Adjuvant treatment with repetitive transcranial magnetic stimulation in freshly diagnosed alcohol-dependence syndrome patients from an industry: An outcome study

ABSTRACT

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Background: Studies have suggested that repetitive transcranial magnetic stimulation (rTMS) could be efficacious in the treatment of major depression and other psychiatric indications. Alcohol-dependence syndrome is difficult to treat, and the relapse rate is high, even following the standard treatment protocol. No study has been done so far in India for the use of rTMS as an adjuvant therapy in the relapse prevention of patients with alcohol-dependence syndrome. Hence, the current study is an open-label study to explore the same. Aim: The aim of this study was to study the feasibility of rTMS in alcohol-dependence syndrome patients, the side effects if any, and the number of relapses that they may suffer from vis-a-vis patients with standard treatment protocols. Materials and Methods: In a prospective, open-label study design, 100 freshly diagnosed cases of alcohol-dependence syndrome were included, and after suitable randomization, half of them were given adjuvant rTMS along with standard treatment and the rest received only standard treatment. The rates of relapse into drinking were compared for both groups. The data were compiled and analyzed with appropriate statistical methods. Results: Participants given adjuvant rTMS showed significantly less number of relapses into drinking compared to the control group on standard treatment for alcohol-dependence syndrome. Conclusion: In the present study, though the sample size is small, a significant change with this novel treatment has been found. Whether this change is maintained over a period of time is to be seen by other longitudinal studies.

Keywords: Repetitive transcranial magnetic stimulation, Alcohol Dependence Syndrome, adjunctive treatment

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain.[1-3] From therapeutic and rehabilitative perspectives, the main interest of repetitive transcranial magnetic stimulation (rTMS) resides in the persistence of clinical changes well beyond the time of stimulation. The duration of such after-effects increases with the number of stimuli delivered and may persist minutes to hours or even days after the end of rTMS session.[4-8] Many studies have suggested that rTMS could be efficacious in the treatment of major depression and other psychiatric indications.[9]

Alcohol-use disorders in various forms have been in the forefront of the disease burden in the world. The standard methods of treatment include detoxification, forced abstinence, anticraving medications, individual

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and group psychotherapy, and attendance in alcoholics anonymous meetings among other methods. Despite that these disorders are difficult to treat and the relapse rate is high. The community participation to keep these patients sober has traditionally been poor despite various attempts. In such a scenario, the psychiatrist needs to put maximal therapeutic efforts at relapse prevention. The rationale to use rTMS as a treatment for substance addiction and craving is that the dorsolateral prefrontal cortex (DLPFC), which plays a major role in top-down inhibitory control mechanisms and reward mechanisms, is dysfunctional in these disorders.\textsuperscript{[11,12]}

A systematic review of the use of rTMS in alcohol-use disorders selected 70 related articles and suggested that rTMS may serve as an emerging therapeutic option for addiction and related disorders. The major lacunae include important methodological limitations and a dearth of knowledge about the precise mechanism of action.\textsuperscript{[13]}

No study has been done so far in India for the use of rTMS as adjuvant therapy in relapse prevention of patients with newly diagnosed alcohol-dependence syndrome. Hence, the current study is an open-label study to explore the feasibility of rTMS in such patients, the side effects if any, the number of relapses that they may suffer from vis-a-vis patients with standard treatment protocols.

**MATERIALS AND METHODS**

This prospective and open-label study was carried out at a tertiary care hospital. Ethical committee clearance was obtained for this study. All participants gave written informed consent. Hundred freshly diagnosed cases of alcohol-dependence syndrome were included in the study. The International Classification of Diseases (ICD)-10 Diagnostic Criteria for Research (DCR) were followed to establish the diagnosis ratified by two psychiatrists.

**Inclusion criteria**
Freshly diagnosed cases of alcohol-dependence syndrome as per the ICD-10 DCR.

**Exclusion criteria**
1. Previously diagnosed patients of psychiatric and medical illnesses
2. Individuals with a history of seizures or serious medical conditions
3. Participants were needed to stay on a steady dose of anticroaving psychiatric medication for that period
4. Patients who have been treated by rTMS earlier.

**Procedure**
After informed consent and half of the patients were given, adjuvant rTMS along with standard treatment and the rest were treated only with the standard treatment after suitable randomization. After the initial treatment, they were followed up periodically at 3 months, 6 months, and 9 months intervals and their relapses into drinking were documented. The criteria for relapse were decided as per the diagnostic criteria of alcohol-dependence syndrome in ICD-10 DCR. The outcome of treatment was decided based on the total period of relapse-free state from alcohol consumption during the duration of the study. Blinding was not practiced as the effects or side effects of rTMS were not possible to be concealed. The average length of hospital stay of the inpatients was calculated and compared. The rates of relapse into drinking were compared for both groups.

**Protocol for repetitive transcranial magnetic stimulation treatment**
In depression, the USFDA approved protocol is 10 Hz, 120% Resting motor threshold (RMT), 4 s run time followed by 26 s off time per train; for 75 such train over the (dominant) DLPFC. This is the conventional protocol. Burst protocol in depression is iTBS (intermittent theta-burst stimulation) to the left DLPFC at 100% RMT for 1800 pulses (600 bursts) with 2 s run time and 8 s off time per train. A further continuous theta-burst stimulation (cTBS) to this on the right DLPFC can be added at 100% for 1800 pulses.

In our study, there has been no preexisting protocol for addictive disorders in general and alcohol dependence in particular. Hence, we have used iTBS on the right DLPFC and cTBS on the left DLPFC for 600 pulses at 90% for craving reduction.

**RESULTS**

Table 1 shows the data in respect of the total number of relapses into alcohol consumption in test and control groups, respectively.

Table 2 shows the time to relapse in the test and control groups. In the control group, there is early relapse for a significant number of people, followed by further relapses by another small number of people.

**Table 1: Total number of relapses into alcohol consumption in test and control groups, respectively**

| Treatment group          | Number of patients | Number of relapse |
|--------------------------|--------------------|-------------------|
| Patients with rTMS (test group) | 50                | 9                 |
| Patients without rTMS   | 50                 | 36                |

rTMS – Repititative transcranial magnetic stimulation
However, the trend shows better results in test group, further analyzed by ANOVA [Table 3].

The above ANOVA analysis shows that there are significant differences in the means of control and test group. Thus, the null hypothesis (there is no significant difference in the relapse rates of alcoholics with standard treatment for alcoholism vs. standard treatment along with rTMS therapy) is rejected. rTMS therapy significantly impacts on the number and time to relapse since treatment is in a positive way. If we take the above values as closest to the nearest integers, then a statistical analysis with the help of Chi-square test shows that the Chi-square statistic is 2.1333. The \( P = 0.144127 \). This result is not significant at \( P < 0.05 \). Hence, the difference between groups as for the average length of stay in the hospital is not statistically significant. Tables 4 and 5 shows age group wise distribution of relapses at 3, 6 and 9 months with rTMS in test and control groups, respectively. Table 6 shows the average length of stay of patients during initial admission with alcohol dependence syndrome with and without rTMS.

**Table 2: Time distribution and the number of relapses in each group**

| Period (months) | Number of relapse (control group) | Number of relapse (test group) |
|-----------------|-----------------------------------|--------------------------------|
| 3               | 17                                | 5                              |
| 6               | 9                                 | 3                              |
| 9               | 9                                 | 1                              |
| Total           | 35                                | 09                             |

**Table 3: Results of ANOVA**

| Source             | SS         | df | MS         | F         |
|--------------------|------------|----|------------|-----------|
| Between-treatments | 67.6       | 1  | 67.6       | 2.81667   |
| Within-treatments  | 192        | 8  | 24         |           |
| Total              | 259.6      | 9  |            |           |

The \( f \)-ratio value is 2.81667. The \( P \leq 0.05 \) (significant). SS – Sum of squares; MS – Mean squares

**Table 4: Age group wise distribution of relapses with repetitive transcranial magnetic stimulation (test group)**

| Age group     | Months | Total |
|---------------|--------|-------|
| Below 30      | 3      | 6     | 9     |
| 30-40         | 2      | 1     | 3     |
| Above 40      | 2      | 1     | 3     |
| Total         | 5      | 3     | 1     | 9     |

**Table 5: Age group wise distribution of relapses without repetitive transcranial magnetic stimulation (control group)**

| Age group (years) | Months | Total |
|-------------------|--------|-------|
| 30-40             | 12     | 4     | 7     | 23    |
| Above 40          | 5      | 5     | 2     | 12    |
| Total             | 17     | 9     | 9     | 35    |

**Table 6: Average length of stay of patients with alcohol-dependence syndrome**

| Length of stay (days) with rTMS | Initial admission | Relapse |
|----------------------------------|-------------------|---------|
| with rTMS                        | 28                | 14.07   |
| without rTMS                     | 28                | 26.16   |

rTMS – Repititative transcranial magnetic stimulation

**Discussion**

Analysis of the data clearly showed that the treatment group with rTMS had a significantly less number and frequency of relapses into drinking compared to the control group of standard treatment for alcohol-dependence syndrome. However, the difference between groups as for the average length of stay was not statistically significant. Result from our study was similar as some previous studies which have highlighted the potential of TMS as an innovative, safe, and cost-effective treatment for some SUDs.[14] Probable hypothesis could be that rTMS influences neural activity in the short and long term by mechanisms involving neuroplasticity both locally, under the stimulating coil, and at the network level, throughout the brain. The long-term neurophysiological changes induced by rTMS have the potential to affect behaviors relating to drug craving, intake, and relapse.[14,15] Other studies have also suggested alcohol-dependence may result in altered cerebral hemodynamic parameters, which can be improved with high-frequency rTMS application.[16]

**Strengths and limitations**

rTMS was initially approved for the treatment of resistant depression but has gained some interest in treating other neurobehavioral disorders including psychiatric syndromes. In the present study, though the sample size is small, a significant change with this novel treatment has been found. Whether this change is maintained over a period of time is to be seen by other longitudinal studies. Since the rTMS machine is now available in psychiatry centers, similar protocols for rTMS can be used on freshly diagnosed patients of alcohol-dependence syndrome and they may be followed up to observe the effect of this novel treatment. The intervention is easily administered, noninvasive, and free of any major side effects, hence the acceptance rate among patients is high and dropout rates are almost nil.

**Future implications**

If the efficacy of rTMS in reducing relapses in alcohol-dependence syndrome cases needs to be established on a par with other existing treatment modalities, the
abovementioned difficulties must be overcome, and if this can be done, this procedure is definitely a better option considering the following: it is very good safety profile; it is well tolerated and easy to administer for the clinician. This study is one of the few of its kind in India and it is worthwhile conducting more trials using larger sample sizes and more rigorous research design in our setting.

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**Conflicts of interest**
There are no conflicts of interest.

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