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NERVE STIMULATION ENHANCES TASK-ORIENTED TRAINING FOR MODERATE-TO-SEVERE HEMIPARESIS 3–12 MONTHS AFTER STROKE: A RANDOMIZED TRIAL

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Abstract

Objective—Determine whether somatosensory stimulation affects outcomes of motor training for moderate-to-severe upper extremity hemiparesis less than 12 months post-stroke.

Design—55 adults participated in 18 intervention sessions pairing 2 hours of active (n=33) or sham (n=22) somatosensory stimulation with 4 hours of intensive task-oriented motor training. Wolf Motor Function Test, Action Research Arm Test, Fugl-Meyer Assessment, and Stroke Impact Scale were administered at baseline, post-intervention, and 1- and 4-month follow-up.

Results—Statistically significant between-groups differences favored the active condition on Wolf Motor Function Test at post (p=0.04) and Action Research Arm Test at post (p=0.02), 1-month (p=0.01), and 4-month (p=0.01) but favored the sham condition on Stroke Impact Scale at

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1-month ($p=0.03$). There were no significant between-groups differences on Fugl-Meyer Assessment.

Conclusion—Somatosensory stimulation can improve objective outcomes of motor training for moderate-to-severe hemiparesis less than 12 months after stroke, although the magnitude of between-groups differences in this study needs to be determined if they are clinically relevant. Future studies should investigate the intervention's impact on disability and functional recovery for this population as well as neurophysiological mechanisms underlying intervention effects.

Keywords

upper extremity; occupational therapy; humans; transcutaneous electric nerve stimulation; neuronal plasticity

Introduction

Neuroplasticity (ie, the capacity for reorganization of the central nervous system) is a basis for functional recovery after stroke¹. Repetitive sensory activation has been shown to modulate neuroplasticity (ie, enlarge motor cortical representation) and improve motor function in animal models². This evidence indicated that sensory stimulation can modulate motor cortical plasticity, thus establishing a mechanism by which sensory input plays a role in motor skill acquisition²⁻⁴. A therapeutic intervention based on this mechanism in humans is called somatosensory stimulation (SS). SS applies repetitive, non-invasive, low-level electrical currents to activate large cutaneous and proprioceptive sensory fibers without producing muscle contractions⁵. There is some evidence that SS modulates neuroplasticity and can enhance upper extremity (UE) motor function in humans after stroke⁶⁻⁸. For example, Sawaki and colleagues conducted a sham-controlled study of the effects of 2 hours of SS on voluntary thumb movement in 7 subjects with mild hemiparesis (ie, able to perform isolated movement of paretic thumb) at >6 months after stroke. Results demonstrated that SS increased encoding of kinematic details of movements evoked with transcranial magnetic stimulation⁸. In addition, Laufer and colleagues' systematic review of randomized and quasi-randomized trials concluded that SS may enhance motor recovery after stroke⁷. However, the majority of the 15 reviewed studies were conducted during the chronic stage of recovery; and the review did not aim to establish how severity of deficit may determine intervention responsiveness. In sum, it has not yet been established how SS may impact moderate-to-severely impaired UE function in the 3-12 month period after stroke.

Intensive, task-oriented motor training has been associated with extensive neuroplastic change, as well as more significant functional gains than usual and customary care, in cases of mild-to-moderately impaired UE motor function after stroke⁹. Similarly, studies showing that SS can enhance outcomes of intensive task-oriented motor training have primarily targeted mild-to-moderate impairment^{10-13, 14}. The purpose of the present study was to investigate whether active SS would enhance outcomes of intensive task-oriented motor training significantly more than sham SS in subjects with moderate-to-severely impaired UE motor function in the 3-12 month period following stroke.

Methods

In accordance with the Declaration of the World Medical Association (www.wma.net), this study was approved by the authorized institutional human research review board governing the research (ie, the University of Kentucky and Cardinal Hill Hospital in Lexington, KY). All subjects provided written informed consent after receiving a verbal and written explanation of the purposes, procedures, and potential hazards of this study. All study procedures were followed in accordance with institutional guidelines. Subjects were recruited from communities, hospitals, and clinics in the local and regional areas surrounding the study site. The study was conducted at a neurorehabilitation research lab located at HealthSouth Cardinal Hill Rehabilitation Hospital in Lexington, KY. *Inclusion Criteria:* The first tier of inclusion criteria included a) having sustained a single ischemic or hemorrhagic stroke during the 3- to 12-month period preceding enrollment; b) inability at the time of screening to demonstrate active extension of the paretic metacarpophalangeal and interphalangeal joints at least 10° and the wrist, 20°; and c) 18 years of age or older. The second tier of inclusion criteria included having a baseline score of 47 or lower on the modified 30-item Fugl-Meyer Assessment (FMA) that measures UE motor function¹⁵. Subjects with impaired sensation at baseline were not excluded, and subjects with various degrees of impaired sensation were enrolled. *Exclusion criteria* were selected to minimize potential confounding variables. These criteria included a) history of carpal tunnel syndrome and/or documented peripheral neuropathy; b) addition or change in the dosage of drugs known to exert detrimental effects on motor recovery within 3 months of recruitment¹⁶; and c) aphasia or cognitive deficit severe enough to preclude informed consent.

This study was a randomized controlled parallel group superiority trial. Standardized evaluations of UE motor function were administered by an occupational therapist at baseline, after completion of the intervention period, and at 1-month and 4-month follow-up timepoints. Following baseline evaluation, the principal investigator (PI) used a computer program to generate a simple random allocation sequence for assigning subjects into 2 groups (ie, either active SS paired with intensive task-oriented training; or sham (control) SS paired with intensive task-oriented training). The only independent variable was SS. In order to maximize enrollment and completion of the study, eligible participants were randomized into a 1.5 active /1 sham ratio. One of the members of the research study staff (LS) enrolled all participants and made all assignments to interventions according to the randomizer program. Each intervention session took place 3 times per week for 6 weeks (18 total sessions) and consisted of either active or sham SS (2 hours) immediately preceding intensive task-oriented motor training (4 hours). Subjects, care providers, and evaluators of motor function were blinded to group assignment (i.e., they were not provided with information about which SS condition any subject received). SS was delivered by one of the members of the research study staff (LS) or a biomedical engineer. Therapists who evaluated motor function or who administered intensive task-oriented training did not administer SS.

Sample Size

Sample size was calculated based on preliminary data in 7 subjects with chronic, UE hemiparesis after stroke. In the preliminary study, 4 subjects received 2-hour daily hand SS

preceding 4-hour motor training for 10 consecutive weekdays. The remaining 3 patients received sham SS preceding 4-hour motor training for 10 consecutive weekdays. The difference of changes in scores on WMFT (logarithm scaled) after intervention for experimental and control groups was 0.07, and the common standard deviation was about 0.09. To detect the same effect size as that observed in the preliminary study with 80% power, assuming a similar standard deviation in the change, a total of 55 subjects were enrolled in the present study.

Evaluation and Outcome Measures

The WMFT served as the primary outcome measure. The time-based portion of the WMFT encompasses a battery of 15 tasks that simulate functional tasks and that are ordered according to complexity⁹. WMFT scoring calculates the mean of the 15 time-based tasks. Because of the skewed distribution of the WMFT, a logarithmic transformation is performed on the mean of these 15 time-based WMFT measures. There are no units, as it is a logarithm. Values are denoted as log (mean WMFT). The WMFT has established reliability and validity and has been extensively applied in research to evaluate UE motor capacity after stroke^{9, 17}. The minimal clinically important difference (MCID) for WMFT has been cited as 1.5 to 4 seconds¹⁸ (0.18 to 0.6 log scaled); however, there is no available data on MCID for WMFT as measured in stroke populations with severely impaired motor function. Secondary outcome measures included the FMA UE motor score, the Action Research Arm Test (ARAT), and the Stroke Impact Scale (SIS). The FMA is a quantitative measure of motor recovery, sensation, coordination, and speed and is based on the principle that motor recovery occurs in a predictable progression¹⁹. The FMA has an extensive history of clinical and research application in stroke populations¹⁹ as well as high inter-rater reliability ($=0.89\sim0.98$ according to the subset for lower or UE) and test-retest reliability ($=0.99$)²⁰. The modified 30-item FMA¹⁵ does not calculate reflex scores and is a unidimensional measure of volitional movement in which the highest possible motor score for a tested UE is 60²¹. The MCID for FMA is 9 to 10 points¹⁸; however, the MCID for the modified 30-item FMA¹⁵ has not been established relative to any level of motor impairment after stroke. The ARAT measures grasp, grip, pinch, and other indices of rehabilitation-related change in UE motor capacity^{17,22}. The highest possible ARAT score for a tested UE is 57. The MCID for ARAT has been cited as 5.7 points¹⁸; however, there is no available data on MCID for ARAT as measured in stroke populations with severely impaired motor function. The SIS is a 59-item measure that assesses 8 domains: strength; hand function; activities of daily living (ADL)/instrumental activities of daily living (IADL); mobility; communication; emotion; memory and thinking; and participation/role function. Each item is rated on a 5-point Likert scale. Scores range from 0-100. Several studies have proven its reliable psychometric attributes, including reliability, validity, and sensitivity to change^{23, 24}.

Intervention Component 1: SS (currently still an investigational device per FDA)

SS was delivered for 120 minutes at the beginning of each session. Optimal positions to stimulate the Erb's point, radial, and median nerves were determined by applying a surface bar electrode with the cathode placed distally on the paretic UE. During identification of the optimal site for stimulation, the irradiation of the stimulation was recorded in cases where subjects could feel the SS. Where subjects could not feel the SS, the investigators elicited

movements of the muscle that corresponded to the nerve that investigators wanted to stimulate. Once the location was set, the intervention stimulation was set to evoke compound muscle action potentials of 50-100 μV in the deltoid, triceps, and opponens pollicis brevis, respectively, which in most cases fell below sensory threshold (i.e., non-perceived afferent stimulation; Figure 1). When subjects had substantially impaired sensation, optimal stimulation sites were identified by visualizing muscle contractions of the deltoid, triceps, and opponens pollicis brevis muscles, respectively. To stimulate each nerve trunk, 10 mm gold-plated stimulating electrodes were placed on the skin to stimulate sites concurrently with the cathode positioned proximally over each of the optimal positions identified by the bar electrode⁵. The stimulation consisted of 10Hz trains of 5 pulses, with each pulse lasting 1ms. Trains of pulses were delivered at 1Hz. Disposable surface EMG electrodes were placed over the belly of the deltoid, triceps, and opponens pollicis brevis muscles. EMG activity was amplified and filtered (bandpass, 10-3000Hz) and recorded using a data collection program written in LabVIEW (National Instruments, Austin, TX). For active SS, the stimulus intensity was adjusted to elicit small compound muscle action potentials of approximately 50 to 100 μV without visible muscle movements⁵. This low stimulus intensity and the stimulus duration of 1ms has been shown to preferentially activate large cutaneous and proprioceptive sensory fibers without producing muscle contractions⁵. While efferent activation can occur at a small level with this intensity, the PNS electrode montage was set to direct the majority of current from distal to proximal. For sham SS, an identical protocol was implemented except that the stimulator amplitude was set to 0V after compound muscle action potentials were identified. Each subject was informed in each session that he or she might or might not feel sensations associated with SS and that sensations did not indicate whether SS was being delivered. Since attention appears to play an important role in neuroplastic change²⁵, subjects were required to stay awake during SS. During stimulation, subjects sat with the paretic arm over a pillow in a comfortable position per subject report during TV watching or reading.

Intervention Component 2: Intensive task-oriented UE motor training

In each session, each subject participated in 4 hours of intensive task-oriented UE motor training immediately following SS. An occupational therapist blinded to SS condition administered the training. Training focused on highly repetitive use of the paretic UE in unilateral and bilateral task-oriented motor activities. Tasks had progressive difficulty in order to elicit movement skill just beyond the level already achieved (ie, shaping)²⁶. Each session incorporated tasks eliciting progressive increase in endurance. These tasks occupied a minimum of 2 hours of training and a maximum of 3.5 hours of training by the end of the second week of training. The remainder of the 4-hour window in each session was used for rest or bathroom breaks. The total time for rest or bathroom breaks varied across subjects and sessions according to each subject's fatigue or personal needs. Tasks were repeatable and targeted functional goals (such as activities of daily living) or prerequisites to function (eg, releasing; grasping; reaching; supination). Training included rest breaks and grading of activities according to subject fatigue and impairment. There was no movement monitoring system, but therapists provided each subject with verbal or visual (graph) feedback on the quality of task performance during training. Rest breaks lasted no longer than the practice segment. The target range for repetitions of any given task was 10 to 50 according to the

demands of the task as well as reported levels of fatigue and engagement of each subject with a given task. Therapy took place in a 1:1 therapist-to-subject ratio. Missed sessions were rescheduled so that each participant completed all 18 sessions.

Statistics

For each outcome of interest, a longitudinal repeated measures model that accounts for categorical time, trial arm, and their interaction was fit. Each model incorporates an unstructured working covariance matrix, and the Kenward and Roger²⁷ degrees of freedom method was used for inference. These analyses correspond to the use of repeated measures MANOVA, but with the allowance of missing data. Primary interest was in the comparison of mean changes in outcomes from baseline to immediately post-intervention and to 1- and 4-month follow-up for the 2 trial arms. To ensure the appropriateness of statistical assumptions for inference, the square root was applied to ARAT and log(mean WMFT) values. With the WMFT, log(mean WMFT) values were subtracted from the maximum sample value of 2.08 before applying the square root. To convey the clinical relevance of results, estimated means and standard errors are presented on the original scale for ARAT and WMFT. All available data were utilized for analyses. All tests were 2-sided, with statistical significance pre-specified as $P < 0.05$. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Supplemental Digital Content 1 shows how this study met the CONSORT checklist for randomized controlled trials. Table 1 summarizes baseline scores and demographics of the sample. Figure 2 depicts the study flow. The date range defining the periods of data collection was 07/08-02/15.

The trial ended because funding was completed. There were no complications or serious adverse events related to the study. No evidence of unintended effects in each group was found. Analysis was by original assigned groups. Figure 3 depicts between-group differences as well as within-group mean change associated with each intervention condition. Results of all analyses are presented in Tables 2–4. For more detail from the models, the separate impacts of each trial arm on the mean change of each outcome are presented.

Statistically significant between-groups differences favored active SS on the following evaluations at the following timepoints: WMFT at post; and ARAT at post, 1-month, and 4-month. No significant between-groups differences on FMA were present at any time. Statistically significant between-groups differences favoring sham SS were evident on SIS at 1-month.

Statistically significant improvement was associated with active SS as indicated by within-group mean change on the following evaluations at the following timepoints: WMFT at post, 1-month, and 4-month; ARAT at post, 1-month, and 4-month; FMA at post, 1-month, and 4-month; and SIS at post and 4-month.

Statistically significant improvement was associated with sham SS as indicated by within-group mean change on the following evaluations at the following timepoints: FMA at post, 1-month, and 4-month; and SIS at post, 1-month, and 4-month. No statistically significant within-group mean change on WMFT or ARAT was associated with sham SS at any timepoint.

Discussion

With regard to the main hypothesis, between-groups analyses revealed that active SS enhanced outcomes of intensive task-oriented training significantly more than sham SS. In addition, there was statistically significant within-group improvement associated with active SS on all timepoints for all outcome measures except SIS at 1-month follow-up. In contrast, sham SS was associated with statistically significant within-group improvement on only 2 of the 4 outcome measures. Thus, SS appears to have potential to serve as a clinical strategy for significantly improving outcomes of intensive task-oriented motor training in cases of moderate-to-severe UE hemiparesis during the 3-12 month period after stroke. However, more studies are needed in this regard, in part because the ARAT was the only outcome measure that reflected statistically significant differences between groups at every timepoint following intervention. Additionally, as the MCID for each outcome measure has not been established with regard to severely impaired motor function after stroke, it is unclear what conclusions are warranted about the clinical significance of this study's findings. Even though some findings reflected statistical significance, the clinical effects may be small.

The FMA predominantly measures body structure and function²⁸; whereas WMFT, ARAT, and SIS predominantly measure activity^{17, 28}. Specifically, WMFT and ARAT measure what an individual can do in a standardized environment²⁹; and questionnaires such as the SIS measure perceived performance¹⁷. Thus, based on the present study's statistical findings, active SS paired with motor training can be considered to have improved not only body structure and function (ie, FMA) but also activity (ie, WMFT; ARAT; SIS). Because sham SS did not significantly improve any outcomes measured by ARAT and WMFT, motor training alone may be insufficient to improve what can be performed in a standardized environment. Future studies incorporating measures that are sensitive and specific to effects at home or outside the lab (e.g., movement monitoring with accelerometers; actual performance; activity limitations; participation restrictions), as well as how these measures relate to disability and clinical relevance, are recommended. Additionally, there were no obvious indications that impaired sensation affected outcomes; but future studies should investigate this possibility.

Findings from this study should be considered in light of possible limitations. First, WMFT was pre-specified as the primary outcome in this study because the WMFT was used in the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial, which showed that constraint-induced movement therapy led to more significant motor improvements than usual care in 222 subjects with mild-to-moderate hemiparesis at 3-9 months after stroke⁹. However, other studies have indicated that the WMFT may not be optimal in cases of severely impaired motor function^{17, 30} because the instrument becomes susceptible to floor effects, as well as non-normal distribution of data, in such cases³⁰. A second limitation in

the present study is that the FMA's possible lack of sensitivity to change in cases of chronically impaired motor function³¹ may have obscured finding significant differences between groups on what the FMA purports to measure. Additional limitations included unequal allocation ratio as well as losses to follow-up at the 1 month and 4 month time points that reduced the statistical power and value of the outcomes at those times. While unequal allocation has been cited as an acceptable approach in double-blind randomized trials³², use of equal allocation ratio should be investigated in future studies. Finally, to aid in interpretation of this study's statistically significant findings, further research is needed to establish the MCID on each outcome measure relative to stroke populations with severely impaired motor function.

Conclusions

Active SS appears to have potential for translation to a clinical strategy that may optimize outcomes of intensive task-oriented motor training for people with moderate-to-severe UE hemiparesis in the 3-12 month period after stroke. Future studies should measure actual performance, activity limitations, and participation restrictions in order to substantiate how SS paired with motor training can impact disability and functional recovery for this population. Additionally, in order to elucidate neurophysiological mechanisms underlying the effects of intervention, future studies should incorporate outcome measures that quantify neuroplastic change.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Electrode Position and Pulse Train. This figure illustrates the placement of electrodes on the paretic upper extremity (UE) for delivery of somatosensory stimulation (SS) to the targeted nerves. The image in the lower left corner illustrates the timing of the pulse train.

Figure 2.
Study Flow.

Figure 3.

Graphs of Change on All Outcomes. Intervention-related changes on Wolf Motor Function Test (WMFT), Action Research Arm Test (ARAT), Fugl-Meyer Assessment (FMA), and Stroke Impact Scale (SIS) are shown. All graphs indicate mean change in score relative to baseline for each group. Change associated with active somatosensory stimulation is shown in the darker shade. To ensure the appropriateness of statistical assumptions, the square root was applied to ARAT and $\log(\text{mean WMFT})$ values. WMFT and ARAT values were back-transformed to raw values to calculate the means and standard errors shown in order to facilitate interpretation of the results. However, the statistics shown are based on the transformed values. For WMFT, improvement is represented as a negative change along the y-axis. For ARAT, FMA, and SIS, improvement is depicted as positive change along the y-axis. Significant within-group change is denoted with a single asterisk. Significant between-groups difference is denoted with a double asterisk. Error bars denote 1 standard error of the mean (SEM).

Table 1

Baseline Scores and Demographics of the Sample. For each outcome measure, group mean scores and standard deviations (in parentheses) at baseline are shown.

Baseline Scores/Demographics	Active Somatosensory Stimulation (SS)(n=33)	Sham SS (n=22)
Wolf Motor Function Test (WMFT)	1.85 (0.32)	1.81 (0.35)
Fugl-Meyer Assessment (FMA)	18.48 (12.75)	18.23 (13.34)
Action Research Arm Test (ARAT)	11.58 (12.80)	13.36 (14.68)
Stroke Impact Scale (SIS)	56.29 (11.99)	54.68 (11.96)
Mean age at enrollment (years)	58 (12.10)	63 (11.78)
Mean time since stroke (months)	7.48 (2.48)	6.86 (2.52)
Sex (number of women/number of men)	14/19 (42%/58%)	13/9 (59%/41%)
Stroke type (ischemic/hemorrhagic)	25/8 (76%/24%)	17/5 (77%/23%)
Stroke location (cortical/subcortical)	23/10 (70%/30%)	14/8 (64%/36%)
Handedness before stroke (right/left)	31/2 (94%/6%)	19/3 (86%/14%)
Paretic upper extremity (right/left)	19/14 (58%/42%)	7/15 (32%/68%)

Table 2

Estimated means, standard errors and p-values corresponding to mean change on all outcomes from baseline to post-intervention. To ensure the appropriateness of statistical assumptions, the square root was applied to ARAT and log(mean WMFT) values.

Outcome Measure	Test Portion	Post-intervention — Baseline		
		Active	Sham	Active - Sham
Wolf Motor Function Test (WMFT; primary outcome measure)	Timed upper extremity (UE)	-7.64 (1.58) $p<0.0001$	-3.97 (2.00) $p=0.10$	-3.67 (2.55) $p=0.04$
Fugl-Meyer Assessment (FMA; secondary outcome measure)	Motor: paretic UE	6.40 (0.98) $p<0.0001$	5.54 (1.23) $p<0.0001$	0.86 (1.57) $p=0.59$
Action Research Arm Test (ARAT; secondary outcome measure)	Paretic UE	4.80 (0.99) $p<0.0001$	3.02 (1.26) $p=0.07$	1.78 (1.61) $p=0.02$
Stroke Impact Scale (SIS; secondary outcome measure)	All	3.47 (1.05) $p=0.002$	5.86 (1.37) $p=0.0001$	-2.39 (1.73) $p=0.18$

Table 3

Estimated means, standard errors, and p-values corresponding to mean change on all outcome measures from baseline to 1-month follow-up. To ensure the appropriateness of statistical assumptions, the square root was applied to ARAT and log(mean WMFT) values.

Outcome Measure	Test Portion	1-month follow-up — Baseline		
		Active	Sham	Active - Sham
Wolf Motor Function Test (WMFT; primary outcome measure)	Timed paretic upper extremity (UE)	-7.37 (1.89) $p=0.0003$	-3.20 (2.27) $p=0.13$	-4.17 (2.95) $p=0.19$
Fugl-Meyer Assessment (FMA; secondary outcome measure)	Motor: paretic UE	6.86 (1.00) $p<0.0001$	4.67 (1.21) $p=0.0003$	2.19 (1.57) $p=0.17$
Action Research Arm Test (ARAT; secondary outcome measure)	Paretic UE	4.57 (0.90) $p<0.0001$	1.59 (1.09) $p=0.23$	2.98 (1.42) $p=0.01$
Stroke Impact Scale (SIS; secondary outcome measure)	All	2.45 (1.22) $p=0.05$	6.89 (1.50) $p<0.0001$	-4.44 (1.93) $p=0.03$

Table 4

Estimated means, standard errors, and p-values corresponding to mean change on all outcomes from baseline to 4-month follow-up. To ensure the appropriateness of statistical assumptions, the square root was applied to ARAT and log(mean WMFT) values.

Outcome Measure	Test Portion	4-month follow-up — Baseline		
		Active	Sham	Active - Sham
Wolf Motor Function Test (WMFT; primary outcome measure)	Timed: paretic upper extremity (UE)	-7.13 (2.51) <i>p</i> =0.004	-5.07 (2.74) <i>p</i> =0.11	-2.06 (3.72) <i>p</i> =0.43
Fugl-Meyer Assessment (FMA; secondary outcome measure)	Motor: paretic UE	8.01 (1.33) <i>p</i> <0.0001	5.74 (1.50) <i>p</i> =0.0004	2.27 (2.01) <i>p</i> =0.26
Action Research Arm Test (ARAT; secondary outcome measure)	Paretic UE	6.12 (1.17) <i>p</i> <0.0001	2.49 (1.31) <i>p</i> =0.11	3.63 (1.76) <i>p</i> =0.01
Stroke Impact Scale (SIS; secondary outcome measure)	All	4.20 (1.54) <i>p</i> =0.01	6.86 (1.64) <i>p</i> =0.0002	-2.66 (2.25) <i>p</i> =0.25