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Transcranial magnetic stimulation in treatment-resistant depressed patients: A double-blind, placebo-controlled trial

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Abstract

This 5-week, randomized, double-blind, placebo-controlled trial investigated the efficacy and tolerability of high frequency repetitive transcranial magnetic stimulation (rTMS) directed to the left prefrontal cortex in drug-resistant depressed patients. Fifty-four patients were randomly assigned to receive 10 daily applications of either real or sham rTMS. Subjects assigned to receive active stimulation were divided into two further subgroups according to the intensity of stimulation: 80% vs. 100% of motor threshold (MT). At study completion, the response rates were 61.1% ($n=11$), 27.8% ($n=5$) and 6.2% ($n=1$) for the 100% MT group, 80% MT group and sham group, respectively. A significant difference (Pearson χ^2 test) was found between the 100% MT and sham groups, while the 80% MT group did not differ significantly from the sham group. Between the two active groups, a marginally significant difference was observed. Analysis of variance with repeated measures on Hamilton Depression Rating Scale scores revealed a significantly different decrease over time of depressive symptomatology among the three treatment groups. Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded, and on the whole the technique was well tolerated. The results of this double-blind trial showed that rTMS may be a useful and safe adjunctive treatment for drug-resistant depressed patients.

Keywords: TMS; Resistant major depression; Motor threshold; Left dorsolateral prefrontal cortex

1. Introduction

Since its introduction by Barker et al. (1985), transcranial magnetic stimulation (TMS) has been used in the study of the functions of several brain regions (Inghilleri et al., 2003; Sakihara et al., 2003), and in the treatment of various neurological conditions (Cantello et al., 2002; Theodore et al., 2002; Canavero et al., 2003; Kanda et al., 2003; Tassinari et al., 2003) and psychiatric disorders (Greenberg et al., 1997; Grisaru et al., 1998; Alonso et al., 2001; Sachdev et al., 2001; D'Alfonso et al., 2002; Franck et al., 2003; Hoffman et al., 2003;

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Kaptsan et al., 2003). In particular, major depression is the mental disorder in which repetitive TMS (rTMS) has been most extensively applied, mainly as an adjunctive treatment for drug-resistant patients (George et al., 1995, 2000; Pascual-Leone et al., 1996; Berman et al., 2000; Padberg et al., 2002; Conca et al., 2002; Fitzgerald et al., 2003; Grunhaus et al., 2003).

Lesion, neuroimaging and electroencephalographic studies have suggested that a relative decrease in function in the prefrontal cortex may be involved in the pathophysiology of depression (Baxter et al., 1989; Bench et al., 1992; Mayberg, 1994; Hirono et al., 1998; Garcia-Toro et al., 2001a; Davidson et al., 2002). On the other hand, rapid rTMS has been shown to have an activating effect on the cortex underlying the site of stimulation and on functionally connected areas, while slow rate rTMS has been shown to have an opposite effect (Speer et al., 2000).

Different research groups have investigated the efficacy of TMS over the dorsolateral prefrontal cortex (DLPFC) in drug-resistant depression with conflicting results (for meta-analysis, see Burt et al., 2002; Martin et al., 2003; commentary in Holtzheimer et al., 2004). Differences in efficacy observed in many studies could be due both to the heterogeneity in stimulation parameters, such as number of pulses per day, intensity of stimulation and number of days of stimulation, as well as heterogeneity of the concomitant drug treatments.

As for the intensity of stimulation, it has been shown that higher intensities evoke more pronounced changes in the electrical (Kahkonen et al., 2005) and metabolic (Nahas et al., 2001) activity of the brain. Moreover, Padberg et al. (2002) found a difference, albeit small, between the antidepressant response to high-frequency rTMS at 90% and 100% MT; in general, the rate of responders in high-intensity studies is higher than for low-intensity trials (Gershon et al., 2003).

The aim of the present study is that of a dose-finding trial, assessing the efficacy of two different active stimulation intensities (80% MT vs. 100% MT) compared with sham rTMS, as well as the safety of rTMS in a sample of depressed patients defined as resistant to pharmacological antidepressant treatments.

2. Methods

2.1. Sample

Fifty-four right-handed patients, consecutively admitted to the mood disorders center of our department, were included in the study. All patients were suffering from a severe and drug-resistant major depressive episode without psychotic features. Patients were considered to suffer from a severe depressive episode when the Hamilton Rating Scale for Depression (HAM-D) score was 26 or higher (Bech et al., 1993); patients were defined as drug-resistant when they showed a lack of improvement to at least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode (Helmchen, 1990). In particular, our patients were resistant to at least two antidepressant drugs, different for mechanism of action and administered for an adequate length of time (at least 6 weeks). More specifically, they had shown resistance to selective serotonin or norepinephrine reuptake inhibitors (e.g., fluvoxamine, 300 mg/day; sertraline, 200 mg/day; or venlafaxine, 300 mg/day) and to one tricyclic antidepressant (e.g., imipramine, 250–300 mg/day). The treatment with the last antidepressant administered before entering the study did not produce a reduction of more than 20% on the total HAM-D score in any patient during the last 6 weeks. During the trial, 20 patients were on venlafaxine, 16 on fluvoxamine, 10 on sertraline and 8 on imipramine. All drugs were maintained at a stable dosage during the duration of the trial. Moreover, no other psychotrophic medication was allowed with the exception of lormetazepam (up to 2 mg at 10 p.m.) and lithium carbonate in bipolar patients (see Table 1). No patient had undergone electroconvulsive therapy (ECT) during the index episode, but five of them had successfully received ECT during previous episodes. Two of them were in the 100% group, one in the 80% group and two in the sham group.

Lifetime diagnosis of major depressive disorder was established by experienced trained psychiatrists and supervised by an independent senior psychiatrist on the basis of unstructured clinical interview and medical records according to DSM-IV criteria (American Psychiatric Association, 1994) and following a best estimate procedure (Leckman et al., 1982).