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ORIGINAL COMMUNICATION

A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients

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Abstract Motor excitability is increased in both hemispheres in stroke patients during motor recovery. Pharmacologically controlled changes of cortical excitability might be beneficial for synaptic plasticity and therefore facilitate functional recovery after a brain lesion. In particular, it has been suggested that antidepressant drugs can modulate motor excitability. Several recent reports suggest the possibility of monitoring pharmacological effects on brain excitability through transcranial magnetic stimulation (TMS). The aim of this study was to investigate motor area excitability in patients with stroke after oral administration of citalopram. We conducted a prospective randomised placebo controlled study. Twenty patients with unilateral stroke were included in the study: ten patients treated by antidepressive drug and ten patients with placebo. A selective serotonergic drug (citalopram) or a placebo was administered using a mean dosage of 10 mg/day in combination with physiotherapy. Motor cortex excitability was studied by single and paired transcranial magnetic stimulation. TMS recording was tested before (T1) and 1 month after (T2) beginning drug treatment. Patients treated by the serotonergic drug, compared to patients that received a placebo, showed a significant improvement in neurological status as measured by NIHSS and a decrease of motor excitability over the unaffected hemisphere, while no differences were observed over the affected hemisphere. Our findings suggest that treatment with serotonergic drugs can bring about a significant decrease of the motor cortex excitability in stroke patients with effects on both the affected and unaffected hemispheres associated with a better motor recovery.

Keywords Stroke · Motor recovery · TMS · Drugs · Rehabilitation

Introduction

After focal ischemic lesions, the brain restores lost functions through various strategies, although the mechanisms underlying post-stroke recovery, termed cerebral plasticity, remain unclear. After the resolution of perilesional edema and diaschisis, several phases take place including redundancy, recovery of function through a neural cells disinhibitory mechanism known as unmasking, cortical map expansion and relearning [6, 8, 27]. These phenomena can be modulated through pharmacological intervention. Increasing interest has been directed to the possible role that drugs can play in the recovery of cerebrovascular lesions. However, the effects can be beneficial or harmful, and to date only limited information is available in this regard. Many studies with different drugs, whose benefits are still not well defined, await further clinical confirmation [2, 3, 21, 29]. Antidepressant drugs play a relevant role in improving depression symptoms and reducing the negative impact of post-stroke depression on functional outcome [10, 23]. It has been suggested that serotonergic agents may improve motor recovery, independently of their antidepressant action, by modulating cerebral sensory-motor activation [9] and improving motor skills of the affected side [24]. Transcranial magnetic stimulation (TMS) is a widely used tool in clinical neurophysiology that permits

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painless evaluation in vivo of the motor impairment of pyramidal tracts and motor excitability in central nervous system lesions. Recently TMS has been demonstrated to have prognostic value providing important additional information on the motor excitability in patients affected by stroke [30]. The technique of paired-pulse TMS is particularly sensitive in activating cortico-cortical circuits, thus providing information on cortical reorganization after brain injury. In the acute phase after stroke there is a motor disinhibition over both hemispheres. During motor recovery there is a return to balanced excitability. Rapid normalization of the excitability of unaffected hemisphere is related to better outcome [21]. TMS allows changes in motor excitability to be measured in patients after application of various therapies [7]. Several studies have been conducted in normal subjects and stroke patients using TMS to assess the different effects of pharmacological substances on motor cortical excitability, without any effect on mood [17, 18, 25, 34, 36]. We have previously demonstrated that a single oral dose of citalopram, a selective serotonin reuptake inhibitor (SSRI), can alter motor cortex excitability in normal subjects [25].

The aim of this study was to investigate the effect of citalopram, given its selective serotonergic action and effect on motor excitability [25], in motor areas in stroke patients during motor recovery. We investigated motor/functional recovery in two groups of patients after unilateral ischemic stroke in the territory of the middle cerebral artery; patients were treated with rehabilitation therapy in combination with citalopram or a placebo.

Materials and methods

Subjects

Twenty consecutive unselected and eligible patients were enrolled in the study (Table 1), and were randomly divided in two groups using computer-generated random numbers: the first group (group A) received pharmacological treatment with a selective serotonergic antidepressant drug (citalopram 10 mg/day), while the second group (group B) received a placebo of identical appearance; both groups received the pill before rehabilitation. Antidepressive treatment lasted at least 4 months.

Patients, outcome assessors and physiotherapists were blinded to the treatment group. TMS was performed by outcome assessors. The inclusion criteria were monohemispheric lesions, CT or MRI documenting a single monohemispheric lesion, age below 80 years, and first attack. Exclusion criteria were pacemakers, metal in the head, concomitant neuropathies, systemic vasculopathies, major affective disorders, alcohol abuse, and dementia leading to uncooperative behavior. All patients and healthy control subjects provided written informed consent. The experimental protocol was approved by the local ethics committee. Clinical improvement was evaluated using current standardized scales: the National Institute of Health (NIHSS) scale for neurological status [15], the Barthel Index for disability (BI) [16], and the Lindmark scale for hand and arm functionality (LS) [14]. Depressive symptoms were rated with the Hamilton Depression Rating Scale (HDRS) [11] and the Beck Depression Inventory (BDI) [27]. In patients with severe brain lesions, depressive symptoms were mainly inferred from signs of agitation, anger, weeping, weight loss, appetite and sleep alterations, and degree of participation in the rehabilitation program and social activities. During hospitalization after stroke, patients underwent daily rehabilitation treatment based mainly on the Bobath approach [4]. Rehabilitation treatment started within the first 10 days after the stroke and was performed for at least 30 min a day by the same team of hospital physiotherapists focusing on transfers, control of posture, independent walking, reduction of muscle tone, and on increasing the range of motion and function in the arms. The two recording sessions were scheduled at 15–20 days and 45–50 days after the stroke. Potential side effects of citalopram (nausea, insomnia, lack of appetite) were also assessed.

Table 1 Patients' characteristics

	Citalopram group	No drug group
No.	10	10
Mean age	68 (±7)	65 (±9)
Sex (M/F)	6/4	6/4
Cort-subcort/subcort	6/4	7/3
Side of lesion (L/R)	6/4	8/2
NIHSS	5	5.3
BI	61	60
HDRS	9.9	10

BI Barthel Index, *HDRS* Hamilton Depressive Rating Scale

Stimulation procedures

All subjects were seated in an armchair with their elbows semi-flexed; the forearm was pronated, fully relaxed and supported by the arm of the chair. Control and conditioned motor evoked potentials (MEPs) were recorded from the right and left thenar eminence (TE) muscles by surface electrodes in all subjects. The amplified and band pass filtered (50–20 kHz) EMG signal was fed into a Basis Esaote Machine (Esaote Company, Florence, Italy) with a sampling rate of 5,000 Hz. An auditory feedback EMG signal was given to ensure complete voluntary relaxation of target muscles. Trials in which voluntary EMG activity

occurred were discarded from further analysis. TMS was applied through a figure-of-eight focal magnetic coil (maximum magnetic field 2.5 Tesla) using a Magstim 200 magnetic stimulator (The Magstim Company, Whitland, Dyfed, UK). The following were tested:

1. The "motor threshold" (MT) intensity was defined as the lowest stimulator output intensity capable of inducing MEPs of at least 50 μV peak-to-peak amplitude in the TE muscles in at least half of 10 trials. MT was determined in relaxed TE muscles [26]. Throughout, stimulus intensities were expressed as a percentage of the maximum stimulator output.
2. Peak-to-peak MEP amplitudes were measured in the resting TE at a stimulus intensity of 120% of the resting motor threshold. A total of 7 stimuli were delivered to each muscle in each session. The size of the MEPs induced by TMS was measured as a percentage of the compound motor action potential (cMAP) elicited by peripheral stimulation of the median nerve. Both MEP and cMAP were recorded by the same electrodes placed over the TE. This parameter was used to avoid errors in measuring the amplitudes of MEPs related to different placements of the electrodes across multiple recording sessions.
3. Paired TMS was performed in each subject using a standardized paradigm in order to investigate early inhibition [12]. For this purpose, two magnetic stimulators were connected to one coil using a Bistim device (The Magstim Company). The first conditioning stimulus was subthreshold (70%) and was delivered through the same magnetic coil at interstimulus intervals (ISIs) of 2, 3, and 4 ms before a suprathreshold test stimulus. The test stimulus intensity was adjusted to 120% of the RMT [35]. This procedure allows measurement of intracortical inhibition (ICI), which many reports suggest reflects the excitability of short inhibitory interneuronal circuits within the motor cortex [35]. Conditioned MEPs in paired TMS paradigms were recorded at randomly varying ISIs; 7 MEPs were recorded for each ISI. Unconditioned MEPs were recorded after every third conditioned MEP at different ISIs applied randomly. Early ICI was then calculated by averaging the ratios across ISIs 2–4. All parameters were investigated in all patients in both hemispheres. The mean duration of the recording sessions was 60 min. Each subject received a mean number of approximately 200 stimuli in each recording session.

Statistical analysis

We used nonparametric tests to evaluate the evolution of neurophysiologic and clinical data because of the sample's size. To test the effects of treatment between subjects we used the Mann–Whitney test (MW). Wilcoxon signed ranks test (WT) was used to test the evolution of data within subjects. To find correlations between clinical scores and neurophysiologic data we performed the Spearman's rho correlation coefficient. A $P < 0.05$ value was assumed to be significant.

Results

Clinical findings

The degree of neurological impairment, functional status and depressive symptoms at entry into the study was similar among groups (MW: NIH, $Z = -1.5$; $P = 0.1$; BI, $Z = -0.1$; $P = 0.9$; LS, $Z = -0.6$; $P = 0.7$; HDRS, $Z = -0.1$; $P = 0.9$; BDI, $Z = -0{,}5$; $P = 0.6$). After 1 month, significant improvements from baseline values were observed in both groups (Table 2). However, at the second time point (T2), the mean NIHSS score in treated patients was significantly lower than that in patients who received placebo (treated mean NIHSS 2.3 vs placebo group NIHSS 3.5, $Z = -2.12$; $P = 0.03$, MW test). Other neurological and functional scales showed no difference between the two groups (Table 2, Fig. 1). An improvement in depressive symptoms was present in both groups (WT: group A: HDRS, $Z = -2.8$; $P = 0.01$; BDI, $Z = -1.9$; $P = 0.04$; group B: HDRS, $Z = -2.3$; $P = 0.02$; BDI, $Z = -1.8$; $P = 0.05$), with a difference between groups (MW: HDRS, $Z = -1.9$; $P = 0.04$; BDI, $Z = -0.54$; $P = 0.06$).

Table 2 Neurological, functional and depressive symptoms course state

	Citalopram group		No drug group	
	T1	T2	T1	T2
NHSS	5 (±2.5)	2.3*, ** (±2)	5.3 (±1.5)	3.5* (±1.3)
LS	60 (±8)	71* (±10)	54 (±13)	67* (±10)
BI	61 (±25)	82* (±28)	60 (±30)	75* (±25)
HDRS	9.9 (±3.5)	6.6*, ** (±3.6)	10 (±2)	8* (±3)
BDI	7.4 (±2)	5.4* (±2.3)	7 (±2.5)	6* (±2)

There is a significant improvement in mean scores of neurological, functional status and depressive symptoms in both groups at T2. Patients taking citalopram showed better neurological improvement at T2. Standard deviations are shown in brackets

LS Lindmark Scale, *BI* Barthel Index, *HDRS* Hamilton Depressive Rating Scale, *BDI* Beck Depression Inventory

*$P < 0.05$ Wilcoxon signed rank test. Significant improvement between T1 and T2

**$P < 0.05$ Mann–Whitney test. Significant differences at T2 between citalopram group and no drug group

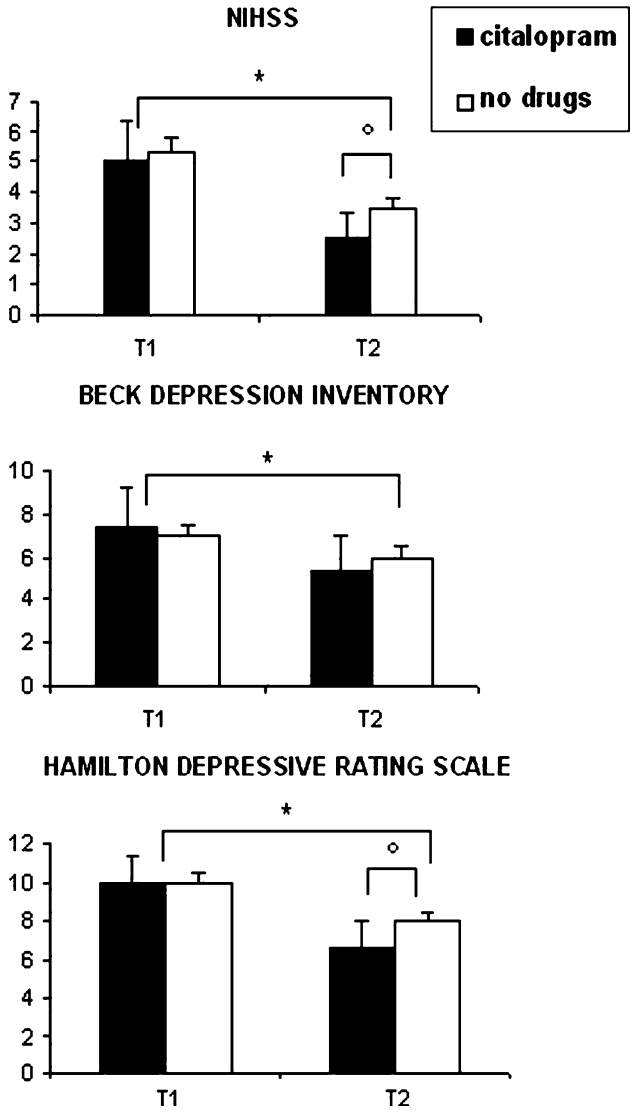

Fig. 1 Neurological impairment and depressive symptoms score in patients taking citalopram and patients without drug. There is a significant improvement in neurological, functional status and depressive symptoms in both groups from T1 to T2. This improvement is greater in patients taking citalopram. *Asterisk* $P < 0.05$ Wilcoxon signed rank test. Significant improvement between T1 and T2. *Open circle* $P < 0.05$ Mann–Whitney test. Significant differences at T2 between citalopram group and no drug group

TMS parameters

Affected hemisphere (AH)

Both groups presented a progressive increase of MEP size (group A; $Z = -1.15$; $P = 0.14$; group B; $Z = -1.7$; $P = 0.9$) and a significant reduction of rMT (group A; $Z = -1.9$; $P = 0.04$; group B; $Z = -2.3$; $P = 0.02$) over AH at T2. No groups effects were observed (MW: MT, $Z = -0.36$; $P = 0.7$; ICI, $Z = -0.53$; $P = 0.6$; MEP, $Z = -1.1$; $P = 0.27$).

Unaffected hemisphere (UH)

An increase of ICI was present in both groups (WT: group A, $Z = -2.7$; $P = 0.01$; group B, $Z = -2.3$; $P = 0.02$). The rMT increased only in the treated group (WT: group A, $Z = -1.9$; $P = 0.04$; group B, $Z = -0.9$; $P = 0.4$). Patients taking the drug showed a larger increase of ICI (MW: $Z = -1.9$; $P = 0.04$) and rMT (MW: $Z = -2.1$; $P = 0.03$) over UH. Other measures, MEP amplitude and MEP latency, were not modified by citalopram treatment (Table 3, Fig. 2).

Correlations

We analyzed correlations between neurophysiologic variables and clinical data between time T1 (baseline) and time T2 (follow-up). We made correlations between the modifications of these parameters (ΔT1–T2). We failed to demonstrate any correlation between the time course of neurophysiologic and clinical data, both in the citalopram and the placebo group. Neurophysiologic data and mood (HDRS-rMT UH: $R = -0.09$, $P = 0.59$; HDRS-rMT AH: $R = -0.15$, $P = 0.36$; HDRS-ICI UH: $R = 0.154$, $P = 0.37$) and neurological status (NIH-rMT UH: $R = -0.19$, $P = 0.28$; NIH-rMT AH: $R = 0.18$, $P = 0.3$; NIH-ICI UH: $R = 0.16$, $P = 0.34$) are not related. Neurological status and mood scores are also not related (NIH-HDRS: $R = 0.26$, $P = 0.12$; NIH-BDI: $R = -0.1$, $P = 0.6$).

Discussion

One novel aspect of this study is the concomitant registration of clinical and neurophysiologic parameters in patients taking a serotonergic drug after stroke. We evaluated the degree of recovery from a single hemispheric stroke in response to rehabilitation therapy alone or when associated with the serotonergic drug citalopram. Patients taking citalopram exhibited a decrease of excitability over the unaffected hemisphere and better clinical improvement without notable side effects. A limit of this study could be the severity of patients' stroke that is quite low, mean NIHSS scores 5, and therefore conclusions may be drawn only for patients with minor stroke.

Depressive symptoms

Depression represents the most frequent mood/emotional disorder after stroke, being found in 10–25% of patients [10]. Post-stroke depression appears to correlate with poorer functional outcome [5, 22] and antidepressants are generally prescribed to improve quality of life and active participation in rehabilitation programs [1]. In this study,

Table 3 Neurophysiological parameters during recovery

	Citalopram		No drugs	
	T1	T2	T1	T2
Affected side				
Motor threshold	72 (±23)	64* (±20)	73 (±18)	61* (±15)
Intracortical inhibition	87 (±28)	76 (±29)	71 (±22)	68 (±27)
MEP amplitude	0.3 mV (±0.3)	0.5 mV (±0.3)	0.47 mV (±0.2)	0.7 mV (±0.2)
Unaffected side				
Motor threshold	51 (±9)	60*, ** (±8)	54 (±7)	53 (±7)
Intracortical inhibition	72 (±24)	38*, ** (±25)	60 (±21)	49* (±20)
MEP amplitude	0.51 mV (±0.4)	0.64 mV (±0.4)	0.89 mV (±0.6)	0.9 mV (±0.6)

Mean scores are reported. Standard deviations are presented in brackets

Affected side both groups had a significant reduction of rMT at T2; other neurophysiological parameters did not show significant modification. There are no group effects

Unaffected side patients taking citalopram showed a significant decrease of rMT. The % conditioned MEP at T2 was significantly lower in the treated group than in the untreated group (ICI increase)

*$P < 0.05$ Wilcoxon signed rank test. Significant improvement between T1 and T2

**$P < 0.05$ Mann–Whitney test. Significant differences at T2 between citalopram group and no drug group

after 1 month both groups improved their motor performance significantly, but the treated group showed more improvement. Our patients, according to the HDRS and BDI scores, were not depressed. Therefore, although treated patients had smaller HDRS scores, efficacy of citalopram in terms of functional outcome based on differences in depressive symptoms between groups after treatment is presumably marginal. We did not find any correlation between mood scores and neurological scores. While the effects of antidepressive drugs on behavior and motivation in rehabilitative training cannot be excluded, in these patients this effect was associated with changes in motor excitability mainly in the motor areas of the unaffected hemisphere.

Motor cortex excitabiltiy

A balanced excitability over both hemispheres appears to correlate with a better degree of motor recovery [30], with a possible role attributed even to the unaffected hemisphere, as demonstrated in previous neurophysiologic [19] and neuroimaging studies [33, 34]. A decrease in motor intracortical inhibition in patients affected by stroke may be responsible, similarly to that observed in experimental animals [22, 28], for a decrease in GABAergic activity over the affected and unaffected hemispheres. Over the affected hemisphere, motor disinhibition may have an immediate role in facilitating motor outputs and may also be important in functional reorganization of the cortex, although this hypothesis must be confirmed in long-term studies [30]. In patients with different degrees of impairment we did not register any differences in motor inhibition

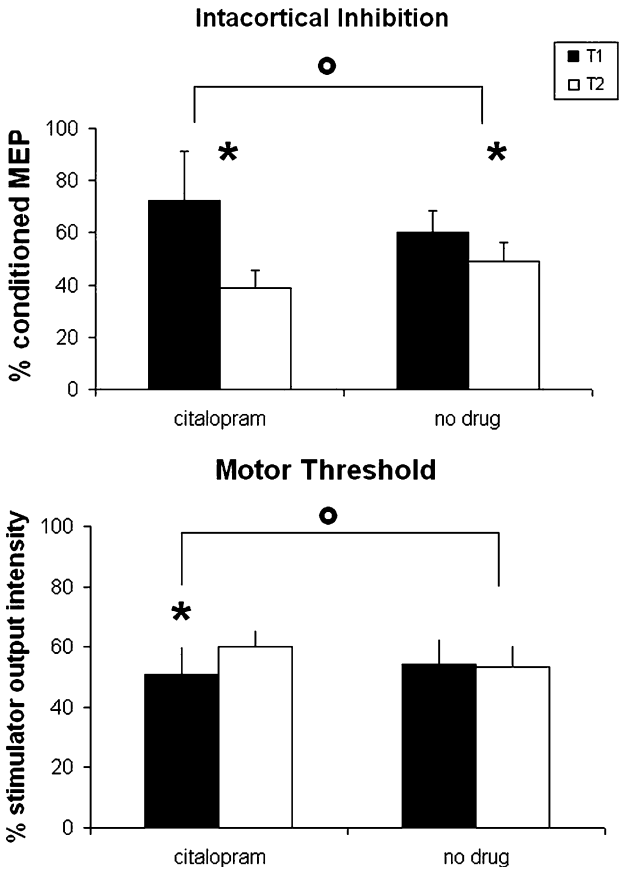

Fig. 2 Time course of neurophysiological parameters over the unaffected side. A percentage of conditioned MEP amplitude decrease reflects an ICI increase. *Asterisk* $P < 0.05$ Wilcoxon signed rank test. Significant improvement between T1 and T2. *Open circle* $P < 0.05$ Mann–Whitney test. Significant differences at T2 between citalopram group and no drug group

in the acute phase, from 15 to 20 days after stroke onset. As discussed by Liepert et al. [13], motor inhibition was reduced in those patients with partial sparing of motor areas. Liepert and coworkers postulated that this disinhibition might be indicative of compensatory mechanisms involved in recovery-related reorganization. In our study, in the acute phase there is a motor disinhibition over the unaffected hemisphere, representing an expression of unmasking of normally suppressed or inhibited pathways, rather than a sign of restorative change to compensate for the motor deficit. During motor recovery, a return to balanced excitability is related to better recovery. The persistence of disinhibition in the unaffected hemisphere is associated with poorer motor recovery, as reported in precedent studies [20]. The intrinsic mechanism of the physiological phenomena could be attributable to transcallosal inhibition as well as to focal intracortical mechanisms [20]. Decreased excitability over the unaffected hemisphere after treatment agrees with previous studies demonstrating a possible role of serotonergic drugs in the modulation of motor cortical excitability [25, 34, 36]. This modulation of cortical excitability is prevalent on the unaffected side where the motor areas and the inhibitory and facilitator circuits are preserved in comparison to the motor areas of the affected hemisphere. A possible role of increased inhibition over the unaffected hemisphere in motor recovery can be only presumed.

Motor cortex excitability modulation or anti-depressive effects?

The modification of TMS parameters after drug intake represents only effects on the motor system. In previous studies, a single oral administration of an anti-depressive drug can modify motor excitability without any effect on mood [25]. The association with the anti-depressive effect is the expression of a wider and more complex brain mechanism. We could even say that inhibition of the motor system after drug intake can be considered as a side effect. Therefore the significant differences in brain inhibition between treated and untreated patients suggest a possible useful side effect of this drug on the motor system in this kind of patient. No correlation exists between TMS parameters and mood, so we can postulate that antidepressive effects and brain excitability modulation are two different consequences of drug intake.

In this study we observed that the motor excitability modifications of the unaffected hemisphere induced by the serotonergic drug citalopram are associated with better motor recovery. However, given the sample's small size, we cannot prove with full certainty any independent effect of citalopram on recovery. The greater inhibition induced by the drug over the unaffected hemisphere could accelerate the normalization of excitability balance between the two hemispheres. The possibility of acting on the disinhibition of the unaffected hemisphere motor areas using pharmacological treatment represents a new clinical possibility in rehabilitation of stroke patients.

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