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Brain SPECT guided repetitive transcranial magnetic stimulation (rTMS) in treatment resistant major depressive disorder

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential treatment in treatment resistant major depressive disorder (MDD). However, there is no consensus about the exact site of stimulation for rTMS. Single-photon emission computed tomography (SPECT) offers a potential technique in deciding the site of stimulation. The present study was conducted to assess the difference in outcome of brain SPECT assisted rTMS versus standard protocol of twenty sessions of high frequency rTMS as add on treatment in 20 patients with treatment resistant MDD, given over a period of 4 weeks. Thirteen subjects (group I) received high frequency rTMS over an area of hypoperfusion in the prefrontal cortex, as identified on SPECT, whereas 7 subjects (group II) were administered rTMS in the left dorsoslateral prefrontal cortex (DLPFC) area. Improvement was monitored using standardized instruments. Patients in the group I showed a significantly better response compared to those in the group II. In group I, 46% of the subjects were responders on MADRS, 38% on BDI and 77% on CGI. The parallel figures of responders in Group II were 0% on MADRS, 14% on BDI and 43% on CGI. There were no remitters in the study. No significant untoward side effects were noticed. The study had limitations of a small sample size and non-controlled design, and all the subjects were also receiving the standard antidepressant therapy. Administration of rTMS over brain SPECT specified area of hypoperfusion may have a better clinical outcome compared to the standard protocol.

1. Introduction

Depressive disorders are one of the commonest psychiatric illnesses with a lifetime prevalence of about 16% in adults over 18 years of age (Kessler et al., 2003). A range of treatments including pharmacological agents as well as non-pharmacological therapies are available for management of depression. Despite availability of so many treatment modalities, non-response to the standard treatments is not uncommon with about one-third of patients not responding satisfactorily to the first antidepressant prescribed (Fava, 2003; Rush et al., 2003). Up to 15% of patients fail to achieve a satisfactory improvement despite use of multiple interventions including aggressive pharmacologic and psychotherapeutic approaches (O'Reardon and Amsterdam, 1998). Repetitive Transcranial Magnetic Stimulation (rTMS) has shown promise in treatment of resistant depressive disorders (Lam et al., 2008). rTMS has emerged as an alternative form of treatment for the patients looking for non-pharmacological treatment. Daily left prefrontal rTMS has been found to be associated with a large effect size compared to the sham treatment (Holtzheimer et al., 2001; Kozel and George, 2002).

One recent multicentric study on 190 subjects with depression (not treatment resistant) achieved remission in 14.1% of the subjects given rTMS compared to 5% in those on sham treatment (George et al., 2010). A meta-analysis of 24 studies with 1092 patients with depression with one failed treatment found overall response rate of 25% for rTMS given over dorso lateral pre frontal cortex (DLPFC), with remission rate of 17% (Lam et al., 2008). However, certain recent studies have reported better outcome with rTMS by administering stronger or accelerated dosing regimens, longer treatment course, bilateral stimulation protocol, individually-tailored stimulation frequencies, new coil geometries, more precise neuronavigation technologies, and more accurate

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methods than the traditional "5 cm rule" for locating the DLPFC (Daskalakis et al., 2008; Downar and Daskalakis, 2013). A recently released evidence based guideline on the therapeutic use of rTMS (Lefaucheur et al., 2014) has put the antidepressant effect of high frequency-rTMS on the left DLPFC at level A (definite efficacy) and of low-frequency (LF) rTMS on the right DLPFC at level B (probable efficacy). rTMS has also a potential for treatment in treatment resistant depression (Ciobanu et al., 2013; Fitzgerald et al., 2012).

The target site for cortical stimulation is decided based on pathophysiological changes underlying depressive disorders. Functional brain imaging in such patients has shown a decrease in rCBF as well as glucose and oxygen consumption in the left frontal regions (Kennedy et al., 1997) reflecting a hypometabolic state and with concomitant hypermetabolism in the right prefrontal regions (Bench et al., 1995). To understand the rTMS antidepressant pathophysiology in TRD, pre and post rTMS cerebral glucose metabolism have been measured, which has been found to be low in bilateral DLPFC and anterior cingulum, and high in several limbic and subcortical regions. After successful rTMS treatment, a reversal of metabolic imbalances has been observed (Li et al., 2010). Another study did not support the general hypothesis of increased antidepressant effects of high-frequency rTMS using PET guided hypometabolism area in prefrontal cortex for stimulation (Paillère Martinot et al., 2010). Weiduschat and Dubin (2013) reported greater resting state blood flow in left DLPFC as a predictor of response to high frequency rTMS in patients with depression.

Single-Photon Emission Computed Tomography (SPECT) offers another option to identify the cerebral cortical area of hypoperfusion/metabolic derangement for stimulation, and administering rTMS at the site. 99mTc-ethyl cysteinate dimer (99mTc-ECD) SPECT is a potential tool to investigate regional cerebral blood flow (rCBF) in a range of psychiatric disorders including depression (Rigucci et al., 2010), and hence can be used to localize the site of stimulation for rTMS. Differences in outcome with varying rTMS parameters like frequency, bilateral vs unilateral administration, and left vs right administration have helped in setting optimal standards. A recent meta-analysis has shown that both high frequency rTMS on left DLPFC and low frequency rTMS on right DLPFC are equally effective therapies for major depressive disorder (MDD). However, treatment given on left DLPFC produces fewer side effects and is more protective against seizures (Chen et al., 2013). Simultaneous rTMS of the right and left DLPFC in patients with MDD does not provide marginal benefits in terms of efficacy or acceptability (Chen et al., 2014).

Usefulness of SPECT in identifying the area of stimulation for rTMS needs further investigation. The current study was planned to assess the difference in clinical outcome of high frequency rTMS using SPECT to identify the site of stimulation verses high frequency rTMS on left DLPFC in patients with treatment resistant MDD.

2. Method

2.1. Sample selection

The study was conducted in an outpatient setting in a tertiary care general hospital in Northern India. Patients attending the service with diagnosis of MDD and not responding to the standard treatment over the study period (October, 2011–April, 2012) were screened. To be included in the study, subjects needed to be in the age group 18–65 with a diagnosis of MDD as per DSM-IV-TR, with a failure to respond to a minimum of two distinctly different classes of antidepressant medications given for 6–8 weeks duration each (stage II or III, definition of Thase and Rush, 1997) and consenting for the study. Patients with any comorbid substance abuse or dependence except nicotine, psychotic symptoms, active suicidal ideation, history of prior treatment with rTMS or ECT, history of seizures, neurosurgical metallic implant, cardiac pacemaker, inner ear prosthesis, medication pumps, pregnancy and unstable medical conditions were excluded from the study. Patients with a recent change in medication i.e. six weeks prior to the study were also excluded from the study. Twenty eight right handed subjects were found suitable for the study, but only 20 could be recruited. Among them, 5 patients were on imipramine, 4 each were on venlafaxine or a combination of venlafaxine and mirtazapine, 3 were on sertraline and lithium, 2 were on paroxetine and mirtazapine and 2 were on escitalopram with thyroxin supplementation.

Medication management of the subjects remained with the treating team, and the study in no way interfered with the decisions of clinical team regarding treatment. A written informed consent was taken from the patient as well as from the legal guardian explaining them the purpose of the study. The study was approved by the Institute's Ethics Committee.

2.2. SPECT procedure and analysis

To identify the area of hypoperfusion, brain SPECT was performed after giving injection 740MBq (20mCi) 99mTc-labeled ECD. The patients lied with eyes closed in a quiet, dark, or dimly lit environment for at least 10 min prior to and 5 min after injection. For image acquisition, the patients were positioned supine in the scanner, with their arms down. Step and shoot mode was used with an angular step of 3 degrees. The head was placed naturally so that the patients felt comfortable and motion could be minimized during the acquisition. The image data were acquired on a Siemens Symbia T6 scanner 30 min after injection of the tracer. The field of view of the image contained the entire brain. The projection data were processed with filtered back projection, and Chang attenuation correction was applied. The region of hypo perfusion was chosen visually.

Based upon brain SPECT findings, the subjects were divided into two groups: subjects in whom an area of hypo perfusion was identified in the prefrontal cortex, constituted the Group I, and the subjects, in whom hypo perfusion was found elsewhere, formed the Group II.

2.3. Repetitive transcranial magnetic stimulation (rTMS) protocol

rTMS was administered using a Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK) with 70-mm figure-of-8 coils that were interchanged to allow cooling at times during the treatment sessions. The figure-of-8 coils generate a more focused magnetic field at the intersection point of the two loops. Similar coils were used for both the groups. The scalp position of the lowest motor threshold for the right abductor pollicis brevis muscle was determined using single pulse TMS. Resting motor threshold (MT) was defined by the lowest power setting producing a visible muscle contraction in $\geq$5 of 10 trials.

High frequency rTMS was administered 5 days a week for consecutive four weeks. All the subjects received 50 trains of 40 stimuli each, given over 2 s with an inter train interval of 60 s. 20 Hz stimulation was used at 110% of the estimated resting MT. The site of rTMS administration in Group I was the area of hypo perfusion in the prefrontal cortex, as identified and localized on SPECT. Hypoperfusion was defined as gross visual disparity, substantiated by a decrease in ratio of perfusion in the mirror region of interest by more than 10%. In group II, rTMS was administered over the left DLPFC, as per the standard procedure, determined by moving the TMS coil 5.0 cm anterior to the MT