# Intramuscular Electrical Stimulation for Shoulder Pain in Hemiplegia: Does Time From Stroke Onset Predict Treatment Success?

John Chae, MD, Alan Ng, MD, David T. Yu, MD, Andrew Kirsteins, MD, Elie P. Elovic, MD, Steven R. Flanagan, MD, Richard L. Harvey, MD, Richard D. Zorowitz, MD, and Zi-Ping Fang, PhD

*Background.* A randomized clinical has shown the effectiveness of intramuscular electrical stimulation for the treatment of poststroke shoulder pain. *Objective.* Identify predictors of treatment success and assess the impact of the strongest predictor on outcomes. *Method.* This is a secondary analysis of a multisite randomized clinical trial of intramuscular electrical stimulation for poststroke shoulder pain. The study included 61 chronic stroke survivors with shoulder pain randomized to a 6-week course of intramuscular electrical stimulation (n = 32) versus a hemisling (n = 29). The primary outcome measure was Brief Pain Inventory Question 12. Treatment success was defined as ≥ 2-point reduction in this measure at end of treatment and at 3, 6, and 12 months posttreatment. Forward stepwise regression was used to identify factors predictive of treatment success among participants assigned to the electrical stimulation group. The factor most predictive of treatment success was used as an explanatory variable, and the clinical trials data were reanalyzed. *Results.* Time from stroke onset was most predictive of treatment success. Subjects were divided according to the median value of stroke onset: early (< 77 weeks) versus late (> 77 weeks). Electrical stimulation was effective in reducing poststroke shoulder pain for the early group (94% vs 7%, $P < .001$) but not for the late group (31% vs 33%). Repeated-measure analysis of variance revealed significant treatment ($P < .001$), time from stroke onset ($P = .032$), and treatment by time from stroke onset interaction ($P < .001$) effects. *Conclusions.* Stroke survivors who are treated early after stroke onset may experience greater benefit from intramuscular electrical stimulation for poststroke shoulder pain. However, the relative importance of time from stroke onset versus duration of pain is not known.

Key Words: *Poststroke shoulder pain—Electrical stimulation.*

Shoulder pain is a common complication following stroke.[1] Surface electrical stimulation (ES) has been shown to reduce shoulder subluxation and improve pain-free range of motion (ROM).[2] However, despite demonstrated benefits, surface ES has not been adopted by the clinical community due to pain of stimulation, need for skilled personnel to ensure reliable stimulation, and lack of third-party payer reimbursement.

To address the limitations of surface ES, a novel percutaneously placed intramuscular ES system was developed. Preliminary studies demonstrated that intramuscular ES is well tolerated, may be effective in reducing shoulder pain, is reliable in producing muscle contraction, and is easily managed in the home by the user or caregiver without skilled personnel.[3-6] These findings were confirmed in a multicenter randomized clinical trial, which demonstrated significant reduction in shoulder pain to at least 12 months posttreatment.[7,8]

The primary outcome measure for the multicenter clinical trial was Brief Pain Inventory Question 12 (BPI 12), which asks participants to rank their worst

From the Cleveland Functional Electrical Stimulation Center (JC, DTY), Cleveland, Ohio; Departments of Physical Medicine and Rehabilitation (JC, DTY, AN) and Biomedical Engineering (JC), Case Western Reserve University, Cleveland, Ohio; Charlotte Institute for Rehabilitation (AK), Charlotte, North Carolina; Kessler Medical Rehabilitation Research and Education Corporation (EPE), West Orange, New Jersey; Department of Rehabilitation Medicine (SRF), Mt Sinai School of Medicine, New York; Rehabilitation Institute of Chicago (RLH), Chicago, Illinois; Department of Rehabilitation Medicine (RDZ), University of Pennsylvania, Philadelphia; NeuroControl Corporation (Z-PF), North Ridgeville, Ohio. Dr Yu is now affiliated with Virginia Mason Medical Center, Seattle, Washington, and Bioness Incorporated, Santa Clarita, California. Dr Kirsteins is now affiliated with Moses Cones Health System, Greensboro, North Carolina. Dr Zorowitz is now affiliated with Johns Hopkins Bayview Medical Center, Baltimore, Maryland. This work was presented in part at the 2006 annual meeting of the Association of Academic Physiatrists, Daytona, Florida, March 2006.

Address correspondence to John Chae, MD, Department of Physical Medicine and Rehabilitation, Case Western Reserve University, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109. E-mail: jchae@metrohealth.org.

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shoulder pain in the previous 7 days on a 0 to 10 numeric rating scale (NRS), where 0 represents "no pain" and 10 represents "pain as bad as you can imagine."[9] Participants were assessed at baseline, the end of treatment (EOT), and 3, 6, and 12 months posttreatment. At 12 months posttreatment, the ES group experienced a mean reduction of 65% in shoulder pain compared to 35% for the control group. However, not all participants in the ES group experienced clinically relevant reduction in shoulder pain. Of the 32 ES participants, only 20 (62%) satisfied the success criterion of a minimum reduction of 2 points[10] on BPI 12 relative to baseline at all assessment periods.

To maximize the treatment effect of intramuscular ES and the efficiency of resource utilization, factors predictive of treatment success must be identified. Thus, the objectives of this secondary analysis of a randomized clinical trial of intramuscular ES for poststroke shoulder pain are to 1) identify factors predictive of treatment success and 2) reassess the treatment effect by reanalyzing the data based on the factor most predictive of treatment success.

## METHOD

### Participants

Participants were greater than 12 weeks poststroke (hemorrhagic or nonhemorrhagic) and at least 18 years of age. Participants had 1) shoulder pain graded as at least 2 on BPI 12, 2) at least 1/2 fingerbreadth of inferior glenohumeral separation by palpation with the affected limb in a dependent position without manual traction, and 3) cognitive ability to fulfill study requirements (able to recall 3 objects after 30 minutes and use an NRS). Patients were excluded if they had a history of arrhythmia with hemodynamic instability, recurrent stroke with persistent neurologic deficit from a previous stroke, prestroke shoulder pathology, complex regional pain syndrome, any implantable stimulator, or uncontrolled seizures (>1/month).

### Clinical Trial

The details of the clinical trial, including implantation procedure, stimulator, stimulation parameters, outcome measures, assessment protocol, and analyses, have been published.[7,8] A brief description is provided. A total of 61 participants were enrolled in the clinical trial, with 32 randomized to the ES group and 29 to the control group. The ES group received percutaneous intramuscular electrodes to the upper trapezius, supraspinatus, middle deltoid, and posterior deltoid via a minimally invasive procedure under local anesthesia. After 1 week of electrode stabilization, the ES group received 6 hours of stimulation per day for 6 weeks. The control group was issued a hemisling with instructions to wear the sling for at least 6 hours per day for the same time period. At EOT, electrodes were removed and the hemisling was returned for the ES and control groups, respectively. Outcomes were assessed in a blinded manner at EOT and at 3, 6, and 12 months posttreatment with BPI 12 as the primary outcome measure.

Intent-to-treat analyses were carried out using 2 approaches. First, treatment success was defined as a minimum of a 2-point reduction in BPI 12 relative to baseline at all posttreatment outcome assessment periods. That is, for a participant to be deemed "successfully treated," the participant must experience a minimum of a 2-point reduction in BPI 12 by the EOT and maintain this level of pain reduction throughout the rest of the clinical trial. Second, BPI 12 data were analyzed using repeated-measure analysis of variance (ANOVA). The study protocol was approved by the institutional review boards at each institution. As investigational devices, the percutaneous electrode and stimulator were evaluated under an Investigational Device Exemption granted by the US Food and Drug Administration.

### Factors Predictive of Treatment Success

Factors predictive of treatment success were identified via forward stepwise logistic regression using intent-to-treat data from the ES group of the clinical trial. The dependent variable was "treatment success," defined as a minimum of a 2-point reduction in BPI 12 relative to baseline at all posttreatment time points. Factors entered in the model included patient and stroke characteristics and outcome measures at baseline. Patient and stroke characteristics included gender, age (years), stroke type (nonhemorrhagic vs hemorrhagic), time from stroke onset to study entry (weeks), and side of hemiparesis. Outcome measures at baseline included BPI 12,[9,11] pain interference with daily activity as measured by BPI 23,[9,11] radiographic inferior subluxation,[12,13] pain-free external rotation ROM,[14] poststroke motor impairment as measured by the upper limb component of the Fugl-Meyer Motor Assessment,[15,16] flexor hypertonia at the elbow on the affected side as measured by the Modified Ashworth Scale,[17] and activities of daily living as measured by the self-care component of the Functional Independent Measure (FIM)[18] and the Arm Motor Ability Test (AMAT).[19]

## Impact of the Factor on Primary Outcome

The factor most predictive of treatment success was used to reanalyze the clinical trial's primary outcome (BPI 12) data based on a predefined decision rule. If the predictive factor was binary, the factor was used directly as an explanatory factor. If the predictive factor was continuous, a median value was calculated. The factor was converted to binary by redefining the factor as ≤ median value or > median value. To assess the sensitivity to different cutoff values, analyses were repeated using the 25th and 75th percentile values.

Participants were characterized with respect to demographics, stroke characteristics, and baseline values according to the predictive factor and treatment assignment. The comparability of the ES and control groups, divided according to the predictive factor, was assessed using the independent *t* test and the Fisher exact test for continuous and binary data, respectively.

**Table 1.** Results of Forward Stepwise Regression for Identification of Factors Predictive of Treatment Success Among Participants Treated With Intramuscular Electrical Stimulation

| Variable | Score | *P* Value |
|---|---|---|
| Time from stroke onset | 5.21 | .022 |
| Functional independence measure—self-care | 4.38 | .036 |
| Modified Ashworth Scale | 2.84 | .092 |
| Brief Pain Inventory Question 12 | 2.02 | .125 |
| Inferior subluxation | 1.92 | .166 |
| Stroke type | 0.77 | .378 |
| Side of hemiplegia | 0.75 | .387 |
| Fugl-Meyer Motor Assessment | 0.60 | .438 |
| Gender | 0.31 | .581 |
| Brief Pain Inventory 23 | 0.20 | .652 |
| Pain-free external rotation range of motion | 0.17 | .677 |
| Age | 0.01 | .918 |
| Arm Motor Ability Test—Function | 0.01 | .930 |

**Table 2.** Baseline Characteristics of ES and Control Participants

| | Early | | | Late | | |
|---|---|---|---|---|---|---|
| Variable | ES (n = 16) | Control (n = 14) | *P* | ES (n = 16) | Control (n = 15) | *P* |
| Age, years | 61.6 (11.3) | 59.1 (13.8) | .60 | 57.1 (11.9) | 55.6 (11.8) | .73 |
| Gender (% female) | 37.5 | 35.7 | 1.00 | 50.0 | 53.3 | 1.00 |
| Stroke onset to study entry, weeks | 35.4 (16.4) | 28.6 (14.2) | .23 | 211.4 (191.3) | 227.2 (191.3) | .82 |
| Side of hemiparesis (% left) | 56.3 | 64.3 | .72 | 75.0 | 53.3 | .27 |
| Stroke type (% hemorrhagic) | 18.8 | 28.6 | .68 | 12.5 | 6.7 | 1.00 |
| Brief Pain Inventory 12 | 8.0 (1.9) | 6.5 (2.2) | .06 | 7.2 (2.3) | 6.5 (2.4) | .45 |
| Brief Pain Inventory 23 | 4.7 (3.1) | 4.1 (2.9) | .56 | 4.7 (2.8) | 3.5 (2.5) | .23 |
| Radiographic inferior subluxation, mm | 8.0 (9.6) | 6.0 (7.9) | .54 | 6.5 (6.4) | 8.8 (10.2) | .46 |
| Pain-free external rotation ROM, degrees | 30.1 (20.7) | 39.1 (16.0) | .19 | 40.6 (27.0) | 39.7 (21.1) | .92 |
| Upper extremity Fugl-Meyer | 16.4 (14.8) | 19.2 (12.5) | .58 | 21.7 (14.1) | 17.5 (8.2) | .32 |
| Modified Ashworth Scale | 1.9 (1.5) | 1.4 (1.0) | .33 | 1.9 (1.0) | 1.8 (1.2) | .85 |
| Functional independence measure—self-care | 27.4 (6.8) | 27.1 (7.5) | .91 | 33.9 (7.6) | 32.9 (7.6) | .72 |
| Arm Motor Ability Test—Function | 1.0 (1.0) | 1.1 (1.1) | .71 | 1.2 (1.4) | 0.8 (0.5) | .23 |

All values are means (SD), unless specified. ES = electrical stimulation; ROM = range of motion.

In the initial analyses of BPI 12 outcomes, 2 success criteria were defined. The first criterion was identical to the one used in the clinical trial[7] and the above logistic regression analysis: ≥2-point reduction in BPI 12 at all posttreatment assessments relative to baseline. To account for possible differences in baseline BPI 12, a second criterion of ≥30% reduction was also used. Separate analyses were carried out, divided according to the predictive factor. The success rates between the ES and control groups were compared with the Fisher exact test. A similar analysis was carried out to compare success rates within each group (ES or control), divided according to the predictive factor.

Longitudinal analysis was carried out using repeated-measure ANOVA with posttreatment BPI 12 as the dependent variable. Between-subject factors were treatment assignment, and the logistic regression identified predictive factor with time (posttreatment assessment periods—EOT, 3, 6, and 12 months) as the within-subject factor. Baseline BPI 12, radiographic inferior subluxation, pain-free external rotation ROM, Fugl-Meyer Motor Assessment score, and Modified Ashworth Scale scores were entered as covariates. Post hoc pairwise comparisons of change in BPI 12 scores relative to baseline for the ES and control groups at each posttreatment assessment were carried out with the independent *t* test. The *P* value was adjusted to .006 (.05/8) to account for multiple testing as the level of significance.

## RESULTS

Results of logistic regression analysis are shown in Table 1. The analysis identified time from stroke onset as the factor most predictive of treatment success. Participants with shorter duration from stroke onset were more likely to exhibit sustained response to the intramuscular ES. The median value was calculated as 77.5 weeks, with a range of 16 to 845 weeks. All actual values were either <77 weeks or >77 weeks. The study population was divided according to this predictive factor and denoted as "early" and "late" groups, respectively. Participant characteristics and baseline values for the ES and control participants according to the early and late designations are shown in Table 2. There was a trend toward higher BPI 12 scores for the ES group relative to control for the early group. Otherwise, there were no significant differences between groups.

Figure 1 shows the success rates for the ES and control groups for the early and late groups using the 2-point reduction success criterion. For the early group, the ES group exhibited a significantly higher success rate compared to controls. However, the difference was not significant in the late group. Among ES subjects, the early group exhibited a significantly higher success rate compared to the late group. However, among control subjects, there was no significant difference between early and late groups. Figure 2 shows similar results using the 30% reduction success criterion.

Tables 3 and 4 show the success rates for the ES and control groups according to the 25th (29 weeks) and 75th percentile (140 weeks) cutoff values, respectively, for time from stroke onset. Among subjects in the ≤25th percentile group, the ES group exhibited a significantly higher rate of treatment success compared to controls using either success criterion. Among subjects in the >25th percentile group, the differences between the ES and control groups were not significant. Similar statistical

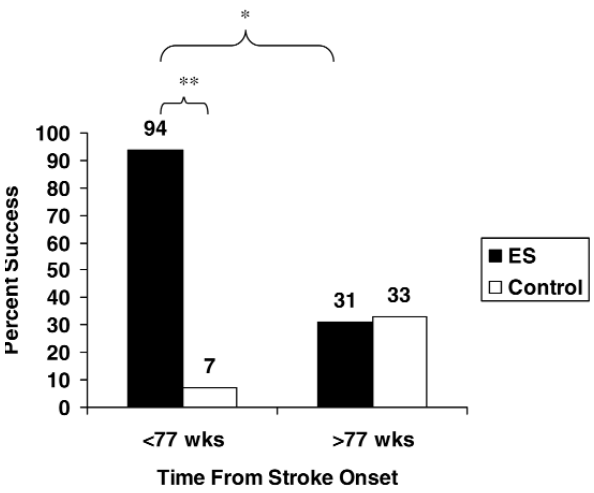


**Figure 1.** Percent of treatment successes based on the 2-point success criterion. ES = electrical stimulation. **P* = .001. ***P* < .001.

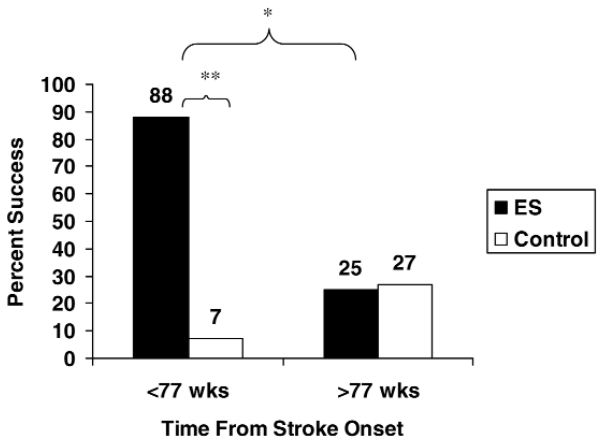


**Figure 2.** Percent of treatment successes based on the 30% success criterion. ES = electrical stimulation. **P* = .001. ***P* < .001.

results were noted using the 75th percentile cutoff value. Based on the 2-point reduction success criterion, the probability of treatment success for the ES group was highest when the median cutoff value (94%) was used, followed by the 25th (88%) and the 75th percentile (74%) values. Going from the 25th percentile to the median cutoff value increased the number of successfully treated patients from 7 to 15 without the cost of a single treatment failure. However, going from the median to the 75th percentile cutoff value increased the number of treatment successes by only 2 additional subjects at the cost of 5 treatment failures.

Figure 3 shows the mean BPI 12 scores from baseline to 12 months posttreatment. The repeated-measure ANOVA model yielded significant treatment ($F = 28.9$,

**Table 3.** Comparison of Success Rates (%) for the Electrical Stimulation (ES) and Control Participants Based on the 2-Point and 30% Reduction Criteria Using the 25th Percentile Cutoff Value for Time From Stroke Onset

| | ≤25th Percentile | | | >25th Percentile | | |
|---|---|---|---|---|---|---|
| Criterion | ES | Control | *P* Value | ES | Control | *P* Value |
| 2 point | 88 (7/8) | 0 (0/9) | <.001 | 54 (13/24) | 30 (6/20) | .135 |
| 30% | 75 (6/8) | 0 (0/9) | .002 | 50 (12/24) | 25 (5/20) | .124 |

**Table 4.** Comparison of Success Rates (%) for the Electrical Stimulation (ES) and Control Participants Based on the 2-Point and 30% reduction Criteria Using the 75th Percentile Cutoff Value for Time From Stroke Onset

| | ≤75th Percentile | | | >75th Percentile | | |
|---|---|---|---|---|---|---|
| Criterion | ES | Control | *P* Value | ES | Control | *P* Value |
| 2 point | 74 (17/23) | 14 (3/22) | <.001 | 33 (3/9) | 43 (3/7) | 1.000 |
| 30% | 65 (15/23) | 14 (3/22) | .001 | 33 (3/9) | 29 (2/7) | 1.000 |

**Table 5.** Mean (SE) Change in BPI 12 Scores at EOT and at 3, 6, and 12 Months Posttreatment for the ES and Control Participants in the Early Treatment (<77 Weeks) Group

| | ES (n = 16) | Control (n = 14) | Mean Difference | 95% Confidence Interval | *P* Value |
|---|---|---|---|---|---|
| EOT | 5.5 (0.8) | 0.9 (0.8) | 4.6 (1.1) | 2.4, 6.9 | <.001 |
| 3 months | 6.5 (0.7) | 0.21 (0.4) | 6.3 (0.8) | 4.7, 7.9 | <.001 |
| 6 months | 6.6 (0.6) | 1.2 (0.8) | 5.4 (1.0) | 3.4, 7.5 | <.001 |
| 12 months | 6.8 (0.4) | 2.4 (0.9) | 4.5 (1.0) | 2.5, 6.5 | <.001 |

BPI 12 = Brief Pain Inventory Question 12; EOT = end of treatment; ES = electrical stimulation.

**Table 6.** Mean (SE) Change in BPI 12 Scores at EOT and at 3, 6, and 12 Months Posttreatment for the ES and Control Participants in the Late Treatment Group (>77 Weeks)

| | ES (n = 16) | Control (n = 15) | Mean Difference | 95% Confidence Interval | *P* Value |
|---|---|---|---|---|---|
| EOT | 3.6 (0.8) | 0.9 (0.6) | 2.7 (1.0) | 0.7, 4.7 | .010 |
| 3 months | 2.4 (0.8) | 1.1 (0.6) | 1.2 (1.0) | –0.8, 3.3 | .232 |
| 6 months | 2.3 (0.8) | 1.5 (0.7) | 0.7 (1.1) | –1.5, 2.9 | .508 |
| 12 months | 3.2 (0.9) | 2.3 (3.3) | 0.9 (1.2) | –1.6, 3.4 | .462 |

BPI 12 = Brief Pain Inventory Question 12; EOT = end of treatment; ES = electrical stimulation.

$P < .001$) and time from stroke onset ($F = 4.9$, $P = .032$) effects. The "treatment" by "time from stroke onset" interaction term was also significant ($F = 10.9$, $P = .002$). Among covariates, only baseline BPI 12 was significant ($F = 21.5$, $P < .001$). Table 5 shows the results of the post hoc comparisons of change in BPI 12 scores at each posttreatment assessment for the early group. The ES group exhibited significantly greater reduction in BPI 12 scores at all posttreatment assessments. Table 6 shows the results of the post hoc comparisons of change in BPI 12 scores at each posttreatment assessment for the late group. The ES group exhibited greater reduction in BPI 12 scores at EOT compared to controls, although the difference did not reach statistical significance. The reduction in BPI 12 scores at subsequent visits was similar between groups.

## DISCUSSION

This secondary analysis of a multisite clinical trial suggests that stroke survivors with poststroke shoulder pain are more likely to respond to intramuscular ES if they are treated within 77 weeks of their stroke onset. Based on

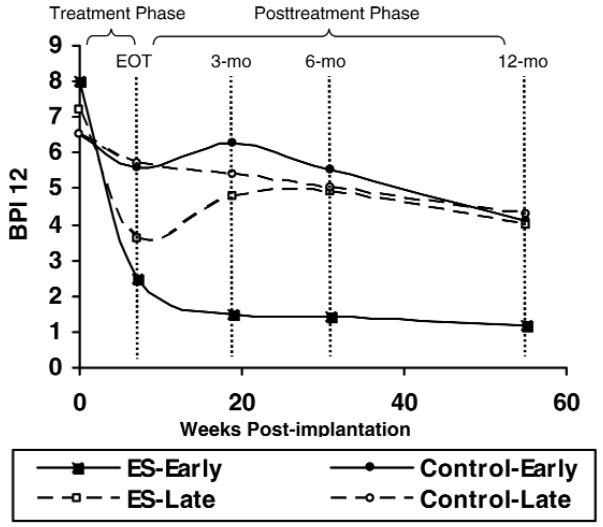


**Figure 3.** Time course of mean Brief Pain Inventory Question 12 (BPI 12) scores for the electrical stimulation (ES) and control participants according to early (solid lines) versus late (dashed lines) intervention. EOT = end of treatment.

the 2-point reduction criterion, data suggest that treating patients within 77 weeks of their stroke improves the likelihood of treatment success from 65% in the original clinical trial to 94% in the present secondary analysis (Figure 1). As shown in Figure 3, participants who were treated early experienced a 68.8% reduction in shoulder pain by EOT, which continued to improve to 85% reduction by final evaluation. In contrast, participants treated late experienced substantial pain reduction by EOT, but the effect dissipated with time, eventually approximating the profile of control subjects.

The improved therapeutic benefit of intramuscular ES for the early treatment group may be due to the presumed timing effect of ES-mediated motor relearning. Previous studies have shown that ES is associated with improvements in motor impairment.[20] Intramuscular ES may mediate its therapeutic benefit by improving the mechanical stability of the poststroke shoulder.[6] Animal studies have shown that motor relearning strategies are more likely to be effective when applied earlier poststroke than later.[21] Accordingly, improvements in motor impairment after ES appear to be maintained for acute stroke survivors[22,23] but not for chronic stroke survivors.[24,25] Consistent with these findings, a recent meta-analysis showed that ES is effective in improving shoulder subluxation among acute stroke survivors but not among chronic stroke survivors.[26]

Assuming that the early and late groups fundamentally have the same disease, the nonsustained therapeutic effect for the late group has several implications for future clinical trials. The patient population should be clearly defined with respect to time from stroke onset, and at the very least, subjects should be stratified according to this factor. If the intervention remains unchanged, future studies should consider excluding this population. Alternatively, it is possible that the prescribed dose was suboptimal. Participants in the late group may require greater than 6 hours of stimulation per day and for greater than 6 weeks. However, increasing the daily dose and overall duration of treatment may increase the risk of infection and retained fragments. Sustained therapeutic benefit may not be possible in this group, regardless of dosage. However, as shown in Figure 3, the late group did experience some short-term benefit. Thus, future trials may investigate an entirely different system such as a permanently implanted device[27] that provides periodic redosing to treat this refractory population.

It is also possible that the participants in the early and late groups are fundamentally different. Is it possible that the late group is actually suffering from chronic pain syndrome? Increasing chronicity of pain is more likely to result in central sensitization of pain at the spinal cord level. Wide dynamic range sensory receptors become converted to nociceptors, and secondary spinothalamic afferents in the dorsal horns are excited by a lower firing frequency of the primary nociceptors.[28] The short-term beneficial effect of ES in the late group may be a neuromodulation effect that temporarily reduces activation of the spinothalamic pathways but mediates no long-term benefit. This would also mean that the pain issues in this late group are more complex, requiring specialized interdisciplinary care rather than a targeted treatment approach.

The study has several limitations. First, it is not clear whether the actual predictive factor is time from stroke onset to study entry or duration of shoulder pain. This information was difficult to obtain as most participants could not recall the precise onset date for their shoulder pain. Second, because this is a post hoc analysis, cause and effect are difficult to invoke with certainty. A larger clinical trial that stratifies participants according to time from stroke onset may address this question. Third, the 77-week cutoff for time from stroke onset to study entry was rather arbitrary, based on a "median" value. Nevertheless, sensitivity analyses using the 25th and 75th percentile values suggest that the median was a reasonable cut-off value, capturing 75% of all treatment successes at the cost of only 1 treatment failure. However, more sophisticated approaches for identifying optimal cutoff points for clinical decision making may be appropriate.[29]

In summary, this secondary analysis suggests that stroke survivors with poststroke shoulder pain are more likely to benefit from intramuscular ES if they are treated early. Those who are treated late may experience short-term benefit, but pain is likely to worsen with long-term response approximating the untreated population. In

view of the post hoc nature of this investigation, specific clinical recommendations must await confirmation in a larger clinical trial that stratifies participants into early and late treatment groups.

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## DISCLOSURES

Conflict of interest: NeuroControl Corporation (NCC), North Ridgeville, Ohio, supported this clinical trial and has direct interest in the content of this article with respect to a device the company intends to commercialize. John Chae, MD, is a consultant to NCC and received clinical trials support. Zi-Ping Fang, PhD, is an employee of NCC. At the time of the study, David Yu, MD, was a consultant to NCC and received clinical trials support but is no longer affiliated with the company. All remaining authors, with the exception of Alan Ng, MD, received clinical trials support.

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