Case Report

Role of Repetitive Transcranial Magnetic Stimulation in Maintenance Treatment of Resistant Depression

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ABSTRACT

Troublesome side-effects and lack of efficacy of the pharmacotherapy are the two major limitations in the depression treatment. Inspite of the established modalities like switching, combination and augmentation, using pharmacological and non-pharmacological agents, nearly one-third patients do not achieve complete remission. Repetitive Transcranial Magnetic Stimulation (rTMS) is one such somatic treatment which has been extensively studied for treatment for acute depression. Drop-out rates due to adverse effects have been found to be extremely low. However, literature regarding the role of rTMS in maintenance treatment in recurrent depression is scarce, and there is no existing literature from India. In this case-report we highlight the role of rTMS in the maintenance treatment of TRD in a patient who has been followed up for about three years (four episodes). Emphasis is placed on improvement in symptoms and functioning without use of any pharmacological treatment. Further, the need for systematic study and standardization of various aspects of rTMS therapy for maintenance treatment is emphasised.

Key words: *Antidepressants, functioning, maintenance, repetitive transcranial magnetic stimulation, side-effects, treatment resistant depression*

INTRODUCTION

The pharmacological management of depression faces two major challenges viz. troublesome side-effects and lack of efficacy in a subset of patients. The former is an important cause of non-compliance and latter may result in treatment-resistant depression (TRD). The 12-month prevalence of Stage 1 and Stage 2 TRD using the Thase-Rush Treatment Resistant depression Staging Method,[1] is estimated to be 3% and 2% respectively.[2] Currently augmentation, switching of antidepressants and combination pharmacotherapy are considered as the mainstay in management of TRD,[3] but in spite of that, one-third patients do not achieve complete remission.[4]

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/0253-7176.106039	

The above strategies to manage TRD also result in significant and sometimes, intolerable side-effects, resulting in non-compliance.[5] Studies have reported lifetime prevalence of non-compliance to be as high as 70%,[6] and treatment dropout rates upto 23% to 44%,[5,7] depending upon the type of antidepressants. The above issues pertaining to efficacy and side-effects among the currently available treatment modalities necessitates the need for newer treatment approaches like Repetitive Transcranial Magnetic Stimulation (rTMS).

Multiple RCTs have found rTMS to be effective for acute treatment for depression with verylow drop-out rates.[8] Though meta-analysis did not find a strong evidence in support of rTMS for acute treatment (10-12 sessions), longer periods of treatment (>2 weeks) have

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shown antidepressant efficacy.[9,10] Few studies have demonstrated that still longer sessions (maintenance rTMS) are associated with sustained anti-depressant effect,[10] though the concept is still relatively new and unexplored. Further, these studies have used parameter as for acute treatment of depression, leaving many questions unanswered about these issues. The regimen used in these studies have been either regular sessions (1-2 times/week) irrespective of stage of remission,[11,12] or daily sessions only during periods of relapses.[13-15] Li *et al*.[11] studied effect of weekly sessions of TMS for a year on a small sample of three adults with bipolar depression who responded acutely to TMS at 110% motor threshold, 5Hz for eight seconds for 40 trains over the left prefrontal cortex. All the subjects completed one year of study and maintained only partial remission with average Hamilton Rating Scale for Depression of 13 (sd=5.9) over the year. O'Reardon *et al*.[12] studied effect of maintenance rTMS on ten adults suffering from Major Depressive Disorder upto 6 years.Seven of the 10 subjects experienced moderate benefit, but only three cases maintained without antidepressants with 1-2 session/week at 100% motor threshold, 10Hz for 5s for 40 trains over the left prefrontal cortex.

Fitzgerald *et al*.[14] studied the effect of rTMS sessions in relapse episodes on 19 subjectsusing 1500 pulses per session at 100% motor threshold (MT), 13-20 sessions per episode. Only three subjects completed the 3rd and 4th episode and showed adequate response but did not reach remission. Demirtas-Tatlidede *et al*. [15] studied 12 subjects for three depressive episodes. With a total of nine sessions per episode, 1600 pulses per session at 90% motor threshold (MT), the mean treatment interval was only 4.9 months. All the above-mentioned studies assessed only the severity of symptoms as outcome measure but not quality of life or dysfunction. All of them were non-comparative, non-blinded, follow-up studies with small sample size and inadequate follow-up period.

Till date, there is no available literature from India exploring the effect of maintenance rTMS with/without pharmacotherapy. The aim of this case report is to demonstrate the concept of maintenance rTMS, its duration of anti-depressant effect on medication-free patient without any significant side-effects due to the antidepressants and the improvement in functioning.

CASE REPORT

Ms. P, a 30 year old married female with well-adjusted pre-morbid personality, had an episodic depressive illness which made its onset in the year 2007 with a depressive episode which lasted for 9 months and was precipitated by academic failure and interpersonal conflict. Patient frequently contemplated self-harm and had socio-occupational dysfunction, poor personal care and disturbed biological functions. Her treatment records showed two trials of SSRIs [Table 1], with which she maintained partial remission with impaired functioning till November 2009, when she presented to the Psychiatry OPD with the 2nd major depressive episode of two months duartion. This was a breakthrough episode as patient was compliant with previous treatment [Table 1]. The symptoms were characterized by sustained and pervasive depressive mood, anhedonia, feeling of decreased energy, poor appetite and insomnia. She had poor concentration, ideas of hopelessness, guilt, decreased self-esteem and occasional ideas of self-harm. No psychotic symptoms were present. All these were associated with anxiety, irritability and occasional crying episodes. She lost her job during the episode, called-off relationship with her boy-friend and would remain confined to her room. Medical history and investigations did not reveal any co-morbid physical illness. The SSRI was cross-tapered with a tricyclic antidepressant, with which she started experiencing daytime sedation and dryness of mouth at sub-maximal dose (Imipramine 150mg; Table 1). Modafinil 200mg/day was added to decrease daytime sedation and as an augmenting agent, but the patient perceived no improvement even after 8 weeks with the above combination. Later, Lamotrigine 100mg/

Table 1: Illness course, intervention and response

Number of depressive episodes	Duration	Treatment received (duration, response)	Baseline MADRS score	Final MADRS score	Condition in inter-episodic period	Duration of inter-episodic period
1st episode (February, 2007)	9 months	• Escitalopram 20mg/day. • Sertraline 200mg/day	Not available	Not available	Partial remission with dysfunction	3 months
2nd episode (November, 2009)	3 months	• Imipramine 150mg/day plus; Modafinil 200mg/day plus; Lamotrigine 100mg/day. • rTMS 20 sessions (3 weeks)	30	4	Complete remission, no dysfunction	6 months
3rd episode (July, 2010)	1 month	rTMS (5 sessions)	26	6	Complete remission, no dysfunction	7 month
4th episode (February, 2011)	2 months	rTMS (20 sessions)	20	4	Complete remission	12 months
5th episode (January, 2012)	2 month	rTMS (20 sessions)	28	4	Complete remission	2 months and continuing

day was added as an augmenting agent. The above combination was continued for another 8 weeks without any significant improvement [Table 1]. Due to poor response and continuing side-effects with the above combination, the patient declined to continue medication further and also refused to undergo further trial with pharmacotherapy.

Due to progressive worsening of symptoms, along with treatment resistance (Thase-Rush Staging Method stage 3)[1] and patient's refusal for pharmacotherapy;it was decided to start treatment with rTMS (Magstim Super Rapid magnetic stimulator; The Magstim Company Ltd). The parameters were 15Hz frequency, train duration 10sec, 20 trains per session and inter-train duration of 60sec (total 3000 pulses). Over the next three weeks 15 sessions were carried out with same parameters [Table 1]. Patient's symptoms started showing improvement by 15 sessions. After further 5 sessions, her symptoms remitted further and she started pursuing all her daily activities. During the period of remission she started preparation for competitive examinations again and she got married as well.

The third depressive episode of one month duration was moderate in intensity which resolved with 5 sessions of rTMS and then, patient became non-compliant for further sessions. Over the next 2 years, there were two moderate depressive episodes of 3 months each. In each of the episode she required 20 rTMS sessions. The parameters in each of the session was intensity 100% of Motor Threshold, 20Hz frequency, train duration of 10sec, 20 trains per session and inter-train duration of 60sec. During the inter-episodic period of remission and even during the depressive episodes she did not have any significant psychosocial, familial or occupational dysfunction and she was able to continue her occupation as a journalist.

DISCUSSION

The case highlights the efficacy of rTMS as a maintenance treatment for depressive illness, without any significant side-effect. It can be especially useful in situations where pharmacotherapy is not effective or not tolerated well. In the present case, the patient was resistant to three adequate trials of antidepressants and augmentation strategy. In addition, patient had distressing side-effects and was not willing to continue pharmacotherapy despite being severely dysfunctional. Therefore, rTMS provided a safe and effective alternative to long term pharmacotherapy for TRD.

The patient was adequately followed-up for significant duration of 3 years covering 4 episodes after starting of rTMS with the average duration of remission period of seven months with good inter-episodic socio-occupational functioning and without any side-effects. The parameter used was 100% MT, but 2000 pulses per session, total 20 sessions per episode. This is more than the parameters used in the previous studies on maintenance rTMS. As there are no parameters recommended for maintenance rTMS, different parameters need to be explored for the optimal response with minimal side-effects.

This case-report raises some of the issues like the optimal parameters for the relapse episodes, the need to measure functioning along with the symptoms and choice between continuous maintenance with rTMS vs. its application only for relapses. Further, studies are required to determine the parameter, scalp location, number of sessions needed according to the symptom severity. Variables like functioning, efficacy, cost-effectiveness and side-effect profile is also warranted.

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How to cite this article: Chatterjee B, Kumar N, Jha S. Role of repetitive transcranial magnetic stimulation in maintenance treatment of resistant depression. Indian J Psychol Med 2012;34:286-9.

Source of Support: Nil, **Conflict of Interest:** None.