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EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AS AUGMENTATION OF ANTIDEPRESSANT TREATMENT IN PATIENTS WITH SEVERE DEPRESSIVE DISORDER AND IT'S COMPARISON WITH LITHIUM

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ABSTRACT Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well-being. Aims of the present study are to evaluate the efficacy of rTMS as an augmentation therapy in patients with severe depressive disorder who were nonresponsive or partial responsive to antidepressant treatment, To assess the tolerability and adverse effect profile of rTMS treatment, and To compare the efficacy of rTMS and Lithium as augmentation agent for the treatment of these patients.The study was carried out on 20 patients, who were divided in two groups (rTMS group and Lithium group), and both the groups were assessed at baseline, at 2 weeks and 4 weeks interval. It was found that rTMS augmentation is more efficacious in severe depressive disorder patients who had nonresponsive or partial responsive to antidepressant treatment than lithium augmentation and also better in side effect profile.

KEYWORDS : Severe depressive disorder, nonresponsive, rTMS, Lithium

INTRODUCTION

The term depression itself was derived from the Latin verb deprimere, "to press down". [1] It is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well-being. [2] The report on Global Burden of Disease estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. [3]

A recent large population-based study from Chennai using Patient Health Questionnaire (PHQ)-12 reported overall prevalence of depression to be 15.1% after adjusting for age using the 2001 census data. [4]

The depressive episode should usually last at least 2 weeks, but if the symptoms are particularly severe and of very rapid onset, it may be justified to make this diagnosis after less than 2 weeks. [5] Patients afflicted with only major depressive episodes are said to have major depressive disorder or unipolar depression.[6] Despite pharmacologic advances in the treatment of MDD, 30%–46% of patients fail to respond adequately to their initial antidepressants and only 25%–35% achieve symptom remission.[7] Patients with MDD who show partial or no response to an adequate trial of 1 or more antidepressants are considered to have treatment-resistant depression (TRD).[8] Between 10% and 30% of depressed patients taking an antidepressant are partially or totally resistant to the treatment.[9] Co-morbid psychiatric and medical disorders, poor compliance, and adverse effects of pharmacotherapy are few causes of partial or non-response.[10]. Non-antidepressant agents widely used for the augmentation strategy include lithium, atypical antipsychotics (AAs), and thyroid hormones. [11] Clinical guidelines recommend lithium augmentation as a first-line treatment strategy for non-responding depressed patients. [12] And the role of lithium augmentation in the management of major depressive disorder. [13]

Lithium (Li) is a monovalent ion, is a member of the group IA alkaline metals on the periodic table. [14] It is used as an augmentation drug when other treatments are not effective in a number of other conditions, including major depression, schizophrenia, and some psychiatric disorders in children. [15] The most common role for lithium in major depressive disorder is as an adjuvant to antidepressant use in persons who have failed to respond to the antidepressants alone. About 50 to 60 percent of antidepressant nonresponders do respond when lithium, 300 mg three times daily, is added to the antidepressant regimen. [14]

repetitive Transcranial magnetic stimulation (rTMS) is a non-invasive application of pulsed magnetic field near an area of scalp. In rTMS, a powerful electrical current is passed through a small coil applied to the scalp. This current generates a focused magnetic field of 1.5 to 2.0T that passes through the scalp and is largely unimpeded by bone or tissue. At cellular level, mechanisms of electroconvulsive therapy (ECT) and rTMS are the same. [14] For treatment-resistant major depressive disorder, HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC) appears effective and low-frequency (LF) rTMS of the right DLPFC has probable efficacy [16].

In our country, there are not so many studies on the effect of rTMS as augmentation therapy in severely depressed patients. It is indeed very important to determine its utility as a novel modality for treating depression. Hence this study has been planned to assess the efficacy of rTMS as augmentation therapy for severe depression and compare it with lithium.

AIMS & OBJECTIVES

1) To evaluate the efficacy of rTMS as an augmentation therapy in patients with severe depressive disorder who were nonresponsive or partial responsive to antidepressant treatment.
2) To assess the tolerability and adverse effect profile of rTMS.
3) To compare the efficacy of rTMS and Lithium as augmentation agent for the treatment of these patients.

Selection Criteria

Inclusion criteria

1) Persons with Severe depressive disorder without psychotic features (ICD-10) who were nonresponsive or partial responsive to antidepressant treatment.
2) Age 18–65 years, both sex.
3) Literate enough to read and understand the questionnaires.
4) Has not taken lithium or rTMS for treatment of depression in current episode.
5) Willing to give written informed consent for participating in the

study.

Exclusion criteria
1) Person having comorbid Substance Use disorder.
2) Pregnant females.
3) Person having chronic medical and neurological disorder.
5) Person with Cardiac pacemakers or any metallic implant.

Tool and Technique:
1) Consent form- written informed consent was taken from all the patients.
2) Screening proforma included all inclusive and exclusive criterions.
3) Sociodemographic proforma.
4) ICD-10 clinical descriptions and diagnostic guidelines.
5) Beck's Depression Inventory (by Aaron T Beck, 1961) (Hindi version)
6) Clinical Global Impression (CGI) Scale.
7) World Health Organization Quality of Life- Bref.
8) Semi structured Side effect questionnaire to assess the side effects of rTMS and Lithium.

Methodology
Approval of the Ethical Committee of Sardar Patel Medical College, Bikaner, was taken for conducting the study.

This was a prospective study conducted at the Department of Psychiatry, Sardar Patel Medical College and PBM Hospital, Bikaner. We screened 24 patients for study, diagnosed as severe depressive disorder without psychotic features (ICD-10) who had history of nonresponsive or partial responsive to antidepressant treatment given in adequate doses and for adequate period. Out of 24 patients 4 patients were not fulfilling the eligibility criteria and rejected due to comorbid substance abuse (n=2), unwilling to participate (n=1), pregnant female (n=1).

Initially all the 20 patients were thoroughly investigated with complete blood count, Liver function test, Kidney function test, Thyroid function test and ECG. After that all cases were measured on CGI, BDI and WHO Quality of life - Bref scale for baseline scores. After that all 20 patients were alternatively divided into 2 groups, each group was having 10 patients. One group was augmented with rTMS further called as rTMS group and other group was augmented with lithium further called as Lithium group. One patient from rTMS group was dropped out during the study.

In this study, the rTMS therapy was given on 5 consecutive days of a week and a total 15 therapy sessions were completed over a three weeks period. Stimulation was delivered in trains of 5 seconds duration and 10 Hz stimulation frequency. In each stimulation session, each subject had received 25 trains of stimulation separated by 25 seconds pause. Each stimulation session, therefore last nearly 12.5 minutes and each subject had received a total of 1250 pulses per session.

In this study lithium group patients were augmented with lithium carbonate 300 mg three times a day.

At the end of 2 weeks all patients were again assessed on study tools (CGI, BDI and Quality of life) and both the study groups were compared. At the end of 4 weeks all the participants were thoroughly investigated on all routine laboratory investigations and assessed with study tools. Information so gained and data so collected was subjected to suitable statistical analysis and results and conclusion were drawn.

RESULT
Before participation in this study all the patients were on antidepressant medication (either one or more than one antidepressant medicine) or on antidepressant and augmenting agent (other to rTMS and Lithium augmentation) and failed on at least one trial of antidepressant treatment or above mentioned combinations during the current episode of illness.

Out of 20, 19 patients (95%) were completed the study. One patient from rTMS group dropped out during study. None of the patient was discontinued due to the adverse effects of treatment.

Table 1 shows different socio-demographic variables of the two study groups. Both the study groups were comparable on different socio-demographic variables. The mean ± SD of age for the rTMS group was 43.89±13.233 and for the lithium group was 41.70 ±11.776 years. Out of total 20 patients, 11 were males (57.89%) and 9(47.36%) were females and majority were married (94.73%). In rTMS group majority of subjects were illiterate (n=5) and majority of subjects (n=5) in lithium group were educated up to high school. Most of subjects were employed (n=16) from upper middle socio economic status and belonging to Hindu religion (n=16) and living in joint family and hailed from rural background.

Table 2 shows The mean duration of illness was 11.622 years SD of ±9.6868 for rTMS group and 7.250 years SD ± 6.4517 for lithium group.

Table 3 shows the treatment response of augmentation with rTMS and lithium carbonate on different assessment tools like BDI, CGI. With the help of BDI both groups were assessed at base line (before stating treatment) and at 2 weeks, 4-weeks interval. At base line BDI mean score of rTMS group and lithium group were 44.20(±6.287), 47.20(±8.189) subsequently and there was no statistically significant difference at baseline assessment. After augmentation, assessment at 2 weeks and 4 weeks interval showed statistically significant difference between these two groups. rTMS group shows greater improvement than lithium study group (p value of improvement on BDI at 2weeks and 4 weeks interval respectively 0.017& 0.034).

This table also shows the CGI severity score at base line was 6 of each group.CGI improvement score were assessed and compared at 2 weeks and 4 weeks interval. On CGI improvement score rTMS group showed much more improvement than lithium group (p values of CGI-I score at 2 weeks and 4 weeks interval respectively were 0.005 & 0.006).

Table 4 shows assessment of Quality of life and comparison between the two groups with the help of World Health Organization Quality Of Life- Bref. At the starting of study the base line assessment were not statistically significant in all domains (physical, psychological, social and environmental) of Quality of life. At the end of 4 weeks there were statistically significant results obtained in physical, psychological, social domains of Quality of life between these two groups (p value for physical, psychological, social domains were 0.022, 0.049, 0.036 respectively).

Table 5 shows side effect profile of the study groups. In lithium group majority of patients (70 %) had developed side effects like tremor, polyuria, weight gain, loss of appetite, nausea but in rTMS group only 22% patients reported side effect like headache.

TABLE 1 showing the different Socio-demographic variables of both the study groups.

Variable	rTMS group (n=9)	Lithium group (n=10)	Chi square (df)/t-test	P value
Age (mean)	43.89	41.70	0.382	0.707
Sex			2.554(1)	0.128
Male	3	7		
Female	6	3		
Education			4.579(4)	0.333
Illiterate	5	2		
High school	1	5		
Graduate/ PG	1	1		
Professional	2	2		
Occupation			9.474(6)	0.149
Unemployed	3	0		
Employed	6	10		
Religion			3.206(1)	0.124
Hindu	9	7		
Muslim	0	3		
Socioeconomic Status			4.025(3)	0.259
Upper				
Upper middle	2	3		
Lower middle	2	4		
Upper lower	2	3		
Lower	3	0		
Residence			0.024 (1)	0.630
Rural	6	7		
Urban	3	3		
Family Type			2.956(2)	0.228
Joint	8	8		
Nuclear	1	2		
Marital Status			1.173(1)	0.474
Unmarried/Seperated	1	0		
Married	8	10		

Table 2. Shows different Clinical variables of both the study groups and their comparison.

Variable	rTMS group	Lithium group	t/x2 test	p value
Duration of Illness	11.622	7.250	1.170	0.258
Onset of illness Insidious Acute	 9 0	 10 0	0	1
Past History Yes No	 6 3	 7 3	0.024(1)	0.630
Family History Yes No	 1 8	 2 8	0.281(1)	0.542

Table 3 -showing the augmentation response on different assessment tools and their comparison in between the groups.

Assessment tool	rTMS group Mean (S.D.)	Lithium group Mean (S.D.)	t test	P value
BDI B	44.56(6.287)	47.20(8.189)	-0.782	0.445
BDI 2 WK	20.67(11.747)	35.80(13.011)	-2.649	0.017
BDI 4 WK	14.33(12.010)	27.00(11.972)	-2.299	0.034
CGI S	6	6		
CGI I 2 WK	2.56(0.726)	3.60(0.699)	-3.192	0.005
CGI I 4 WK	1.56(0.882)	2.90(0.994)	-3.102	0.006

BDI B- Beck's Depression Inventory baseline, CGI I- Clinical Global Impression improvement, CGI S- Clinical Global Impression severity.

TABLE 4 -Assessment and comparison of Quality of life in between the groups

Domain of WHO-QOL BREF Scale	rTMS group Mean (S.D)	Lithium group Mean (SD)	t test	P value
Physical health B	7.4286 (1.45686)	7.8286 (0.93508)	0.720	0.481
Psychological B	6.3704 (1.29577)	6.2000 (1.33518)	-0.282	0.782
Social B	9.0370 (2.18864)	9.7333 (1.66889)	0.785	0.443
Environment B	11.3889 (2.05818)	11.1500 (1.90102)	-0.263	0.796
Physical health A	14.6667 (3.84389)	10.5714 (3.26876)	2.510	0.022
Psychological A	15.0370 (4.27020)	10.7333 (4.65554)	2.092	0.049
Social A	13.9259 (2.11986)	11.7333 (2.06559)	2.282	0.036
Environment A	13.3889 (2.64313)	13.0000 (1.39443)	0.407	0.689

B- base line A – after 4 weeks

TABLE 5- Showing side effect profile of different augmentation treatment groups.

Variables	rTMS group	Lithium group
Gastrointestinal tract: nausea Appetite loss, nausea, vomiting,	0	4
Skeletal muscle: pain, muscle contraction, arhralgia	0	0
Psychiatric: anxiety , acute dysphoria, attack of laughter (broca area stimulation), suicidal ideation, induced mania	0	0
Neurological: local pain on the scalp muscles, headache, Seizure, tremor	2	6
Endocrine Thyroid: goiter, hypothyroidism, hyperthyroidism (rare) Parathyroid: hyperparathyroidism	0	0
Renal Polyuria	0	4
Miscellaneous Weight gain, fluid retention	0	2

DISCUSSION

The rTMS protocol used in this study was similar to that of Pascual Leone*et al*. [17] In this study, the therapeutic benefits of rTMS were observed after 15 rTMS treatments by stimulating the left dorsolateral prefrontal cortex. We have used higher magnetic field intensity (100% motor threshold) instead of the Pascual Leone study (90% motor threshold) and a shorter stimulus train with total pulses per session (1250 to 2000 pulses in 12.5 to 20 minutes duration). Although the antidepressant mechanism of action for the rTMS remains unknown, recent works are beginning to examine the neurochemical basis for rTMS and its effects on several animal behavioral models. [18] Similar to ECT and antidepressants, rTMS may alter brain monoamines neurotransmitters. Regional alterations in dopamine, serotonin, and 5-hydroxyindoleacetic acid levels have been reported with rTMS. A recent SPECT study in healthy adults that used left prefrontal repetitive TMS demonstrated that compared with baseline, there was reduced blood flow at the coil site and in the anterior cingulate during stimulation, with increases in brainstem activity.[19] Previous studies have demonstrated that rTMS at similar parameters over the prefrontal cortex results in increases in serum thyroid stimulating hormone, which suggests the possibility of increases in thyrotropin releasing hormone and an indirect effect of repetitive TMS on hypothalamo-pituitary structures.[20,21] Finally, like antidepressants and ECT, rTMS can significantly decrease the number of beta-adrenergic receptors in certain parts of the rat's brain.[22]

The most important finding of this study was that the rTMS can be used safely and effectively as an augmenting treatment method in patients with severe depressive disorder without psychotic feature.

Epstein C, Figiel GS et al. Found that 21 out of 50 patients with depression (42%) responded to rTMS. [23,24] A study conducted by Pascual Leoneet al. reported that 11 out of 17 depressed patients (65%) responded to rTMS.[17]

A substantial number of RCTs and open studies have been conducted on the use of lithium augmentation in refractory depression and majority of studies has demonstrated substantial efficacy of lithium augmentation in partial and non responder to antidepressant treatment. The results of a previous meta-analysis of 9 RCTs also provided firm evidence that lithium augmentation results in a statistically significant improvement in the antidepressant response rate as compared with the effects of placebo .[25]

Overall, RCTs and open studies included, about 50% of patients were responsive to lithium augmentation in these reports. About 20% of patients responded within the first week. [26] Lithium was found to potentiate the therapeutic effects of a broad spectrum of antidepressants, including SSRIs. [27, 28,] Lithium augmentation is generally well tolerated with all classes of antidepressants. The combination of lithium with antidepressants has not been reported to be associated with serious side effects. [29] And therefore has been recommended by many clinicians for treatment resistant depressed patients. [30]

In our study, not a single patient developed epileptic seizure episode during the rTMS treatments is similar to the study conducted by Pascual Leone et al. [17] Headache was reported by two patients in our study. During rTMS treatment there were no cardiovascular, neurological complications, complained of memory impairment or cognitive side effects developed to any patient. These observations are consistent with previous safety reports on rTMS treatment.

In summary, rTMS appears to be safe and effective in treating some medication resistant depressed patients. More research is needed to identify the ways to sustain the therapeutic benefits of rTMS and to identify the optimum techniques for its administration. To find out the potential neurobiological and clinical predictors of response to rTMS will be needed in further study. In lithium study group various side effects developed during the treatment. The rTMS augmentation is better in onset of action, treatment efficacy, shows greater improvement and better safety profile than lithium.

CONCLUSION

The most important finding of this study is that rTMS can be used safely and effectively as an augmentation therapy in patients with severe depressive disorder without psychotic feature who are non responder or partial responder to antidepressant medication.

LIMITATIONS

The principal limitations of this study were the small sample size, an open label design, and lack of a placebo arm. Another limitation of this study is to use the retrospective diagnostic approach of non-responder or partial responder to antidepressant medication because of relatively short duration of the study. Without long term follow up we can't conclude that whether the antidepressant effect of augmentation with rTMS will be maintained after the initial improvement.

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