Authors:

John Chae, MD, ME
David T. Yu, MD
Maria E. Walker, MSE
Andrew Kirsteins, MD
Elie P. Elovic, MD
Steven R. Flanagan, MD
Richard L. Harvey, MD
Richard D. Zorowitz, MD
Frederick S. Frost, MD
Julie H. Grill, MSE
Zi-Ping Fang, PhD

Affiliations:

From the Cleveland Functional Electrical Stimulation Center, Cleveland, Ohio (JC, DTY); the Departments of Physical Medicine and Rehabilitation (JC, DTY) and Biomedical Engineering (JC), Case Western Reserve University, Cleveland, Ohio; Charlotte Institute for Rehabilitation, Charlotte, North Carolina (AK); Kessler Medical Rehabilitation Research and Education Corporation, West Orange, New Jersey (EPE); the Department of Rehabilitation Medicine, Mt. Sinai School of Medicine, New York, New York (SRF); Rehabilitation Institute of Chicago, Chicago, Illinois (RLH); the Department of Rehabilitation Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (RDZ); the Division of Physical Medicine and Rehabilitation, Cleveland Clinic Foundation, Cleveland, Ohio (FSF); and NeuroControl Corporation, Valley View, Ohio (MEW, JHG, ZPF).

Correspondence:

All correspondence and requests for reprints should be addressed to John Chae, MD, ME, Department of Physical Medicine and Rehabilitation, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH 44109.

Disclosures:

Supported, in part, by grants R44HD34996 and K12HD01097 from the National Institute for Child Health and Human Development, grant M01RR0080 from the National Center for Research Resource, and by NeuroControl Corporation, Valley View, Ohio.

Dr. Yu is now affiliated with the Department of Rehabilitation Medicine, University of Washington, Seattle, Washington; Dr. Kirsteins is now affiliated with Moses Cones Health System, Greensboro, North Carolina; Ms. Maria Walker and Ms. Julie H. Grill are now affiliated with New Developments and Innovation in Medical Technology, Cleveland, Ohio.

Presented, in part, at the 65th Annual Assembly of the American Academy of Physical Medicine and Rehabilitation, November 2004, Tuscan, Arizona.

NeuroControl Corporation (NCC), Valley View, Ohio, intends to commercialize the device evaluated in this article. John Chae, MD, ME, and David Yu, MD, are consultants to NCC, which has a financial interest in the contents of this article. Zi-Ping Fang, PhD, is an employee of NCC. Maria Walker, MS, and Julie Grill, MS, were employees of NCC at the time of this clinical trial, but they are no longer affiliated with the company. Zi-Ping Fang, PhD, and Maria Walker, MS, are named on a patent for the device evaluated in this study.

FIM™ is a trademark of the Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Inc.

0894-9115/05/8411-0832/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/01.phm.0000184154.01880.72

RESEARCH ARTICLE

Intramuscular Electrical Stimulation for Hemiplegic Shoulder Pain

A 12-Month Follow-Up of a Multiple-Center, Randomized Clinical Trial

ABSTRACT

Chae J, Yu DT, Walker ME, Kirsteins A, Elovic EP, Flanagan SR, Harvey RL, Zorowitz RD, Frost FS, Grill JH, Fang ZP: Intramuscular electrical stimulation for hemiplegic shoulder pain: A 12-month follow-up of a multiple-center, randomized clinical trial. Am J Phys Med Rehabil 2005;84:832–842.

Objective: Assess the effectiveness of intramuscular electrical stimulation in reducing hemiplegic shoulder pain at 12 mos posttreatment.

Design: A total of 61 chronic stroke survivors with shoulder pain and subluxation participated in this multiple-center, single-blinded, randomized clinical trial. Treatment subjects received intramuscular electrical stimulation to the supraspinatus, posterior deltoid, middle deltoid, and upper trapezius for 6 hrs/day for 6 wks. Control subjects were treated with a cuff-type sling for 6 wks. Brief Pain Inventory question 12, an 11-point numeric rating scale was administered in a blinded manner at baseline, end of treatment, and at 3, 6, and 12 mos posttreatment. Treatment success was defined as a minimum 2-point reduction in Brief Pain Inventory question 12 at all posttreatment assessments. Secondary measures included pain-related quality of life (Brief Pain Inventory question 23), subluxation, motor impairment, range of motion, spasticity, and activity limitation.

Results: The electrical stimulation group exhibited a significantly higher success rate than controls (63% *vs.* 21%, $P = 0.001$). Repeated-measure analysis of variance revealed significant treatment effects on posttreatment Brief Pain Inventory question 12 ($F = 21.2$, $P < 0.001$) and Brief Pain Inventory question 23 ($F = 8.3$, $P < 0.001$). Treatment effects on other secondary measures were not significant.

Conclusions: Intramuscular electrical stimulation reduces hemiplegic shoulder pain, and the effect is maintained for ≥12 mos posttreatment.

Key Words: Stroke, Shoulder Pain, Electrical Stimulation

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

To address the limitations of surface ES systems, 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 and consistent in producing muscle contraction, and is easily managed in the home by the user or caregiver without skilled personnel.[3–6] We confirmed these findings in a multiple-center, randomized clinical trial, which demonstrated significant reduction in shoulder pain to ≥6 mos posttreatment.[7]

All subjects in the multiple-center, randomized clinical trial have now been observed for 12 mos. The objective of this article is to report the sustaining effects of intramuscular ES on hemiplegic shoulder pain at 12 mos. We tested our primary hypothesis that intramuscular ES–mediated reduction in shoulder pain is maintained to ≥12 mos after completion of treatment. We also assessed a series of secondary hypotheses regarding pain-related quality of life, shoulder subluxation, shoulder range of motion, hypertonia, and upper limb motor impairment and activity limitation.

MATERIALS AND METHODS

Subjects

Subjects were recruited from stroke rehabilitation outpatient clinics of seven academic medical centers in the United States. To qualify for study inclusion, subjects had to be >12 wks poststroke (hemorrhagic or nonhemorrhagic) and ≥18 yrs of age. Subjects had to have shoulder pain rated as ≥2 on the 11-point numeric rating scale (NRS) of the Brief Pain Inventory[8] question 12 (BPI 12), have at least one-half fingerbreadth of inferior glenohumeral separation by palpation with the affected limb in a dependent position without manual traction, and possess the cognitive ability to fulfill study requirements (able to recall three objects after 30 mins and use an NRS). Patients were excluded if they had a history of arrhythmia with hemodynamic instability, previous stroke with persistent neurologic deficit, prestroke shoulder pathology, complex regional pain syndrome, any implantable stimulator, or uncontrolled seizures (>1 per month for 1 yr). Subjects were allocated via computer-generated randomization in blocks of four assignments (two treatments and two 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 used in this trial are investigational devices and were evaluated under an Investigational Device Exemption granted by the United States Food and Drug Administration. The electrode, stimulator, and stimulus parameters were previously described.[7] Stimulus intensity (pulse width) was adjusted to provide optimal joint reduction by palpation without discomfort and remained constant during the 6-wk 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 upper trapezius muscles. Compliance was monitored electronically via a built-in data-logging system.

Treatment and Evaluation

Intramuscular electrodes were implanted in ES subjects via a percutaneous approach in the supraspinatus, posterior deltoid, middle deltoid, and upper trapezius muscles using the sterile procedure that was previously described.[7] One week after implantation, ES subjects were prescribed 6-hrs of stimulation per day for 6 wks. All treatment sessions were carried out in subjects' homes. After the 6-wk treatment phase, investigators removed the electrodes by gently pulling on the external portions of the electrodes. ES subjects discontinued stimulation 24 hrs before their end-of-treatment (EOT) assessment 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. Subjects in both groups were allowed to use their hemiparetic arm for activities of daily living during the stimulation and sling-use periods, respectively. Control subjects returned the hemislings after the 6-wk treatment phase. ES subjects were permitted to use a hemisling if prescribed before enrollment, but they were instructed not to use them during ES treatment. Due to ethical considerations, all subjects were allowed to receive concomitant treatments, including pharmacologic (opioid and nonopioid analgesics) and nonpharmacologic (outpatient physical and occupational therapy) interventions as per their primary care physicians.

Blinded evaluations were performed at baseline (within 48 hrs before electrode implantation for the ES group), EOT, and at 3, 6, and 12 mos posttreatment by trained therapists. EOT assessments for ES subjects were performed before removal of electrodes to avoid the confounding effect of any discomfort associated with electrode removal. A bandage was kept over the electrode insertion site for ES subjects and over the comparable site for control subjects to maintain blinding of evaluators.

Outcome Measures

Primary Outcome Measure

The primary outcome measure was the BPI 12. The BPI is a pain questionnaire that assesses both pain intensity (sensory dimension) and the interference (reactive dimension) of pain in daily activities. The BPI has demonstrated both reliability and validity across cultures and languages.[8,9] 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 0–10, in which 0 indicates "no pain" and 10 indicates "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 seven activities on an 11-point NRS, in which 0 indicates "does not interfere" and 10 indicates "completely interferes." The summary score is a composite of scores for seven specific questions that relate to the domains of general activity, mood, walking ability, normal work, interpersonal relationships, sleep, and enjoyment of life. The summary measure is the mean of all seven domains.

Subluxation was assessed radiographically[7] based on modifications of previously described methods.[10,11] Pain-free, passive external rotation range of motion of the glenohumeral joint was measured with a goniometer with the subject in a supine position with the shoulder abducted to 45 degrees while the elbow was held at 90 degrees of flexion with the forearm in a neutral position.[12] Hemiparetic upper limb strength and coordination were assessed with the upper limb component of the Fugl-Meyer motor assessment.[13,14] Resistance to passive elbow extension was assessed with the Ashworth scale.[15] Resistance to shoulder abduction or external rotation were not evaluated due to the potential confounding effect of shoulder pain. Upper limb–related activity limitation was assessed with the self-care (eating, grooming, bathing, upper body dressing, lower body dressing, toileting) portion of the FIM™ instrument[16] and the Arm Motor Ability Test.[17]

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 using standard equivalency tables.[18,19] The protocol initially did not include monitoring of hours of formal outpatient physical and occupational therapies. Therefore, these data were collected retrospectively by reviewing subjects' medical records.

Statistical Analysis

The study was powered based on a superiority test of proportions assuming a one-sided test with alpha of 0.05 and beta of 0.20. A one-sided test was used in view of previous surface ES studies that generally reported positive findings with no evidence of negative effect. The hypothetical "success" proportions at EOT were defined as 70% for the ES group and 40% for the control group for a minimum clinically significant difference between groups of 30%. The power calculation revealed that 33 subjects were required in each group. 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's Exact test and the independent *t* test, respectively.

For those who completed protocol (treatment phase and all follow-up visits), the primary outcome measure (BPI 12) was analyzed using a per-protocol approach. However, because selective drop could bias the study results, BPI 12 data were also analyzed using an intent-to-treat approach.[20] Subjects who violated study protocol but agreed to continue with follow-up maintained their treatment assignments, and available follow-up data were used in the analysis. Missing data were handled in the following manner: If a subject missed a posttreatment visit but came in for an unplanned visit, unplanned visit data were imputed for missing data. If a subject missed a posttreatment visit and did not come in for an unplanned visit but completed diaries, the maximum pain recorded during the 7 days before the scheduled visit was imputed for missing data. For all other missing data, last observations were carried forward.

BPI 12 data were analyzed in three ways. First, local success rates, defined as proportions exhibiting a $\geq$2-point reduction[21] in BPI 12 relative to

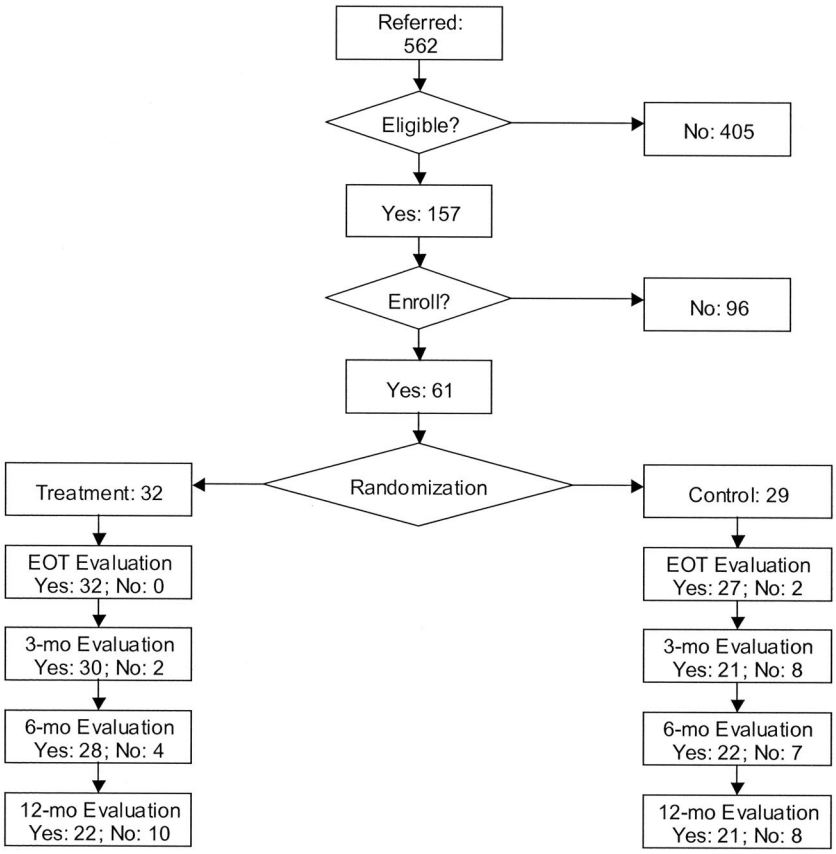

FIGURE 1 *Subject flow diagram.* EOT*, end of treatment.*

baseline at a given posttreatment assessment were compared between groups. Second, overall or global success rates, defined as ≥2-point reduction in BPI 12 relative to baseline at all posttreatment assessments were compared between groups. Success rates between groups were compared with the Fisher's Exact test. Third, longitudinal analyses were carried out using repeated-measure analysis of variance (ANOVA) with posttreatment BPI 12 as the dependent variable, treatment assignment and times of posttreatment assessment (EOT, 3, 6, and 12 mos) as between- and within-subject factors, respectively, and baseline BPI 12 as a covariate. If the global statistic was significant, post hoc comparisons of change in BPI 12 at each posttreatment assessment were carried out with the independent *t* test.

Secondary outcome measures were assessed using a per-protocol approach. Concomitant opioid and nonopioid analgesic therapies and physical and occupational therapies were analyzed using per-protocol and intent-to-treat approaches. Secondary outcome measures and analgesic therapies were analyzed with repeated-measure ANOVA in a manner similar to BPI 12. Cumulative hours of physical and occupational therapies were compared using the independent *t* test.

RESULTS

Subjects and Baseline Characteristics

Figure 1 shows the subject flow diagram. Among the 562 patients screened, 157 (28%) qualified for enrollment. Most common reasons for exclusion were lack of shoulder subluxation (41%), lack of pain (21%), inability to use an NRS (11%), and previous strokes (5.5%). Of those who qualified, 61 (38.8%) 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 ES group and 29 to the control group. All 32 ES subjects completed the treatment protocol. However, ten subjects missed at least one follow-up assessment. Thus, 22 ES subjects (68.8%) completed the study without protocol violations. A total of 27 of 29 control subjects completed the treatment protocol. However, among those who completed the treatment phase, nine subjects missed at least one posttreatment assessment. Thus, 18 control subjects (62%) completed the study without protocol violations. None of the missed visits were due to illnesses, worsening pain, or any issues related to the clinical trial.

Enrollment was terminated before accruing

the target sample of 66 subjects due to lower than expected recruitment rate. In addition, 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 EOT was 53% higher (84.4% *vs.* 31.0%) in the ES group compared with the control group ($P < 0.001$). The target sample size was calculated based on an anticipated 30% difference between groups.

There were no significant differences between groups with respect to baseline characteristics (Table 1). However, the ES group exhibited a trend toward higher BPI 12 score and nonopioid analgesic dose at baseline. ES subjects were 97.2% compliant with their stimulation protocol. ES subjects used the hemisling an average of 1.0 hr/day, whereas control subjects used the hemisling an average of 5.4 hrs/day.

Primary Outcome Measure

Of 305 (61 subjects × 5 data points per subject) possible BPI 12 data points, 40 subjects who completed the protocol contributed 200 data points. These data were used for per-protocol analyses. For intent-to-treat analyses, 64 additional BPI 12 data points were available from subjects who violated protocol but who elected to continue with planned follow-up visits. A total of 41 BPI 12 data points (13.4%) were deemed missing. Three of these data points were imputed by using unplanned visit data and another 3 by diary data. The remaining 35 missing data points were imputed by using the last available data point. Figure 1 shows the timing of missing data with respect to follow-up visits. At 12 mos, of the 61 possible BPI 12 data points, 18 (29.5%) were missing. Two of these were imputed by diary data and 1 by unplanned visit data.

Figure 2 shows the local success rates at each posttreatment assessment. The per-protocol approach exhibited significantly higher success rates for the ES group compared with controls at EOT ($P < 0.001$) but not at 3, 6, and 12 mos. The intent-to-treat approach exhibited significantly higher success rates for the ES group at all posttreatment assessments ($P < 0.001$–0.0029). Figure 3 shows the global success rates. The ES group showed significantly higher success rates relative to controls for both per-protocol ($P = 0.005$) and intent-to-treat approaches ($P = 0.001$). Figure 4 shows the mean BPI 12 scores from baseline to 12 mos posttreatment. The per-protocol repeated-measure ANOVA model yielded significant treatment ($F = 9.2$, $P = 0.004$) and baseline BPI 12 ($F = 4.9$, $P = 0.032$) effects on posttreatment BPI 12. Similarly, the intent-to-treat repeated-measure ANOVA model yielded significant treatment ($F = 21.2$, $P < 0.001$) and baseline BPI 12 ($F = 12.4$, $P = 0.001$) effects on posttreatment BPI 12. Time interaction

TABLE 1 Baseline characteristics

	ES ($n = 32$)	Control ($n = 29$)	P Value
Age, yrs	60 ± 11.4	58 ± 12.9	0.43
Sex, % female	42.4	42.9	1.00
Stroke onset to enrollment, wks	123 ± 157	135 ± 171	0.76
Stroke type, % hemorrhagic	18.2	17.9	1.00
Stroke level, % cortical[a]	55.6	73.9	0.24
Etiology, % embolic, lacunar, thrombotic[a]	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
Opioid analgesic dose	0.13 ± 0.35	0.20 ± 0.65	0.61
Nonopioid analgesic dose	0.25 ± 0.37	0.12 ± 0.23	0.10
BPI question 12 (0–10)	7.59 ± 2.12	6.52 ± 2.29	0.06
BPI question 23 (0–10)	4.73 ± 2.88	3.68 ± 2.52	0.13
Pain-free external rotation ROM, degrees	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 (0–66)	19.06 ± 14.47	18.31 ± 10.34	0.82
Ashworth scale (0–4)	1.88 ± 1.21	1.62 ± 1.12	0.40
FIM™–self-care (0–42)	30.66 ± 7.82	30.10 ± 7.99	0.79
Arm Motor Ability Test–FA (0–5)	1.10 ± 1.19	0.96 ± 0.93	0.51
Arm Motor Ability Test–QOM (0–5)	1.02 ± 1.06	0.89 ± 0.85	0.58

ES, electrical stimulation; BPI, Brief Pain Inventory; ROM, range of motion; FA, functional ability; QOM, quality of movement.

Values are mean ± standard deviation unless stated otherwise.

[a] As a percentage of nonhemorrhagic subjects.

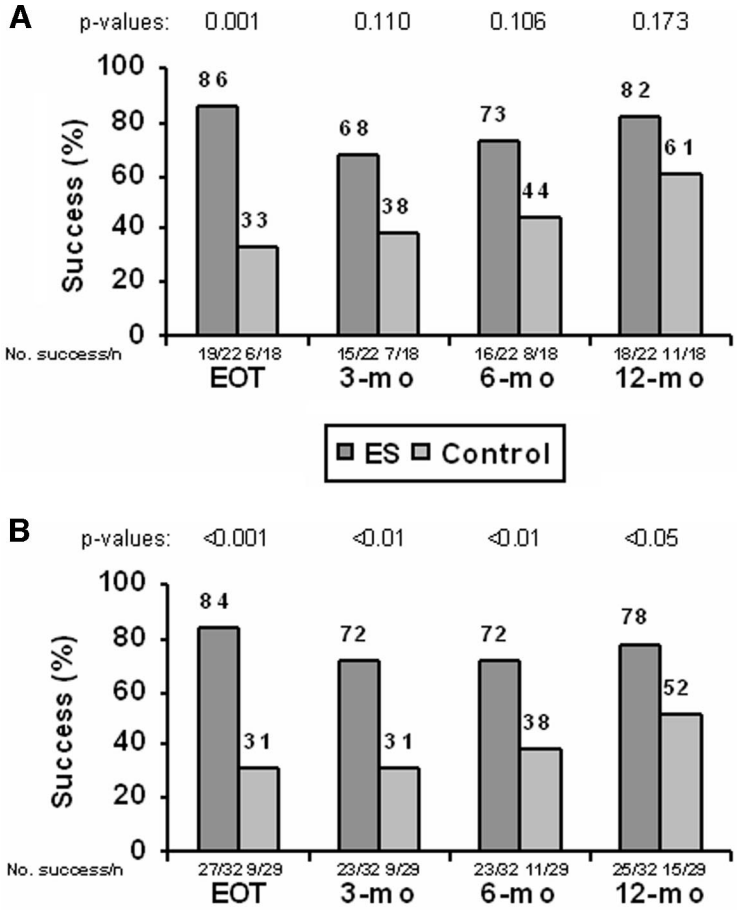

FIGURE 2 *Local success rates for electrical stimulation (*ES*) and control groups based on ≥2-point reduction criterion at each posttreatment assessment using per-protocol (*A*) and intent-to-treat approaches (*B*).* EOT*, end of treatment.*

terms were not significant for either model. Table 2 show the results of the post hoc comparisons of change in BPI 12 at each posttreatment assessment using per-protocol and intent-to-treat approaches. The ES group exhibited significantly greater reduction in BPI 12 at all time points compared with controls for both per-protocol and intent-to-treat approaches.

Secondary Outcome Measures and Concomitant Therapies

The repeated-measure ANOVA model revealed significant treatment ($F = 8.3$, $P < 0.001$) and baseline BPI 23 ($F = 17.9$, $P < 0.001$) effects on posttreatment BPI 23. Table 3 shows the results of the post hoc comparisons of change in BPI 23 at each posttreatment assessment. The ES group exhibited significantly greater reduction in BPI 23 at all time points. Repeated-measure ANOVA failed to demonstrate any significant effect of ES on the remaining secondary measures.

On average, subjects took very low doses of analgesic medications for their shoulder pain. At baseline, the average dose of opioid medications for the ES group was equivalent to 26 mg of codeine per day. The control group's dose was equivalent to 40 mg of codeine per day. At baseline, the average dose of nonopioid medications for the ES group was equivalent to 1000 mg of acetaminophen (or two tablets of Extra Strength Tylenol) per day. The control group's dose was equivalent to 500 mg of acetaminophen per day. The repeated-measure ANOVA showed no significant effect of treatment on posttreatment medication use for both per-protocol and intent-to-treat approaches. Similarly, the differences in the hours of concomitant outpatient physical and occupational therapy sessions were not statistically significant.

Safety

A total of 128 electrodes were implanted in 32 ES subjects. The implantation procedure was well tolerated in all ES subjects. During the treatment phase, all electrodes remained intact and free of infection. Granuloma formation defined as localized tissue inflammation exhibited by redness, swelling, or pain at the electrode exit site was noted for five electrodes (3.9%) in two subjects (6.3%). All granulomas re-

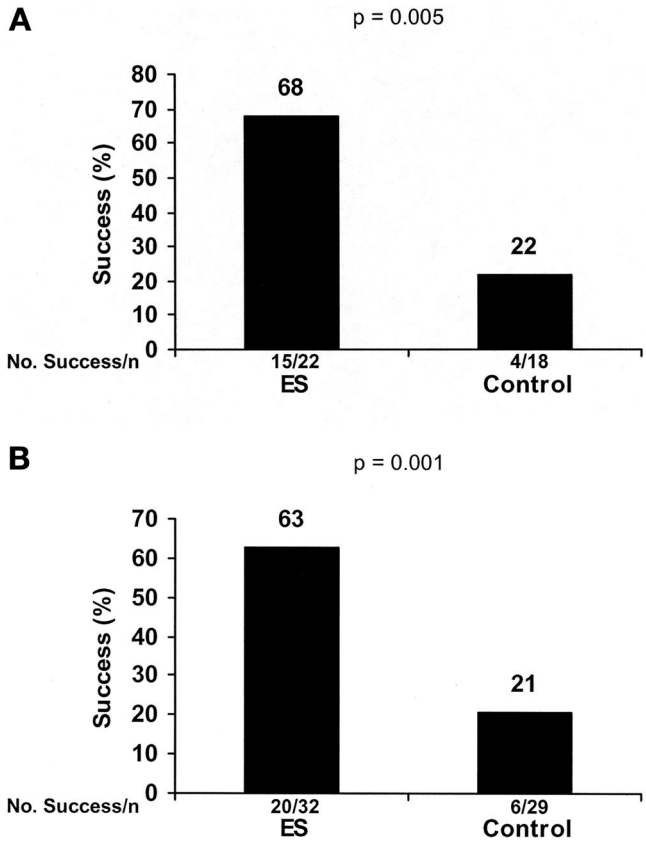

FIGURE 3 *Global success rates for electrical stimulation (*ES*) and control groups based on ≥2-point reduction criterion at all posttreatment assessments using per-protocol (*A*) and intent-to-treat approaches (*B*).*

solved after electrode removal, without additional intervention. The tips of five electrodes (3.9%) among four subjects (12.5%) broke during removal. At 12-mo follow-up, there was no evidence of granuloma formation or infection. The four subjects received an addition physical and radiographic examination an

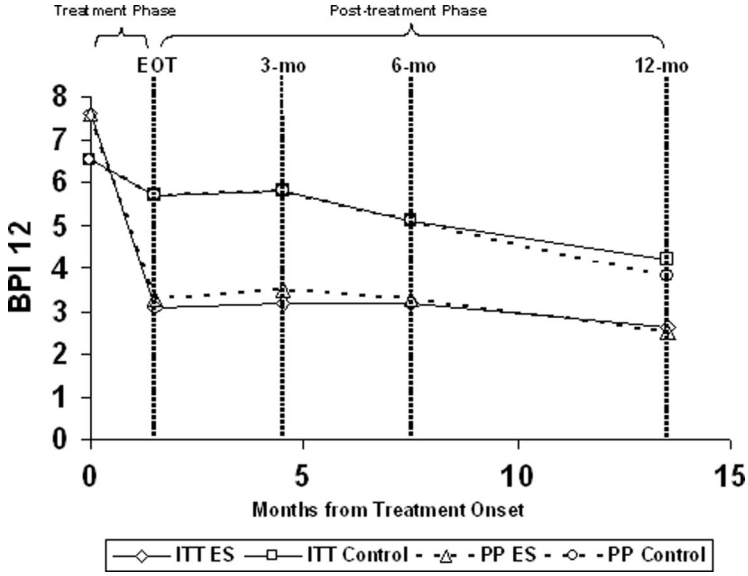

FIGURE 4 *Time course of Brief Pain Inventory (*BPI*) question 12 for electrical stimulation (*ES*) and control subjects using per-protocol (*PP, dashed lines*) and intent-to-treat (*ITT, solid lines*) approaches.* EOT, *end of treatment.*

TABLE 2 Mean change in Brief Pain Inventory question 12 for electrical stimulation (ES) and control groups at end of treatment (EOT) and at 3, 6, and 12 mos posttreatment using per-protocol and intent-to-treat approaches

Time of Assessment	ES (SD)	Control (SD)	Difference	95% Confidence Interval	*P* Value
Per-protocol					
EOT	4.45 (3.36)	1.11 (3.03)	3.34	1.30–5.39	0.002
3 mos	4.31 (3.90)	0.94 (1.80)	3.37	1.47–5.28	0.001
6 mos	4.50 (3.69)	1.67 (3.09)	2.83	0.66–5.00	0.012
12 mos	5.23 (3.22)	2.94 (3.47)	2.28	1.14–4.45	0.040
Intent-to-treat					
EOT	4.53 (3.21)	0.86 (2.51)	3.67	2.20–5.14	<0.001
3 mos	4.44 (3.68)	0.68 (1.85)	3.75	2.27–5.23	<0.001
6 mos	4.44 (3.56)	1.38 (2.81)	3.06	1.42–4.69	<0.001
12 mos	5.00 (3.30)	2.31 (3.21)	2.69	1.02–4.36	<0.001

average of 18.8 mos (range, 12–26 mos) after electrode removal. On examination, there was no evidence of granulomas or infection. Radiographic examination revealed no evidence of electrode fragment migration.

DISCUSSION

The primary finding of this report is that intramuscular ES–mediated pain reduction for the treatment of hemiplegic shoulder pain is maintained to ≥12 mos after completion of treatment. Improvement in pain-related quality of life is also maintained to ≥12 mos after completion of treatment. However, consistent with our 6-mo report, intramuscular ES has no effect on motor impairment, hypertonia, pain-free range of motion, and activity limitation at 12 mos.

Using the 2-point reduction criterion, the per-protocol data yielded a significantly higher success rate for the ES group relative to controls at EOT but not at 3, 6, and 12 mos. The intent-to-treat data yielded significantly higher success rates for the ES group relative to controls at all time points. However, at 12 mos, the difference between groups was smaller (78.1% *vs.* 51.7%) and statistically less significant ($P = 0.036$). These observations are likely due to two factors. First, although the treatment group experienced a dramatic reduction in BPI 12 at EOT, which was maintained at 12 mos, the control group experienced a gradual reduction throughout the entire follow-up phase. By 12 mos, the control group experienced a mean reduction of 2.9 ± 3.5 (SD) and 2.3 ± 3.2 (SD) for per-protocol and intent-to-treat approaches, respectively. Second, the progressive reduction in effect sizes is an artifact of the 2-point reduction criterion. Defining success as a ≥2-point reduction in BPI 12 does not capture the fact that the treatment group experienced a more dramatic reduction in pain than the control group. The mean reduction in BPI 12 at 12 mos for the treatment group was 5.2 ± 3.3 (SD) and 5.0 ± 3.3 (SD) for per-protocol and intent-to-treat approaches, respectively. Accordingly, post hoc analyses of 3-, 6-, and 12-mo per-protocol data using the more stringent 4-point reduction criterion yielded statistically significant differences at all time points (3 mos: 50.0% *vs.* 11.1%, $P = 0.016$; 6 mos: 59.1% *vs.* 22.2%, $P = 0.027$; 12 mos: 72.2% *vs.* 33.3%, $P = 0.024$). Similarly, post hoc analysis of 12-mo intent-to-treat data using the more stringent 4-point reduction criterion yielded a much larger difference between groups (68.8% *vs.* 27.6%) with greater statistical significance ($P = 0.001$).

Although criterion-based analyses at each assessment suggest the benefit of intramuscular ES, the approach has several limitations. First, it is possible that some subjects experience success at EOT, but pain recurs at subsequent assessments. Although the effect is likely to be specific to the intervention, clinical significance is reduced be-

TABLE 3 Mean changes in Brief Pain Inventory question 23 at end of treatment (EOT) and at 3, 6, and 12 mos posttreatment using a per-protocol approach

Time of Assessment	ES (SD)	Control (SD)	Difference	95% Confidence Interval	*P* Value
EOT	−2.71 (3.24)	−0.54 (1.93)	−2.17	−3.54, −0.81	0.002
3 mos	−3.40 (3.18)	−0.20 (2.54)	−3.20	−4.81, 1.58	<0.001
6 mos	−2.93 (2.87)	−1.13 (2.28)	−1.80	−3.26, −0.33	0.017
12 mos	−3.59 (3.03)	−1.37 (2.73)	−2.21	−3.99, −0.44	0.016

cause the effect is not sustained. Second, it is possible that some subjects experience no treatment effect initially but experience reduction in pain in subsequent assessments. If the improvement is >2 points relative to baseline, this subject would be considered a success. However, although the improvement is clearly important to the subject, it would be difficult to justify that the improvement was due to the intervention. Thus, to address these limitations, the 2-point criterion was applied in a global manner such that a subject would be considered a success only if the criterion was satisfied at all assessments. As shown in Figure 3, this approach reduces the overall success rates for both groups. However, the differences between groups were more substantial and the results are more meaningful with respect to specificity of treatment and clinical significance.

The significant reduction in BPI 23 noted at 6 mos was maintained at 12 mos. 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 measures. Thus, data suggest that reduction in poststroke shoulder pain mediated by intramuscular ES is associated with improvements in quality of life, which is maintained to ≥12 mos posttreatment. However, because the study did not formally assess quality of life using a valid and reliable stroke-specific measure, these conclusions must be deemed as tentative.

Data indicate that percutaneous, intramuscular ES 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 five electrodes (3.9%) fractured during electrode removal. Based on our experience with >850 percutaneous electrodes implanted in humans in our laboratory since 1978, approximately 1.5% of retained electrode fragments may lead to migration of electrode fragment toward the skin or infection.[22] Thus, in the present application, the probability of electrode fracture during removal with subsequent development of medical complication is 0.039×0.015 or 0.0006 per electrode. The four subjects with retained electrode fragments have been observed for an average of >18 mos without complications. In view of the demonstrated benefit on shoulder pain and pain-related quality of life, the minimal risk associated with intramuscular ES, in our opinion, is clinically acceptable.

Although data demonstrate that intramuscular ES is safe and effective in treating hemiplegic shoulder pain, the mechanism of action remains uncertain. Previous studies have suggested a relationship between spasticity and shoulder pain and that ES reduces spasticity.[1,23] However, in this study, improvement in spasticity was not observed. Thus, it is unlikely that intramuscular ES mediates pain reduction via reduction in spasticity. This and previous studies with ES were conducted based 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 ES on shoulder subluxation, pain-free external rotation range of motion, or motor impairment. This is consistent with a meta-analysis that demonstrated that ES reduces shoulder subluxation among acute stroke survivors but not among chronic stroke survivors.[24] Thus, it is unlikely that intramuscular ES mediates pain reduction via improvement in glenohumeral biomechanics. However, the study was not powered for these secondary measures. Thus, small but clinically relevant effect of ES on these measures cannot be ruled out. Other possible mechanisms include afferent modulation at the level of spinal cord[25] and sensory modulation resulting in sustained functional reorganization or neuroplasticity of subcortical and cortical brain structures.[26,27] These alternate mechanisms were discussed in greater detail previously.[7]

There are a number of differences in how data were analyzed for the present article compared with our 6-mo report, and this warrants further discussion. First, in addition to being applied locally at each assessment, the 2-point success criterion was applied globally. As noted earlier, this was based on scientific and clinical grounds. Second, for longitudinal analyses, our 6-mo article used the general estimating equation, whereas the present article used repeated-measure ANOVA. We elected the latter because the general estimating equation is more commonly used for binary data.[28] Nevertheless, data were reanalyzed using the general estimating equation, and the results were similar, with treatment effect remaining significant. Third, imputation methods were different. Both the 6-mo article and the present article imputed unplanned visit and diary data first for missing data. However, for the remaining missing data, the 6-mo article imputed baseline values, whereas the present article imputed last available observations. We elected to use the last observation carried forward approach because it is clinically more plausible. It is highly unlikely that subjects who experienced substantial reduction in pain by EOT all reverted back to their high level of baseline pain. This is corroborated by the results of our per-protocol analysis, which showed that ES subjects who did not violate protocol maintained their pain reduction throughout the posttreatment period (Fig. 4). In addition, telephone queries of treatment subjects who

missed visits indicated that missed visits were not due to worsening pain. Nevertheless, the decision to impute last available observation *vs.* baseline value is clearly controversial. Thus, 2-point reduction global criterion–based and longitudinal analyses were repeated using baseline value imputation. As anticipated, the effect sizes are reduced, but both criterion-based (50% success for treatment *vs.* 21% for controls, $P = 0.016$) and longitudinal ($F = 12.4$, $P = 0.001$) analyses continue to show significant differences between groups.

This study has a number of limitations. First, this was not a placebo-controlled trial. Implanted electrodes, even without ES, may provide therapeutic benefit. Implanted electrodes, regardless of ES, may also prompt subjects and caregivers to increase attention to the painful hemiparetic limb. Consequently, subjects may be more careful handling the hemiparetic arm, reducing trauma and thereby reducing pain. 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. This study demonstrates the safety of short-term percutaneous electrodes. Thus, future studies should consider a sham electrode implantation or an active alternative treatment such as surface stimulation.

Second, the ES group had somewhat higher baseline BPI 12 scores compared with controls. It is possible that subjects with higher baseline BPI scores are more likely to show greater improvements (regression to the mean), biasing the study toward the ES group. Indeed, post hoc correlational analysis showed a significant correlation between baseline BPI 12 and reduction in BPI 12 at EOT ($r = 0.402$, $P = 0.023$). However, one can address this problem by converting the absolute change in BPI 12 to percentage change. Accordingly, the correlation between baseline BPI 12 and percentage reduction in BPI 12 at EOT is no longer significant ($r = 0.107$, $P = 0.637$). Data were reanalyzed using a 30% global reduction success criterion. The 30% reduction is roughly equivalent to 2-point reduction on a 0–10 NRS.[21] Per-protocol and intent-to-treat approaches continue to show significant benefit of ES over the control group (per-protocol: 63.6% *vs.* 22.1%, $P = 0.012$; intent-to-treat: 56.3% *vs.* 17.2%, $P = 0.003$).

Third, the rate of protocol violation was high, with a third of all subjects missing at least one posttreatment visit. However, as described above, the selected imputation method is clinically realistic and robust. Post hoc analysis with a more conservative baseline value imputation continued to show significant treatment effect.

Fourth, as with many randomized clinical trials, the restrictive inclusion and exclusion criteria led to a small samples size, which limits the generalizability of study results. The next logical step is to carry out 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.

Fifth, it is not known whether the treatment dose used in this study is optimal. Dose-response trials should be conducted to determine the optimal prescriptive parameters. It is possible that 3 wks of stimulation at 6 hrs/day is just as effective as 6 wks of stimulation. It is also possible that 9 wks of stimulation is significantly more effective. Stimulation intensity and duration are also likely to influence the rate of retained electrode fragments.

Sixth, formal outpatient physical and occupational therapies were not monitored prospectively. Although retrospective review showed no significant differences between groups, potential bias cannot be ruled out. In addition, the timing of therapies with respect to the treatment phase was not available. Thus, it is possible that during the treatment phase, the ES group received more therapies than the control group. Future studies should rigorously monitor such concomitant therapies.

Finally, due to a slower than expected recruitment rate, the sponsor (NeuroControl Corporation), independent of the investigators, elected to terminate the study before accruing the 66 subjects. This is not consistent with accepted standard practice. Interim analyses should be planned and performed by an independent data and safety monitoring board. The decision to stop the study should be based on predetermined stop rules. In general, studies are stopped on safety grounds rather than detection of positive effects.

Although percutaneous intramuscular ES is a promising new tool in the treatment armamentarium of poststroke shoulder pain, additional studies are needed to rule out placebo effect, fully account for concomitant therapies, determine the mechanism of action, define optimal prescriptive parameters, expand clinical indications, and demonstrate long-term effect beyond 1 yr. Though ES is not new, technological advances have enhanced the practicality of clinical implementation, opening the door to explore new preventive and therapeutic applications.

CONCLUSIONS

This multiple-center, randomized clinical trial demonstrates that percutaneously placed intramuscular ES is safe and effective in reducing poststroke shoulder pain and improving pain-related quality of life among chronic stroke survivors with shoulder subluxation and pain. The therapeutic effect is maintained for ≥12 mos posttreatment.

ES 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 rule out a placebo effect, fully account for concomitant therapies, define optimal prescriptive parameters, elucidate mechanisms of action, further expand indications, and demonstrate therapeutic benefit beyond 1 yr.

ACKNOWLEDGMENTS

We thank the clinical coordinators, clinical assessors, and research assistants at each clinical site: Charlotte Institute for Rehabilitation: Mary Andrews, Karyn Grattan, Todd Misura, Rose Harris, and David Levi; MetroHealth Medical Center: Catherine Corrigan, and Theresa Fitzgerald; Kessler Medical Rehabilitation Education and Research Corporation: Stephen Page, Sue Ann Sisto, and Ramon Lansang; Mt. Sinai Medical School: Anousheh Behnegar, Leslie Kane, and Lori McKenna; Rehabilitation Institute of Chicago: Florence Denby, Kari Sheridan, Ela N. Benz, and Michele Zygman; University of Pennsylvania: Lilia Faust, Colleen Gownley, and Tami Berdosh; Cleveland Clinic Foundation: Joe Endredi, Michelle Marcus, and Terry Palmer. We also thank Mindy Liss of Medical Devices Consultants Incorporated, North Attlelboro, MA, for her assistance with data management and statistical analysis.

REFERENCES

1. Van Ouwenaller C, Laplace PM, Chantraine A: Painful shoulder in hemiplegia. *Arch Phys Med Rehabil* 1986;67: 23–6
2. Price CI, Pandyan AD : Electrical stimulation for preventing and treating post-stroke shoulder pain: A systematic Cochrane review. *Clin Rehabil* 2001;15:5–19
3. Chae J, Yu D, Walker M: Percutaneous, intramuscular neuromuscular electrical stimulation for the treatment of shoulder subluxation and pain in chronic hemiplegia: A case report. *Am J Phys Med Rehabil* 2001;80:296–301
4. Yu DT, Chae J, Walker ME, et al: Comparing stimulation-induced pain during percutaneous (intramuscular) and transcutaneous neuromuscular electric stimulation for treating shoulder subluxation in hemiplegia. *Arch Phys Med Rehabil* 2001;82:756–60
5. Renzenbrink GJ, IJzerman MJ: Percutaneous neuromuscular electrical stimulation (P-NMES) for treating shoulder pain in chronic hemiplegia: Effects on shoulder pain and quality of life. *Clin Rehabil* 2004;18:359–65
6. Yu DT, Chae J, Walker ME, et al: Percutaneous intramuscular neuromuscular electric stimulation for the treatment of shoulder subluxation and pain in patients with chronic hemiplegia: A pilot study. *Arch Phys Med Rehabil* 2001;82: 20–5
7. Yu DT, Chae J, Walker ME, et al: Intramuscular neuromuscular electrical stimulation for post-stroke shoulder pain: A multi-center randomized clinical trial. *Arch Phys Med Rehabil* 2004;85:695–704
8. Cleeland CS, Ryan KM: Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23: 129–38
9. Tan G, Jensen MP, Thornby JI, et al: Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain* 2004; 5:133–7
10. Prevost R, Arsenault AB, Dutil E, et al: Shoulder subluxation in hemiplegia: A radiologic correlational study. *Arch Phys Med Rehabil* 1987;68:782–5
11. Boyd EA, Goudreau L, O'Riain MD, et al: A radiological measure of shoulder subluxation in hemiplegia: Its reliability and validity. *Arch Phys Med Rehabil* 1993;74:188–93
12. Andrews AW, Bohannon RW: Decreased shoulder range of motion on paretic side after stroke. *Phys Ther* 1989;69: 768–72
13. Berglund K, Fugl-Meyer AR: Upper extremity function in hemiplegia: A cross-validation study of two assessment methods. *Scand J Rehabil Med* 1986;18:155–7
14. Duncan PW, Propst M, Nelson SG: Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther* 1983;63:1606–10
15. Brashear A, Zafonte R, Corcoran M, et al: Inter- and intrarater reliability of the Ashworth Scale and the Disability Assessment Scale in patients with upper-limb poststroke spasticity. *Arch Phys Med Rehabil* 2002;83:1349–54
16. Hsueh IP, Lin JH, Jeng JS, et al: Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke. *J Neurol Neurosurg Psychiatry* 2002; 73:188–90
17. Kopp B, Kunkel A, Flor H, et al: The Arm Motor Ability Test: Reliability, validity, and sensitivity to change of an instrument for assessing disabilities in activities of daily living. *Arch Phys Med Rehabil* 1997;78:615–20
18. Way WL, Way EL: Opioid analgesics and antagonists. In: Katzung BG, ed. *Basic and Clinical Pharmacology*. Norwalk: Appleton and Lange, 1987:336–349
19. Shearn MA: Nonsteroidal anti-inflammatory agents; nonopiates analgesics; drugs used in gout, in Katzung BG (ed): *Basic and Clinical Pharmacology*. Norwalk, Appleton and Lange, 1987, pp 396–413
20. Lang TA, Secic M: *How To Report Statistics in Medicine: Annotated Guidelines for Authors, Editors and Reviewers. ACP Series: Medical Writing and Communication.* Philadelphia, American College of Physicians, 1997
21. Farrar JT, Young JP, Jr, LaMoreaux L, et al: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58
22. Knutson JS, Naples GG, Peckham PH, et al: Electrode fracture rate and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper-limb functional electrical stimulation application. *J Rehabil Res Dev* 2003;39:671–84
23. Levin M, Hui-Chan W: Relief of hemiparetic spasticity by TENS is associated with improvement in reflex and voluntary motor function. *Electroencephalogr Clin Neurophysiol* 1992;85:131–42
24. Ada L, Foongchomcheay A: Efficacy of electrical stimulation in preventing or reducing subluxation of the shoulder after stroke: A meta-analysis. *Aust J Physiother* 2002;48:257–67
25. Melzak R, Wall PD: Pain mechanisms: A new Theory. *Science* 1965;150:971–9
26. Petersen-Felix S, Curatolo M : Neuroplasticity: An important factor in acute and chronic pain. *Swiss Med Wkly* 2002;132:273–8
27. Flor H: The modification of cortical reorganization and chronic pain by sensory feedback. *Appl Psychophysiol Biofeedback* 2002;27:215–27
28. Kleinbaum D, Klein M: Logistic regression: A self-learning text, in Dietz K, Gail M, Krickeberg K, et al (eds): *Statistics for Biology and Health*. New York, Springer-Verlag, 2002