SHORT REPORT

Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression

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Abstract

A growing number of studies report antidepressant effects of repetitive transcranial magnetic stimulation (rTMS) in patients with major depression. The hypothesis that high frequency (20 Hz) rTMS (HF-rTMS) may speed up and strengthen the therapeutic response to sertraline in MD was tested. Twenty eight patients who had not yet received medication for the present depressive episode (n=12) or had failed a single trial of an antidepressant medication (n=16) were started on sertraline and randomised to receive either real or sham HF-rTMS. HF-rTMS was applied to the left dorsolateral prefrontal area in daily sessions (30 trains of 2 s, 20-40 s intertrain interval, at 90% motor threshold) on 10 consecutive working days. The results suggest that in this patient population, HF-rTMS does not add efficacy over the use of standard antidepressant medication.

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Keywords: major depression; transcranial magnetic stimulation; sertraline; prefrontal area

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of inducing a fairly localised current in the cortex of the human brain. A time varying magnetic field is generated by a brief current pulse passed through a stimulation coil held over the subject's scalp. The magnetic field penetrates the scalp and skull unattenuated. The rapid change of the magnetic field induces a current strong enough to depolarise neurons and thus modify the activity in the targeted cortical area and trans-synaptically in functionally connected brain structures.^{1 2} If appropriate guidelines are followed rTMS is safe and has minimal side effects.³

Most of a growing number of studies on rTMS in depression report antidepressant effects applying high frequency stimulation (HF-rTMS; >1 Hz) over the left prefrontal cortex, whereas others have employed low frequency rTMS (LF-rTMS; <1 Hz) over the right prefrontal cortex (for reviews see George *et al*,¹ Reid *et al*,⁴ and Menkes *et al*).⁵ Nevertheless, few controlled studies have

focused on the effect of rTMS as add on treatment to medications in depression. We report a double blind controlled pilot study of left prefrontal HF-rTMS as adjuvant treatment to sertraline in patients with major depression.

Methods

The local research and ethics review board approved the study. All patients gave their written informed consent before entering the study and after the procedure and objectives had been fully explained to them. We recruited 28 patients older than 18 years of age who had not tried sertraline for the present depression episode and met DSM IV criteria for major depression.⁶ Prospective patients were screened for contraindications for rTMS,³ including personal or family history of seizures, past neurosurgical procedures, implanted pacemaker, inner ear prosthesis, medication pumps, pregnancy, and unstable medical conditions. Patients with a high suicidal risk, based on a structured diagnostic interview were also excluded.

The patients made a first selection evaluation visit in which, after confirming the DSM-IV diagnosis, a wash out period of 1 week off all medications began. Then, in addition to undergoing rTMS, all these patients were started on sertraline (50 mg for 2 weeks, later increased, if necessary, depending on clinical response). All 28 patients, except two, were taking benzodiazepines at the time of entry into the study. These were kept unchanged. Two subjects were left handed, and both of them were randomised to receive sham rTMS.

Stimulation was applied to the left dorsolateral prefrontal cortex⁷ using a Dantec Magpro stimulator (Dantec Medical, Medtronic Inc, Minneapolis, MN, USA) and an 8 shaped coil (each wing measuring 8.5 cm in diameter). Stimulation intensity was 90% of the motor threshold intensity defined according to the current recommendations of the International Federation of Clinical Neurophysiology. Stimulation frequency was 20 Hz. The coil was centred 5 cm anterior to and in the same parasagittal plane as the optimal scalp position for activation of the contralateral abductor pollicis brevis muscle.⁷ The stimulation indices used were within current safety guidelines.³

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Table 1 Summary of results

	Real HF-rTMS	Sham rTMS
Patients (n)	11	11
age (y) (mean (SD))	43.2 (13.1)	45.0 (18.3)
Males	5	5
Inpatients	3	1
Patients with one previous pharmacological trial	5	6
Patients with previous episodes	7	4
Duration of present episode (months)	6.6 (4.2)	8.1 (12.6)
HDRS entry score	25.9 (6.4)	26.6 (6.4)
HDRS 1 week score	20.1 (5.2) (−20.7%)	22.3 (7.0) (−15.3%)
HDRS 2 week score	16.1 (7.7) (−38.2%)	17.9 (8.7) (−34.3%)
HDRS 4 week score	14.3 (7.1) (−45.2%)	14.5 (10.9) (−45.2%)
GCI entry score	5.0 (0.9)	4.3 (1.1)
GCI 1 week score	4.2 (1.1) (−16.0%)	3.9 (1.3) (−9.3%)
GCI 2 week score	3.3 (1.4) (−34.0%)	3.4 (1.6) (−20.9%)
GCI 4 week score	2.5 (1.7) (−50.0%)	2.6 (1.7) (−39.5%)
BDI entry score	27.09 (8.5)	23.18 (6.9)
BDI 1 week score	23.1 (5.1) (−14.4%)	22.3 (8.3) (−3.7%)
BDI 2 week score	19.4 (6.7) (−28.1%)	21.2 (7.9) (−8.2%)
BDI 4 week score	19.5 (7.4) (−27.7%)	18.5 (11.1) (−20.1%)

HDRS=Hamilton depression rating scale; GCI=global clinical inventory; BDI=Beck depression inventory.

Real rTMS was applied with the coil held flat on the scalp and the handle pointing occipitally. Sham rTMS was applied with the stimulation coil angulated 90 degrees away from the scalp. Clinical evaluators and patients were unaware of group assignment. Each patient received 10 rTMS sessions on 10 consecutive working days. Each daily session consisted of 30 trains of 2 seconds duration and 20–40 seconds intertrain intervals (total of 1200 stimuli/session). At the end of each session patients were asked about possible secondary effects.

For assessment of antidepressant effects, we used the 21 item Hamilton depression rating scale (HDRS),⁸ the global clinical inventory (GCI),⁹ and the 17 item Beck depression inventory (BDI).¹⁰ Statistical analysis was performed at a significance threshold of 0.05 using the Windows 95 SPSS software package. Repeated measures analyses of variance (ANOVA) were used to investigate whether there were group differences at baseline, to assess change over time, and to look for interaction effects. When the application of parametric tests was not possible, the Mann-Whitney test was used.

Results

Two patients terminated participation in the study during the 2 weeks of rTMS application (due to intolerance to sertraline in one patient and “fear of brain damage” in the second patient). Four patients were lost in the 2 weeks of follow up after rTMS (three for unacceptable changes in medication, one because of “personal reasons”). The HDRS score was only slightly changed in these patients up to the point of their dropping out of the study. Three of the dropped patients had been receiving sham rTMS and three real rTMS. Their data were excluded from subsequent detailed analysis. The data of the 22 remaining patients were analyzed. The groups receiving real and sham treatment did not differ significantly in sex, age, baseline scores in any of the depression scales, or other clinical variables.

Real HF-rTMS did not result in statistically greater decrements in the HDRS, GCI, and BDI scores than sham HF-rTMS during the

first 2 weeks. At the second week, four of the patients who received HF-rTMS had a >50% decrease in HDRS scores, and four had a >25% decrease (in the sham HF-rTMS three had a >50% decrease in HDRS scores, and five had a > 25% decrease).

The only side effect of rTMS encountered was slight, self limited, and transitory muscle tension headaches affecting three of the 11 patients that received real HF-rTMS.

Discussion

In combination with antidepressant medication (sertraline), real rTMS resulted in a similar antidepressant effect to sham rTMS. In these patients real rTMS seems to have added nothing to the medication regimen alone. It is possible that HF-rTMS was not effective. Alternatively, patients with major depression may have benefited from sertraline enough to obscure a small additional benefit from the rTMS. The placebo effect of rTMS may also have contributed to abolish statistical significance. The lack of a control group receiving medication and no rTMS precludes us from making this distinction. Nevertheless, our results suggest a slight non-statistical tendency for the therapeutic effect for the combination of real rTMS with medication to be faster than that of sham rTMS and medication (table 1). The main limitation of this trial is the relatively small sample size.

There are several studies available which have used rTMS in patients with major depression while they were taking antidepressant drugs. In all these trials the antidepressant effects and potential side effects of rTMS seemed unaffected by the concurrent intake of medication. Conca *et al* were the first to specifically study the potential benefit of rTMS as add on therapy to antidepressant medication in patients with major depression.¹¹ They conducted a controlled clinical trial on 24 patients randomised to receive antidepressant medication with or without concurrent rTMS add on. Patients receiving rTMS add on showed a faster remission of depressive symptoms. Differences between the two patient groups became statistically significant already after the third rTMS session and grew by the end of the study. Our results do not replicate the findings of Conca *et al*, perhaps because in their study the lack of sham rTMS control resulted in a rather different protocol for both patient groups and made the study essentially an open design.¹¹ Other studies using rTMS as an augmentation technique to antidepressant medication have found positive and negative results, but are also difficult to compare with ours because of important differences in the methodology and sample used (medication resistant patients).^{12–13}

In conclusion, in this sample of non-resistant patients with major depression, HF-rTMS seems to have no adjunctive benefit associated with sertraline.

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