excluded from this study.

After screening, patients underwent baseline evaluations and assessments of UEFM, Arm Motor Ability Test (AMAT) scores,[36] the Box and Block Test, structural and functional magnetic resonance imaging (MRI and fMRI), Stroke-Specific Quality of Life Scale (SS-QOL), and a neuropsychological testing battery. The neuropsychological assessments have been described in detail previously.[29] In this article, we evaluate the 4-, 12-, and 24-week assessments of the composite primary efficacy endpoint (ie, UEFM and AMAT scores).

Randomization

Subjects were randomized in a 2 to 1 ratio to an investigational or control group, respectively. Computer-generated randomization was performed at a central location by using a site-specific block design with random block sizes of 3, 6,
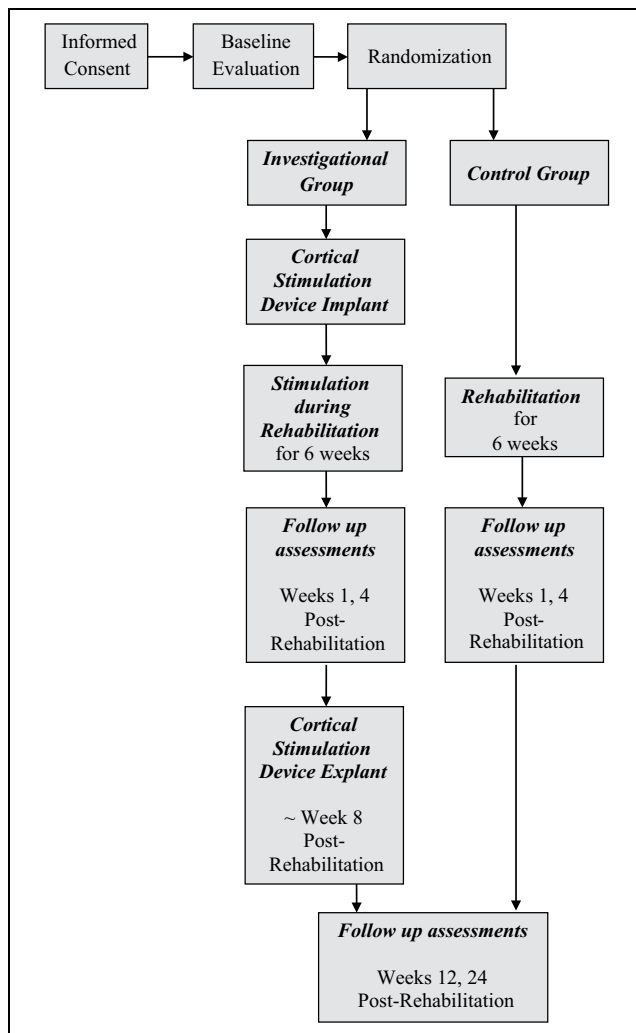
Figure 1. Clinical trial design.

or 9. Investigational group patients were implanted with the EECS system and then received 6 weeks of task-oriented upper limb motor rehabilitation with EECS turned on only during the rehabilitation sessions. Patients in the control group were not implanted; nor did they undergo sham surgery. To parallel the timing of rehabilitation in the investigational group, rehabilitation for control group patients was initiated 2 to 4 weeks after randomization, and also lasted for 6 weeks. Both the investigational and control groups were followed up for 24 weeks after completing the rehabilitation program, with assessment visits occurring at weeks 1, 4, 12, and 24 (Figure 1).

Blinding

Patients and the clinicians involved in patient care were not blinded, but assessors of outcome measures were blinded to treatment group assignment. To maintain assessor blinding, all patients, regardless of group assignment, masked any

evidence of the neurosurgical procedure by wearing a cloth hood during testing.

Imaging

The imaging protocol was previously described.[29] Briefly, structural MRI was used to verify the anatomical location of the stroke, and fMRI was used to identify the cortical target area associated with defined active wrist and hand movements in the affected limb. The fMRI task was a simple block design in which the participant elevated their affected wrist approximately 5° and returned to the neutral position every 2 seconds during the 30-second active block. Participants were instructed to remain still during the 30-second control block. The forearm and wrist were fixed in a plastic holder, and 2 runs of 4 minutes and 30 seconds were collected of the same movement. Data were concatenated if both sessions lacked any movement contamination; else a single uncorrupted run was used to identify the activation. Analysis was conducted in SPM5 after motion correction, slice timing correction, and spatial smoothing (2 times the voxel dimension). Functional data were coregistered to the participant's 3-dimensional anatomical T1 volume to facilitate the surgical placement. The contrast used to generate the functional activation map was active (wrist movement) greater than control (rest). Selection of the stimulation site was limited to the ipsilesional hemisphere and had to be located in (or near) known motor-sensory regions to avoid any artifactual activation. Because of the robust nature of the motor response even in this population, the activation was typically along the intact motor cortex just anterior to the central sulcus. The center of mass of the activation cluster was identified by coordinates that were transferred to the structural scan. The structural scan was then labeled at the coordinate to be used as a target for the surgical placement of the electrode.

Cortical Stimulation System

The EECS system consisted of an implantable pulse generator (IPG), the lead, and a handheld stimulation programmer.[29] Stimulation frequency, pulse width, and stimulation amplitude could be programmed in 5 Hz (range = 5-150 Hz), 25 μs (range = 25-300 μs), and 0.25 mA (range = 0-13 mA) increments, respectively. The EECS lead used a 6-element platinum-iridium electrode grid configured in a flexible 2 by 3 element array encased in a silicone sheath. The electrode contacts were 3 mm in diameter and spaced 9 mm [center-to-center] apart, making the effective stimulation area of the electrode ~1.8 cm^2.[28]

Implantation Procedure

The patient was under general anesthesia during the implant procedure. An extradural craniotomy (~4 cm in diameter)

was performed above the predetermined cortical area. The stimulation electrode was placed on the dura mater over the target location, as predetermined using frameless stereotaxic neuronavigation, and was anchored with dural sutures. The lead was then tunneled beneath the scalp and the skin of the neck and exited at the subclavicular pocket for connection to the IPG.

Cortical Stimulation Programming

Three electrode contacts along one edge of the lead were configured as anodes, and 3 contacts on the opposite edge were programmed as cathodes. Prior to initiation of the 6-week rehabilitation intervention, the stimulator output current level was programmed based on movement threshold (MT) testing. The IPG output current level was adjusted in 1-mA increments up to 13 mA at 50 Hz and 250 μs to determine the minimum current level required to elicit visible or palpable hand or arm muscle response (ie, MT). The stimulation amplitude used during rehabilitation therapy was 50% of the MT. The choice of 50% of MT was based on preclinical data in rat stroke models suggesting that subthreshold (50% of MT) stimulation was superior to suprathreshold stimulation in achieving improved motor skill and dendritic volume during EECS with motor training.[14] If no muscle response could be induced during testing, the stimulator was set at 6.5 mA, which is 50% of maximum pulse generator output. These stimulation parameters were unchanged throughout the rehabilitation intervention. EECS was initiated approximately 5 minutes prior to the start of each rehabilitation session, and was discontinued at the end of each session.

Rehabilitation Protocol

Both investigational and control groups participated in a 6-week rehabilitation program[29,37] that consisted of approximately 2.5 hours of therapy per day (2 sessions per day, 60-75 minutes per session). Rehabilitation was conducted 5 days a week for the first 4 weeks and 3 days a week for the next 2 weeks (total = 26 days or 65 treatment hours). The first session each day focused on motor activities and movements appropriate for the patient (ie, improvements in coordination and the abilities to grasp, release, and reach). After a rest break, the subsequent session focused on activities of daily living and self-selected functional activities using the affected arm and hand. Functional activities were selected using the Canadian Occupational Performance Measure (COPM) performed at baseline.[38,39] During this assessment, the patient selected 5 motor tasks that were most challenging to perform independently. Two of these were selected as focused goals for therapy and the therapist also encouraged the subject to work on these tasks at home during the 6-week rehabilitation period. The EECS system was explanted

approximately 8 weeks after completion of the rehabilitation protocol (Figure 1). On completion of the rehabilitation protocol, investigators instructed patients not to participate in additional physical/occupational therapy (except speech therapy) during the rehabilitation program and the first 4 weeks of follow-up.

Study Outcomes

Two primary outcome measures were used in this study: the UEFM and the AMAT. UEFM is a standardized quantitative assessment of neurological and motor impairment. AMAT is both a qualitative and quantitative assessment of upper limb function in activities of daily living. Raters were trained and their rating skill was tested prior to data collection, and retested every 6 months throughout the course of the study. The primary outcome measure was defined as the percentage of patients with clinically meaningful improvements in both the UEFM and AMAT measures when assessed 4 weeks postrehabilitation. A clinically meaningful improvement was defined a priori as a 4.5-point improvement from baseline in the UEFM (out of a total of 66 points) and a 0.21-point improvement in the AMAT function (out of a total of 5 points). The target criterion for the UEFM and AMAT scales were chosen on the basis of pooled results from prior rehabilitation studies in patients with chronic hemiparesis.[27,28,40]

Secondary outcome measures included (*a*) absolute change from baseline in UEFM and AMAT scores, measured at weeks 4, 12, and 24 postrehabilitation and (*b*) clinically meaningful improvement in UEFM and AMAT at weeks 12 and 24.

Statistical Analysis

The statistical analysis plan was previously described in detail.[29] Briefly, the efficacy of the intervention was tested using intent to treat analysis comparing the proportion of patients in the investigational group achieving success with those in the control group. Missing data were imputed by carrying forward the data from the previous assessment. A z-score was calculated based on the difference of these proportions and tested for significance using a 1-sided test (α = .025). To examine differences in the proportions of subjects in each treatment group who achieve clinical success across time, covariate adjusted analyses of the primary efficacy endpoint were conducted using logistic regression. Covariates included baseline UEFM, time since stroke, handedness, age, gender, and investigational site. Secondary analyses compared mean changes in UEFM and AMAT scores between investigational and control groups at 4, 12, and 24 weeks posttreatment using repeated-measures models. These comparisons accommodated the nonindependence of observations from subjects and allowed for the

comparison of outcomes between treatment groups during the study period and at specific time points (repeated-measures analysis of variance). Follow-up post hoc comparisons between treatment groups at any given time point were done using a 1-sample *t* test. For all secondary analyses, *P* ≤ .05 was considered statistically significant.

Safety Assessments

Details of the description and classification of adverse events (AEs) and serious adverse events (SAEs) have been previously published.[29] In brief, a data and safety monitoring board was responsible for reviewing safety data. Safety assessments included the monitoring of adverse events, concomitant medications, postoperative clinical and neurological examinations, and stimulation system checks. Investigators judged whether each AE was related to the underlying disease state, to the device, or to the study procedure, and this assessment was documented on the case report form. The AEs that were categorized prior to study enrollment were characterized as anticipated events, and any other event recorded was classified as an unanticipated event.

Results

A total of 373 patients consented to participate in the *Everest* study. A total of 164 patients who met the study's inclusion/exclusion criteria were randomized into 104 investigational and 60 control subjects. Of the 104 who were randomized to the investigational group, 94 received a cortical implant (prior to device implantation, 9 subjects declined to continue in the study and 1 subject experienced a second stroke). Out of the 60 subjects randomized to the control group, 58 received the rehabilitation therapy (prior to entering therapy, 2 subjects declined to continue in the study). Each patient completed the study within approximately 8 months, which included 1 to 2 weeks of baseline activities, 6 weeks of treatment, and 24 weeks of follow-up (Figure 1). All 6-weeks of rehabilitation was completed by 97% of the investigational (91/94) and control group (56/58) patients. Because of study attrition, 91, 89, and 87 investigational and 55, 54, and 52 control group patients completed the 4-, 12-, and 24-week assessments, respectively.

Handedness, time since stroke, and National Institutes of Health Stroke Scale score differed between investigational and control groups at baseline (Table 1), with investigational group patients having greater stroke severity and longer time since stroke (*P* < .05). The dominant hand was more often hemiparetic in the investigational group (*P* < .05). We separated the investigational group into those who achieved MT during programing (MT) and those who did not (non-MT). The investigational MT subgroup had significantly smaller lesion volumes (*P* < .01), and the stroke

location was primarily isolated to the basal ganglia and/internal capsule in a majority of the patients (Table 1) when compared with the non-MT subgroup and the control group. None of the other patient characteristics were significantly different between the investigational and control groups.

Primary Outcome Measure

There was not a significant difference between the investigational and control group for the primary outcome measure, as a clinically meaningful improvement was observed in 32% (95% CI 22% to 41%) of investigational, and 29% (95% CI 17% to 41%) of control group patients at 4 weeks postrehabilitation (*P* = .36). After adjusting for differences in baseline UEFM, time since stroke, handedness, age, and gender, results remained nonsignificant between treatment groups at the 4-week follow-up.

Secondary analyses using repeated-measures models that accommodate the nonindependence of observations revealed no significant difference between the investigational and control groups in the proportion of patients reaching the composite primary endpoint at the 12 week assessment. However, at 24 weeks postrehabilitation, a significantly higher number (post hoc comparison, *P* = .003) of investigational group patients (39%) attained or maintained the primary efficacy endpoint compared to the control group (15%; Figure 2, Tables 2 and 3).

Other Secondary Outcome Measures

Repeated-measures secondary analyses revealed no significant treatment group differences in mean UEFM or AMAT scores over time. The average AMAT improvement for investigational group subjects showed a trend toward significantly greater change from baseline than control group subjects at week 4 (*P* = .06). The improvement was generally sustained for both groups throughout the 12-week follow-up, but the investigational group subjects maintained their performance on the primary outcome to a greater degree (*P* = .003) at follow-up week 24 than the control group (Figure 2A). This was especially notable for AMAT scores measured at 24 weeks (Table 2), which were significantly different between the investigational and control groups (post hoc comparison, *P* < .05).

Post Hoc Subset Analysis

Movements were elicited during MT testing (performed prior to the rehabilitation sessions) in 13 of the 91 (14%) investigational group patients at the 4-week follow-up. A subgroup analysis was conducted to determine whether the MT subgroup achieved significant primary target endpoint outcomes compared with the control group. At 4 weeks postrehabilitation, a significant number (*P* = .002) of the

Table 1. Subject Demographics and Baseline Measures.

Parameter	Investigational (n = 94)	Investigational Non-MT (n = 81)	Investigational MT (n = 13)	Control (n = 58)
Female, n (%)	42 (44.7)	36 (44.4)	6 (46.2)	20 (34.5)
Age, years, mean (SD)	56.4 (11.3)	56.6 (11.1)	55.2 (11.7)	57.4 (10.7)
Caucasian, n (%)	83 (88.3)	72 (88.9)	11 (84.6)	52 (89.7)
Neurological disorder other than index stroke, n (%)	6 (6.4)	5 (6.1)	1 (7.7)	6 (10.3)
Previous TIA, n (%)	12 (12.8)	9 (11.1)	3 (22.1)	10 (17.2)
Dominant hand affected, n (%)	60 (63.8)[a]	52 (64.2)[a]	8 (61.5)[a]	26 (44.8)
Time since index stroke, months, mean (SD)	66.8 (71.0)[a]	75.6 (79.3)[a]	44.2 (51.1)	46.2 (47.7)
Prior rehabilitation, n (%)	93 (98.9)	80 (98.8)	13 (100.0)	55 (94.8)
Prior rehabilitation length, days, mean (SD)	87.3 (74.4)	86.2 (60.5)	94.4 (59.2)	78.4 (83.6)
Lesion volume, cm^3, mean (SD)	23.4 (35.2)	26.3 (26.5)	4.9 (6.32)[a]	30.4 (42.9)
Location of stroke				
Isolated to basal ganglia and/or internal capsule, n (%)	47 (50.0)	36 (44.4)	11 (84.6)[a]	27 (46.6)
Involvement of other brain structures, n (%)	41 (43.6)	39 (48.1)	2 (15.4)[a]	29 (50.0)
NIHSS, mean (SD)	2.9 (1.8)[a]	3.0 (1.5)[a]	2.6 (1.9)	2.3 (1.34)
UEFM, mean (SD)	37.6 (6.1)	37.4 (7.1)	38.3 (5.0)	37.6 (5.90)
AMAT, mean (SD)	2.97 (0.68)	2.94 (0.5)	3.1 (0.7)	3.02 (0.69)

Abbreviations: MT, movement threshold; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; UEFM, upper extremity Fugl-Meyer score; AMAT, Arm Motor Ability Test score.
[a]Significant difference (*P* < .05) when compared with control group.

MT subgroup patients (69%; 95% CI 44% to 94%) achieved clinically meaningful improvement when compared to the control group (29%; 95% CI 17% to 41%). Mean changes in UEFM and AMAT scores also suggest treatment group differences over the 24-week follow-up period. Interestingly, a greater proportion of patients in both the investigational MT and investigational non-MT groups (*P* = .005) achieved clinical success at week 24 compared with the control group (Figure 2B). A post hoc white matter tract analysis[41] on a subset (n = 60) of the 94 investigational group patients showed that the amount of corticospinal tract damage in the MT subgroup was lower than the investigational non-MT subgroup. Investigational group patients who achieved the primary efficacy endpoint had a smaller degree of corticospinal tract damage when compared with the control group.[41]

Safety

Adverse events that occurred during each study phase (pretreatment, implant, rehabilitation, explant, and follow-up) are shown in Table 4. Overall, 244 AEs in 77 patients and 40 SAEs in 25 patients occurred in the investigational group and 43 AEs in 21 patients and 6 SAEs in 6 patients occurred in the control group. From the investigational group, 111

(45%) of the AEs and 27 (67%) of the SAEs were unrelated to the EECS device or procedure. Of the remaining 133 AEs from the investigational group, 4 (3 anticipated) were device related and 126 (85 anticipated) were procedure related (Tables 5 and 6). The most common procedure-related AEs observed were headache (n = 26), pain (n = 19), swelling (n = 7), and infection (n = 7) at the implant site, which occurred in 20, 14, 7, and 7 patients, respectively. There were also 8 occurrences of hematoma/bleeding at the implant site and 1 hemorrhage (Table 5). A majority of the device- and procedure-related AEs resolved without any sequelae and not classified as SAEs. One death occurred in the investigational group after a large recurrent stroke and respiratory failure and was not associated with the study.

Overall, there were 40 SAEs (anticipated SAEs = 11; unanticipated SAEs = 29) in 25 investigational group subjects, and the likelihood of a patient in the investigational group having any SAE was 24% (95% CI 16% to 33%). A majority of these SAEs (77%) occurred either during implant (32%) or postrehabilitation (45%). Eleven SAEs occurred in 9 subjects that were related to implantation or removal of the study device (Tables 5 and 6). Three of these events resulted in early surgical removal of the device, due to wound infection at device implant site, persistent headache after implant, and bleeding between skull and brain.
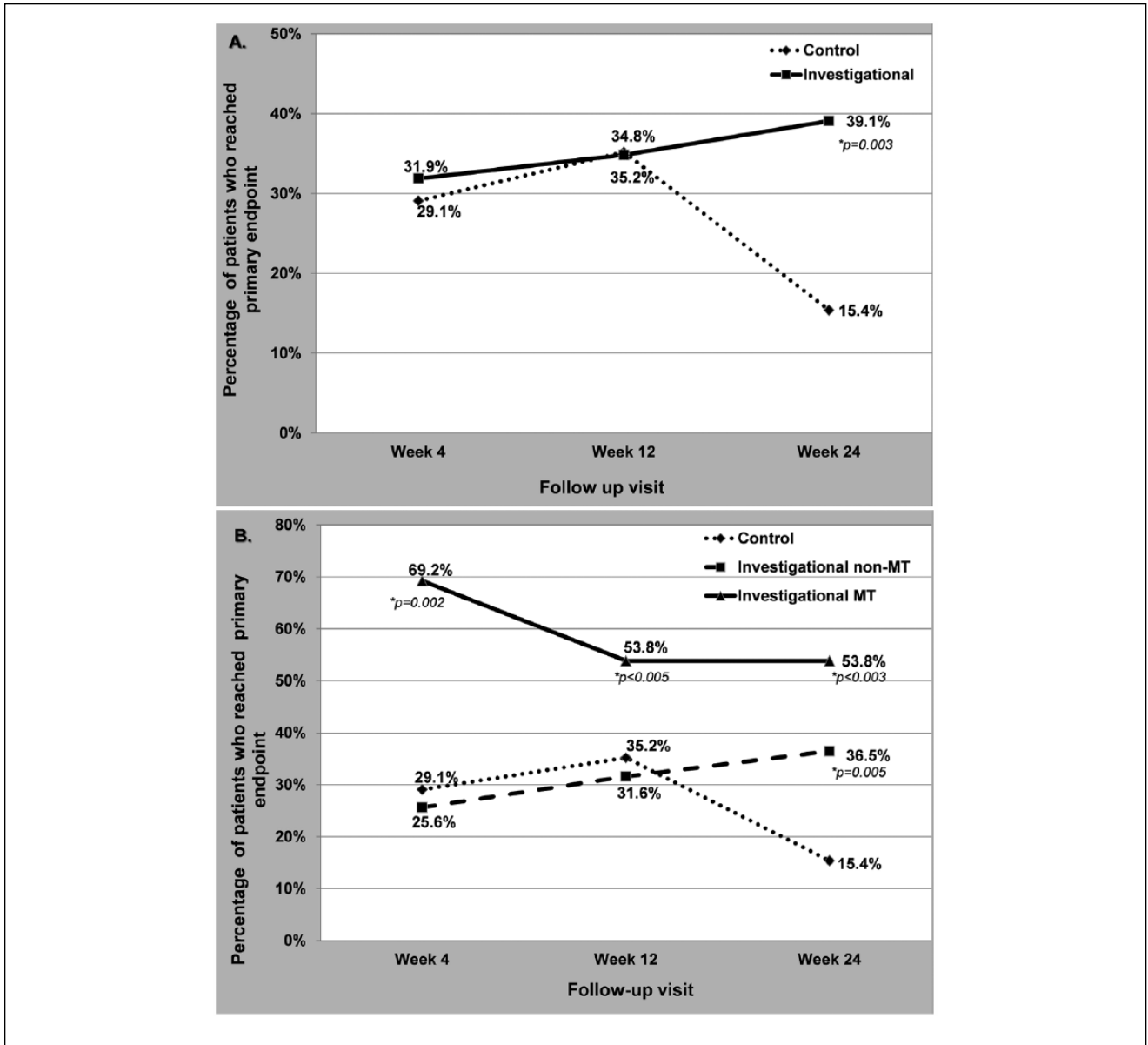
Figure 2. (A) Comparison of percentage of patients who exhibited the defined clinically meaningful improvement within the investigational and control groups. (B) Comparison of percentage of patients who exhibited clinically meaningful improvement between the investigational movement threshold (MT) subgroup, investigational non-MT subgroup, and the control group.
*Post hoc comparisons with significance ($P < .05$) when compared with the control group at the corresponding follow-up visit.

Discussion

We report the primary results of the largest clinical trial to date on application of epidural cortical stimulation during task-oriented motor rehabilitation for recovery of poststroke upper extremity hemiparesis. The percentage of patients demonstrating predefined, clinically meaningful improvements in both UEFM and AMAT scores at 4 weeks postrehabilitation was not significantly different between the control and investigational groups.

Secondary post hoc analysis revealed a statistically significant difference between the proportion of investigational and control group patients who attained the combined primary endpoint at 24 weeks postrehabilitation. Further post hoc analysis of a small subgroup (n = 13) revealed that the MT investigational subgroup patients had a 69% success rate in achieving the primary endpoint, which is significantly greater than the 29% of the control group patients who responded.

This large-scale study also illustrates the safety associated with an epidural cortical stimulation system implant.

Table 2. UEFM and AMAT Scores, and Change From Baseline, Over Posttreatment Follow-up Weeks 1, 4, 12, and 24.

	Week 1	Week 4	Week 12	Week 24
Investigational group, n	91	91	89	87
Control group, n	56	55	54	52
UEFM mean (SD)				
Investigational	41.0 (8.3)	42.0 (8.5)	42.5 (9.1)	42.3 (9.6)
Control	40.7 (7.7)	41.2 (7.4)	41.7 (8.5)	41.0 (9.7)
UEFM change mean (SD)				
Investigational	3.5 (5.2)	4.3 (5.3)	4.8 (5.5)	4.6 (6.3)
Control	3.4 (4.7)	4.0 (4.3)	4.6 (5.4)	3.8 (7.1)
AMAT mean (SD)				
Investigational	3.27 (0.71)	3.36 (0.71)	3.37 (0.76)	3.35 (0.79)[a]
Control	3.25 (0.73)	3.27 (0.75)	3.27 (0.76)	3.19 (0.83)
AMAT change mean (SD)				
Investigational	0.28 (0.44)	0.37 (0.47)	0.36 (0.52)	0.35 (0.49)
Control	0.26 (0.39)	0.26 (0.37)	0.26 (0.45)	0.17 (0.49)

Abbreviations: UEFM, upper extremity Fugl-Meyer score; AMAT, Arm Motor Ability Test score.
[a]Post hoc comparisons with significance ($P < .05$) when compared with control group at the corresponding follow-up visit.

Table 3. Comparison of Changes in UEFM and AMAT Scores From Baseline to Weeks 1, 4, 12, and 24 Between the Investigational Movement Threshold (MT) Subgroup, Investigational Non-MT Subgroup, and the Control Group.

	Week 1	Week 4	Week 12	Week 24
Investigational MT subgroup, n	13	13	13	13
Investigational non-MT subgroup, n	78	78	76	74
Control group, n	56	55	54	52
UEFM mean (SD)				
Investigational MT subgroup	5.9 (3.7)[a]	7.2 (3.3)[a]	6.5 (3.6)[a]	6.1 (6.5)[a]
Investigational non-MT subgroup	3.1 (5.3)	3.9 (5.5)	4.5 (5.8)	4.3 (6.2)
Control	3.4 (4.7)	4.0 (4.3)	4.6 (5.4)	3.8 (7.1)
AMAT change mean (SD)				
Investigational MT subgroup	0.49 (0.45)[a]	0.51 (0.42)[a]	0.45 (0.49)[a]	0.46 (0.49)[a]
Investigational non-MT subgroup	0.25 (0.44)	0.35 (0.47)	0.35 (0.52)	0.33 (0.49)[a]
Control	0.26 (0.39)	0.26 (0.37)	0.26 (0.45)	0.17 (0.49)

Abbreviations: UEFM, upper extremity Fugl-Meyer score; AMAT, Arm Motor Ability Test score.
[a]Post hoc comparisons with significance ($P < .05$) when compared with control group at the corresponding follow-up visit.

Table 4. Classification of Adverse Event (AE) Occurrence in Control and Investigational Group Subjects as a Result of Each Study Phase Starting From Enrollment Through 24 Weeks.[a]

Study Phase	No. of AEs in Investigational Group	No. of Subjects	No. of AEs in Control Group	No. of Subjects
Device-related AEs (including SAEs)			N/A	N/A
Pretreatment	0	0		
Implant	1	1		
Rehabilitation	4	3		
Explant	2	2		
Follow-up	2	2		
Total	9	7		
Procedure-related AEs (including SAEs)			N/A	N/A
Pretreatment	0	0		
Implant	65	38		
Rehabilitation	19	13		
Explant	31	25		
Follow-up	11	10		
Total	126	57		
SAEs				
Pretreatment	2	1	0	0
Implant	13	9	N/A	N/A
Rehabilitation	3	3	0	0
Explant	4	4	N/A	N/A
Follow-up	18	11	6	6
Total	40	25	6	6
Death				
Pretreatment	0	0	0	0
Implant	0	0	N/A	N/A
Rehabilitation	0	0	0	0
Explant	0	0	N/A	N/A
Follow-up	1 (unrelated to device/ procedure)	1	0	0
Total	1	1	0	0

Abbreviations: SAE, serious adverse event; N/A, not applicable.
[a]The row corresponding to the total number of subjects will not tally with the column corresponding to "No. of Subjects" in instances when more than one AE type occurred in the same subject.

Safety information collected through the course of the study suggests that patients implanted with the EECS system were at no greater risk of physical or psychological harm than what was previously appreciated at study initiation. Although the cortical lead implant procedure was invasive, the AEs recorded in this study are common in surgeries associated with this modality. The incidence rates of device-related AEs is substantially lower when compared with other neurostimulation modalities such as spinal cord stimulation,[42] deep brain stimulation,[43,44] and peripheral nerve stimulation.[45] Frequently occurring device- and procedure-related AEs in these other stimulation modalities include lead migration (13% to 30%), lead breakage (5% to 10%), infection (1% to 20%), and pain at the implant site (5% to 20%). Deep brain stimulation implant procedure–related intracranial hemorrhages[43] and postimplant seizures[44] have

Table 5. Characterization of Anticipated Device-, Procedure-, and Adverse Drug/Anesthesia-Related Adverse Events (AEs) and Serious Adverse Events (SAEs) in Investigational Group Subjects From Enrollment Through 24 weeks.[a]

Anticipated AEs	No. of AEs	No. of Subjects
Device-related AEs (including SAEs)		
Fracture of electrode, lead, or implantable pulse generator	1	1
Other (tingling sensation)	2	1
Total	3	2
Procedure-related AEs (including SAEs)		
Bleeding/hematoma at operative site	8	8
Bleeding between skull and brain	1	1
Damage to nerve/vasculature in surgical area	2	2
Headache	26	20
Formation of fibrous tissue/fluid pockets	2	2
Infection at implant site	7	7
Neck pain	6	5
Neural tissue damage	2	1
Clinically significant pain at operative site	19	14
Seizure	2	1
Swelling at operative site	7	7
Unstable blood pressure	3	2
Vertigo/dizziness	1	1
Total	85	46
Adverse drug-/anesthesia-related AEs (including SAEs)		
Fever	2	2
Hypoxia	0	0
Nausea	3	3
Pneumonia	0	0
Urine retention	2	2
Vomiting	5	5
Total	12	11
Procedure-related SAEs		
Bleeding between skull and brain	1	1
Headache	1	1
Infection at operative site	2	2
Clinically significant pain at operative site	1	1
Seizure	2	1
Total	7	6
Adverse drug-/anesthesia-related SAEs		
Fever	1	1
Nausea	1	1
Urinary retention	1	1
Vomiting	1	1
Total	4	4
Other		
Digestive	2	2
Integument	1	1
Musculoskeletal	2	2
Neurologic	7	7
Renal/urogenital	1	1
Other body system	2	2
Total	15	12

[a]The row corresponding to the total number of subjects will not tally with the column corresponding to "No. of Subjects" in instances when more than one AE type occurred in the same subject.

Table 6. Characterization of Unanticipated Device-, Procedure-, and Adverse Drug-/Anesthesia-Related Adverse Events (AEs) and Serious Adverse Events (SAEs) in Investigational Group Subjects.

Unanticipated AEs	No. of AEs	No. of Subjects
Device-related AEs (including SAEs)		
Other (pain associated with implantable pulse generator movement)	1	1
Total	1	1
Procedure-related AEs (including SAEs)		
Cardiovascular	4	4
Digestive	1	1
Integument	4	4
Musculoskeletal	6	6
Neurologic	4	4
Pulmonary	2	2
Renal/urogenital	1	1
Other body system	7	5
Total	29	17
Procedure-related SAEs		
Cardiovascular	1	1
Integument	1	1
Pulmonary	1	1
Renal/urogenital	1	1
Other body system	1	1
Total	5	4

[a]The row corresponding to the total number of subjects will not tally with the column corresponding to "No. of Subjects" in instances when more than one AE type occurred in the same subject.

been reported in 5% and 2% of the patients, respectively. Pain at the lead and/or IPG site is common with any neurostimulation device implant procedure and typically subsides within 2 to 3 weeks. Superficial infections can be treated with antibiotics, but the infections involving hardware require device explantation. SAEs such as fever, nausea, vomiting, and urinary retention occurred in this study due to adverse reactions to the anesthesia procedure associated with the device implant. Overall, considering the number of patients implanted in this study with the EECS device (n = 94), and their medical history, the rate of procedure-related SAEs was consistent with rates seen with other implanted neuromodulation devices used clinically (eg, spinal cord stimulators).

The phase I and II trials leading up to the present study demonstrated the safety and efficacy of EECS delivered during rehabilitation in chronic stroke patients. In the *Adams* trial,[27] 4 patients with EECS during 3 weeks of rehabilitation experienced a sustained 10-point improvement in UEFM, compared with a 2-point improvement for the control group. Likewise, in the *Baker* trial,[28] 12 patients with

EECS during 6 weeks of rehabilitation experienced a 5.5-point improvement in UEFM and a 0.4-point improvement in AMAT, compared with 1.9- and 0.2-point improvements, respectively, for the control group. Observation of greater efficacy in these earlier small-scale studies might be explained by the greater proportion of patients reaching MT, or the lack of blinded trial designs. During study phases I and II, MTs were elicited in 75% and 42% of the patients, respectively. In this phase III study, only 14% of patients exhibited MT during postoperative testing. The inability to reach MT calls to question whether the programmed amplitude of subthreshold stimulation during rehabilitation was sufficient to induce neuroplasticity.[14-16]

Inability to achieve MT in this study might alternately be explained by suboptimal lead placement. Like prior studies,[27,28] *Everest* used fMRI to identify the target in the primary motor cortex innervating the contralateral upper limb. However, unlike the *Adams* study,[27] intraoperative cortical mapping of evoked motor potentials or gross hand movement was not performed to confirm the target. Furthermore, the fMRI hot spot used to locate the target in this study may not be indicative of the complete extent of neural damage. In the present study, investigational patients in whom a motor response could be elicited (MT subgroup) had a higher probability of achieving the primary efficacy endpoint when compared with the non-MT investigational and the control group.[41] The MT subgroup had smaller lesion volumes and the stroke location was isolated to the basal ganglia and/or internal capsule (Table 1) when compared to the non-MT subgroup and the control group. A post hoc white matter tract analysis[41] on a subset (n = 60) of the 94 investigational group patients showed that the amount of corticospinal tract damage in the MT subgroup was lower than in the patients in the investigational non-MT subgroup. Furthermore, all investigational group patients who achieved the primary efficacy endpoint had a smaller degree of corticospinal tract damage.[41] But, a recently published post hoc imaging analysis[46] based on the Everest trial patients (both investigational and control group) revealed a lack of correlation between lesion volume and motor function in patients with mild chronic hemiparesis. This study showed that the anatomical location of the lesion relative to the descending motor pathways was a better predictor of arm and hand motor function gains following rehabilitation than lesion size alone. Based on these findings, future chronic stroke rehabilitation trials should attempt to quantify the anatomical and functional corticospinal tract integrity for patient selection, and to predict treatment outcome. Diffusion tensor imaging[47,48] and TMS[49] have been recently used to predict functional motor outcomes in both subacute and chronic stroke patients. Additionally, epidural or subdural CS system implantation procedures should incorporate intraoperative motor or somatosensory evoked potential mapping to confirm target location during lead placement.

The choice of an appropriate endpoint is vital for studies involving new therapeutic modalities. The a priori definition of clinically meaningful response in the *Everest* trial differed subtly, but notably from the prior safety and feasibility studies using EECS during rehabilitation. In the *Baker* trial,[28] a clinically meaningful improvement was defined as achieving both 0.21-point AMAT improvement and a 3.5-point UEFM improvement, which was realized by 50% of the patients randomized to stimulation. In *Everest*, the threshold for UEFM in the composite endpoint was increased to 4.5 points as per FDA's recommendation. At the time of study initiation, the use of a combined performance metric had not been previously reported in rehabilitation research. However, the method is consistent with the notion of finding clinically meaningful outcomes in both motor impairment (UEFM) and functional activity (AMAT) dimensions, and has been used in other contemporary rehabilitation studies like the EXCITE trial.[6] It should be noted that differences among clinical trials in the outcome measures used to characterize activity and impairment prevents direct comparison of results across different trials.[50]

In addition to selection of the most meaningful outcome measures, assessing them at the appropriate intervals postintervention is also important. In the present study, the primary endpoint was measured at 4 weeks after completing therapy. However in the post hoc secondary analysis, the investigational group had sustained improvements at 24 weeks posttherapy and these effects were not attenuated over time. In contrast, a notable decline in motor performance was observed in the control group between the 12 (35% treatment response rate) and 24 week (15% treatment response rate) assessments. A similar pattern of group differences were also observed in the *Adams*[27] and *Baker*[28] trials, and also in a recent study that used low-frequency rTMS to stimulate the contralesional hemisphere of patients 3 to 9 months poststroke.[51] At 1 month postrehabilitation, there was no significant difference in the UEFM scores between treatment and sham groups. But, at 24 weeks posttherapy treatment group patients had a clinically significant improvement, while the sham group's performance declined.[51] The investigational group response rate at 24 weeks suggests that the EECS intervention induced sustained functional motor improvements, but it could have also provoked delayed gains in motor function. Structural and functional plasticity resulting from EECS in preclinical animal stroke models is observed immediately,[14-16] but its long-term sustainability has not been studied in detail. The positive trend in the investigational group responder rate at the 12- and 24-week assessments could be attributed to a delayed translation of the EECS-induced structural alterations into gains in motor performance. Neuroprotective, neural repair, and neurorestorative mechanisms different from the ones responsible for the initial response to neuronal stimulation have been observed in cerebral ischemic

animal models[52], and can be potentially responsible for the long-term consolidation of motor learning seen in the investigational group. In severely impaired animal stroke models, EECS failed to significantly enhance the efficacy of task-oriented rehabilitation, but movement abnormalities were reduced during skilled motor tasks.[53] Reduced dependence of the investigational group on compensatory strategies postrehabilitation, and a shift in the control group's movement strategy from optimally restored movements to suboptimal compensation-induced motor control[54,55] could explain the decline of the control group's performance over time.

Finally, the single-blinded design of the present study is a notable limitation. For ethical considerations a sham surgery trial was not supported by the FDA, and patients and clinicians charged with their care were not blinded to treatment assignment. Determining the safety of a novel device is mandatory and supersedes adherence to standards for research design. However, after the safety of targeted combined subthreshold CS with rehabilitation has been established, a sham-controlled neurosurgical trial may be permissible, especially if a late crossover to treatment is provided for patients randomized to sham.

Conclusions

The *Everest* phase III trial was unsuccessful in attaining its primary efficacy endpoint at 4 weeks posttreatment. Cortical stimulation delivered during task-oriented upper limb rehabilitation did not result in significantly higher functional motor gains in investigational group patients when compared to the control group patients who underwent only rehabilitation. Although secondary post hoc analyses showed that investigational group patients exhibited significantly better functional improvements 24 weeks postrehabilitation, the results should be viewed with caution due to the inability to rule out a Hawthorne effect (ie, more attention from the investigators to the investigational group), and also due to the lack of a sham surgery control group. These concerns are equally relevant for the small subgroup (n = 13) of patients whose stimulators were able to evoke hand movements. The *Everest* trial confirmed a consistent finding that stroke patients with mild to moderate upper extremity hemiparesis could realize improvements even long after the occurrence of an ischemic insult in the brain. Finally, we established that the safety profile of cortical stimulation in a large-scale multicenter clinical trial is consistent with other similar neurostimulation modalities. Future trials with an enhanced study design, patient selection, and lead localization techniques may be able to overcome the limitations of this trial, and may show promise in establishing cortical stimulation as an accepted treatment modality during stroke rehabilitation.

Authors' Note

Everest Trial investigators: Robert Levy, MD, PhD, Northwestern University, Chicago, Illinois; Martin Weinand, MD, University of Arizona, Tucson, Arizona; Randall Benson, MD, Wayne State University, Detroit, Michigan; Stephen J Page, PhD, University of Cincinnati, Cincinnati, Ohio; Gary Abrams, MD, University of California San Francisco, San Francisco, California; Don Smith, MD, Colorado Neurological Institute, Englewood, Colorado; Charles Hodge, MD, State University of New York, Upstate Medical University, Syracuse, New York; Elizabeth Noser, MD, The University of Texas, Health Science Center at Houston, Houston, Texas; Robert Gross, MD, PhD, Emory University, Atlanta, Georgia; Sean Ruland, DO, University of Illinois at Chicago, Chicago, Illinois; Jaimie Henderson, MD, Stanford University, Stanford, California; Helmi Lutsep, MD, Oregon Health & Science University, Portland, Oregon; Carolee Winstein, PT, PhD, University of Southern California, Los Angeles, California; Elaine Skalabrin, MD, University of Utah, Salt Lake City, Utah; Douglas Kondziolka, MD, MSc, University of Pittsburgh, Pittsburgh, Pennsylvania; Gordon Baltuch, MD, University of Pennsylvania, Philadelphia, Pennsylvania; Ross Zafonte, MD, Spaulding Rehabilitation Hospital, Boston, Massachusetts; Steve Flanagan, MD, The Mount Sinai School of Medicine, New York, New York; Ryder Gwinn, MD, Swedish Medical Center, Seattle, Washington; Brad Steinle, MD, St. Luke's Health System, Kansas City, Missouri; Scott Silliman, MD, University of Florida College of Medicine, Jacksonville, Florida.

References

1. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry*. 1987;50:714-719.

2. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*. 2003;34:2181-2186.

3. Sunderland A, Tinson D, Bradley L, Hewer RL. Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator. *J Neurol Neurosurg Psychiatry*. 1989;52:1267-1272.

4. Wade DT, Langton-Hewer R, Wood VA, Skilbeck CE, Ismail SM. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry*. 1983;46:521-524.

5. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1994;75:394-398.

6. Wolf SL, Winstein CJ, Miller JP, et al; EXCITE Investigators. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA*. 2006;296:2095-2104.

7. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. *Disabil Rehabil*. 1999;21:357-364.

8. Lincoln NB, Parry RH, Vass CD. Randomized, controlled trial to evaluate increased intensity of physiotherapy treatment of arm function after stroke. *Stroke*. 1999;30:573-579.

9. Cramer SC, Nelles G, Benson RR, et al. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*. 1997;28:2518-2527.

10. Johannson BB. Brain plasticity and stroke rehabilitation. The Willis Lecture. *Stroke*. 2000;31:223-230.

11. Kato H, Izumiyama M, Koizumi H, Takahashi A, Itoyama Y. Near-infrared spectroscopic topography as a tool to monitor motor reorganization after hemiparetic stroke: a comparison with functional MRI. *Stroke*. 2002;33:2032-2036.

12. Nudo RJ, Friel KM. Cortical plasticity after stroke: implications for rehabilitation. *Rev Neurol (Paris)*. 1999;155:713-717.

13. Nudo RJ. Plasticity. *NeuroRX*. 2006;3:420-427.

14. Adkins-Muir DL, Jones TA. Cortical electrical stimulation combined with rehabilitative training: enhanced functional recovery and dendritic plasticity following focal cortical ischemia in rats. *Neurol Res*. 2003;25:780-788.

15. Kleim JA, Bruneau R, Vandenberg P, MacDonald R, Mulrooney R, Pocock D. Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. *Neurol Res*. 2003;25:789-793.

16. Plautz EJ, Barbay S, Frost SB, et al. Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol Res*. 2003;25:801-810.

17. Ameli M, Grefkes C, Kemper F, et al. Differential effects of high-frequency repetitive transcranial stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol*. 2009;66:298-309.

18. Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology*. 2005;65:466-468.

19. Kim YH, You SH, Ko MH, et al. Repetitive transcranial magnetic stimulation–induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke*. 2006;37:1471-1476. Erratum in *Stroke*. 2006;37:2861.

20. Yozbatiran N, Alonso-Alonso M, See J. Safety and behavioral effects of high-frequency repetitive transcranial magnetic stimulation in stroke. *Stroke*. 2009;40:309-312.

21. Boggio PS, Nunes A, Rigonati SP, Nitche MA, Pascual-Leone A, Fregni F. Repeated sessions of non-invasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restor Neurol Neurosci*. 2007;25:123-129.

22. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*. 2005;128:490-499.

23. Harvey RL, Nudo RJ. Cortical brain stimulation: a potential therapeutic agent for upper limb motor recovery following stroke. *Top Stroke Rehabil*. 2007;14(6):54-67.

24. Opitz A, Zafar N, Bockermann V, Rohde V, Paulus W. Validating computationally predicted TMS stimulation areas using direct electrical stimulation in patients with brain tumors near precentral regions. *Neuroimage Clin*. 2014;4:500-507.

25. Deng ZD, Lisanby SH, Peterchev AV. Electric field depth–focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. *Brain Stimul*. 2013;6:1-13.

26. Wongsarnpigoon A, Grill WM. Computer-based model of epidural motor cortex stimulation: effects of electrode position and geometry on activation of cortical neurons. *Clin Neurophysiol*. 2012;123:160-172.

27. Brown JA, Lutsep HL, Weinand M, Cramer SC. Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery*. 2006;58:464-473.

28. Levy R, Ruland S, Weinand M, Lowry D, Dafer R, Bakay R. Cortical stimulation for the rehabilitation of patients with hemiparetic stroke: a multicenter feasibility study of safety and efficacy. *J Neurosurg*. 2008;108:707-714.

29. Harvey RL, Winstein CJ. Design for the Everest randomized trial of cortical stimulation and rehabilitation for arm function following stroke. *Neurorehabil Neural Repair*. 2009;23:32-44.

30. Berglund K, Fugl-Meyer AR. Upper extremity function in hemiplegia: a cross-validation study of two assessment methods. *Scand J Rehabil Med*. 1986;18:155-157.

31. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther*. 1983;63:1606-1610.

32. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglin S. The post stroke hemiplegic patient I: a method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7:13-31.

33. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, action research arm test and box and block test: a multicentre study. *Clin Rehabil*. 2005;19:404-411.

34. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther*. 1993;73:447-454.

35. Gladstone DJ, Daniells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of tis measurement properties. *Neurorehabil Neural Repair*. 2002;16:232-240.

36. Yozbatiran N, Der-Yeghianian L, Cramer S. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair*. 2008;22:78-90.

37. Bravi L, Stoykov ME. New directions in occupational therapy: implementation of the task-oriented approach in conjunction with cortical stimulation after stroke. *Top Stroke Rehabil*. 2007;14(6):68-73.

38. Cup EH, Scholte op Reimer WJ, Thijssen MC, van Kuyk-Minis MA. Reliability and validity of the Canadian Occupational Performance Measure in stroke patients. *Clin Rehabil*. 2003;17:402-409.

39. Eyssen IC, Beelen A, Dedding C, Cardol M, Dekker J. The reproducibility of the Canadian Occupational Performance Measure. *Clin Rehabil*. 2005;19:888-894.

40. Chae J, Labatia I, Yang G. Upper limb motor function in hemiparesis: concurrent validity of the arm motor ability test. *Am J Phys Med Rehabil*. 2003;82:1-8.

41. Nouri S, Cramer SC. Anatomy and physiology predict response to motor cortex stimulation after stroke. *Neurology*. 2011;77:1076-1083.

42. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg*. 2004;100(3 suppl spine):254-267.

43. Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *J Neurosurg*. 2012;116:84-94.

44. Coley E, Farhadi R, Lewis S, Whittle IR. The incidence of seizures following deep brain stimulating electrode implantation for movement disorders, pain and psychiatric conditions. *Br J Neurosurg*. 2009;23:179-183.

45. Falowski S, Wang D, Sabesan A, Sharan A. Occipital nerve stimulator systems: review of complications and surgical techniques. *Neuromodulation*. 2010;13:121-125.

46. Page SJ, Gauthier LV, White S. Size doesn't matter: cortical stroke lesion volume is not associated with upper extremity motor impairment and function in mild, chronic hemiparesis. *Arch Phys Med Rehabil*. 2013;94:817-821.

47. Lindenberg R, Zhu LL, Rüber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. *Hum Brain Mapp*. 2012;33:1040-1051.

48. Jang SH, Kim K, Kim SH, Son SM, Jang WH, Kwon HG. The relation between motor function of stroke patients and diffusion tensor imaging findings for the corticospinal tract. *Neurosci Lett*. 2014;572:1-6.

49. Kwon YH, Son SM, Lee J, Bai DS, Jang SH. Combined study of transcranial magnetic stimulation and diffusion tensor tractography for prediction of motor outcome in patients with corona radiata infarct. *J Rehabil Med*. 2011;43(5), 430-434.

50. Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in contemporary stroke trials. *Int J Stroke*. 2009;4:2000-2005.

51. Harvey RL, Roth HR, Tappan RS, Kermen R, Laine J, Stinear J, Rogers LM. The Contrastim Stroke Study: improving hand and arm function after stroke with combined non-invasive brain stimulation and task-oriented therapy—a pilot study. *Stroke*. 2014;45(suppl 1):A152.

52. Morimoto T, Yasuhara T, Kameda M, et al. Striatal stimulation nurtures endogenous neurogenesis and angiogenesis in chronic phase ischemic stroke rats. *Cell Transplant*. 2011;20:1049-1064.

53. Adkins DL, Hsu JE, Jones TA. Motor cortical stimulation promotes synaptic plasticity and behavioral improvements following sensorimotor cortex lesions. *Exp Neurol*. 2008;212:14-28.

54. Levin M, Kleim JA, Wolf SL. Point of view: enhancing interdisciplinary perspectives: what do motor recovery and compensation mean in patients following stroke? *Neurorehabil Neural Repair*. 2009;23:313-319.

55. Kitago T, Liang J, Huang VS, et al. Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation? *Neurorehabil Neural Repair*. 2013;27:99-109.