J Rehabil Med 2012; 44: 125–130

ORIGINAL REPORT

DOSAGE OF NEUROMUSCULAR ELECTRICAL STIMULATION: IS IT A DETERMINANT OF UPPER LIMB FUNCTIONAL IMPROVEMENT IN STROKE PATIENTS?

Shu-Shyuan Hsu, PhD[9], Ming-Hsia Hu, PhD[1,2,3], Jer-Junn Luh, PhD[1,3], Yen-Ho Wang, MD[4,5], Ping-Keung Yip, MD[7,8] and Ching-Lin Hsieh, PhD[4,6]

From the [1]School and Graduate Institute of Physical Therapy, College of Medicine, [2]Graduate Institute of Brain and Mind Sciences, National Taiwan University, [3]Physical Therapy Center, [4]Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, [5]Department of Physical Medicine and Rehabilitation, National Taiwan University College of Medicine, [6]School of Occupational Therapy, College of Medicine, National Taiwan University, Taipei [7]Department of Neurology, Cardinal Tien Hospital, [8] School of Medicine, Fu-Jen Catholic University, New Taipei City and [9]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei, Taiwan

Objective: **To investigate the predictors related to upper extremity functional recovery, with special emphasis on neuromuscular electrical stimulation dose-response in patients after stroke.**

Subjects: **Ninety-five patients with stroke who received a 4-week neuromuscular electrical stimulation intervention.**

Design: **Prospective predictive analysis.**

Methods: **The change score of the Action Research Arm Test (ARAT) was used as the main outcome. Baseline subject characteristics, stroke-related data, and intervention-related data were collected. Multiple linear regression analysis was applied to identify the potential predictors related to main outcome.**

Results: **The regression model revealed that the initial Fugl-Meyer upper limb score was the most important predictor for ARAT change score post-test, followed by time since stroke onset and location of stroke lesion. At 2-month follow-up, the neuromuscular electrical stimulation dosage became a significant determinant in addition to the above predictors.**

Conclusion: **Initial motor severity and lesion location were the main predictors for upper limb functional improvement in stroke patients. Neuromuscular electrical stimulation dosage became a significant determinant for upper limb functional recovery after stroke at 2-month follow-up. More intensive neuromuscular electrical stimulation therapy during early rehabilitation is associated with better upper limb motor function recovery after stroke.**

Key words: neuromuscular electrical stimulation; stimulation dosage; stroke; upper extremity function.

J Rehabil Med 2012; 44: 125–130

Correspondence address: Ming-Hsia Hu, School and Graduate Institute of Physical Therapy, College of Medicine, National Taiwan University, No. 17 XuZhou Road, Taipei, Taiwan ROC, 100. E-mail: mhh@ntu.edu.tw

Submitted November 22, 2010; accepted October 10, 2011

INTRODUCTION

Paresis of the upper extremities is one of major impairments following stroke (1). Impaired upper extremity motor function frequently limits the ability to perform activities of daily living independently (2, 3). More than half of stroke survivors demonstrate moderate to severe arm dysfunction 6 months after stroke and only 5–20% recover fully (3, 4). Previous studies have found that stroke-related factors, such as lesion location (5), shoulder subluxation (6), muscle tone (7), sensory impairment (8), and initial motor severity of affected limbs (9, 10), are related to upper extremity motor functional recovery after stroke. Stroke patients with more severe sensori-motor deficit tend to recover upper limb function more poorly than those with less severe initial deficit (9). To facilitate the early return of voluntary hand and arm movement in stroke patients, early exercise intervention has been advocated (11). However, patients with severe paresis have difficulty participating actively in exercise programmes in the acute flaccid stage. For these patients, neuromuscular electrical stimulation (NMES) is a valuable alternative rehabilitative modality to facilitate motor recovery in the absence of active voluntary upper limb movement for stroke patients in the acute stage.

Evidence has shown that NMES facilitates improvement in sensori-motor recovery (12–14), passive range of motion (15), and arm function (13, 14). NMES also helps to reduce shoulder subluxation (16) and shoulder pain in stroke patients (17). Although NMES has been suggested as an adjunct therapy for post-stroke rehabilitation, the stimulation dosage of NMES varied widely among studies (18). The total hours of stimulation dosage ranges from as little as 6 h over 2 weeks (19) to as much as 220 h over 12 weeks (20). Our previous study found that higher intensity of rehabilitation therapy is associated with better functional outcome for patients with more severe stroke (10). The question remains as to whether higher doses of NMES lead to better arm function recovery than lower doses of NMES. The answer is unclear because of the wide range of stimulation doses of NMES reported (18). More studies are needed to investigate the effect of NMES dosage on upper limb function after stroke.

From the above review, it is apparent that stroke-related characteristics and NMES parameters are important factors related to upper limb function recovery in stroke patients.

The present study is a predictive analysis of potential predictors related to upper limb function recovery, with special emphasis on the effects of dosage of NMES during post-stroke rehabilitation.

METHODS

Subjects

From May 2004 to December 2008, 95 stroke patients were recruited into the current study investigating the effects of NMES on upper limb functional recovery. The inclusion criteria were: (*i*) unilateral stroke and onset within the last 3 months; (*ii*) Brunnstrom stage ≤IV; and (*iii*) able to follow directions to complete major assessment. The study protocol was approved by the ethics committees of the two participating medical centres.

Treatment intervention

All subjects were allocated randomly to groups of varying treatment intensities. There were 4 groups, each of which received 0, 15, 30, or 60 min per session, 5 times per week, of NMES. The NMES was provided to subjects in addition to their regular inpatient rehabilitation during the study period. However, due to occasional absence of subjects (sick-leave, household chores, early discharge from hospital), the actual total stimulation hours per subject varied between 0 to 20 h. The NMES intervention programme was individualized and the content of stimulation varied based on each subject's initial motor severity of the affected upper extremity. The placement of stimulation electrodes was based on the following principles: (*i*) if subjects had shoulder subluxation, one channel was placed over the supraspinatus and the posterior deltoid; (*ii*) if subjects had some visible grasping movement or moderate flexor spasticity (Modified Ashworth Scale >2), electrodes were placed over the extensor digitorum communis and extensor carpi radialis to produce hand opening; (*iii*) if the hand was completely paralysed, electrodes were placed over the extensor digitorum communis, extensor carpi radialis, and flexor digitorum communis to produce alternating hand grasping and opening. The stimulation pulse was a symmetrical biphasic waveform, with a pulse width of 250–400 μs and frequency of 25–50 Hz. The intensity, frequency, and pulse width of the electrical current were adjusted for each subject in order to produce visible limb movements that were as large as possible while the subject remained subjectively comfortable. The duty cycle was adjusted every 2 weeks, with a duty cycle of 10 s on and 10 s off in the first 2 weeks and 10 s on and 5 s off in the second 2 weeks.

Dependent variables

The Action Research Arm Test (ARAT) (21) was selected as the main outcome measure to assess function of the affected upper extremity prospectively following recruitment to this study. The change scores of the ARAT at the end of treatment and at follow-up from initial baseline were used as dependent variables. This test contains 4 subscales: grasp, grip, pinch and gross movement. The test consists of 19 items and the total score ranges from 0 to 57. The ARAT was assessed at baseline, at the end of 4-week treatment, and at 2 months after the completion of the treatment (follow-up).

Independent variables

Potential variables that were entered into the prediction model included demographic, stroke-related, and intervention-related data. The demographic data included age and gender. The intervention-related data included the actual NMES stimulation dosage (total hours). The stimulation dosage was defined as the number of hours of NMES administered to the affected upper limb of the subjects. The stroke-related data comprised: (*i*) type of stroke (infarction or haemorrhage); (*ii*) localization of stroke lesion; lesion sites were divided into several brain areas, namely the cortex, internal capsule and corona radiata, basal ganglia and thalamus, pons and medulla, and large middle cerebral artery (MCA) territory, by neuroimaging report; (*iii*) onset time of stroke, i.e. the number of days from stroke onset to baseline test; (*iv*) side of hemiplegia (right=0, left=1); (*v*) aphasia (no=0, yes=1); (*vi*) cognitive function measured by Mini Mental State Examination (22) (MMSE <24=0, MMSE 24 ≥=1); (*vii*) hemi-neglect (no=0, yes=1); (*viii*) hemi-anopsia (no=0, yes=1); (*ix*) initial sitting balance (the score on sitting balance item of Postural Assessment Scale for Stroke) (23); (*x*) initial sensory impairment in upper extremity (no=0, yes=1); (*xi*) shoulder subluxation (no=0, yes=1); (*xii*) post-stroke shoulder pain (no=0, yes=1); (*xiii*) initial range of motion of upper extremity (no limit=0, limited=1); (*xiv*) muscle tone assessed by modified Ashworth Scale (0–5 points) (24); (*xv*) severity and extent of hemiplegia of affected extremities assessed by the Brunnstrom motor recovery scale (25) and the upper extremity motor section of the Fugl-Meyer Motor Assessment Scale (FMA-UE) (26). A higher Brunnstrom stage or FMA-UE score indicated better upper extremity motor recovery.

Table I. *Subject characteristics (*n = *95)*

Variables	Value
Age, years, mean (SD)	62.6 (12.2)
Males, *n* (%)	61 (64.2)
Time since stroke onset, days, mean (SD)	23.3 (20.3)
Ischaemic stroke, *n* (%)	68 (71.6)
Previous stroke, *n* (%)	14 (14.7)
Paretic side, left, *n* (%)	50 (52.6)
Lesion location, *n* (%)	
Cortex	7 (7.4)
Basal ganglia/thalamus	27 (28.4)
Internal capsule/corona radiata	15 (15.8)
Pons/medulla	15 (15.8)
Large MCA territory	29 (30.5)
Others	2 (2.1)
Aphasia, *n* (%)	27 (28.4)
MMSE ≥24, *n* (%)	49 (51.6)
Hemi-neglect, *n* (%)	11 (11.6)
Hemi-anopsia, *n* (%)	23 (24.2)
Post-stroke shoulder pain, *n* (%)	21 (22.1)
Shoulder subluxation, *n* (%)	42 (44.2)
Limited range of motion of shoulder, *n* (%)	18 (18.9)
Limited range of motion of hand, *n* (%)	6 (6.3)
Sensory impaired, *n* (%)	64 (67.4)
Muscle tone, *n* (%)	
Normal tone	27 (28.4)
Hypertone	14 (14.7)
Hypotone	54 (56.8)
Brunnstrom stage of upper extremity, *n* (%)	
Stage I–II	81 (85.3)
Stage III–IV	14 (14.7)
Brunnstrom stage of lower extremity, *n* (%)	
Stage I–II	37 (38.9)
Stage III–V	58 (61.1)
Baseline FMA-UE score, mean (SD)	
Total score, 0–66	7.8 (6.2)
Shoulder/elbow/forearm, 0–36	7.3 (5.6)
Wrist/hand, 0–30	0.5 (1.4)
Baseline ARAT score, mean (SD)	
Total score, 0–57	0.6 (1.2)
Grasp, 0–18	0
Grip, 0–12	0
Pinch, 0–18	0
Gross movement, 0–9	0.6 (1.2)

MCA: middle cerebral artery; MMSE: Mini-Mental State Examination; FMA-UE: upper extremity motor section of Fugl-Meyer Motor Assessment Scale; ARAT: Action Research Arm Test; SD: standard deviation.

Statistical analysis

SPSS for Windows version 13.0 was used for all statistical analyses. Univariate analysis was applied to identify the potential variable related to main outcomes. All univariate potential factors with a *p*-value < 0.2 were entered into the multivariate linear regression model. Collinearity among potential variables was evaluated. Variables with moderate to high intercorrelations ($r \geq 0.5$ or $r \leq -0.5$) were regarded as collinear, and only one was entered into the regression model. The forward stepwise approach was used. Last-observation-carried-forward was used as an intention-to-treat method for dealing with missing data. The significance level was set at 0.05.

RESULTS

During the study, 95 stroke patients were recruited into the study and completed the baseline assessment. A total of 89 subjects completed the post-treatment assessment (dropout rate 6.3%) and 81 subjects completed the follow-up assessment (dropout rate 14.7%). The characteristics of the stroke patients are shown in Table I. After 4 weeks of intervention, the ARAT scores of all subjects improved by an average of 5.9 points, and this improvement was maintained at follow-up. Seventeen percent of subjects had regained some dexterity in the affected upper extremity (ARAT ≥ 10) after intervention, and 31% had recovered some dexterity at follow-up.

The results of the univariate analysis to identify potential predictors of improvement on ARAT score at the end of intervention and at follow-up are shown in Table II. Table III shows the significant predictors entered into the multiple regression model at the end of the 4-week intervention. In the model, the baseline FMA-UE score, time since stroke onset, and lesion location of stroke were significant predictors of ARAT change score at the end of intervention ($F_{3,89}=29.90$, $p=<0.001$). These 3 predictors accounted for 49% of the total variance. The initial motor severity measured by FMA-UE was the most important predictor, explaining 36% of the ARAT change score ($r=0.61$, $p<0.001$). The other two factors explained 13% of the total variance.

The results of multiple regression model for predicting the improvement in the ARAT score at 2-month follow-up are listed

Table II. *Results of univariate analysis for prediction of the Action Research Arm Test (ARAT) change score at post-test and follow-up*

Variables	Post-test β (95% CI)	At follow-up β (95% CI)
Age	–0.21 (–0.39 to –0.03)**	–0.36 (–0.63 to –0.08)**
Male	–3.23 (–7.93 to 1.47)*	–3.8 (–10.88 to 3.28)
Time since stroke onset	–0.09 (–0.20 to 0.02)*	–0.12(–0.29 to 0.45)*
Left handedness	10.06 (–2.78 to 22.90)*	7.61 (–11.86 to 27.08)
Left hemiplegia	–1.49 (–6.04 to 3.05)	–4.68 (–11.45 to 2.1)*
Previous stroke	–2.34 (–8.74 to 4.06)	–0.26 (–9.9 to 9.37)
Haemorrhagic type	4.35 (–0.62 to 9.31)*	7.35 (–0.07 to 14.77)*
Lesion site, IC/CR/large MCA territory	–7.57 (–11.86 to –3.28)***	–13.29 (–19.57 to –7.01)***
Lesion site, BG/thalamus	2.49 (–2.42 to 7.4)	4.34 (–3.02 to 11.7)
Lesion site, pons/medulla	5.55 (–0.58 to 11.68)*	10.81 (1.71 to 19.91)**
Aphasia	–2.18 (–6.49 to 2.14)	–1.02 (–7.52 to 5.49)
MMSE ≥ 24	4.35 (–0.22 to 8.92)*	5.37 (–1.52 to 12.26)*
Hemi-anopsia	–3.17 (–8.44 to 2.10)	–3.95 (–11.88 to 3.99)
Hemi-neglect	–1.97 (–9.07 to 5.12)	0.59 (–10.08 to 11.27)
Sitting balance	5.36 (0.57 to 10.14)**	7.58 (0.38 to 14.78)**
Shoulder subluxation	–2.34 (–6.94 to 2.17)	–1.89 (–8.76 to 4.97)
Post-stroke shoulder pain	–0.86 (–6.43 to 4.72)	–2.84 (–11.2 to 5.51)
Limited shoulder ROM	–4.91 (–10.5 to 0.69)*	–8.59 (–16.96 to –0.24)**
Limited hand ROM	–6.15 (–15.41 to 3.12)*	–10.46 (–24.33 to 3.42)*
Sensory impaired	–1.58 (–3.6 to 0.45)*	–1.82 (–5.44 to 1.79)
MAS score	–6.53 (–12.1 to –0. 96)**	–9.62 (–17.99 to –1.25)**
Shoulder MAS score	–4.33 (–8.6 to 0.06)*	–7.17 (–13.55 to –0.79)**
Elbow/forearm MAS score	–5.35 (–9.55 to –1.15)**	–7.79 (–14.11 to –1.47)**
Wrist MAS score	–3.84 (–10.51 to 2.83)	–2.61 (–12.68 to 7.47)
Hand MAS score	–2.4 (–9.44 to 4.64)	–0.37 (–10.24 to 10.97)
Hypotone	–6.45 (–12.73 to –0.17)**	–8.64 (–18.11 to 0.83)*
Brunnstrom stage-uep ≥ III	10.54 (6.38 to 14.7)***	12.41 (5.85 to 18.97)***
Brunnstrom stage-ued ≥ III	11.82 (5.88 to 17.75)***	13.98 (4.78 to 23.18)***
Brunnstrom stage-le ≥ III	7.32 (2.3 to 11.73)***	11.68 (5.11 to 18.26)***
Baseline FMA-UE score	1.08 (0.79 to 1.37)***	1.19 (0.69 to 1.68)***
Baseline ARAT score	4.01 (2.35 to 5.67)***	4.42 (1.8 to 7.05)***
NMES dosage	0.18 (–0.13 to 0.49)	0.43 (–0.03 to 0.89)*

*$p<0.2$; **$p<0.05$; ***$p<0.001$.

β: regression coefficient; CI: confidence interval; IC: internal capsule; MCA: middle cerebral artery; MMSE: Mini-Mental State Examination; FMA-UE: upper extremity motor section of Fugl-Meyer Motor Assessment Scale; CR: corona radiata; BG: basal ganglia; ROM: range of motion; MAS: modified Ashworth Scale; Brunnstrom stage-uep: Brunnstrom stage of upper extremity proximal part; Brunnstrom stage-ued: Brunnstrom stage of upper extremity distal part; Brunnstrom stage-le: Brunnstrom stage of lower extremity; NMES: neuromuscular electrical stimulation.

Table III. *Multiple regression model for the prediction of Action Research Arm Test improvement at the end of intervention (*n = *89)*[a]

Variables	β value (β error)	Standardized β value	95% CI for β	Accumulated model adjusted R^2	*p*-value
Intercept	3.67 (1.82)		0.05 to 7.29		0.047
Baseline FMA-UE	1.06 (0.14)	0.60	0.80 to 1.33	0.36	<0.001
Lesion site, IC/CR/large MCA territory	–6.56 (1.68)	–0.29	–9.90 to (–3.23)	0.44	<0.001
Time since stroke onset	–0.12 (0.04)	–0.22	–0.20 to (–0.04)	0.49	0.004

[a]Intention-to-treat analysis.
β: regression coefficient; FMA-UE: upper extremity motor section of Fugl-Meyer Motor Assessment Scale; MCA: middle cerebral artery; IC/CR: internal capsule/corona radiata; CI: confidence interval.

in Table IV. The change in the ARAT at follow-up was significantly predicted by baseline FMA-UE score, lesion location, NMES dosage, time since stroke onset, motor stage of affected lower extremity, and side of hemiplegia. The whole model explained 45.3% of the total variance ($F_{6,86} = 13.68$, $p = < 0.001$). Initial motor impairment of paretic extremity accounted for 22% of the variance (FMA-UE: $r = 0.45$, $p < 0.001$; Brunnstrom stage of lower extremity: $r = 0.33$, $p = 0.001$), followed by lesion sites involving internal capsule, corona radiata, and large MCA territory ($r = –0.42$, $p < 0.001$), NMES dosage ($r = 0.18$, $p = 0.04$), time since stroke onset ($r = –0.14$, $p = 0.08$), and side of hemiplegia ($r = –0.14$, $p = 0.08$).

DISCUSSION

The present study showed that the functional improvement of the affected upper limb measured by the ARAT at the end of the 4-week NMES intervention was significantly predicted by the initial motor severity of the affected upper limb, lesion location, and time since stroke onset. At 2-month follow-up, the regression model showed that the initial motor severity of affected limbs, lesion location, NMES dosage, time since stroke onset, and side of hemiplegia were significant predictors of improvement on the ARAT scores. In summary, 4 stroke-related factors (initial motor severity, lesion location, time since stroke onset, and hemiplegic side), and 1 intervention-related factor (NMES dosage) predict the functional recovery of the affected upper extremity up to 2 months after stroke rehabilitation.

The initial motor severity, as indicated by the FMA-UE scores, was the most important predictor of upper extremity function in our stroke population at post-test and follow-up. Patients with high baseline FMA-UE scores showed good upper limb function recovery. Patients who presented with some basic voluntary synergy movement (FMA-UE ≥ 10) initially had an 81% probability of regaining some upper extremity function after intervention. This result is in agreement with the findings from previous studies (4, 27), which show that stroke patients with initial voluntary shoulder or hand grasping movement had a good prognosis of recovery of arm function. In addition to initial upper limb severity, the degree of lower limb paresis was a significant predictor of upper extremity function at follow-up. Stroke patients with a higher motor stage of the affected lower extremity (Brunnstrom stage ≥ III) demonstrated better recovery of upper limb function than those subjects with more severe lower extremity impairment. This finding is in agreement with a previous study reporting that stroke patients with lower limb paralysis tend to have poor recovery in the upper limb compared with those subjects with some synergy movement in the lower limb (5).

Lesion location of stroke has been shown to be another factor for upper limb function after stroke (5). Our results are in agreement with previous findings, in that they show that patients with lesions in the corona radiata, internal capsule, or large MCA territory have poorer upper limb motor function recovery. The cortico-spinal tract from the motor cortex passes through the corona radiata and internal capsule to the lower motor neuron. If the lesion involves these brain areas, the cortico-spinal tract is probably interrupted. Furthermore, the MCA supplies most brain areas that control upper limb motor function. Stroke involvement in the large MCA territory suggests severe and extensive damage of these motor areas.

Table IV. *Multiple regression model for the prediction of Action Research Arm Test improvement at 2-month follow-up (*n = *81)*[a]

Variables	β value (β error)	Standardized β value	95% CI for β	Accumulated model adjusted R^2	*p*-value
Intercept	8.21 (3.81)		0.62 to 15.80		0.034
Baseline FMA-UE	1.00 (0.23)	0.37	0.54 to 1.46	0.19	<0.001
Lesion site, IC/CR/large MCA territory	–11.31 (2.61)	–0.34	–16.50 to (–6.13)	0.32	<0.001
NMES dosage	0.57 (0.19)	0.24	0.20 to 0.93	0.36	0.003
Time since stroke onset	–0.21 (0.07)	–0.25	–0.33 to (–0.08)	0.39	0.002
Left hemiplegia	–7.11 (2.63)	–0.21	–12.34 to (–1.88)	0.42	0.008
Brunnstrom stage-le	7.20 (3.02)	0.21	1.19 to 13.20	0.45	0.019

[a] Intention-to-treat analysis.
β: regression coefficient; CI: confidence interval; FMA-UE: upper extremity motor section of the Fugl-Meyer Motor Assessment Scale; IC/CR: internal capsule/ corona radiata; MCA: middle cerebral artery; NMES: neuromuscular electrical stimulation; Brunnstrom stage-le : Brunnstrom stage of lower extremity.

Stroke onset time and side of hemiplegia were significant predictors at follow-up. Our results showed that patients with shorter duration since the onset of stroke (within 1 month) had better recovery compared with those subjects with longer onset duration. Previous studies have reported that stroke patients achieve most recovery in the upper limb function within 3 months post-stroke and that recovery occurs fastest in the first month (3, 4). Subjects with left hemiplegia in our study tended to have less recovery in the upper limb function than subjects with right hemiplegia. This result is in agreement with a previous study showing that patients with right hemisphere stroke had poor functional outcome (28). However, the issue regarding the influence of the side of cerebral lesion remains inconclusive (28, 29). In brief, our study found that stroke patients with severe motor impairment, stroke sites in the motor-related regions, with left hemiplegia, and with longer duration since stroke onset at baseline could be predicted to have poorer motor recovery of the affected upper extremity.

In addition to the above stroke-related predictors, the effect of rehabilitation intensity is an important focus of current research in the field of stroke rehabilitation (30). Our study found that the dosage of NMES was a significant determinant of the upper limb functional improvement at 2-month follow-up. Increasing the stimulation dose of NMES led to greater improvement in the ARAT score. Similarly, more intensive arm exercise leads to better enhancement of upper limb dexterity during stroke rehabilitation (31). Hence, both NMES dose and exercise intensity during stroke rehabilitation seemed to follow the law of effect, i.e. a positive relationship between number of practice trials, or the stimulation dosage, and motor performance improvement.

In addition, we also note that the dosage of NMES was entered into the regression model only for predicting ARAT improvement at 2-month follow-up, but not immediately at the end of intervention. This suggests that there may be some latent effect of NMES on upper limb function. We found that the dosage of NMES was significantly associated with motor recovery measured by FMA-UE score ($\beta = 0.4$, $p = 0.05$) at the end of 4 weeks of NMES intervention. These results show that the NMES-induced motor improvement (FMA-UE score at post-test) precedes functional improvement (ARAT change score at follow-up) in stroke patients.

Was the dose effect revealed in our study influenced by the initial severity of our participants? Past studies have shown that neurological severity may influence the treatment intensity that patients receive. More severely affected patients tend to receive lower intensity of rehabilitation than less severely affected patients (32, 33). In our study, subjects were allocated randomly to 4 groups of varying treatment intensities, and the baseline motor severity was equivalent among groups ($F3,91 = 0.99$, $p = 0.4$). Since some subjects received doses that were lower than assigned due to sick leave or early discharge, the actual stimulation doses for each subject may vary. Hence, for the current regression analysis, the NMES dosage was coded using the actual treatment hours received for each subject instead of the assigned dosage of the group. No significant relationship was found between the NMES dose and initial motor severity ($r = –0.09$, $p = 0.41$). In conclusion, our study did not reveal a relationship between initial motor severity and NMES dosage. The NMES dosage and the initial motor severity were both significant predictors for recovery of arm function after stroke.

An interesting implication for clinical practice of NMES, i.e. the electrode placement, was noted during experiment. In our study, the placement of electrodes was based on the individual's ability to flex the hand at baseline. Due to high correlation between the ability to flex the hand and baseline FMA-UE score ($r = 0.62$, $p < 0.001$), the FMA-UE score, and not the electrode placement factor, was included in the regression analysis to avoid a problem with multicollinearity. Thus, the effect of electrode placement was not analysed statistically. The electrode placement indicated the stimulation strategy selected. Two stimulation strategies are commonly used for upper limb NMES therapy, alternating stimulation of the hand extensor and flexor muscles or stimulation of hand extensors only (34). We observed that stroke patients who received stimulation on both flexor and extensor muscles showed significantly better improvement than those who received stimulation on extensor muscles only. This finding was inconsistent with a previous study suggesting that the two stimulation strategies were similarly effective (34). It is noted that most (85%) of our subjects were totally paralysed in the upper limb at baseline assessment, whereas all subjects in the previous study preserved some hand opening and grasping movement. Hence, it seems that patients with some preservation of upper limb motor function may benefit from either type of stimulation strategy, whereas those with no initial function might benefit more from alternating flexor and extensor stimulation. We must remember that the electrode placement was significantly correlated with initial motor severity; therefore, it is possible that the differential electrode placement effect observed was influenced by the initial severity of the subjects. We considered an individualized NMES program based on each subject's severity to be a better treatment method to enhance recovery. Thus, further research is needed to investigate the effects of varying stimulation strategies on stroke patients at different recovery stages.

There were some limitations in the present study. Our study attempted to investigate the factors related to improvement of function in the affected upper limb. Many conceivable predictors, such as demographic, stroke-related, and intervention-related data, were included in the prediction model. However, our predictive models reached only moderate strength of fitting, and some variance was not explained. Thus, there remain some important predictors of upper limb recovery that need to be investigated in future studies. Secondly, we found that the dosage of NMES was significantly associated with arm function. However, the NMES dosage in our study was limited to 0–20 h. This range is narrower than those used in most studies on the treatment effect of NMES, from 6 hs to more than 200 h. We thought that our range was more practical for clinical application. However, our results cannot be generalized to clinical practice where the total treatment time exceeds 20 h nor can our results be applied to treatment programmes exceeding 1 h/session. More

studies are needed to develop the dose-response curve and to find the optimal NMES dosage or minimal effective dosage in improving upper limb function.

In conclusion, the present study found that more intensive NMES dosage was positively associated with better upper limb function, independent of initial motor severity, side of hemiplegia, lesion location, and the time since stroke onset. Patients who initially preserve some voluntary movement of the affected limbs may benefit more from intervention of 4-week NMES combined with regular rehabilitation. Furthermore, stroke patients with shorter duration since the onset of stroke benefited more from higher dosage NMES.

ACKNOWLEDGEMENTS

This study was supported partially by the Bureau of Health Promotion, Department of Health, ROC (DOH93-HP-1114–DOH94-HP-1114) and Taipei Veterans General Hospital (V95-A-108).

REFERENCES

1. Lai SM, Studenski S, Duncan PW, Perera S. Persisting consequences of stroke measured by the Stroke Impact Scale. Stroke 2002; 33: 1840–1844.
2. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke 2001; 32: 1279–1284.
3. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil 1994; 75: 394–398.
4. Sunderland A. Arm function after stroke: an evaluation of grip strength as a measurement of recovery and prognostic indicator. J Neurol Neurosur Psychiatry 1989; 52: 1267–1272.
5. Shelton FN, Reding MJ. Effect of lesion location on upper limb motor recovery after stroke. Stroke 2001; 32: 107–112.
6. Paci M, Nannetti L, Taiti P, Baccini M, Rinaldi L. Shoulder subluxation after stroke: relationships with pain and motor recovery. Physiother Res Int 2007; 12: 95–104.
7. Feys H, De Weerdt W, Nuyens G, van de Winckel A, Selz B, Kiekens C. Predicting motor recovery of the upper limb after stroke rehabilitation: value of a clinical examination. Physiother Res Int 2000; 5: 1–18.
8. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. Disabil Rehabil 1999; 21: 357–364.
9. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke 2003; 34: 2181–2186.
10. Hu MH, Hsu SS, Yip PK, Jeng JS, Wang YH. Early and intensive rehabilitation predicts good functional outcomes in patients admitted to the stroke intensive care unit. Disabil Rehabil 2010; 32: 1251–1259.
11. Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? Stroke 2000; 31: 2984–2988.
12. Chae J, Bethoux F, Bohine T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. Stroke 1998; 29: 975–979.
13. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke 1999; 30: 1384–1389.
14. Hsu SS, Hu MH, Wang YH, Yip PK, Chiu JW, Hsieh CL. Dose-response relation between neuromuscular electrical stimulation and upper-extremity function in patients with stroke. Stroke 2010; 41: 821–824.
15. Pandyan AD, Granat MH, Stott DJ. Effects of electrical stimulation on flexion contractures in the hemiplegic wrist. Clin Rehabil 1997; 11: 123–130.
16. Wang RY, Yang YR, Tsai MW, Wang WT, Chan RC. Effects of functional electric stimulation on upper limb motor function and shoulder range of motion in hemiplegic patients. Am J Phys Med Rehabil 2002; 81: 283–290.
17. Chantraine A, Baribeault A, Uebelhart D, Gremion G. Shoulder pain and dysfunction in hemiplegia: effects of functional electrical stimulation. Arch Phys Med Rehabil 1999; 80: 328–331.
18. de Kroon JR, Ijzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med 2005; 37: 65–74.
19. Cauraugh J, Light K, Kim S, Thigpen M, Behrman A. Chronic motor dysfunction after stroke: recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. Stroke 2000; 31: 1360–1364.
20. Alon G, Levitt AF, McCarthy PA. Functional electrical stimulation enhancement of upper extremity functional recovery during stroke rehabilitation: a pilot study. Neurorehabil Neural Repair 2007; 21: 207–215.
21. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res 1981; 4: 483–492.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–198.
23. Benaim C, Perennou DA, Villy J, Rousseaux M, Pelissier JY. Validation of a standardized assessment of postural control in stroke patients: the Postural Assessment Scale for Stroke Patients (PASS). Stroke 1999; 30: 1862–1868.
24. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67: 206–207.
25. Sawner KA, Lavigne JM. Recovery stages and evaluation procedures. 2nd ed. New York: JB Lippincott Press; 1992.
26. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 1975; 7: 13–31.
27. Katrak P, Bowring G, Conroy P, Chilvers M, Poulos R, McNeil D. Predicting upper limb recovery after stroke: the place of early shoulder and hand movement. Arch Phys Med Rehabil 1998; 79: 758–761.
28. Macciocchi SN, Diamond PT, Alves WM, Mertz T. Ischemic stroke: relation of age, lesion location, and initial neurologic deficit to functional outcome. Arch Phys Med Rehabil 1998; 79: 1255–1257.
29. Yavuzer G, Kucukdeveci A, Arasil T, Elhan A. Rehabilitation of stroke patients: clinical profile and functional outcome. Am J Phys Med Rehabil 2001; 80: 250–255.
30. Whitall J. Stroke rehabilitation research: time to answer more specific questions? Neurorehabil Neural Repair 2004; 18: 3–8.
31. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet 1999; 354: 191–196.
32. Bode RK, Heinemann AW, Semik P, Mallinson T. Relative importance of rehabilitation therapy characteristics on functional outcomes for persons with stroke. Stroke 2004; 35: 2537–2542.
33. Chen CC, Heinemann AW, Granger CV, Linn RT. Functional gains and therapy intensity during subacute rehabilitation: a study of 20 facilities. Arch Phys Med Rehabil 2002; 83: 1514–1523.
34. de Kroon JR, MJ IJ, Lankhorst GJ, Zilvold G. Electrical stimulation of the upper limb in stroke: stimulation of the extensors of the hand vs. alternate stimulation of flexors and extensors. Am J Phys Med Rehabil 2004; 83: 592–600.