

The prognostic value of motor-evoked potentials in motor recovery and functional outcome after stroke – a systematic review of the literature

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Summary

The aim of this study was to systematically review published data on the value of motor-evoked potentials (MEPs) in predicting motor recovery of the upper extremity and general functional outcome early after stroke.

We searched PubMed for original prognostic studies. Only full-text original papers evaluating the prognostic value of MEPs elicited by transcranial magnetic stimulation (TMS) in motor function recovery of the upper extremity were included in this review.

Data from the studies included in the review are presented in two tables: one shows the general characteristics of the studies and the other gives methodological details and results.

Of 842 publications, only 15 met the criteria for inclusion in this review.

Data from 14 trials provided evidence that TMS of the motor cortex, eliciting MEPs, is a reliable tool for predicting motor recovery as well as functional outcome. The interpretation of the results was complicated by methodological differences between the included studies.

KEY WORDS: arm function, motor evoked potentials, outcome, stroke, transcranial magnetic stimulation

Introduction

Stroke is a severe social problem. It is the third most frequent cause of death and a major cause of disability in adults (1). Despite advances in treatment of acute stroke and post-stroke rehabilitation, the dependency rate after stroke still reaches 20-30% (1). Therefore, there is a need for prognostic tools for recovery after stroke that would help in early decision making on acute-stage treatment and rehabilitation. The grade of

paresis in the early stage of stroke is generally well recognized as a predictor of motor recovery (2,3).

Transcranial magnetic stimulation (TMS) is an electrophysiological technique in which the brain cortex, particularly the motor area, is stimulated with magnetic field in order to obtain information about the function of motor pathways of the central nervous system. This method was introduced in 1985, when Barker et al. developed a magnetic stimulator able to excite the human motor cortex (4). TMS can be used to stimulate the primary motor cortex (M1) and elicit motor evoked potentials (MEPs) in target muscles of the contralateral upper limb. MEPs (electrophysiological parameters: e.g. latency and amplitude), or their absence, provide indicators of the functional integrity and excitability of the corticomotor pathway and make it possible to evaluate a related motor impairment at the time of testing (5).

There have been several attempts to predict motor recovery after stroke through the use of MEPs (6-11). However, the value of MEPs elicited with TMS in the acute and subacute stage of stroke is still poorly investigated. Several studies suggest a prognostic value of MEPs recorded from the affected upper limb, but this thesis has yet to be proved in a large prospective trial. Some studies conducted in the acute phase of stroke showed, using MEP threshold and MEP amplitude measurements, a relationship between motor recovery and the degree of motor system impairment (7,9,12,13). However, other data argue against the hypothesis that MEPs are a good prognostic tool (14). The heterogeneous methodologies applied in these studies may complicate the interpretation of their results.

The identification of a reliable predictor of upper limb recovery would promote individualization of rehabilitation programs. The availability of reliable prognostic data (potentially MEPs) could be an additional criterion of eligibility for rehabilitation unit transfer after acute stroke. The aim of this systematic review of the literature was to summarize up-to-date evidence about the usefulness of TMS and MEPs in predicting motor recovery after stroke.

Materials and methods

This systematic review was undertaken according to the relevant criteria of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (15).

We searched the PubMed database from 1966 to January 2012 for original studies in patients with acute stroke, which evaluated the predictive value of TMS and MEPs for residual upper limb paresis/paralysis and overall clinical outcome. We additionally searched the reference lists of the included publications.

We applied a broad search strategy including the terms: “TMS” OR (“transcranial” AND “magnetic” AND “stimulation”) AND stroke.

Studies were eligible for inclusion if: i) they evaluated the prognostic value of MEPs elicited with TMS in the acute and subacute phase of stroke; ii) they included individuals with an upper limb deficit (paresis/paralysis) as a result of stroke; iii) TMS was performed to obtain MEPs from the paretic hand within 14 days of stroke; iv) there was a follow-up evaluation of motor or functional recovery (we did not specify a minimum period of follow-up).

We excluded: i) case reports; ii) studies in which MEPs were recorded from muscles other than upper limb muscles; iii) studies in which electrophysiological techniques other than TMS were used to elicit MEPs; iv) studies in which no follow-up evaluation was available.

The positive predictive value of MEPs for outcome in the patients participating in the reviewed studies was determined on the basis of improvement in: motor function of the upper extremity and/or general outcome (evaluated using neurological scales: NIHSS – National Institutes of Health Stroke Scale; mRS – modified Rankin Scale, BI – Barthel Index; SSS – Scandinavian Stroke Scale; CANS – Canadian Neurological Scale, MRCS – Medical Research Council Scale, Gusev-Skvortsova Scale, Or-gogozo scale, Toronto Stroke Scale).

All identified trials fulfilling the inclusion criteria and not fulfilling any of the exclusion criteria were included in this review. JB and KK selected potentially eligible studies (using a standardized form) which were independently reviewed by those authors. Extracted data (standardized form) included study sample size, type of stroke, time of MEP evaluation, technical details of TMS and MEP recording, degree of limb paresis, clinical scales used, follow-up examination and predictive value of MEPs. Any disagreement was resolved by discussion with the third author (MK).

We did not perform a meta-analysis as the study designs were very heterogeneous (inclusion criteria for subjects, interventions, evaluation of clinical outcomes). Indeed, conducting a meta-analysis using these data would not have been appropriate.

Results

The PubMed search identified 842 publications. Only 15 trials evaluated the prognostic value of MEPs in the acute and subacute stage of stroke (within max. 14 days of stroke onset). Of these trials, which met our criteria and were included in this review, 14 proved the predictive value of upper limb MEPs in stroke patients. The general characteristics of the included studies (7-11,13,14,16-23) and relative methodological details and results are presented in Tables 1 and 2.

The studies included a total of 480 patients with ischemic (n=463) or hemorrhagic (n=17) stroke (acute or subacute) and 97 control subjects. The sample sizes ranged from six (23) to 84 participants (32 of whom formed the control group) (18). In 14 trials a Magstim 200 stimulator was used. The number of recorded MEPs ranged from two (20,21) to six (10). In two trials the number of discharges was unclear (11,22). There

emerged significant discrepancies in terms of upper limb muscle selected for evaluation. The studies also used a wide range both of scales to measure the clinical outcome (see Table 1), and of follow-up periods – ranging from two weeks (7,21) to one year (9,16,22). All but one (14) of the studies supported the predictive value of MEP evaluation in the acute and subacute phase of stroke.

Discussion

The results of our review suggest that MEP evaluation in the acute and subacute phase of stroke may be helpful in predicting functional recovery. Methodological differences between the reviewed studies constitute a limitation of this systematic review as they did not allow us to meta-analyze the results of the reviewed studies. These differences concerned, for example: the type of stroke, the clinical scales used, the duration of the follow-up period, the type of stimulator and coil, the stimulation protocol, the localization of the stimulated area, the time from stroke onset and timing of MEP evaluation, and the degree of arm paresis.

In the literature there is a lack of data on MEPs as a predictive factor of upper limb recovery in this particular group of patients – i.e. patients in the acute and subacute phase of stroke. In the recent literature on prognostic variables relating to upper limb recovery following stroke, MEPs are not recognized as predictors of upper limb recovery (24). However, this latter review did not concentrate on acute and subacute stroke patients, but rather aimed to extract predictive factors for upper limb recovery from a very broad spectrum of factors. Predictor variables considered within the studies reviewed included age, sex, lesion site, initial motor impairment, MEPs and somatosensory-evoked potentials (24). Only initial measures of upper limb impairment and function impairment were found to be the most significant predictors of upper limb recovery with odds ratio 14.84 (95% confidence interval, CI, 9.08-24.25) and 38.62 (95% CI 8.40-177.53), respectively. A previous systematic review (published in 2009) stated that neurophysiological measures and initial sensorimotor abilities were the best predictors of arm movement recovery (25).

Some neurological scales proved to have prognostic value in predicting outcome: mRS (26-28), NIHSS (28,29), Orrington Prognostic Scale (30). Residual strength of the paretic muscles (31) and observation of the recovery over the first four weeks (32) may also provide clinical indicators of functional recovery.

Some authors suggest combining electrophysiological methods with clinical evaluation to obtain better predictive value for recovery after stroke (33).

The decision about further rehabilitation in a rehabilitation unit is sometimes difficult and controversial. It is well known that post-stroke rehabilitation is a lengthy and expensive process. Moreover, some patients may not gain the expected benefits from it. Hence the need for specific and sensitive criteria to select the patients who would fully benefit from rehabilitation. The presence or absence of MEPs could constitute an additional criterion for the prognosis of upper limb function recovery as well as general outcome after stroke. There is still a need for further trials conducted on large

Table 1 - Characteristics and results of the included trials

Number of patients	Control group	Stroke type	Time of inclusion in study	Localization of lesion	Neurological deficit	MEP evaluation following stroke onset	Follow-up			Ref. no.
							When	Outcome measures		
								Hand specific	General scales	
25	16 healthy subjects	Ischemic stroke	Within 48 hours of stroke onset	11 cortico-subcortical, 7 subcortical and 7 limited capsular infarcts	Complete hand palsy	Within 48 hours	6 months	MRCS	NIHSS, mRS, BI	11
31	20 age-matched healthy subjects	First ischemic stroke in the MCA territory	Within 24 hours of stroke	Cortical or cortico-subcortical infarct	MRC 0-2 points	1 st and 8 th day	8 th , 30 th , 90 th , 180 th and 360 th day after stroke	MRCS	NIHSS, mRS, BI	16
12	12 subjects	Supratentorial	1-7 days post-stroke	Lacunar, hemorrhagic, ischemic, supratentorial	2 paresis, 10 plegia	1 st -7 th days, 30 th day and 3 months after stroke	3 months	Degree of paresis (no paresis, mild to severe paresis, plegia)	BI	17
52	32 healthy subjects	Ischemic	Within 3 days of admission	Cortico-subcortical locations, cortical lesions or foci located in the depth of the hemispheres (unclear)	Unclear	Single evaluation within 3 days of stroke	20-25 days	No	Gusev-Skvortsova Scale, CANS, and Orgogozo scale	18
15	No	Ischemic, first-ever stroke	Within 48 hours post-stroke	MCA territory that was due to either thrombosis or embolism	Complete hand palsy	On day 1 and after 1 year	After 1 year	MRCS	NIHSS, BI	9
26	No	Ischemic stroke	Within the first 24 hours of stroke onset	First-ever ischemic stroke in the MCA territory	Complete hand palsy	Days 1 and 14	14 days	MRCS	mRS at day 1, NIHSS at days 1 and 14, and BI at day 14	7
21	No	First-ever strokes, 16 ischemic and 5 hemorrhagic	1-5 days post-stroke	Single vascular lesion	SSS 0-6 points	Days 1-5	6 months	SSS	Clinical evaluation 1-5 days, 15 days and 6 months after stroke	10
50	No	Ischemic	Within 24 hours	Cortical, corticosubcortical, subcortical, vertebrobasilar	MRC 0-4 points	3-7 days	6 months	MRCS	CANS and BI	13
33	No	Ischemic	Within 7 days	First-ever stroke from the MCA territory	MRC 0-4 points	Within 7 days	4 months	MRCS, Motricity Index (upper limb subscale score) (MI)	NIHSS	19
44	No	Ischemic	Within 10 days of stroke	No data	Complete paralysis of the upper or lower extremity	Within 10 days and then 40 days post-stroke	26 weeks	Fugl-Meyer motor assessment	SSS	20
50	No	Ischemic	Within 4 days	MCA territory, cortical and subcortical	No data	Within 4 days and after 6 weeks and 3 months	3 months	no	BI and mRS	8
38	17 healthy subjects	Ischemic	1 st day	Occlusion of the MCA	Hemiplegia	Days 1 and 14	2 weeks	Hemiplegia, no specific scale	BI, mRS, Modified CANS (MCNS),	21
50	No	Acute ischemic stroke	Within 24 hours	Cortical and subcortical	No data	1, 3, 30 and 90 days after stroke	1 year	No	mRS, Toronto Stroke Scale	22
27	No	19 ischemic and 8 hemorrhagic strokes	Within the first 7 days	19 acute ischemic stroke and 8 hemorrhagic stroke	0-4 pts (muscle strength: 0, no strength; 5, full strength)	Within 1 week and 3 to 6 months after the event	3 and 6 months	No specific scale: muscle strength: 0, no strength; 5, full strength	mRS and BI	14
6	No	Ischemic stroke	Within 8 hours	No data	Hemiparesis, mean NIHSS 2 in paretic limb	Within 89 hours and after 15 days	15 days	NIHSS	No	23

Abbreviations: NIHSS=National Institutes of Health Stroke Scale; mRS=modified Rankin Scale score; BI=Barthel Index; SSS=Scandinavian Stroke Scale; CANS=Canadian Neurological Scale, MRC=Medical Research Council scale, MCA=middle cerebral artery

Table 2 - Methodological details and results of the included studies

Type of stimulator	Type of coil	Time of MEP evaluation	Number of repeats to be averaged for each state	Stimulus intensity	Coil placement	Target muscle	Predictive value for outcome after follow-up period	Electrophysiological measure	Ref no.
Magstim 200 stimulator	Figure-of-eight coil (7 cm diameter)	Within 48 h and after 6 months	Unclear	TMS intensity was initially set at maximal stimulator output (100%)	Tangentially to the scalp with the handle held backward	FDI and biceps brachii muscles	Yes (positively correlated with better scores on Barthel Index items reflecting bimanual coordination)	Latency, amplitude, and shape of ipsilateral responses	11
Magstim 200 stimulator (Magstim Ltd, Whitland, Dyfed, UK)	Figure-of-eight shaped coil (7 cm diameter)	Days 1 and 8	5 stimuli	Maximal output (100%)	The coil was placed tangentially to the scalp with the handle held backwards with a 30° downward tilt	FDI	Yes	MEP amplitude (MEP max/Mmax ratio)	16
Novametrix (Magstim model 200)	9 cm diameter circular flat coil	1-7 days, 30 days and 3 months after stroke	4 stimuli	80-100%	Flat on the vertex	ADM and tibialis anterior muscles	Yes	MEP amplitude, CMCT	17
Phasis (OTE Biomedica, Italy) and Neuro-MVP-4 (Neurosoft, Ivanovo, Russia)	No data available	During the first 3 days	At least 3 evoked responses	No data available	"projections of the motor zones of the cortex" (unclear)	APB	Yes	CMCT	18
Magstim Novametrix 200 magnetic stimulator	9 cm diameter circular coil (Novametrix Inc)	Day 1 and after 1 year	4 consecutive responses	Stimulation intensity was set at 100% of maximum stimulator output	"Standard" position	FDI	Yes	CMCT, latency and amplitude of MEPs	9
Magstim 200 magnetic stimulator	Circular coil of 9 cm in mean diameter	Days 1 and 14	4 consecutive responses	Stimulation intensity was 70% of maximal stimulator output or 100% if no response was obtained at 70%	Tangential plane above the vertex	FDI	Yes	CMCT, latency and amplitude of MEPs	7
Magstim 200 stimulator	Circular coil (outer diameter 12 cm)	Days 1-5	6 stimuli at the maximum stimulator output	10% up to 100% of the stimulator output	Was centered over a point marked on the scalp at either C3 or C4 (International 10-20 System) with the handle pointing posterior	Thenar muscles	Yes	1) The size (area of the rectified EMG signal) and latency of 'contralateral' and 'ipsilateral' MEPs elicited at the maximum stimulator output (100%). 2) The ratio between the size of 'contralateral' and 'ipsilateral' MEPs elicited in the same muscle	10
Magstim Novametrix 200 magnetic stimulator	9 cm diameter coil, capable of generating a 2-T maximum field intensity (Novametrix Inc)	3-7 days	3 successive discharges with maximum output	20% above-threshold and maximal stimulation output	Maximum stimulation band fitted tangential 3 to 4 cm lateral and posterior to the vertex to study the arm	APB	Yes	Amplitude and latency of the facilitated MEPs	13
Magstim 200 stimulator (Magstim Ltd, UK)	12 cm diameter circular coil	Within 7 days	3 stimulations	100% output intensity	Above the vertex	FDI of both upper limbs	Yes	Amplitude and latency of the facilitated MEPs	19
Magstim 200 magnetic stimulator (Magstim, Whitland, South West Wales)	9 cm mean diameter circular coil	Within 10 days and then at 40 days after stroke	At least two responses	80%-100% (maximum output)	Placed in a tangential plane above the vertex	ADM, biceps brachii, vastus medialis, and tibialis anterior	Yes	CMCT and latencies of MEPs	20
Medicor Magstim 200 magnetic stimulator	7 cm figure-of-eight coil for cortical stimulation	4 days, 6 weeks, and after 3 months	At least three MEPs were recorded, and the shortest one was taken	Increasing intensity (stepwise 40-100% output)	No data available	ADM	Yes	CMCT and latencies of MEPs	8
Magstim Model 200	9 cm diameter coil (unclear – circular or figure-of-eight)	1.78±0.98 (day 1) and 12.36±4.05 (day2) days after stroke onset	2 MEP were recorded	The stimulus intensity was set at 100% power to all patients	Placed tangentially over the vertex	APB	Yes	Amplitude of MEP and CMCT	21
Magstim (Novametrix) apparatus	1.5 Tesla circular coil (outer diameter 14 cm and inner diameter 4.5 cm)	1, 3, 30 and 90 days after stroke	Unclear	No data available	Over the vertex	Hypothenar, biceps brachialis, gastrocnemius and quadriceps	Yes	The shortest latency (or CMCT) and the highest amplitude of MMEPs in four responses	22
Magstim 200 stimulator	Circular coil with an outer diameter of 9 cm	Within the first week and 3 to 6 months after the event	At least 3 MEPs were recorded, and the one that had the shortest latency was taken	No data available	Over the vertex	Thenar and tibialis anterior muscles bilaterally using surface electrodes	No	Amplitude and latency of the facilitated MEPs	14
Magstim 200 stimulator	Figure-of-eight coil (no data regarding size)	Within 8 hours	5 stimuli	Maximal magnetic stimulator output	Motor cortex (unclear precise location)	ADM bilaterally	Yes	Amplitude, latency and CMCT	23

Abbreviations: CMCT=central motor conduction time; MEP=motor evoked potential; ADM=abductor digiti minimi; FDI=first dorsal interosseous; APB=abductor pollicis brevis, EMG=electromyography; ABP=abductor pollicis brevis.

groups of patients with acute stroke in order to confirm the available preliminary results (presented in this review).

This systematic review of the literature supports the thesis that MEP evaluation early after stroke onset may be helpful in predicting motor recovery of the arm. It may facilitate the process of identifying candidates for intensive inpatient rehabilitation. However, further, well-designed studies, conducted on large groups of patients, are necessary to define its potential role in everyday clinical practice.

Limitations

This review, as mentioned, has certain limitations, including methodological differences between the studies (the most important concerning: number of discharges, coil positioning, scales used to evaluate the motor deficit as well as general neurological status and dependency, follow-up period). Indeed, the reviewed studies used a wide range of follow-up periods. Finally, only 15 studies (representing a total of 480 patients and 97 controls) met the criteria for inclusion in our review. This sample size is too small to draw firm conclusions and further studies are necessary.

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