ARAŞTIRMA YAZILARI **ORIGINAL ARTICLE**

PROGNOSTIC VALUE OF TRANSCRANIAL MAGNETIC STIMULATION IN ACUTE STROKE PATİENTS DUE TO MIDDLE CEREBRAL ARTERY INFARCTION

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ABSTRACT:
Objective: Although it is important to know the prognosis of stroke in the early stages of the event, it is not easy to evaluate the prognosis only with clinical examination on admission. Purpose: The aim of our study is to determine the prognostic value of transcranial magnetic stimulation (TMS) in a homogeneous group of patients with ischemic stroke due to middle cerebral artery territory infarction.
Patients and Methods: Fifteen healthy subjects and forty patients with acute stroke due to middle cerebral artery territory infarction were studied. After the first TMS evaluation was performed within the three days after the event, the TMS test was repeated at the end of the first month. Bilateral hemispheres of the control subjects and the healthy hemispheres of the patients, healthy and lesioned hemispheres of the patients were compared. The functional recovery was assessed at fourth month with Orgogozo's MCA scale, NIH-NINDS score and Barthel index.
Results and Conclusion : Statistically significant functional improvement was found in patients with MEP response at the end of fourth month. Our results showed that TMS technique provides a useful early prognostic indicator of functional recovery in ischemic stroke patients when used togethet with clinicical predictors.
Key Words: Transcranial magnetic stimulation, ischemic stroke, prognosis

ORTA SEREBRAL ARTER SULAMA ALANI İNFARTINA BAĞLI OLARAK AKUT İSKEMİK İNME GEÇİREN HASTALARDA TRANSKRANYAL MANYETİK STİMÜLASYONUN PROGNOSTİK DEĞERİ

Amaç: İnme sonrası erken dönemde prognozu tahmin etmek tedavi ve rehabilitasyon planı açısından önemlidir. Ancak sadece klinik muayene bulgularıyla prognozu tahmin etmek kolay değildir. Bu çalışmanın amacı orta serebral arter sulama alanı infarktına bağlı olarak iskemik inme geçiren homojen bir hasta populasyonunda transkranyal manyetik stimülasyonun (TMS) prognostik değerini araştırmaktır.
Hastalar ve Metodlar: Onbeş sağlıklı gönüllü ve orta serebral arter sulama alanında akut infarkt gelişen 40 hasta çalışmaya alındı. İnme gelişiminden sonraki ilk üç günde ilk TMS testi yapıldıktan sonra takip eden birinci ayın sonunda TMS değerlendirmesi tekrarlandı. Kontrol vakalarının her iki hemisferi, hastaların sağlam ve lezyonlu hemisferlerinden elde edilen TMS yanıtları karşılaştırıldı. Fonksiyonel düzelme dördüncü ayın sonunda Orgogozo'nun MCA skalası, NIH-NINDS skoru ve Barthel indeksi ile değerlendirildi. Sonuçlar ve Yorum : Dördüncü ayın sonunda MEP cevabı elde edilebilen hastalarda istatistiksel anlamlı derecede fonksiyonel düzelme gözlendi. Sonuçlarımız TMS'nin klinik prediktörlerle birlikte kullanılmasının iskemik inme prognozunu belirlemede faydalı olabileceğini gösterdi.
Anahtar Sözcükler: Transkranyal manyetik stimülasyon, iskemik inme, prognoz

INTRODUCTION:

In the early stages of the stroke, it is difficult to estimate the prognosis of functional recovery in stroke patients (1-3). The poor prognostic factors in the subacute phase after stroke were reported as age, female gender, presence of previous stroke, sitting inbalance, nonlacunar stroke type, cognitive dysfunctions, paresis of arm and leg, not alert as initial level of consciousness, homonymous hemianopia, visual extinction, constructional apraxia, no transfer to the stroke unit, visuospatial construction problems and urinary incontinence (4,5). However, the establishment of early prognosis of functional recovery in stroke patients seems to be difficult on the basis of only clinical data (2,3). To stimulate human motor cortex through intact scalp and skull with transcranial magnetic stimulation (TMS) was shown previously (6-11). TMS allows activation of neurons in the cortex and produces an electric field in the brain by electromagnetic induction (11,12). It has been used to evaluate motor pathways in neurological diseases such as stroke, and to clarify the functional prognosis after stroke in the early stage of the event. This may have great value for optimizing rehabilitation strategies and treatment prothocol (13-16).

Athough previous studies suggested cortical MEP as a prognostic indicator, other studies reported no signifcant predictive value of MEP in acute stroke (17-19). In recent years, systematic reviews for early prediction of functional outcome after stroke revealed the prognostic value of MEP,

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Geliş Tarihi: 06.01.2006 Kabul Tarihi: 15.06.2006 Received: 06.01.2006 Accepted: 15.06.2006

and suggestions for further studies about this subject were offered (20-22).

The aim of our study was to evaluate the value of TMS in predicting functional outcome after ischemic stroke in a homogenous group due to middle cerebral artery territory infarction.

MATERIAL AND METHOD:

Forty patients with first ever ischemic stroke due to middle cerebral artery (MCA) territory infarction, and 15 healthy age matched controls were enrolled in the study. The patients had no prior history for stroke. The patients were hospitalized within the first 24 hours after ischemic stroke, and all of them had significant hand weakness at onset (strength < 2/5), muscle strength was assessed by the Medical Research Council (MRC) Scale. Stroke due to MCA territory infarction was diagnosed by medical history and clinical examination of the patients at the admission day. The infarcts in MCA territory were demonstrated with computed tomographic (CT) scans on the following days. Patients with primary intracerebral hemorrhage, lacunar infarcts or hemorrhagic transformation were excluded. The patients with small vessel disease (lacunar infarcts) who initially presented as MCA territory infarctions with medical history and neurological examination (four patients) were also excluded after the lesion was demonstrated with neuroimaging techniques (CT and/or MRI). Neurological examination and first TMS evaluations were performed simultaneously within the first three days and TMS studies were performed at the end of the first month after stroke onset again.

TRANSCRANIAL MAGNETIC STIMULATION:

The patients were studied by TMS within the first three days after the stroke onset and at the end of the first month by the same researcher. Magnetic stimulation was performed by use of a Magstim Novametrix 250 magnetic stimulator with a 9 cm mean diameter circular coil while the patients were lying in supine position. Stimulation was performed with the coil held tangentially 3-4 cm lateral and posterior to the vertex, and both hemispheres were stimulated at rest. We performed the TMS study without fascilitation because background voluntary contraction causes difficulty in measurement of MEP onset latency and increases the individual amplitude variation, and the consciousness of some patients was not enough for fascilitation. Stimulation intensity was set at 100% of maximum stimulator output. Counterclockwise current was applied for left hemisphere, and clockwise current was applied for right hemisphere stimulation. When the muscle remained inexcitable with the coil in the standard position, it was moved slightly around and the stimulation was repeated at least 10 times to ensure that no response could be elicited. Recordings were taken from bilateral abductor pollicis brevis muscle with cup shaped surface electrodes. Medelec Synergy EMG machine was used for amplification with gains of 20 microvolt and 1 mV/division. A 100 miliseconds poststimulus period was analyzed. Peak to peak amplitudes were obtained, and latencies were measured between the stimulation artifact and the onset of first negative departure from the baseline. If the response was obtainable, TMS was repeated at least five times to obtain the MEP response with shortest latency. The time taken by the response in traveling from the cortex to the target muscle was termed total conduction time. To calculate central motor conduction time (CMCT), we also studied M and F latencies of median nerves, and then CMCT was calculated with the formulation of " MEP latency- [(F latency + M latency -1) /2]". The patients divided into three groups according to the MEP responses: 1- patients with absent MEP, 2- patients with delayed CMCT, 3- patients with normal CMCT. Delayed CMCT was considered prolonged at > (CMCT of the control subjects + 2,5 SD) (8,5 msn).

The amplitude and latency of MEP responses, CMCT obtained from lesioned hemispheres were compared with the values obtained from healthy hemispheres. The values of the healthy hemispheres were also compared with the values obtained from the bilateral hemispheres of control subjects. It is reported that the cause of the absent or reduced MEP response in the first few days after stroke may be due to perilesional edema and ischemic penumbra (3). For this reason we performed the TMS test again at the end of the first month after the ischemic event, and after we compared the values between the two TMS tests to be sure of the reliability of the values with paired samples t test.

The clinical status of the patients was determined with Orgogozo's MCA scale, Barthel

index and Stroke scale of national institute of health- national institute of neurological disorders and stroke (NIH-NINDS scale) within the first three days and at fourth month (23-26). The functional improvement of the patients with and without MEP responses, and the functional improvement of the patients with normal and delayed CMCT were compared at fourth month.

The study was approved by the local ethics committee and informed consent was obtained from a close relative of patients. Subject consent was obtained according to the decleration of Helsinki.

The Man Whitney-u test was used to compare the amplitude, latency of MEP, and CMCT between the lesioned and healthy hemispheres of the patients, and between the healthy hemispheres of the patients and the healthy subjects. The MEPs obtained within the first three days after stroke onset and obtained at the end of the first month were compared with paired samples T test. The Wilcoxon matched pair test was used to asses the changes in Orgogozo's MCA scale, Barthel index, and NIH-NINDS scale at fourth month. The value of $p<0,05$ was accepted as statistically significant and the values were given as mean ± SD in the text.

RESULTS:

Forty patients (16 male, 24 female) with MCA territory infarction and 15 healthy volunteers (6 male, 9 female) were included in the study. Mean age of patients was 68,0 ± 11,8 and mean age of control subjects was 60,5 ± 8,1 years. Difference for age between the two groups was found not to be statistically significant ($p>0,05$). Left hemisphere was dominant in all patients. Nineteen of the patients had right and 21 of them had left hemisphere lesion. Bilateral TMS tests were performed on both sides of the patients and healthy subjects and the latency and amplitude of MEP and CMCT were measured. In the first TMS evaluation, MEP response could not be obtained from 16 (40%) of 40 patients, where as sixteen patients (40%) had normal and eight patients (20%) had delayed CMCT.

Eight patients died during the follow up period of 4 months. Six of them (four of them due to central herniation, and 2 of them due to infection) were from the patients without MEP response, and two of them (due to infection) were from the patients with MEP response. None of the patients with MEP response died because of central herniation.

No significant difference was found for mean amplitude and latency of MEP and CMCT between the healthy hemispheres of the patients and the bilateral hemispheres of the control subjects (Table1). There was also no significant difference for latency, amplitude of MEP and CMCT of healthy and lesioned hemispheres between the two TMS tests performed within three days and at the end of the first month (Table 2).

Table 1: Comparison of age, mean amplitude, latency of MEP, CMCT between the healthy hemisphere of the patients and healthy controls

	Stroke patients (n=40)	Healthy control subjects (n=15)	p value
Mean age	68,0 ± 11,8	60,5 ± 8,1	
Latency of MEP (msec)	21,2 ± 1,1	21,3± 0,8	>0,05
Amplitude of MEP (mV)	2,8 ± 1,5	2,8 ±0,8	>0,05
CMCT (msec)	7,3 ± 0,6	7,1 ± 0,6	>0,05

Table 2 : Comparison of the mean amplitude, latency of MEP, and CMCT between the two TMS tests performed within the first three days and at the end of the first month

	Healthy hemisphere	Lesioned hemisphere				
	I. TMS evaluation	II. TMS evaluation	p value	I . T M S evaluation	I I . T M S evaluation	p value
Latency of MEP (msec)	21,2 ± 1,1	21,4 ± 1,2	0,203	23,3 ± 1,5	23,2± 1,5	0,552
Amplitude of MEP (mV)	2,9 ± 1,4	2,6 ± 1,2	0,122	1,4 ± 1,2	1,3 ± 0,8	0,485
CMCT (msec)	7,2 ± 0,6	7,0 ± 0,7	0,128	8,5 ± 1,4	8,5 ± 1,3	0,864

There was significantly lower mean amplitude of MEP on the affected side of the stroke patients compared with the data recorded from the healthy hemispheres of the stroke patients in both TMS tests (1,4 ± 1,1 mV vs 2,9 ± 1,4 mV for the first TMS test and 1,2 ± 0,8 mV vs 2,6 ± 1,2 mV for the second TMS test) ($p<0,001$) . A more prolonged mean CMCT (8,5 ± 1,3 msec vs 7,0 ± 0,7 msec for the first TMS test and 8,5 ± 1,4 msec vs 7,3 ± 0,6 msec for the second TMS test) and MEP latency (23,3 ± 1,5 msec vs 21,2 ± 1,1 msec for the first TMS test and 23,2 ± 1,5 msec vs 21,4 ± 1,2 msec for the second TMS

test) was found on the lesioned hemispheres of the patients compared with the healthy hemispheres and healthy controls in both TMS tests (p<0,001) (Table 3).

Table 3. Comparison of mean amplitude, latency of MEP, CMCT between the lesioned and healthy hemispheres in two TMS evaluation performed within the first three days and at the end of the first month

	I. TMS evaluation			II. TMS evaluation		
	Healthy hemisphere	Lesioned hemisphere	p value	Healthy hemisphere	Lesioned Chemisphere	p value
Latency of MEP (msec)	21,2 ± 1,1	23,3 ± 1,5	<0,001	21,4±1,2	23,2±1,5	<0,001
Amplitude of MEP (mV)	2,9 ± 1,4	1,4 ± 1,1	<0,001	2,6±1,2	1,2±0,8	<0,001
CMCT (msec)	7,3 ± 0,6	8,5 ± 1,4	<0,001	7,0±0,7	8,5±1,3	<0,001

Table 4. Comparison of age, gender, side and type of the lesion, initial Orgogozo's MCA scale, Barthel index, and NIH-NINDS score between the patients with and without MEP response

	Patients with MEP response n=24	Patients without MEP response n=16	p value
Age	66,8	69,8	0,292
Gender (M/F)	10/14	6/10	
Side of the lesion (R/L)	11/13	8/8	
Lesion type (branch MCA / large MCA territory infarction)	7/17	3/13	
Initial Orgogozo's MCA scale	39,4 ± 14,9	36,3 ± 12,3	0,924
Initial Barthel index	31,5 ± 16,9	18,7 ± 7,6	0,202
NIH-NINDS score	22,9 ± 4,4	23,5 ± 4,6	0,817

No significant difference was found for initial Orgogozo's MCA scale (p=0,924), Barthel index (p=0,202) and NIH-NINDS score (p=0,817) between the patients with and without MEP response, but initial Barthel index value of the patients with MEP response was higher than the patients without MEP response (Table 4). We observed a better clinical outcome at fourth month in the patients in whom there was a recordable MEP within the first three days. The patients with MEP response had significantly better mean scores recorded at fourth month of MCA scale (60,0 ± 16,5 vs 40,0 ± 7,1), Barthel index (49,5 ± 20,7 vs 25,5 ± 6,8), and NIH-NINDS score (14,5 ± 5,9 vs 20,2 ± 5,9) (p<0,001). However, we found no significant difference for clinical improvement between the patients with normal and delayed CMCT(p>0,05). Comparison of Orgogozo's MCA scale, NIH-NINDS score and Barthel index obtained within the first three days and at fourth month between patients with and without MEP response and between patients with normal and delayed CMCT were shown in Table 5 and 6.

Table 5. Comparison of Orgogozo's MCA scale, NIH-NINDS score and Barthel index obtained within the first three days and at fourth month between patients with and without MEP response

		I. evaluation	II.evaluation	p value
Patients with MEP response (n= 24)	MCA scale	39,4 ± 14,9	60,0 ± 16,5	< 0,001
	NIH-NINDS score	22,9 ± 4,4	14,5 ± 5,9	< 0,001
	Barthel index	31,5 ± 16,9	49,5 ± 20,7	< 0,001
Patients without MEP response (n=16)	MCA scale	36,3 ± 12,3	40,0 ± 7,1	0,468
	NIH-NINDS score	23,5 ± 4,6	20,2 ± 5,9	0,015
	Barthel index	18,7 ± 7,6	25,5 ± 6,8	0,096

Table 6. Comparison of Orgogozo's MCA scale, NIH-NINDS score and Barthel index obtained within the first three days and at fourth month between patients with normal and delayed CMCT

		I. evaluation	II. evaluation	p Value
Patients with normal CMCT (n= 16)	MCA scale	45,0 ± 12,6	64,4 ± 13,9	< 0,001
	NIH-NINDS score	21,8 ± 4,2	13,6 ± 5,5	< 0,001
	Barthel index	35,6 ± 14,0	54,3 ± 15,8	< 0,001
Patients with delayed CMCT (n= 8)	MCA scale	28,1 ± 13,3	48,3 ± 18,6	0,05
	NIH-NINDS score	25,0 ± 4,4	16,6 ± 6,9	0,07
	Barthel index	23,1 ± 19,8	36,6 ± 28,1	0,158

DISCUSSION:

The capacity of functional recovery is one of the important factors for the prognosis of stroke. The poor prognostic factors in the subacute phase after stroke were known as age, female gender, previous stroke, nonlacunar stroke type, cognitive

dysfunctions, severity of paralysis, sitting inbalance, decreased initial level of consciousness, homonymous hemianopia, visual extinction, constructional apraxia, no transfer to the stroke unit, bad social support, visuospatial construction problems and urinary incontinence (4,5). In order to planning the treatment procedure it is important in stroke patients to know the prognosis. However only with clinical data on admission the early determination of the prognosis seems to be difficult. TMS allows the simple and painless evaluation of human motor cortex. Additionally the technique of TMS is easy to perform, safe and rapid (3,27,28).

The underlying mechanism of functional improvement in ischemic stroke patients is reported as unmasking of existing but functionally inactive pathways, sprouting of fibers of surviving neurons to formation of new synapses, and reorganisation of central nervous system circuit allowing to alternative pathways (29). TMS has been used for determining the prognosis of ischemic strokes since early 1990, however previous studies had controversy results about the prognostic value of TMS in the acute phase of the event (2,3,13,18,19,30). Heald et al (13) reported the largest TMS study with 118 ischemic stroke patients, and concluded that the presence of MEP response in the early phase of the event is able to differentiate good from the poor prognosis. In contrast to the studies which support the prognostic value of TMS, Zgur et al (18) and Arac et al (19) reported that TMS had no value for determining the prognosis of ischemic stroke. However, these studies were heterogenous, included ischemic and hemorrhagic strokes and also patients with variable degree of motor deficit. The prognostic value of MEP was suggested in recent studies, and systematic reviews for early prediction of functional outcome after stroke (20-22). In Hendricks study, five of 85 potentially relevant study were analyzed, and obvious evidence for the prognostic value of MEP for functional recovery after stroke was reported.

In our study, we evaluated the prognostic value of TMS in a homogeneous group of ischemic stroke patients with significant motor deficit (MRC score< 2/5) at onset due to infarct in the MCA territory. NIH-NINDS score, Orgogozo's MCA scale and Barthel index were performed for clinical evaluation within the first three days and at fourth month. It is known that most of the patients were not able to come to the outpatient clinics for control after stroke because of the mobility difficulties. For this reason, we followed up the patients for four months. Although functional recovery may proceed until one year, Kwakkel et al (5) reported that most of functional recovery occurs within the first few months, especially within the first two months after stroke. Therefore we thought that four months follow-up period is enough for determination the early prognosis after stroke. These was suggested by Rapiserda et al (31) who performed a TMS study with 26 acute ischemic stroke patients and Vang et al (17) with 38 stroke patients with shorter follow up period periods (14 days). In this respect Escudero et al (3) also evaluated the prognostic value of MEP in fifty four patients with acute ischemic stroke for six months period.

Timmerhuis et al (20) reported that MEP and age were valuable prognostic parameters in predicting stroke outcome when used together with Barthel index. Our findings were in accordance with Timmerhuis' study. In our study, mean Barthel Index at admission day was higher in patients with MEP response than the patients without MEP response (31,5 ± 16,9 vs 18,7 ± 7,6 and p=0,202), but the initial values for Orgogozo's MCA scale and NIH-NINDS score were statistically no difference. We also found no significant difference for age between the two groups (66,8 years vs 69,8 years, p=0,69).

In the early stages of ischemic stroke, it is reported that the perilesional edema and ischemic penumbra may affect the MEP response (3). Therefore, we performed the TMS tests within the first three days after the event and repeated the TMS test after one month, and compared the results between these two tests. No significant difference was found for latency, amplitude of MEP, and CMCT between the two tests. We also found no significant difference for latency and amplitude of MEP and CMCT between the healthy hemispheres of the patients and the bilateral hemispheres of the control subjects.

Sixteen (40%) of our patients had no initial MEP response, and none of these patients had MEP response in the second evaluation after one month. Sixteen (40%) of the remaining 24 patients had normal CMCT and eight (20%) of them had delayed CMCT. The ratios of our study were found similar to the ratios of Escudero's study (patients without MEP: 40%, patients with normal CMCT: 34%, and patients with delayed CMCT: 26%). The

ratios were similar because the upper limit of CMCT normality used by Escudero's study was also similar to our own (> 8,13 versus >8,5 msec, respectively).

Rapisarda et al (31) reported that the MEP amplitude is the most sensitive parameter to use for determining the prognosis, but it is known that MEP amplitude varies with the stimulation point and the position of the coil (10,32,33). For this reason, although we found statistically significant difference for MEP amplitudes between the lesioned hemispheres and healthy hemispheres, we prefered the latency (CMCT) for determining the prognosis. We also performed the TMS studies without fascilitation because background voluntary contraction causes difficulty in measurement of MEP onset latency and increases the individual amplitude variation (34). We only evaluated the MEPs from upper limbs because interpretation of lower limb MEP is difficult.

We found statistically significant improvement for Orgogozo's MCA scale, NIH-NINDS score and Barthel index in patients with MEP response with either delayed or normal CMCT during the four months of follow-up period. Escudero et al (3) reported a better clinical improvement in patients with normal CMCT than the patients with delayed CMCT, but in our study, there was no difference for prognosis between the patients between normal and delayed CMCT.

In conclusion, our study suggest that the TMS technique may have value to identify the patients with greater possibility for recovery in the early stages after acute ischemic stroke when used together with clinical predictors, especially with Barthel index.

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