REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN MEDICATION-RESISTANT BIPOLAR DEPRESSION

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SUMMARY

OBJECTIVES: Repetitive transcranial magnetic stimulation (rTMS) has been demonstrated to be effective in depressive disorders in many studies. But this promising method has not been specifically studied in bipolar depression in which antidepressant medications can precipitate a manic episode and lead to rapid-cycling disorder.

METHODS: Eight patients having drug-resistant severe bipolar depression were applied rTMS with antidepressant drugs in an open and uncontrolled study. The Hamilton Depression Rating Scale was given to the patients both before the treatment and after ten sessions of rTMS. Fifty percent decrease in the score was evaluated as ‘response’. The patients also used antipsychotic and/or mood stabilizing drugs.

RESULTS: Five patients responded to the rTMS therapy recovering from depression. Three patients shifted to manic episodes.

COCNLUSION: rTMS may be an effective method in the treatment of bipolar depression. However, the fact that three patients out of eight switched to mania raises questions about its safety even though all of these patients were also taking antidepressant medications.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a promising research and clinical tool in a number of neurological and psychiatric disorders. Its efficacy in depression has been demonstrated in many studies (1,2,3,4,5,6,7,8). Fewer studies have investigated rTMS in bipolar disorder.

Bipolar depression is an area of clinical challenge. Antidepressant drugs may cause a switch to mania and rapid-cycling disorder. With respect to the high prevalence of bipolar disorder and the extent of morbidity and mortality it causes, it is clear that novel therapeutic approaches may be very imporant. We have investigated the efficacy and safety of rTMS in treatment-resistant bipolar depression.

METHODS

Eight patients having drug-resistant severe bipolar depression were applied rTMS with antidepressant drugs in an open and uncontrolled prospective study. Four were females and four were males. The average age of the patients was 31.1. The diagnosis of depression was made according to the DSM-IV. Drug-resistant depression was described as the failure to respond adequately both to the addition of or increase in the dose of lithium and to two succesive courses of monotherapy with pharmacologically different antidepressants given in adequate doses for sufficient time. The seventeen-item Hamilton Depression Rating Scale (HDRS) were given to the patients both before the treatment and after ten sessions of rTMS. Severe depression was described as having at least 22 points on the HDRS. A fifty percent decrease in the scale was evaluated as ‘response’. The patients also used antipsychotic and/or mood stabilizing drugs.

rTMS was applied over the lef prefrontal cortex (Magstim, rapid, superrrapid high frequency magnetic stimulator). Its intensity was the motor threshold that caused muscle movement when it was applied over the motor cortex. Other values of rTMS were 10 seconds, 25 Hz, 210 pulses and 70 trains. All patients gave written informed consent.

RESULTS

The average of HDRS scores of the patients was 28.2. All responded to the rTMS therapy, that is, showed at least 50 percent decrease in HDRS scores. However, three patients shifted to manic episodes.

In eight patients having medication-resistant severe bipolar depression, rTMS resulted in response to the therapy in 100 percent of patients. However, mania as an adverse effect occured in 37.5 of patients. Therefore, it seems that 62.5 of patients benefited from rTMS.

DISCUSSION

The fact that all eight patients having bipolar depression responded to rTMS is promising; however, high rate of switch to mania raises questions about the safety of this method.

There are case reports showing that transcranial magnetic stimulation has induced mania in patients suffering from bipolar depression (9,10,11,12,13). A study including both unipolar and bipolar patients compared rTMS and electroconvulsive therapy (ECT) and found significant difference neither in mania scores nor in improvement in depression (14). Another study conducted on 23 patients having bipolar depression who received either active or sham rTMS produced a trend but not statistically significant greater improvement in daily subjective mood ratings post-treatment, and no one switched to mania (15). Significant mood improvement was reported by bipolar disorder subjects who underwent an echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) in comparison with those who underwent sham EP-MRSI and with healthy subjects who underwent actual EP-MRSI (16).

On the other hand, TMS was tried in the treatment of mania. Sixteen manic patients received right or left prefrontal TMS in a double-blind, controlled trial, and significantly more improvement was observed in those treated with right than with left stimulation(17) in contrast to the application of TMS in depression, which improves more significantly with left stimulation. In a later study 25 manic patients entered and 19 completed, either right active TMS or right sham TMS was applied and right TMS was no more effective than sham (18). The authors concluded that previous results reporting higher efficacy of right TMS were due to an effect of left TMS to worsen mania or to the fact that their patient population had much more psychosis than in the previous study (depression studies have reported that psychosis is a poor prognostic sign for TMS response). In an open and prospective study, nine manic patients treated with right prefrontal rapid TMS for four weeks showed a sustained reduction of manic symptoms (19). However, TMS of right prefrontal cortex has also been reported to induce mania (12).

Regarding literature and the present study, it seems that left prefrontal TMS leads to improvement in unipolar or bipolar depression while inducing mania; on the other hand, right prefrontal TMS may be useful for mania. High and low frequency TMS may cause opposite effects in brain and mood (20). The high rate of switch to mania in our trial may be due to higher doses given to the patients than reported in the literature. An article reviewing TMS in the treatment of mood disorder concluded that the antidepressant and antimanic effects of TMS depend on clinical considerations such as stimulus frequency, intensity, and magnetic coil placement; in addition, biological heterogeneity among the patients treated with TMS may also contribute to differing efficacy accross clinical trials (21).

CONCLUSION

rTMS may be an effective method in the treatment of bipolar depression. However, the fact that three patients out of eight switched to mania raises questions about its safety even though all of these patients were also taking antidepressant medications. The effects of rTMS on mood are related to stimulus frequency, intensity and coil placement. Elaboration of practical issues on the clinical application of rTMS may lead to an important development in the treatment of bipolar disorders. However, further studies conducted in larger samples of subjects in a controlled and double-blind design are needed.

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