Motor evoked potentials: prognostic value in motor recovery after stroke

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Summary

Accurate motor and functional prognosis after stroke is important for the optimal planning of a personalised rehabilitation programme, and clinical, demographic and radiological data are commonly employed for this purpose. It is becoming increasingly apparent that motor evoked potentials (MEPs), obtained through transcranial magnetic stimulation, can furnish complementary prognostic information on motor outcome after stroke, particularly when initial hand palsy is present.

To evaluate the prognostic value of early MEPs together with other clinical variables, 19 subjects with first-ever stroke in the middle cerebral artery territory and hand palsy at onset, were evaluated in the acute phase. These cases were retrospectively selected out of a sample of 33 subjects.

Multivariate analysis was carried out using amplitude of MEPs, National Institutes of Health Stroke Scale score (NIH) and Motricity Index as independent variables, and Medical Research Council scale score (MRC) as the dependent outcome variable at 4 months after stroke.

The best model, which combined NIH and MEP data, accounted for 75.44% of the variability of the MRC. Our results suggest that the NIH and MEPs may yield information useful for predicting hand motor outcome after stroke in the presence of initial hand palsy, a condition in which a prognosis made on the basis solely of clinical data is deemed more difficult.

KEY WORDS: MEP, motor recovery, prognosis, stroke, upper extremity.

Introduction

The accurate prediction of functional and motor outcome after stroke is crucial to the planning of an optimal rehabilitation programme, especially in the most severely impaired subjects.

An accurate prognosis can allow a more carefully tailored and personalised selection of rehabilitation techniques from among the various neurofacilitatory and compensatory methods available, and also of the most appropriate rehabilitation setting after discharge. Many prognostic factors have been proposed, including age, history of stroke, radiological parameters, and somatosensory evoked potentials (SSEPs); among the early clinical prognostic factors, urinary incontinence, altered consciousness, disorientation in time and space, severity of motor impairment and impaired balance have been advocated as useful. A patient’s activities of daily living score on admission and level of social support are also considered to be of prognostic value.

Following the early work on transcranial magnetic stimulation (TMS) (3), many studies have employed this safe and non-invasive technique to assess the residual integrity of motor corticospinal pathways after stroke, recording motor evoked potentials (MEPs), especially from intrinsic hand muscles, in order to provide an early prognosis of motor outcome (5-9). The prognostic value of MEPs has already been shown to be an important factor in the planning of post-stroke rehabilitation (10): MEPs allow more personalised selection of techniques, avoidance of learned non use, and the identification of realistic functional goals.

Most TMS studies exploring this question have recorded MEPs from intrinsic hand muscles, which are more directly under the control of the corticospinal system (11), with some authors investigating groups of patients homogeneous for initial hand palsy, a condition in which a prognosis made on the basis solely of clinical data is deemed more difficult (11-14). In spite of the fact that most authors agree about the prognostic value of MEPs after stroke, few have examined the relationship between acute-stage clinical, demographic and neurophysiological prognostic data and motor or functional outcome at follow up using a multivariate approach (15-18); moreover, only one study (19) used multivariate analysis to consider samples homogeneous for early motor impairment.

The aim of the present study was to assess the predictive value of the National Institutes of Health Stroke Scale score (NIH) and Motricity Index (upper limb subscale score) (MI), together with acute-phase MEPs, in relation to hand motor recovery at 4 months in a sample of patients with initial hand palsy. A retrospective study of a sample of patients with first-ever ischaemic stroke in the middle cerebral artery territory evaluated by TMS was carried out; only subjects with hand palsy at onset were considered and multiple regression analysis was employed on the data set.

Materials and methods

A sample of 33 subjects with first-ever ischaemic stroke in the middle cerebral artery territory, confirmed by MR or CT
imaging, were examined. The observations were collected over a period of three years and clinical and instrumental data were recorded in a database at our centre. All the patients underwent a rehabilitation programme based on the Bobath approach, which emphasises control of muscle tone and facilitation of recruitment in functional conditions. When needed, the patients also received speech and cognitive therapy. The rehabilitation programme was continued at least until the follow up at 4 months after stroke. All the subjects underwent TMS to establish their motor prognosis during the first week of the acute phase. All the neuropsychological tests were performed by the same physician. Subjects with severe clinical conditions or presenting technical contraindications to TMS (20) were excluded; another exclusion criterion was the presence of minor or fast recovering motor upper limb impairment. Previous nerve conduction velocity tests ruled out peripheral neuropathies. Motor evoked potentials were performed using a Magstim 200 stimulator (Magstim Ltd, UK) with a 12-cm diameter circular coil above the vertex and recording with surface electrodes from first dorsal interosseous (FDI) of both upper limbs. A Viking Quest electromyograph (Nicolet Viasys, USA) was employed. Clockwise stimulation was used for the right hemisphere and anticlockwise stimulation for the left hemisphere. Threshold was established if five MEPs of at least 50 µV were recorded in a series of 10 stimulations at rest, or with facilitation techniques if no potentials were recorded in the rest condition. Motor evoked potentials were recorded at rest and with slight FDI isometric recruitment with stimulation output 20% above the threshold; if hand palsy was present, facilitated MEPs were recorded with contralateral contraction. The amplitude of the facilitated MEPs was calculated as the maximal peak-to-peak value out of a series of five MEPs and expressed as a percentage of compound motor action potential amplitude (MEP%M) after supramaximal stimulation of the ulnar nerve at the wrist. Motor evoked potentials were judged absent if not recorded with 100% output intensity. In three stimulations in the facilitated condition. Facilitated latency was recorded and central conduction time (CCT) was calculated according to the F wave method. During the acute phase, the MRC, NIH and MI scales were administered. MRC scale scores were also recorded at the 4 months follow up. Through retrospective assessment of acquired data, 19 subjects (9 men and 10 women) showing complete hand palsy in the acute phase (MRC=0) were selected for the study; 6 of them had right and 13 had left palsy; their mean age was 69.1±9.4 years.

A multiple regression analysis (21) was carried out, selecting NIH, MEP%M and MI as independent variables and the MRC scale score at 4 months as the dependent variable. MEP%M was scored 0 if MEPs were absent, 1 if MEP%M was < 5%, and 2 if MEP%M was > 5%. To rule out multicolinearity, univariate Spearman's rho (ρ) correlation analysis between independent variables was previously calculated; a non parametric test was chosen in view of the distribution of the data, which were skewed for MEP and MI variables. Subsequently, a multiple stepwise backward regression was performed. The significance of regression analysis was determined by t test and analysis of variance. The Durbin-Watson test

| Subjects | Age | Lesion site | Lesion side | MI | NIH | Threshold of MEPs in % | Latency of MEPs in msec | CCT, msec | MEP%M | MRC |
|----------|-----|-------------|-------------|----|-----|-----------------------|------------------------|-----------|-------|-----|-----|
| 1        | 16  | Cortical-subcortical | right | 66 | 12  | 0                      | 0                      | 0         | 0     | 0   | 0   |
| 2        | 26  | Cortical     | left | 9  | 15  | 0                      | 0                      | 0         | 0     | 0   | 0   |
| 3        | 72  | Brainstem    | left | 9  | 7   | 85                     | 21.4                   | 7.2        | 1     | 4   |     |
| 4        | 63  | Cortical-subcortical | left | 9  | 12  | 0                      | 0                      | 0         | 0     | 0   | 0   |
| 5        | 65  | Subcortical  | left | 0  | 14  | 0                      | 0                      | 0         | 0     | 0   | 0   |
| 6        | 64  | Subcortical  | left | 39 | 11  | 50                     | 21                     | 6.4        | 2     | 5   |     |
| 7        | 79  | Cortical-subcortical | left | 0  | 16  | 0                      | 1                      | 0         | 0     | 0   |     |
| 8        | 60  | Cortical-subcortical | left | 28 | 14  | 0                      | 0                      | 0         | 0     | 0   | 0   |
| 9        | 72  | Cortical-subcortical | left | 1  | 0   | 0                      | 0                      | 0         | 0     | 0   |     |
| 10       | 51  | Subcortical  | left | 0  | 9   | 0                      | 0                      | 0         | 0     | 0   |     |
| 11       | 82  | Cortical     | left | 0  | 19  | 95                     | 19                     | 4.4        | 1     | 0   |     |
| 12       | 69  | Subcortical  | right | 0 | 12  | 0                      | 0                      | 0         | 0     | 0   |     |
| 13       | 88  | Subcortical  | right | 0 | 9   | 75                     | 24.8                   | 7.3        | 1     | 3   |     |
| 14       | 75  | Subcortical  | left | 0 | 15  | 0                      | 0                      | 0         | 0     | 0   |     |
| 15       | 64  | Subcortical  | left | 0 | 12  | 0                      | 0                      | 0         | 0     | 0   |     |
| 16       | 74  | Cortical-subcortical | right | 0 | 9   | 0                      | 0                      | 0         | 0     | 0   |     |
| 17       | 69  | Subcortical  | left | 0 | 10  | 0                      | 0                      | 0         | 0     | 0   |     |
| 18       | 54  | Subcortical  | left | 9 | 5   | 0                      | 2                      | 0         | 0     | 0   |     |
| 19       | 80  | Cortical     | right | 14| 7   | 0                      | 0                      | 0         | 0     | 0   |     |

*69.1±9.4 (0-66) **0 (5-19) **76.25±19.31 **21.55±2.41 **6.32±1.35 **0 (0-2) **0 (0-5)

Abbreviations and symbols: MI = Motricity Index scale score; NIH = National Institutes of Health Stroke Scale score; MEPs = Motor evoked potentials; CCT = central conduction time; MEP%M= facilitated MEP amplitude expressed as a percentage of compound motor action potential amplitude; MRC = Medical Research Council scale score. * mean ± SD; ** mode (range).
was also carried out to check for any significant correlation in the order of occurrence of residuals. For all the statistical analyses, alpha was set at 0.05 and the Statgraphics Centurion package (Statpoint Inc., USA) was used. All the subjects gave their written informed consent to participate in the study.

Results

Descriptive statistics of the clinical and neurophysiological data are reported in Table I. MEPs were recorded in subjects 3, 6, 11, and 13 in the acute phase. In subjects 3, 11, and 13, MEP%M was < 5% and the threshold was increased; in subject 6, MEP%M was >5% and the threshold was normal. Latency and CCT were prolonged in subjects 3, 6 and 13. Various degrees of MRC improvement were observed in three of the four subjects with MEPs present in the acute phase, and also in two cases with absent MEPs. Patient 11, in whom MEPs were recorded but who did not have an MRC improvement, showed MEPs with normal latency, high threshold and very low amplitude. The correlation analysis among independent variables is reported in Table II. Since the data correlations tested using Spearman’s rho were low and not significant, multiple regression analysis was performed using NIH, MEP%M and MI (Table III). The multiple regression equation was significant ($F = 17.92, p = 0.000$) with adjusted $R^2$ equal to 73.8%; since MI was not significant, this variable was excluded in the backward regression analysis. The final model, combining NIH and MEP data, was significant ($F=28.65, p=0.000$) with adjusted $R^2$ explaining 75.44% of the variability of outcome RMC scores (Table IV). Since the Durbin-Watson test gave a result of 1.61 with $p=0.20$, serial autocorrelation of the residuals was ruled out.

Discussion

A minority of stroke patients with initial hand palsy show, over some months, a significant motor and functional hand recovery. Motor evoked potentials, used to assess the residual direct corticospinal pathways that underpin much of the motor improvement as well as neuroplasticity and the compensating phenomenon, make it possible to obtain a more accurate motor prognosis. This study investigated the prognostic value of clinical and MEP variables in relation to hand motor recovery after stroke when initial hand palsy was present. Employing multiple regression analysis, MEP%M together with NIH scale were shown to be the best model yielding useful prognostic information, explaining 75.4% of the variability of the dependent outcome variable, MRC. A previous model that included the MI scale score was discarded on the basis of a backward stepwise analysis, as this variable was not found to be significant. In four of the 19 subjects it was possible to record MEPs in the acute phase: these patients recovered various degrees of hand strength even though this could be deemed have some functional significance only in the three with an MRC of at least 3. Motor evoked potentials with very low amplitude and normal latency were recorded in case 11, who did not show hand motor recovery. In this case, it is possible that the high value of the output stimulator employed and the circular coil type used did not allow a focal stimulation of the selected hemisphere and that, as a result, ipsilateral MEPs were recorded. The functional value of ipsilateral motor pathways after stroke has yet to be clarified (22).

Our results agree with other studies on the additional prognostic value of MEPs, considered together with other clinical parameters; however, the selected variables are not always the same, and methodological differences have also been observed in previous MEP analysis studies. Even though many authors have studied the prognostic value of MEPs on motor recovery after ischaemic stroke, few have investigated the relationships among the various available prognostic factors by

<table>
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<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
<th>T Statistic</th>
<th>P-Value</th>
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<tr>
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<tr>
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<td>0.000</td>
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<tr>
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<td>-0.112</td>
<td>0.912</td>
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</table>

Abbreviations: NIH=National Institutes of Health Stroke Scale score; MEP%M=facilitated MEP amplitude expressed as a percentage of compound motor action potential amplitude; MI=Motricity Index scale score.

Analysis of variance: $F=17.92$, $p=0.000$

Adjusted $R^2=73.82$

Standard error of the estimate=0.80

Durbin-Watson statistic=1.589 ($p=0.16$)
means of multivariate analysis in order to improve predictions of motor outcome or disability. In particular, to our knowledge, only one study (19) has investigated this aspect in a group of subjects homogeneous for early motor impairment; the authors found that the early presence of MEPs in a sample of patients with complete upper extremity paralysis predicted functional recovery and that the addition of clinical, radiological and age data did not yield a better prognostic model. Timmerhuis et al. (18) studied the prognostic value of MEPs, SSEPs, age, Barthel Index Scale and radiological parameters, employing the Rankin scale as outcome disability variable; their results showed MEPs, computing CCT and age to be significant variables. Other authors (15) found that MEPs and SSEPs, together with motor arm performance, muscle tone and disability, predicted arm motor recovery, highlighting that neurophysiological data alone were of limited value. D’Olhaberriague et al. (16) demonstrated that two parameters — presence of MEPs and CCTs — increased the possibility of predicting degree of disability after stroke, together with infarction size, laboratory data and age. Escudero et al. (17) investigated the CCT of MEPs, hand MRC, neurological status and Barthel Index in relation to Barthel and MRC improvement, finding that MEP helped to predict MRC outcome regardless of initial MRC or Barthel score.

One limitation of our study, apart from the retrospective design, is that in spite of the number of prognostic factors considered to be important, only two clinical variables were considered for analysis together with MEP amplitude; however, the relatively small size of the sample would not have allowed the inclusion in the analysis of a greater number of prognostic variables (21). Moreover, the MRC scale, whose reliability has been evaluated in stroke subjects (23), was used as an indicator of motor outcome and the results should be considered to refer to hand strength as opposed to hand function recovery, even though a high correlation exists between the two constructs, as demonstrated by previous studies in chronic hemiparetic stroke subjects (24,25). In particular the authors (25), assessing the strength of various upper limb muscle groups with a dynamometer, concluded that hand strength combined with shoulder flex- or strength correlates best with upper limb function.

From a clinical perspective, a functional outcome scale would have been more useful; however it has been demonstrated that MEPs, at least in subcortical strokes, are more related to strength recovery as they are linked to the integrity of corticospinal pathways; conversely, they are not directly related to the cortical neuroplasticity that underpins the more slowly developing functional hand recovery (26). On the other hand, caution is warranted when the prognostic value of MEPs is studied employing disability scales as measures of recovery outcome (17); these data are in fact dependent not only on the recovery of motor pathways and on the neuroplasticity phenomenon, but also on rehabilitation programs carried out, and on social and environmental factors.

The fact that MI did not add prognostic information with regard to hand motor recovery might be related to the fact that the corticospinal system exerts less influence over proximal muscles (27), whose strength determined the MI scores in our study.

The low excitability of the motor cortex area of the affected hemisphere after stroke, as confirmed by this study in a population with initial hand palsy, has recently been related to a high transcallosal inhibitory drive of the unaffected hemisphere (28). This phenomenon would hinder the motor recovery underpinned by the neuroplasticity process of the affected hemisphere and, on the other hand, would support a maladaptive plasticity of the unaffected hemisphere (29). In order to reduce transcallosal inhibition, repeated TMS has been employed on the unaffected hemisphere yielding a better functional hand performance (30). These findings suggest the need for further research in rehabilitation techniques that, like constraint-induced movement therapy, might allow a better functional outcome through a better control of the neuroplasticity process, as demonstrated by TMS studies (31).

In conclusion, the results of this study support the hypothesis that early MEPs, together with clinical general neurological conditions, can help to predict hand motor recovery after stroke when initial hand palsy is present. Further studies should assess neurophysiological, clinical, radiological and laboratory data in larger, homogeneous groups of subjects, particularly when an initial limb paresis is present and the additional prognostic value of the MEPs is less clear.

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