The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: A randomized, double blind sham controlled study

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Abstract

BACKGROUND: Transcranial magnetic stimulation (rTMS) can modulate cortical activity. The goal of our study was to assess whether rTMS would facilitate effect of serotonin reuptake inhibitors in patients with panic disorder.

METHODS: Fifteen patients suffering from panic disorder resistant to serotonin reuptake inhibitor (SRI) therapy were randomly assigned to either active or to sham rTMS. The aim of the study was to compare the 2 and 4 weeks efficacy of the 10 sessions 1 Hz rTMS with sham rTMS add on SRI therapy. We use 1 Hz, 30 minutes rTMS, 110% of motor threshold administered over the right dorso-lateral prefrontal cortex (DLPFC). The same time schedule was used for sham administration. Fifteen patients finished the study. Psychopathology was assessed using the rating scales CGI, HAMA, PDSS and BAI before the treatment, immediately after the experimental treatment and 2 weeks after the experimental treatment by an independent reviewer.

RESULTS: Both groups improved during the study period but the treatment effect did not differ between groups in any of the instruments.

CONCLUSION: Low frequency rTMS administered over the right dorso-lateral prefrontal cortex after 10 sessions did not differ from sham rTMS add on serotonin reuptake inhibitors in patients with panic disorder.

ORIGINAL ARTICLE

Introduction

Panic disorder is chronic psychiatric disorder. Only approx. 25% patients reach full remission after drug therapy over four years follow up (Katschnig et al., 1995). One way to increase proportion of patients with full remission is cognitive behavioral therapy. This kind of therapy is effective but is not available to all patients. So another therapeutic modality in patients with panic disorder are tested. Repetitive transcranial magnetic stimulation (shortly rTMS) is based on the electromagnetic field induction (duration of 100–200 ms, 2T intensity) using the coil placed over the skull. The effect is neuronal depolarisation within the depth of 2cm (depending on distance of coil from underlying cortex) from head surface (George, et al., 1999). Mechanism of action of TMS in neuropsychiatric disorders is not yet fully known. It was observed that low frequency TMS reduced cerebral glucose metabolism in cortical and subcortical regions immediately after application as revealed by PET and SPECT imaging studies (Speer et al., 2003) . Nevertheless, there are completely opposite findings (Stallings et al., 1997, Kimbrell et al., 1999). Studies using high frequency TMS as treatment of depression disorders coupled with SPECT mapping of cerebral activity and rCBF showed increased rCBF in the site of stimulation (over the left dorso-lateral prefrontal cortex – LDPFC) as well as changes in remote regions (Catafau et al., 2001, Nahas et al., 2001). Prefrontal rTMS can affect memory (Pascual-Leone et al. 1996), mood (George et al. 1996) in healthy individuals and may act as an antidepressants (Pacual-Leone at al. 1996). There are only few studies using rTMS in panic disorder**.**

One case report described application of low frequency rTMS (1Hz) over the righ dorso-lateral prefrontal cortex in patient with panic disorder resulting in a marked improvement, maintained for 4 weeks (Zwanger et al., 2002). Second small case-series presented a modest and partial symptom improvement in three patients with panic disorder but improvement did not seem to be clinically relevant (Garcia-Toro et al., 2002). This finding is in agreement with our study where we found correlation of symptomatology with regional metabolic changes in patients with panic disorder in rest conditions (Paskova et al., 2003). Positive correlation between severity of symptoms and intensity of ^{18}FDG PET uptake in right fronto-temporal area were detected. These areas seem to be possible candidate locations for rTMS. Positive correlation between metabolism and intensity of symptoms suggested further application of low frequency rTMS, which decrease metabolism in the area of administration.

The general aims of our randomized, double blind, sham controlled rTMS study was to assess the therapeutic effect the low frequency rTMS add to SRI in patienst with panic disorder. Null hypothesis was:

- rTMS will have no impact on the symptomatology in the patients with panic disorder

Alternative hypothesis was:

- rTMS will have significant impact on the symptomatology of panic disorder comparing with sham rTMS.

Methods

Subjects

Fifteen patients with panic disorder according to ICD-10 research diagnostic criteria for panic disorder or for panic disorder with agoraphobia; treated with SRIs minimaly for 6 weeks before the study and did not respond to this medication, were randomly allocated to active rTMS or sham rTMS after initial assessment.

Including criteria:

a, ICD-10 research critaria for panic disorder or for panic disorder with agoraphobia
b, Non-responders on SRIs (at least 6 weeks treatment)
c, Age 18–45 years
d, Written informal consensus

Excluding criteria:

a, Major depressive disorder
b, Risk of suicidality
c, 17-item HAMD more than 16
d, Organic psychiatric disorder
e, Psychotic disorder in history
f, Abusus of alcohol or other drugs
g, Serious somatic disease
h, Patients using non-prescribed medication
i, Gravidity or lactation
j, Epilepsy or pathological EEG
k, Patients with implantats of pacemakers

Including criteria were confirmed with 2 independent raters.

Criteria for exclusion during the study (drop out):

a, Fulfilling the excluding criteria
b, Patient do not collaborate
c, Decision of researcher in the case of health problems of patients

The study was designed as a double-blind, therefore rTMS was performed by a psychiatrist trained in rTMS application and rating was provided by another trained psychiatrist blind to rTMS therapy. Patients were randomly assigned to the two treatment groups:

- 1st group – treated with active rTMS
- 2nd group – treated with sham rTMS

Technical devices

Magstim Super Rapid stimulator (Whitland, UK) with an air cooled, figure-eight 70-mm coil was used for 10 sessions (5 sessions per week for 2 weeks) The frequency of 1Hz rTMS at 110% of motor threshold (MT) was administered over the right DLPFC for 30 min., with

the total number of 1 800 pulses per session. The right DPLFC stimulation site was defined as the region 5 cm rostral in the same sagittal plane as the optimal site for MT production in the left abductor pollicis brevis. MT was assessed as the lowest strength of TMS needed to elicit 5 or more electromyographic responses (EMG, Neurosign 400 equipment) ≥50 μV within ten trials. The sham stimulation was defined with a coil diverted by 90 degrees over the same area and same intensity and design as real rTMS.

Ratings

General psychopathology was assessed by Clinical Global Impression (CGI – Guy 1976); anxiety was objectively measured with HAMA – Hamilton Rating Scale for Anxiety (Hamilton 1959) and self report BAI – Beck Anxiety Inventory (Beck a Emery 1985). Severity of symptomatology was measured with PDSS – Panic Disorder Severity Scale (Shear et al 1997). Rating scales were administered the day before first rTMS administration (week 0), then after 2 weeks (after 10 stimulation) (week 2) and after 4 weeks (2 weeks after last stimulation) (week 4).

Ethical issues

Investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the written informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The local ethic Committee of Prague Psychiatric Center and Mental Hospital Bohnice approved this project.

Table 1. Time table for using the measures.

Measurements	Week 0	Week 2	Week 4
ICD-10	X		
MINI	X		
CGI-S	X	X	X
PDSS	X	X	X
HAMA	X	X	X
BAI	X	X	X

ICD-10 = The International Classification of Disorders, 10th revision
MINI = Mini-International Neuropsychiatric Interview
CGI-S = Clinical Global Impression-Severity
PDSS = Panic Disorder Severity Scale
HAMA = Hamilton Anxiety Rating Scale
BAI = Beck Anxiety Inventory

Table 2. Patients included and excluded from the study.

Patients referred to the PCP	33
Including diagnostic criteria reached	21
Signed informed consensus	15
Completers	15

Statistics

All data are presented as the mean and SD. Patient's demographic and baseline clinical characteristics were compared between treatment groups and analyzed using the two-sample t-test or the Mann-Whitney U test and chi-square test or Fisher's exact test for continuous and categorical variables, respectively. Results were analyzed using non-parametric repeated measure analysis of variance (Friedman's test with post hoc Wilcoxon signed rank test with a Bonferroni correction for multiple comparisons) and Mann-Whitney U-tests for intra- and inter-group comparisons respectively. Results were considered significant if $p<0.05$. Statistical computing was performed with Statsoft Statistica version 7.0 software.

RESULTS

Description of the patient groups

There were thirty three patient referred to the Prague Psychiatric centre for resistant panic disorder. Twenty one of them fulfilled the diagnostic including criteria to the study but only fifteen signed informed consensus (Table 2). Fifteen patients was randomized to two study groups. The patients had been receiving stable pharmacological treatment (antidepressants) for 6 weeks before study enrollment and during the study.

There were no statistically significant differences between the active and sham groups in terms of demographic characteristics such as age, marital status, duration of the disorder and dose of antidepressant medication (calculated to the paroxetine equivalents: paroxetine 20 mg = citalopram 20 mg or fluoxetine 20 mg, or sertralin 50 mg or venlafaxin 75 mg). The groups significantly differed in education; more patients from the sham group finished secondary school than from rTMS group. The demographic and medication baseline data of completers are presented in the Table 3.

There were no statistically significant differences between the active and sham groups in the average scores of psychopathology rating scales of CGI, HAMA,

Table 3. Demographic data.

	rTMS	Sham	Statistics
number	7	8	
age	33.7±9.2	33.8±12.2	UTT: n.s.
gender; male : female	1:6	3:5	chi^2: n.s.
education: basic : secondary : university	5: 1: 1	1 : 6 : 1	chi^2: $p< 0.05$
single : married	2 : 5	2:6	FET: n.s.
antidepressant medication (equivalent of paroxetine)	20.0±1.6 mg	22.5±17.5 mg	UTT: n.s.
duration of disorder (years)	9.9±6.1	9.1±6.9	UTT: n.s.

UTT – unpaired t-test; FET - Fischer's exact test,
chi^2 – Chi-square test with Yates' correction

PDSS and BAI. The baseline data from rating scales are presented in the Table 4.

Pharmacotherapy

All patients followed with medication (SSRIs) which they used before without any change during the study. The average doses of antidepressant medication given on Table 3. The mean doses (unpaired t-test) of the psychopharmacs not differ between groups.

Rating scales

CGI – severity

There were not significant differences in the severity scores of Clinical Global Impression (CGI) in both groups at the beginning (see Table 5). Severity scores dropped significantly in both groups during the treatment, but the differences between the groups after two week of treatment and after another two weeks were not significant (Mann Whitney U test: n.s.). Only one patient from rTMS and 2 patients from sham rTMS groups reached the score 2 immediately after treatment.

HAMA

HAMA is an objective rating scale for measuring general symptoms of anxiety (not solely focused on panic symptoms). At the beginning there were not significant differences in the severity of HAMA scores between the two groups. During the tretment statistically significant decrease of total HAMA scores occurred in sham group but not in rTMS group. However, no significant difference in mean total scores was found between two groups after two week of treatment and after another two weeks (Mann Whitney U test: n.s (p=0.054) – see Table 5). There were 3 patients from rTMS group and 2 patients from sham rTMS group who reached the 50% decrease of the HAMA score after treatment.

PDSS

Panic Disorder Severity Scale (PDSS) is an instrument for specific assessment of panic disorder. It is the most sensitive instrument for this disorder. There were not significant differences in the severity scores of PDSS in both groups at the beginning (see Table 5). At the end of

Table 4. The rating scales before the treatment.

	rTMS		sham		Statistics test: p-value
	mean	SD	mean	SD	
CGI – S	5.286	0.7559	4.625	1.188	MW: n.s.
HAMA	21.43	4.791	21.13	5.111	MW: n.s.
PDSS	17.86	3.338	16.25	4.464	MW: n.s.
BAI	34.86	10.07	25.38	14.21	MW: n.s.

MW = Mann-Whitney U test

Table 5. Mean scores in rating scales during the treatment.

		rTMS		sham		Statistics test: p-value
		mean	SD	mean	SD	
CGI – S	**Week 0**	5.286	0.7559	4.625	1.188	n.s.
	Week 2	4.143	1.345	3.75	1.488	n.s.
	Week 4	3.714	0.488	2.75	1.165	n.s.
HAMA	**Week 0**	21.43	4.791	21.13	5.111	n.s.
	Week 2	18.43	11.41	13.13	6.175	n.s.
	Week 4	15.86	4.914	10.75	3.845	n.s. (p=0.054)
PDSS	**Week 0**	17.86	3.338	16.25	4.464	n.s.
	Week 2	14.57	4.429	10.75	6.431	n.s.
	Week 4	11.71	4.071	8.25	4.95	n.s.
BAI	**Week 0**	34.86	10.07	25.38	14.21	n.s.
	Week 2	24.14	11.57	15.63	7.891	n.s.
	Week 4	23.86	10.43	14.5	6.164	n.s. (p=0.072)

treatment there was a significant decrease in total PDSS scores in both groups. The difference between the groups was not statistically significant in week 2 and week 4 (Mann Whitney U test: n.s.). No one from rTMS group and 2 patients from sham rTMS group reached the 50% decrease of the PDSS score after treatment.

BAI

There were no significant differences in the severity of Beck Anxiety Inventory (BAI) scores between the two groups at the beginning. Time path of BAI scores is similar to that of HAMA. Statistically significant decrease of total scores during the treatment occurred in sham group but not in rTMS group. However, the difference in the mean BAI total scores between the two treatment groups was not statistically significant in week 2 and week 4 (Mann Whitney U test: n.s ($p=0.072$) – see Table 5). There were 2 patients from rTMS group and 1 patient from sham rTMS group who reached the 50% decrease of the BAI score after treatment.

Tolerability and safety

There were no seizures, headaches, neurological and cognitive difficulties occurred.

Discussion

According to our hypotheses, the study has confirmed the null hypothesis – low frequency rTMS of right dorsolateral prefrontal cortex had no significant impact on the symptomatology in the patients suffering with the panic disorder who did not respond to SSRIs. There were sligthly better results in sham rTMS group. But no significant differences between treatment groups were detected. However the two groups were too small to generalize these results. Our negative findings may be related to type II error. Also we treated chronic patients suffering with panic disorder in this study. There was relatively long mean previous duration (9 years) of the disorder in these patients. The question is how can rTMS work in less chronic patients? How do patients respond without any medication? Another question is wheather the place of stimulation, duration and low frequency of rTMS is optimal for patients with panic disorder? Some studies indicated that for rTMS efficacy are very important parameters of intensity, number of pulses or number of sessions (Gerson et al., 2003). Some rTMS studies in patients with depression showed that 10 sessions could be insufficient even in therapy in patients with depression (Gerson et al., 2003). Maybe for rTMS effect in patients with panic disorder is necessary rTMS therapy longer than 10 sessions. Another question is, if the place of stimulation and low frequency of stimulation are optimal for panic disorder patients? In our case study (Zalesky et al., 2004) we presented patient with panic disorder and agoraphobia which was treated with high-frequency rTMS administered over the left dorsolateral prefrontal cortex for 2 weeks. After the treatment there was an improvement in the scores of rating scales. However the symptoms have worsened again after the end of the treatment. This could indicate insufficient duration of the therapy. Another case study described effective high-frequency rTMS over the left frontal cortex after the failure of low frequency rTMS over right frontal cortex (Guaiana et al., 2005). That suggests that high-frequency rTMS and application over the left-frontal cortex could be effective. Choice of the place and low frequency in our study was done according results of hypermetabolism in panic patients on PET in this region (Paskova et al., 2003). According the Hoffman and Cavus (2002) hypothesis the low frequency rTMS reduces hypermetabolism and hyperexcitability in the brain regions. Functional neuroimaging studies (Shin et al., 1997) suggest that patients with posttraumatic stress disorder have the similar right-sided frontal activation as our patients with panic disorder. Grisaru et al. (1998) reported a pilot study of 10 patients with posttraumatic stress disorder who received slow rTMS to both the left and right motor cortex. Their symptoms improved for 1–7 days after the trial. That was not the case in our study with panic disorder patients. Maybe we should consider the possible indirect propagated effect of slow rTMS. Neuroimaging data for patients with depression and epilepsy, for instance, have suggested that greater suppressive effect of 1 Hz rTMS are obtained in the cortical region contralateral to that being stimulated (Speer et al., 2000). If indirect effect of rTMS are distinct from direct effects, this finding would be important in designing intervention studies based on known cortical patterns of pathological activation. Further studies in this area need to be undertaken.

Conclusion

Low frequency rTMS administered over the right dorso-lateral prefrontal cortex during 10 sessions did not differ from sham rTMS in facilitating the effect of SRIs in patients with panic disorder in our study. Further studies are indicated to assess the efficacy of rTMS in panic disorder and to clarify the optimal stimulation characteristics.

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