# Intramuscular Neuromuscular Electric Stimulation for Poststroke Shoulder Pain: A Multicenter Randomized Clinical Trial

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ABSTRACT. Yu DT, Chae J, Walker ME, Kirsteins A, Elovic EP, Flanagan SR, Harvey RL, Zorowitz RD, Frost FS, Grill JH, Feldstein M, Fang Z-P. Intramuscular neuromuscular electric stimulation for poststroke shoulder pain: a multicenter randomized clinical trial. Arch Phys Med Rehabil 2004;85: 695-704.

**Objective:** To assess the effectiveness of intramuscular neuromuscular electric stimulation (NMES) in reducing poststroke shoulder pain.

**Design:** Multicenter, single-blinded, randomized clinical trial.

**Setting:** Ambulatory centers of 7 academic rehabilitation centers in the United States.

**Participants:** Volunteer sample of 61 chronic stroke survivors with shoulder pain and subluxation.

**Intervention:** Treatment subjects received intramuscular NMES to the supraspinatus, posterior deltoid, middle deltoid, and trapezius for 6 hours a day for 6 weeks. Control subjects were treated with a cuff-type sling for 6 weeks.

**Main Outcome Measure:** Brief Pain Inventory question 12 (BPI 12), an 11-point numeric rating scale administered in a blinded manner at the end of treatment, and at 3 and 6 months posttreatment.

**Results:** The NMES group exhibited significantly higher proportions of success based on the 3-point or more reduction in BPI 12 success criterion at the end of treatment (65.6% vs 24.1%, $P<.01$), at 3 months (59.4% vs 20.7%, $P<.01$), and at 6 months (59.4% vs 27.6%, $P<.05$). By using the most stringent "no pain" criterion, the NMES group also exhibited significantly higher proportions of success at the end of treatment (34.4% vs 3.4%, $P<.01$), at 3 months (34.4% vs 0.0%, $P<.001$), and at 6 months (34.4% vs 10.3%, $P<.05$).

**Conclusions:** Intramuscular NMES reduces poststroke shoulder pain among those with shoulder subluxation and the effect is maintained for at least 6 months posttreatment.

**Key Words:** Electric stimulation; Shoulder pain; Rehabilitation; Stroke.



SHOULDER PAIN IS A COMMON complication after stroke.[1] There are many postulated etiologies of poststroke shoulder pain.[2,3] However, shoulder subluxation is among the most commonly cited causes,[1,4] although a causal relationship remains controversial.[5] To date, the only treatment option for poststroke shoulder dysfunction supported by randomized controlled trials (RCTs) is surface neuromuscular electric stimulation (NMES), which has been shown to reduce shoulder subluxation and improve pain-free range of motion (ROM). However, systematic reviews of RCTs have failed to demonstrate significant effect of surface NMES on activity-dependent or resting poststroke shoulder pain.[6,7] Furthermore, despite demonstrated benefits on shoulder subluxation and ROM, surface NMES has not been adopted by the clinical community due to pain caused by stimulation, inability to focally stimulate deep muscles, need for skilled personnel to ensure reliable stimulation, and lack of third-party payer reimbursement. Accordingly, in 1986, Baker and Parker, the authors of the first RCT of surface NMES for shoulder subluxation, wrote "Until implanted electrode systems become available . . . long-term use of surface electrical stimulation can be managed by only a few patients with hemiparesis and their families."[8(p1937)]

To address the limitations of surface NMES systems and prior study designs, a multicenter, single-blinded RCT of intramuscular NMES with clinically relevant shoulder pain as the primary outcome measure was carried out. Preliminary studies showed that intramuscular NMES is better tolerated than surface NMES, is able to focally stimulate deep muscles, is reliable and consistent in producing muscle contraction, and is easily managed by the user or caregiver.[9-11] The purpose of this study was to show the effectiveness and safety of percutaneous intramuscular NMES in treating poststroke shoulder pain. We

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tested our primary hypothesis that intramuscular NMES provides significant and sustained reduction of shoulder pain among chronic stroke survivors with shoulder subluxation and pain. We tested a series of secondary hypotheses that intramuscular NMES reduces interference of shoulder pain on daily activities, shoulder subluxation, motor impairment, limitations on ROM, and disability.

## METHODS

### Participants

Subjects were recruited from stroke rehabilitation outpatient clinics at 7 academic medical centers in the United States. To qualify for study inclusion, subjects had to be more than 12 weeks poststroke (hemorrhagic or nonhemorrhagic) and at least 18 years of age. Subjects had to have shoulder pain rated as at least 2 on the 11-point numeric rating scale (NRS) of the Brief Pain Inventory[12] question 12 (BPI 12), at least one-half fingerbreadth of inferior glenohumeral separation by palpation with the affected limb in a dependent position without manual traction, ability to understand study requirements, and ability to recall 3 objects after 30 minutes.

Subjects also had to show ability to use an NRS. Specifically, they were asked to assess the pain associated with 3 scenarios, "a mosquito bite," a "stubbed toe," and a "broken arm." The scenarios were presented in a random order, and they were asked to rank them from the least to most painful. Subjects were excluded if they were unable to rank the pain in the following order: (1) "mosquito bite," (2) "stubbed toe," and (3) "broken arm." Patients were excluded if they had history of ventricular arrhythmias or any other arrhythmia with hemodynamic instability, previous stroke with persistent neurologic deficit, prestroke shoulder pathology, complex regional pain syndrome, and any implantable stimulator or uncontrolled seizures ($>$1/mo for 1y). Subjects were allocated via computer-generated randomization in blocks of 4 assignments (2 treatments, 2 controls). The institutional review board at each site approved the study protocol and all subjects signed informed consent.

### Stimulation System and Stimulation Parameters

The percutaneous electrode and stimulator[a] used in this trial are investigational devices and were evaluated under an investigational device exemption granted by the US Food and Drug Administration. Both the electrode and stimulator were previously described.[11] The stimulator "on" time of 20 seconds consisted of 5 seconds of ramp up, 10 seconds of plateau, and 5 seconds of ramp down. The "off" time was 10 seconds. The current amplitude was kept constant at 20mA. Adjusting the pulse width from 10 to 200$\mu$s regulated the stimulus intensity. Stimulus intensity was adjusted to provide optimal joint reduction by palpation without discomfort and remained constant during the 6-week treatment phase. To minimize muscle fatigue and repetitive vertical translation of the humeral head on the glenoid fossa, the stimulation of posterior deltoid and supraspinatus muscles were alternated with stimulation of middle deltoid and trapezius muscles. Compliance was monitored electronically with a built-in data-logging system.

### Treatment and Evaluation

NMES subjects were implanted with intramuscular electrodes via a percutaneous approach in the supraspinatus, posterior deltoid, middle deltoid, and upper trapezius muscles using a sterile technique. The electrode exit sites were localized to the superior lateral aspect of the shoulder just medial and posterior to the acromion. Motor points of the target muscles were initially localized by using monopolar needle stimulation using standard electyromyographic needle insertion sites.[13] Various sites around the standard site were also stimulated, and the site associated with the best reduction of the subluxation by inspection and manual palpation was selected as the implantation site. The paths between the motor points and anticipated electrode exit sites were anesthetized with 2% lidocaine. A 19-gauge hypodermic needle loaded with a percutaneous electrode was tunneled subcutaneously from the electrode exit site toward the motor point. The electrode was stimulated during the tunneling procedure to facilitate electrode positioning. After reaching the optimal location, the needle was slowly withdrawn while pressure was maintained at the muscle belly to anchor the barb of the electrode and leave the electrode in place. After needle removal, electrode position was again confirmed by stimulating the electrode and observing the reduction in subluxation. If there was insufficient reduction, the electrode was removed and another electrode was implanted. The procedure was repeated for the other muscles. The subcutaneous tunneling procedure allows multiple electrodes to exit from the same site, facilitating skin care and connection with the external stimulator.

One week after implantation, subjects given NMES were prescribed 6 hours of stimulation per day for 6 weeks. However, subjects were allowed to receive the stimulation during any part of the day, and they were allowed to divide the stimulation to 2 or 3 equal duration sessions per day to facilitate compliance. All treatment sessions were carried out in subjects' homes. Subjects were allowed to be seated, standing, or ambulating during the stimulation as long as their arms were unsupported to "gravity load" the muscles during stimulation. Accordingly, when seated, subjects were not allowed to use a lapboard, and they were not allowed to be supine. After the 6-week treatment phase, investigators removed the electrodes by gently pulling on the external portions of the electrodes. NMES subjects discontinued stimulation 24 hours before the end of treatment assessments to eliminate short-term effects of the stimulation.

Control subjects were given a cuff-type hemisling with instructions to use the sling whenever the upper limb was unsupported. As with the NMES group, control subjects were allowed to be seated, standing, or ambulating during sling use. When seated, they were not allowed to use a lapboard and they were not allowed to be supine. Subjects in both groups were allowed to use their hemiparetic arm for activities of daily living (ADLs) during the stimulation and sling use periods, respectively. However, they were instructed not to place their shoulders in painful positions such as extremes of abduction and external rotation. Control subjects returned the hemislings after the 6-week treatment phase. Subjects given NMES were permitted to use a hemisling if prescribed before enrollment but were instructed not to use them during NMES treatment. Because of ethical considerations, all subjects were allowed to receive concomitant treatments including pharmacologic (opioid and nonopioid analgesics) and nonpharmacologic (outpatient physical [PT] and occupational [OT] therapy) interventions as per their primary care physicians.

Blinded evaluations for both groups were performed at baseline (within 48-h before electrode implantation for the NMES group), at the end of treatment, and at 3 and 6 months posttreatment by trained occupational therapists. Subjects were asked not to discuss their treatments with the blinded assessor at each visit. The end-of-treatment assessments for subjects given NMES were performed before removal of electrodes to avoid the confounding effect of any discomfort associated with

electrode removal. Bandages were placed on the shoulder of both NMES and control subjects to maintain blinding.

### Outcome Measures

***Primary outcome measure.*** The primary outcome measure was the BPI 12. The BPI is a pain questionnaire, which assesses both pain intensity (sensory dimension) and the interference (reactive dimension) of pain in daily activities. The BPI has shown both reliability and validity across cultures and languages.[12] The developers of the BPI suggested that BPI 12, the "pain worst" rating, may be selected as the primary response variable. The question asks subjects to rate their worst shoulder pain in the last week on an 11-point NRS of 0 (no pain) to 10 (pain as bad as you can imagine).

***Secondary outcome measures.*** The degree to which shoulder pain interfered with daily activities was assessed with the BPI question 23 (BPI 23), which assesses 7 activities on an 11-point NRS, from 0 (does not interfere) to 10 (completely interferes). The summary score is a composite of scores for 7 specific questions that relate to the domains of general activity, mood, walking ability, normal work, interpersonal relationships, sleep, and enjoyment of life.

The effect of percutaneous intramuscular NMES on inferior subluxation was assessed radiographically based on modifications of previously described methods.[14,15] Subluxation was measured on true anteroposterior radiographs by using the vertical distance between the center of the glenoid fossa to the center of the humeral head. The frame of reference was defined as the superior, inferior, medial, and lateral aspects of the glenoid fossa, which accounted for scapular rotation in the hemiplegic shoulder. Changes in subluxation were evaluated in millimeters as measured through comparison of radiographs of the affected side and the unaffected side.

Pain-free, passive external rotation ROM of the glenohumeral joint was measured with a goniometer with the subject in a supine position with the shoulder abducted to 45°, whereas the elbow was held at 90° of flexion with the forearm in a neutral position.[16] Hemiparetic upper-limb strength and coordination were assessed with the upper-limb component of the Fugl-Meyer Motor Assessment.[17,18] Resistance to passive elbow extension was assessed with the Ashworth Scale.[19] We elected not to evaluate resistance to shoulder abduction or external rotation because of the potential confounding effect of shoulder pain. Upper limb–related disability was assessed with the self-care portion of the FIM instrument[20] and the Arm Motor Ability Test[21] (AMAT).

***Diary data.*** In view of the fluctuating nature of pain and to corroborate the results of the primary outcome measure, subjects were asked to rate their shoulder pain daily by using BPI question 15 (BPI 15). BPI 15 asks subjects to rate their pain at a given point in time on an 11-point NRS as used in BPI 12. Subjects were asked to rate their pain at the conclusion of their morning ADLs. Scores were recorded daily during the baseline week, during each day of the 6-week treatment phase, and during 1 week before the 3- and 6-month evaluations.

### Concomitant Therapies

During each study visit, all pharmacologic analgesic agents and their doses were recorded. Subjects were also asked to record their daily medication use in diaries. To compare doses between subjects and between groups, daily doses of opioid and nonopioid analgesics were normalized to equivalent daily doses by using standard equivalency tables.[22,23] The protocol initially did not include monitoring of hours of formal outpatient PT and OT. Therefore, these data were collected retrospectively by reviewing subjects' medical records. Although this information was collected retrospectively, the information is likely to be as accurate or more accurate than prospectively collected subject reports because medical records document actual treatments rendered, including duration and frequency of treatment, and are less likely to be affected by subjects' reliability.

### Statistical Analysis

The study was powered based on a superiority test of proportions assuming a 1-sided test with $\alpha$ of .05 and $\beta$ of .20. We used a 1-sided test in view of previous surface NMES studies that generally reported positive findings with no evidence of negative effect. The hypothetical "success" proportions at the end of treatment were defined as 70% for the NMES group and 40% for the control group for a minimal clinically significant difference of 30%. The power calculation revealed that 33 subjects were required in each groups. Success of randomization was assessed via univariate analysis of specific baseline demographic, stroke, and outcomes variables. Nominal and continuous data were analyzed with the Fisher exact test and the independent *t* test, respectively.

The primary outcome measure (BPI 12) was analyzed with an intent-to-treat approach using multiple inputations. When subjects missed their evaluation, but came in for an unplanned visit, unplanned visit data were imputed for missing data. When subjects missed their evaluation and did not come in for an unplanned visit, but completed their diaries, the maximum pain recorded during the 7 days before the scheduled visit was imputed for the missing data. For all other missing data, values at baseline were imputed. BPI 12 data were initially assessed with respect to predefined success criterion. The primary success criterion was defined as 2-point or more reduction in pain. More stringent 3- and 4-point or more reduction and "no pain" criteria were also used. The differences in proportion of successes between groups at each evaluation point were initially assessed with the Fisher exact test. To account for the potential confounding effect of baseline BPI 12, data were reanalyzed by using logistic regression with baseline BPI 12 as a covariate.

A longitudinal analysis of BPI 12 by using a general estimating equation (GEE) was also performed[b] with baseline BPI 12 as a covariate. The statistical software fits the appropriate GEE longitudinal model to all available data, including imputed data for missing data. The model includes a main effect for treatment, a main effect for time, and an interaction term relating the 2 main effects. The model is equivalent to fitting 2 arbitrary quadratic equations to the data, one for each group. The model was run by using an arbitrary (unstructured) correlation matrix, which makes no assumptions about the correlation between pairwise measurements. Variance estimates for the regression coefficients were estimated by using a robust estimate. If the treatment or interaction term was significant, post hoc pairwise analyses were performed with the independent *t* test with *P* value adjusted for multiple testing ($P \leq .017$). Secondary outcome measures were also assessed with the GEE longitudinal analysis but by using a per-protocol approach.

Concomitant opioid and nonopioid analgesic therapies were analyzed by using an intention-to-treat approach using multiple imputations. First, missing data were imputed using diary data. For missing baseline data, the average daily dose during the week before the start of treatment was used. For data missing from the end of treatment or 3- and 6-month visits, the average daily doses during the week before each visit were used. Second, unscheduled visit data were imputed for missing data from missed scheduled visits. Third, "worst case" imputation was used for medications that were entered only as needed. Treatment subjects were assigned the recommended maximum

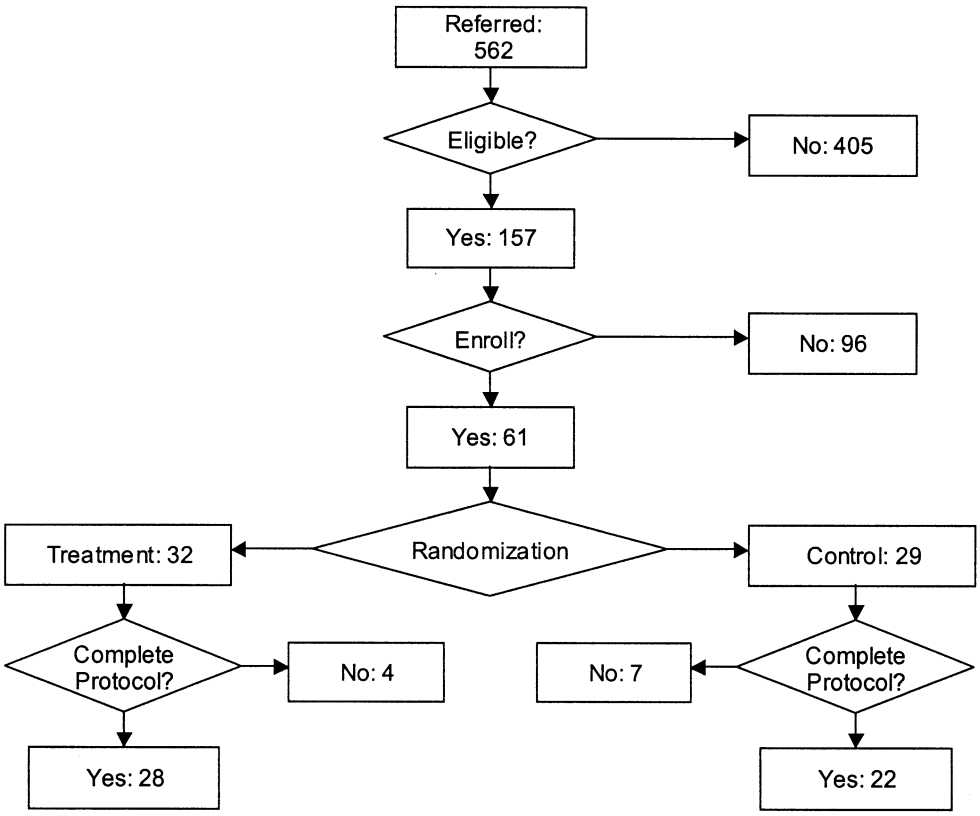


**Fig 1. Subject flow diagram.**

daily dose, whereas control subjects were assigned 0. Finally, all remaining missing data were imputed by carrying the last value forward.

Mean changes in normalized dose of opioid and nonopioid medications at the end of treatment, 3 months, and 6 months were compared between groups using the independent *t* test. To evaluate concomitant pain medication as a confounding factor on the primary outcome measure BPI 12, additional series of logistic regressions were carried out with opioid and nonopioid analgesic doses entered as covariates. As with original analyses, outcomes were assessed for all success criteria based on BPI 12 (≥2-, ≥3-, ≥4-point pain reduction and "no pain") at the end of treatment and at 3 and 6 months. The regression model included 4 covariates (opioid and nonopioid medications at baseline and at time of evaluation), in addition to the constant term and the treatment effect.

The cumulative hours of OT and PT were analyzed by using an intention-to-treat approach using worst-case imputation. Control subjects were assigned 0 hours of therapies; treatment subjects were assigned 118 hours. In clinical practice, typical formal outpatient therapy programs for chronic stroke survivors do not exceed 3 hours of a given therapy a week. If a subject received this amount of weekly therapy for the entire duration (nearly 8mo) of the study, he/she would receive 118 hours. Thus, 118 hours is a reasonable worst-case imputation for treatment subjects. Therapy hours were compared between groups by using the independent *t* test. To evaluate concomitant therapies as a confounding factor on the primary outcome measure, logistic regression was also carried out with the cumulative number of hours of formal outpatient OT and PT entered as covariates. As with original analyses, outcomes were assessed for all success criteria based on BPI 12 (≥2-, ≥3-, ≥4-point pain reduction, and "no pain"). However, we limited our analysis to the 6-month evaluation visit because we monitored the cumulative number of hours of therapies during the entire study period, and outcome at 6 months has the highest clinical significance. The model included 2 covariates (OT, PT), in addition to the constant term and the treatment effect.

## RESULTS

### Subjects and Baseline Characteristics

Figure 1 shows the subject flow diagram. Among the 562 patients screened, 157 (27.9%) qualified for enrollment. Most common reasons for exclusion were lack of shoulder subluxation (40.9%), lack of pain (21.0%), failure to pass the cognitive screening test (11.1%), and prior strokes (5.5%). Of those who qualified, 61 (38.9%) gave consent for randomization. The primary reason for not giving consent was concerns for risks associated with an invasive procedure. Thirty-two subjects were assigned to the NMES group and 29 to the control group. Four (12.5%) subjects given NMES dropped out of the study. One subject became severely depressed and was unable to communicate after the 3-month follow-up, and another subject experienced medical complications unrelated to the intervention after completion of treatment and withdrew consent. Two subjects were lost to follow-up after completion of the 3-month follow-up. Seven (24.1%) control subjects dropped out of the study. One subject who was immune compromised experienced exacerbation of liver failure and died of sepsis before completion of the treatment phase. One subject experienced recurrent medical complications of stroke including seizures, depressed level of alertness, headaches, and anxiety and withdrew consent. One subject missed 3- and 6-month follow-up evaluations because of out-of-town engagements. One subject missed a 6-month follow-up evaluation because of a scheduling

**Table 1: Baseline Characteristics**

| | NMES (n=32) | Control (n=29) | *P* Value |
|---|---|---|---|
| Age (y) | 60±11.4 | 58±12.9 | 0.43 |
| Gender (% female) | 42.4 | 42.9 | 1.00 |
| Stroke Variables | | | |
| Onset to enrollment (wk) | 123±157 | 135±171 | 0.76 |
| Type (% hemorrhagic) | 18.2 | 17.9 | 1.00 |
| Level (% cortical)* | 55.6 | 73.9 | 0.24 |
| Etiology (% embolic/lacunar/thrombotic)* | 21.7/21.7/56.6 | 17.4/17.4/65.2 | 0.85 |
| Right hemiparesis (%) | 36.4 | 42.9 | 0.79 |
| Sensory impairment (%) | 15.6 | 27.6 | 0.35 |
| Aphasia (%) | 18.2 | 28.6 | 0.37 |
| Neglect (%) | 15.6 | 17.2 | 1.00 |
| Analgesic dose | | | |
| Opioid | 0.13±0.35 | 0.20±0.65 | 0.61 |
| Nonopioid | 0.25±0.37 | 0.12±0.23 | 0.10 |
| Assessments | | | |
| BPI 12 | 7.59±2.12 | 6.52±2.29 | 0.06 |
| BPI 23 | 4.73±2.88 | 3.68±2.52 | 0.13 |
| Pain-free external rotation ROM (deg) | 35.31±24.28 | 39.41±18.47 | 0.46 |
| Inferior subluxation (mm) | 7.25±8.04 | 7.45±9.12 | 0.77 |
| Fugl-Meyer Motor Assessment | 19.06±14.47 | 18.31±10.34 | 0.82 |
| Ashworth Scale | 1.88±1.21 | 1.62±1.12 | 0.40 |
| FIM | 30.66±7.82 | 30.10±7.99 | 0.79 |
| AMAT FA | 1.10±1.19 | 0.96±0.93 | 0.51 |
| AMAT QOM | 1.02±1.06 | 0.89±0.85 | 0.58 |

NOTE. Values are mean ± standard deviation (SD) unless stated otherwise.
Abbreviations: FA, functional ability; QOM, quality of movement.
*As a percentage of nonhemorrhagic subjects.

difficulty. Two subjects reported transportation difficulty after completing the treatment phase and withdrew consent. One subject was lost to follow-up after completion of treatment due to relocation. None of the subjects dropped out because of illness related to the clinical trial, worsening pain, or dissatisfaction with treatment.

Enrollment was terminated before accruing the target sample of 66 subjects because an interim analysis of 61 enrolled subjects yielded a substantially larger effect of treatment than anticipated. The proportion of subjects meeting a priori success criterion (≥2-point reduction) at end of treatment was 53.4% higher (84.4% vs 31.0%) in the NMES group compared with the control group ($P<.001$). The target sample size was calculated based on an anticipated 30% difference between groups in proportions of subjects meeting the success criterion.

There were no significant differences between groups with respect to baseline characteristics (table 1). However, the NMES group exhibited a trend toward higher BPI 12 score and higher nonopioid analgesic dose at baseline. NMES subjects were 97.2% compliant with their stimulation protocol. Subjects given NMES and their caregivers reported on user surveys that the NMES treatment was easy to use and did not interfere with ADLs or any ongoing therapies. Subjects given NMES used the hemisling an average of 1 hour a day, whereas control subjects used the hemisling an average of 5.4 hour a day.

### Primary Outcome Measure

Of 244 possible primary outcome measure data points for baseline and 3 follow-up evaluations, 22 (9%) were missing. Table 2 shows the results of intent-to-treat analyses of the primary outcome measure BPI 12. Based on the 2-point reduction criterion, the NMES group exhibited significantly higher proportion of successes at the end of treatment, and at 3 months posttreatment, and a trend toward significance at 6 months posttreatment. By using more stringent 3- and 4-point or more reduction and "no pain" criteria, the NMES group exhibited a significantly higher proportion of successes compared with controls at all evaluations. Logistic regression demonstrated persistence of significant treatment effect after adjustment for baseline BPI 12.

GEE analysis of BPI 12 revealed a significant main effect for treatment ($z=-5.38$, $P<.001$), and time by treatment interaction ($z=2.00$, $P=.046$), indicating a significant treatment effect. Figure 2 shows the average reduction in BPI 12 at each evaluation point. Post hoc analyses showed that the NMES group exhibited significantly greater reduction in BPI 12 compared with controls at the end of treatment (difference=3.7; 95% confidence interval [CI], 2.2–5.2; $P<.001$), at 3 months (difference=3.3; 95% CI, 1.8–4.9; $P<.001$), and at 6 months (difference=2.3; 95% CI, 0.7–4.0; $P=.006$).

### Secondary Outcome Measures

GEE analysis of BPI 23 revealed nonsignificant main effects for time ($z=-1.25$, $P=.213$) and treatment assignment ($z=1.53$, $P=.126$). However, the interaction term involving treatment and time was highly significant ($z=-3.74$, $P<.001$), indicating a significant treatment effect. Figure 3 shows the average reduction in BPI 23 at each evaluation point. Post hoc analyses showed that the NMES group exhibited significant reduction in BPI 23 compared with controls at the end of treatment (difference=2.2; 95% CI, 0.8–3.6; $P=.002$), at 3 months (difference=3.2; 95% CI, 1.5–4.9; $P<.001$), and at 6 months (difference=1.8; 95% CI, 0.3–3.4; $P=.017$). GEE analyses of the remaining secondary measures did not show significant differences between groups. Nonparametric analy-

**Table 2: Results of Primary Outcome Measure (BPI question 12)**

| Success Criterion | NMES (%) (n=32) | Control (%) (n=29) | OR (95% CI), *P* Value |
|---|---|---|---|
| End of treatment | | | |
| ≥2 points | 27 (84.4) | 9 (31.0) | 12.0 (3.5–41.3), <.001 |
| ≥3 points | 21 (65.6) | 7 (24.1) | 6.0 (2.0–18.4), <.01 |
| ≥4 points | 19 (59.4) | 5 (17.2) | 7.0 (2.1–23.1), <.01 |
| No pain | 11 (34.4) | 1 (3.4) | 14.7 (1.8–122.7), <.01 |
| 3 months | | | |
| ≥2 points | 21 (65.6) | 9 (31.0) | 4.2 (1.5–12.4), <.05 |
| ≥3 points | 19 (59.4) | 6 (20.7) | 5.6 (1.8–17.6), <.01 |
| ≥4 points | 17 (53.1) | 3 (10.3) | 9.8 (2.5–39.1), <.001 |
| No pain | 11 (34.4) | 0 (0.0) | <.001* |
| 6 months | | | |
| ≥2 points | 20 (62.5) | 11 (37.9) | 2.7 (1.0–7.7), .07 |
| ≥3 points | 19 (59.4) | 8 (27.6) | 3.8 (1.3–11.3), <.05 |
| ≥4 points | 16 (50.0) | 6 (20.7) | 3.8 (1.2–11.9), <.05 |
| No pain | 11 (34.4) | 3 (10.3) | 4.5 (1.1–18.4), <.05 |

NOTE. Values are proportions meeting success criterion.
Abbreviations: OR, odds ratio; CI, confidence interval.
*Unable to calculate OR due to 0% success for the control group.

ses of ordinal data yielded similar results, and, therefore, only results of parametric analyses are presented.

### Diary Data

Of 3843 possible diary data points for daily pain level, BPI 15, a total of 1242 (32.3%) were missing. In view of the large number of missing data, formal statistics were not carried out. Figure 4 shows the daily mean values for BPI 15 for both groups. The average BPI 15 scores of NMES and control subjects were similar at baseline. During the treatment phase, the NMES and control subject scores began to diverge so that at 3 and 6 months, substantially larger differences between groups were observed.

### Concomitant Therapies

Approximately 18% of analgesic medication data were deemed missing. On average, subjects took very low doses of analgesic medications for their shoulder pain. At baseline, the average dose of opioid medications for the NMES group was equivalent to 26mg of codeine per day. The control group's dose was equivalent to 40mg of codeine per day. At baseline, the average dose of nonopioid medications for the NMES group was equivalent to 1000mg of acetaminophen (or 2 tablets of Extra Strength Tylenol) per day. The control group's dose was equivalent to 500mg of acetaminophen per day. Table 3 shows the mean change in normalized doses of opioid and nonopioid medications at each follow-up visit relative to baseline. Although subjects given NMES tended to exhibit decreases in pain medication doses relative to baseline, the differences between groups were not significant.

Ten percent of formal outpatient PT and OT data were deemed missing. Table 4 shows the mean cumulative number of hours of formal outpatient OT and PT sessions. The differences between groups were not significant. Logistic regression analyses of BPI 12 with adjustment for these concomitant therapies continued to show significant effect of NMES.

### Safety

A total of 128 electrodes were implanted in 32 subjects given NMES. The implantation procedure was well tolerated in all

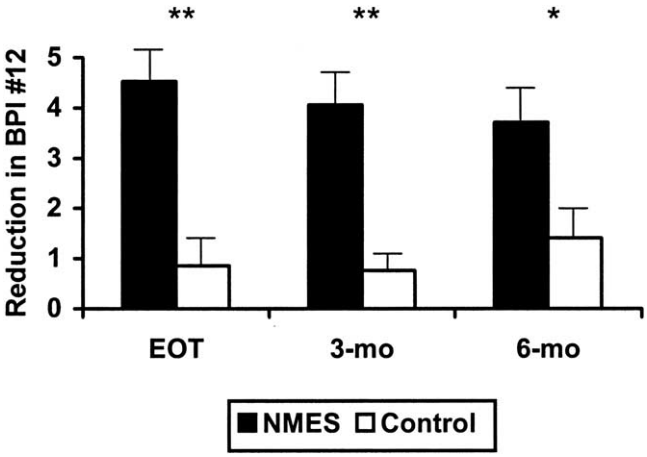


**Fig 2. Mean reduction in primary outcome measure (BPI 12) at end of treatment (EOT) and at 3 and 6 months posttreatment relative to baseline. Bars indicate standard error (SE). *$P$<.01; **$P$<.001.**

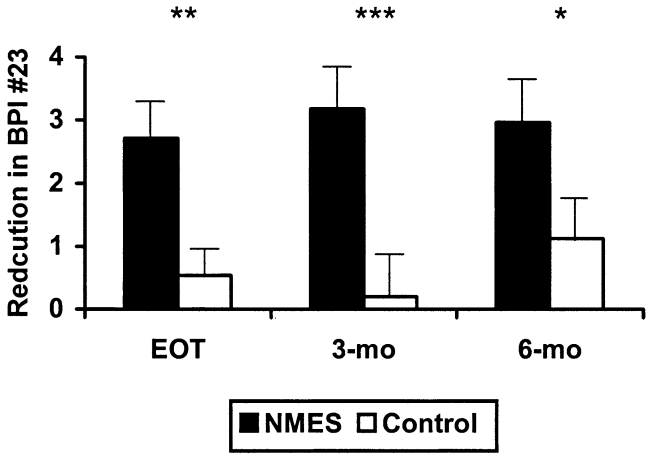


**Fig 3. Mean reduction in pain interference with daily activities (BPI 23) at end of treatment and at 3 and 6 months posttreatment relative to baseline. Bars indicate SE. *$P$<.05; **$P$<.01; ***$P$<.001.**

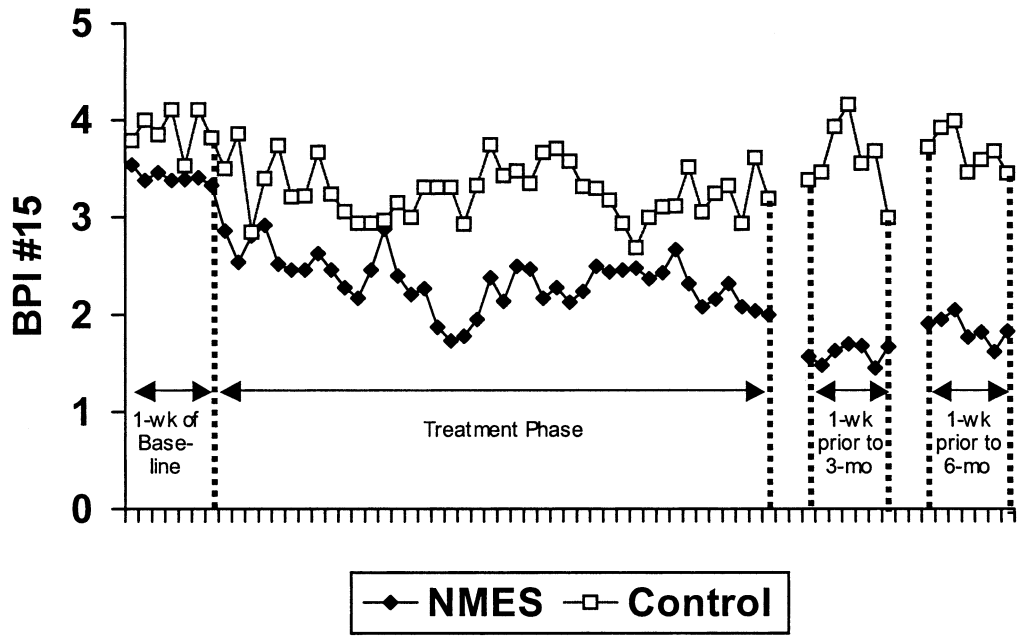


**Fig 4. Mean daily pain scores (BPI 15) after morning ADLs from diaries.**

NMES subjects. During the treatment phase, all electrodes remained intact and free of infection. Granuloma formation, defined as localized tissue inflammation exhibited by redness, swelling, and or pain at the electrode exit site, was noted for 5 (3.9%) electrodes in 2 (6.3%) subjects. All granulomas resolved after electrode removal without additional intervention. The tips of 5 (3.9%) electrodes among 4 (12.5%) subjects broke during removal. Among the 4 subjects with retained electrode fragments, the fragments have remained for an average of 18.8 months (range, 12–26mo) without evidence of granulomas or infections.

## DISCUSSION

Based on 3- and 4-points or more reduction in BPI 12 and no pain criteria, significantly greater proportions of subjects given NMES were successfully treated for shoulder pain compared with controls at all evaluation points. The lack of significance at 6 months using the less stringent 2-point success criterion was likely because of the higher than anticipated spontaneous improvement of control subjects as well as inherent variability in pain over time within individual subjects. Treatment effect was maintained after adjustment for baseline BPI 12 and concomitant pharmacologic and nonpharmacologic therapies. Longitudinal analysis corroborated the results of success criteria-based analyses, with the NMES group exhibiting significant greater improvements in BPI 12 compared with controls. Diary data also corroborated the results of primary analyses.

In contrast to prior studies, our study evaluated clinically relevant poststroke shoulder pain by using BPI 12. In general, prior NMES studies evaluated pain by assessing passive pain-free external rotation ROM or by assessing pain at rest. Unfortunately, pain-free external ROM and pain at rest evaluate very different constructs, which is the likely explanation for the wide range of incidences of hemiplegic shoulder pain reported in the literature.[3] These measures also have uncertain clinical significance.[3] Passive pain-free external ROM tends to overestimate the incidence and severity of pain because the level of pain experienced can increase when a shortened muscle is stretched or if soft tissue is impinged between the humeral head and acromion process on movement. This approach introduces an artificial environment, which may not be relevant to patients' routine daily activity. However, the measurement of pain at rest likely underestimates the severity and incidence of pain because many patients experience pain only when the affected limb is moved, for example, during ADLs or when the limb is in a dependent position during standing or ambulating. In our study, BPI 12 was used to evaluate shoulder pain; it assessed the worst pain during the previous week without specifying the level of activity so that the pain score was most relevant to subjects' actual experience during their routine daily activities.

Although reduction in shoulder pain itself has high clinical significance, additional clinical relevance of intramuscular NMES is reflected by the significant improvement in BPI 23. In addition to assessing general activity and walking ability, BPI 23 assesses vocation, interpersonal relationships, mood, sleep, and enjoyment of life. These latter domains are more typically elements of quality of life (QOL) measures. Thus, data suggest

**Table 3: Changes in Opioid and Nonopioid Analgesic Doses Relative to Baseline**

| | Opioid | | Nonopioid | |
|---|---|---|---|---|
| Evaluation Period | NMES | Control | NMES | Control |
| End of treatment | −.015±.151 | .052±.855 | −.044±.448 | .063±.384 |
| 3 months | −.055±.184 | .108±.929 | −.084±.451 | −.010±.124 |
| 6 months | −.018±.387 | −.058±.935 | .005±.523 | −.027±.125 |

NOTE. Values are normalized doses ± SD. The differences between NMES and control groups were not statistically significant.

**Table 4: Cumulative Hours of OT and PT Sessions During the Entire Study Period**

| | NMES | Control |
|---|---|---|
| OT | 12.7±30.5 | 11.0±30.1 |
| PT | 11.8±29.9 | 5.8±22.6 |

NOTE. Values are mean hours ± SD.

that reduction in poststroke shoulder pain mediated by intramuscular NMES is associated with improvements in QOL. However, because the study did not formally assess QOL by using a valid and reliable stroke-specific measure, these conclusions must be deemed as tentative.

Although improvements in BPI 23 were observed, there were no improvements in upper-limb disability as reflected by the self-care component of the FIM and AMAT. This apparent inconsistency is because of the difference in constructs behind BPI 23 and the disability measures. A blinded assessor administered the FIM and AMAT to determine if an individual was able to perform specific tasks whether or not they experienced pain while performing the tasks. In contrast, BPI 23 is a self-reported measure that assesses whether pain interferes with the performance of specific tasks. If a person experiences pain when performing the tasks, pain is perceived to interfere with the tasks, whether or not the task is accomplished successfully. Thus, the apparent inconsistency is because of the fact that BPI 23 is more similar to a QOL measure than a disability measure.

Data indicate that percutaneous intramuscular NMES as implemented in this study is safe for the treatment of poststroke shoulder pain. The principal safety issue is retained electrode fragments. The distal tips of 5 electrodes (3.9%) fractured during electrode removal. The electrodes are fabricated from surgical grade stainless steel and are biocompatible. However, potential complications associated with retained electrode fragments include migration of the electrode fragment toward the skin, which may require a minor outpatient procedure to remove the fragment, and infection, which may require oral antibiotics. Based on our experience with over 850 percutaneous electrodes implanted in humans in our laboratory since 1978, approximately 1.5% of retained electrode fragments may lead to 1 or both of these complications.[24] Thus, in our present application, the probability of electrode fracture during removal with subsequent development of medical complication is .039×.015 or .0006 per electrode. The 4 subjects with retained electrode fragments were followed up for an average of more than 18 months without complications. In view of the demonstrated benefit on shoulder pain and daily activities, the minimal risk associated with intramuscular NMES, in our opinion, is clinically acceptable.

Although data show that intramuscular NMES is safe and is effective in treating poststroke shoulder pain among those with shoulder subluxation, the mechanism of action remains uncertain. Prior studies[1,25] have suggested a relationship between spasticity and shoulder pain and that NMES reduces spasticity. However, in our study, improvement in spasticity was not observed. Thus, it is unlikely that intramuscular NMES mediates pain reduction via reduction in spasticity. This and other studies with NMES were conducted on the assumption that impaired biomechanics of the glenohumeral joint is an important factor in the pathogenesis of shoulder pain. However, our study was unable to detect any significant effect of intramuscular NMES on shoulder subluxation, pain-free external rotation ROM, or motor impairment. This lack of significance is consistent with a recent meta-analysis[26] that showed that NMES reduces shoulder subluxation among acute stroke survivors but not among chronic stroke survivors. Thus, it is unlikely that intramuscular NMES mediates pain reduction via improvement in glenohumeral biomechanics. However, because the study was not powered for these secondary measures, small but clinically relevant effect of NMES on these measures cannot be ruled out.

An alternative to the biomechanics mechanism is afferent modulation at the level of the spinal cord. Melzack and Wall[27] showed that stimulation of low-threshold myelinated primary afferent fibers decreases the response of dorsal horn neurons to unmyelinated nociceptors. In addition, blockade of conduction in myelinated fibers enhances the response of dorsal horn neurons. Thus, pain can be modulated by the balance of activity between nociceptive and other afferent inputs at the spinal level. This theory has been the prevailing theoretical mechanism of transcutaneous electric nerve stimulation (TENS) and may be responsible for the short-term effect of percutaneous electric nerve stimulation (PENS) in reducing low back pain.[28] However, the clinical efficacy of TENS remains controversial[29] and pain reduction persisting for up to 6 months after completion of treatment as observed in our study is not consistent with TENS or PENS.[28]

Another hypothesis, which may account for the long-term effects seen in this study, is sensory modulation resulting in sustained functional reorganization or neuroplasticity of subcortical and cortical brain structures. There is now growing evidence that chronic pain is associated with changes at the supraspinal level that maintain the pain experience even when the causative factors are no longer active or are less severe.[30] There is also evidence that cortical plasticity related to chronic pain can be modified by behavioral interventions that provide feedback to the brain areas that were altered by somatosensory pain memories.[31] Thus, it is possible that the significantly greater intensity and duration of afferent stimulation from intramuscular NMES, as compared with TENS and PENS, partially reverses or modifies these changes, which then alters the pain experience.

The plausibility of this hypothesis is supported by studies that show that electric stimulation is a powerful modality for providing feedback to the central nervous system, with resultant neuroplastic changes. Episodic electric stimulation of the nucleus basalis, paired with auditory stimulus, results in massive reorganization of the primary auditory cortex.[32] Electric stimulation of a peripheral nerve decreases intracortical inhibition and has been implicated in cortical reorganization.[33] This mechanism may be responsible for the reported improvements in motor function among some stroke survivors treated with electric stimulation.[34,35] The hypothesis that intramuscular NMES mediates reduction in shoulder pain via neuroplastic changes is speculative. However, in view of the sustained nature of pain reduction in our study in the absence of significant improvements in biomechanics or spasticity, and the growing evidence that the mammalian brain has the ability to undergo significant changes in response to manipulation of afferent input, the hypothesis merits further investigation.

A major limitation of this study is the lack of a placebo. A placebo was not incorporated into the study because safety data at the time of study inception were insufficient to ethically justify a minimally invasive sham procedure. However, a recent review[36] indicated that placebo effect in clinical trials may be less significant than previously thought and are not significant when using binary outcomes such as "pain" versus "no pain." In our study, intention-to-treat analysis revealed significantly higher proportion of subjects with "no pain" in the NMES group versus controls at all evaluations. Thus, the

sustained treatment effect based on the binary outcome suggests that if a placebo effect is present, it is likely to be minimal.

A second limitation of the study is the higher dropout rate among control subjects. A critical follow-up period for this clinical trial is 6 months. At this period, 13% of NMES and 24% of control subjects had missing BPI 12 values. However, by using an intention-to-treat approach, 2 of the control subjects' missing data were replaced by data from unplanned visits, which occurred 1 and 2 months, respectively, beyond the scheduled 6 months visit. Because treatment effect generally declines with time, this was believed to be a conservative strategy. This decreased the percentage of missing values at risk for being imputed automatically as "failures" among control subjects to 17%, which is more comparable to the 13% for the treatment group. Our intention-to-treat approach was designed to provide the most accurate imputations for missing data without incurring a bias toward improved outcomes in the NMES group.

A third limitation is the possibility of a difference in arm use during the stimulation and sling use periods for the NMES and control groups, respectively. A difference could have occurred for 2 reasons. First, it is possible that the sling imposed greater constraint on the shoulder, resulting in decreased mobility with development or worsening of adhesive capsulitis and leading to increased shoulder pain. Alternatively, the substantial reduction in shoulder pain mediated by NMES could have allowed subjects to increase the use of their arm. In the former case, decreased arm use in the control group would clearly be a confounding factor. In the latter case, increased arm use in the NMES groups would clearly be a favorable outcome. We elected not to monitor actual arm use because we were unaware of any valid or reliable method for doing so. However, it is also highly unlikely that a difference in arm use occurred for several reasons. First, the cuff-type sling provides minimal, if any, mechanical constraints on the mobility of the shoulder. Unlike traditional slings, the elbow, wrist, and hand are also free from constraints. Second, if substantial reduction in shoulder pain in the NMES group was because of increased arm use relative to controls, then the difference in arm use between groups must have been substantial. If the difference in arm use was substantial, the NMES group should have exhibited improvements in at least some of the secondary measures, especially pain-free external ROM. However, a lack of difference in any of the secondary measures suggests that a difference in arm use did not occur.

A final limitation of the study is the limited generalizability of study results. As with most RCTs, we imposed restrictive inclusion and exclusion criteria to limit the number of confounding variables. Thus, the study results are applicable only to those who are beyond 3 months since their stroke, have moderate to severe shoulder pain, have shoulder subluxation, and are cognitively intact. Of the 562 stroke survivors screened for inclusion, only 28% were eligible for enrollment. Forty-one percent did not have shoulder subluxation, 21% had mild or no pain, and 11% failed the cognitive screen. Even among those who qualified, only 39% gave consent to participate because of concerns for risks associated with an invasive procedure. Consequently, only 11% of all screened stroke survivors enrolled in the clinical trial. The next logical step is to carry out additional trials to expand the clinical indication to shoulder pain without subluxation. Other indications to consider for future trials include prevention and treatment in the acute stroke population.

Although percutaneous intramuscular NMES is a promising new tool in the treatment armamentarium of poststroke shoulder pain, additional studies are needed to determine the mechanism of action, to define optimal prescriptive parameters, and to expand its clinical indications. The determination of natural history and elucidation of pathophysiology are of paramount importance in developing effective prevention and treatment strategies for poststroke shoulder pain. Implementation of percutaneous intramuscular NMES to prevent shoulder dysfunction in a select group of patients at high risk for developing shoulder pain may be an important cost-effective clinical strategy. Further elucidation of NMES effects and mechanisms may lead to development and evaluation of synergistic interventions such as NMES to provide afferent stimulation and modulation of other pathophysiology such as spasticity or inflammation. Daily and total duration of NMES treatment in this study were based on previous studies with surface NMES. However, optimal prescriptive parameters remains to be elucidated in future studies. Though NMES is not new, technologic advances have enhanced the practicality of clinical implementation, opening the door to explore many new preventive and therapeutic applications.

## CONCLUSIONS

This multicenter RCT showed that percutaneously placed intramuscular NMES is safe, and reduces poststroke shoulder pain and the degree to which shoulder pain interferes with daily activities among chronic stroke survivors with shoulder subluxation and pain. The therapeutic effect is maintained for at least 6 months posttreatment. NMES subjects were highly compliant with the treatment program, and subjects and their caretakers managed the system easily without the need for skilled personnel. Additional studies are needed to define optimal prescriptive parameters, elucidate the mechanism of action, and further expand indications.

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**Suppliers**

a. RestoreStIM; NeuroControl Corp, 8333 Rockside Rd, Cleveland, OH 44125.
b. Stata Corp, 4905 Lakeway Dr, College Station, TX 77845.