A shark-controlled trial of repetitive transcranial magnetic stimulation over left dorsolateral prefrontal cortex and its effects on craving in patients with alcohol dependence

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Aim: The aim of this study is to study the effects of repetitive transcranial magnetic stimulation (rTMS) therapy over the left dorsolateral prefrontal cortex (DLPFC) in craving in drug-naïve male inpatients of alcohol dependence syndrome. Methods: A single-blind randomized sham-controlled study involving sixty inpatients of alcohol dependence syndrome in a tertiary care center. Following detoxification and consent, the patients were allocated into either active or sham groups for rTMS protocol. Daily sessions of rTMS were administered over the left DLPFC at 120% of motor threshold at high-frequency (10 Hz) stimulation with 4 s train, inter-train interval of 26 s, and a total of twenty trains per session. Alcohol craving questionnaire (ACQ-NOW) was administered thrice for each patient, i.e., before rTMS, on completion of rTMS, and 02 weeks following completion of rTMS. Results: Analysis of variance of scores of ACQ NOW pre rTMS and immediately after and 2 weeks post rTMS did not show significant reduction in craving scores. Conclusion: Administration of ten daily sessions of high-frequency rTMS over the left DLPFC did not have significant effect in reducing craving in patients with alcohol dependence syndrome.

Keywords: Alcohol dependence, craving, males, repetitive transcranial magnetic stimulation

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external cues. Abstinence efforts are successful when the capacity to resist craving is improved. Hence, craving can be considered to be a critical therapeutic objective and outcome too. There are a few treatment options today for alcohol dependence. Psychopharmacological and psychosocial measures have not produced significant reduction in relapse rates and have their limitations.[1]

This has lead to felt need for developing newer treatment modalities in the field of alcohol dependence syndrome. Transcranial magnetic stimulation (TMS) for therapeutic use first appeared > two decades ago and has been Food and Drug Administration approved for treatment-resistant depression and obsessive-compulsive disorder.[2] Repetitive TMS (rTMS) technique has been examined in a few studies for efficacy in alcohol and other substance use disorders. It is postulated that rTMS can modulate neuronal activity and influence the behaviors of craving, drug seeking, and eventually drug consumption.[3]

Various studies have proven the safety of this procedure. Mishra et al. conducted a sham-controlled study of high-frequency rTMS to the right dorsolateral prefrontal cortex (DLPFC) to a sample of 45 (30 active and 15 sham) male patients of alcohol dependence syndrome and reported significant reduction in craving post rTMS.[4] However, the sampling was purposive and some of the patients were on anticraving medications too. Mishra et al. in another study reported reduction in craving scores in patients receiving rTMS to either right or left DLPFC and reported no significant differences in between the groups.[5]

Hoppner et al. did not find significant differences in craving in 19 (10 Active and 9 sham) detoxified women with alcohol use disorder who underwent high frequency (20 Hz) rTMS to left DLPFC.[6]

Herremans and Baeken in their prospective sham-controlled study on 36 hospitalized patients of alcohol use disorder did not find much effects on craving scores between the active and sham groups.[7]

Makani et al. in their systematic review using strength of review taxonomy guidelines have rated strength of evidence of efficacy of rTMS in alcohol addiction as level 2 study quality and class B strength.[8]

Although many technical details for optimal stimulation parameters need further investigation and optimization, rTMS appears to deserve careful experimental scrutiny as a potential therapeutic tool in the treatment of alcohol dependence syndrome. Indeed, with its nearly absent side effects, and a low degree of invasiveness, rTMS may offer to be an efficacious, nonpharmacological, and therapeutic intervention and especially in alcohol use disorders having comorbid renal or hepatic impairments where caution has to be exercised in pharmacotherapy.[9]

We did a study with a larger sample size in an Indian population.

**METHODS**

This study was conducted on hospitalized patients in psychiatry ward of a tertiary care multispecialty hospital. Ethical clearance of the study was obtained from the Institutional Ethics Committee of the Hospital. The design was of a prospective, single-blind, sham-controlled study, conducted over a period of 25 months (September 2016 to September 2018). The study sample consisted of sixty right-handed male patients of 25 years to 56 years of age who were diagnosed as a case of alcohol dependence syndrome according to the International Classification of Diseases 10-Diagnostic Criteria for Research. The patients were either admitted due to occupational deterioration or by a family member or were referred by a clinician suspecting alcohol dependence withdrawal features/ alcohol-related sociooccupational dysfunction or medical complications. Patients were recruited in this study only after completion of detoxification. Patients were first screened for any history of seizure (other than withdrawal seizures), stroke, shrapnel, metal fragments, stents/metal implants, pacemaker, etc., and were excluded from the study. Neuroimaging, electroencephalography, and neurology consultation were obtained in needful cases. Handedness was determined by the Edinburgh handedness inventory.[10] Following screening, they were provided with informed choice about the modalities of treatment for alcohol dependence syndrome including rTMS and its possible role in suppression of craving as per existing evidence. They were also informed about possibility of receiving sham rTMS or actual rTMS. Patients apprehensions were allayed by a detailed explanation and displaying a short video of the procedure. A written informed consent was obtained. Most of the patients were also under care of other specialists/sub specialties for the various medical comorbidities. Before the beginning of rTMS sessions, all patients underwent assessment of biochemical profile (mean corpuscular volume, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and serum γ-glutamyl transferase), lifetime alcohol use, CAGE criteria, and alcohol use disorder identification test (AUDIT) criteria were assessed to measure the severity of alcohol dependence syndrome. For assessment and quantification of craving alcohol craving questionnaire (ACQ-Now) was used.[11]

A random number table was used to assigning thirty patients each to active or sham group. The DLPFC of the patient was located by 5 cm rule.[12]
The motor threshold (MT) was determined by the effect on right abductor pollicis brevis using the visual method (to see for muscle twitching) using a figure-of-eight-shaped coil at 1 Hz frequency according to the Rossini–Rothwell algorithm.[13] The study was conducted in a therapeutic room in the hospital with trays with emergency medications for seizure and resuscitation.

MT was determined once at start of therapy for each patient. The process was started with an MT of 36% intensity and

| Table 1: Clinical characteristics of active and sham groups of patients of alcohol dependence syndrome |
|---------------------------------------------|-------------|-------------|---------------|
| Variable                                    | Type        | Active (n=30) | Sham (n=30)   |
| Type of cases                               |             |              |               |
| New                                         | 14          | 19           | 33 (55)       |
| Old                                         | 16          | 11           | 27 (45)       |
| Nature of referral                          |             |              |               |
| From employer                               | 17          | 17           | 34 (56.7)     |
| From medical specialist                     | 10          | 13           | 23 (38.3)     |
| By family members                           | 3           | 0            | 3 (5)         |
| Type of presentation                        |             |              |               |
| Acute intoxication                          | 8           | 10           | 18 (30)       |
| Alcohol withdrawal seizures                 | 8           | 5            | 13 (21.67)    |
| Alcohol withdrawal uncomplicated            | 10          | 11           | 21 (35)       |
| Behavioural oddities                        | 4           | 4            | 8 (13.33)     |
| CIWA-Ar scores                              |             |              |               |
| ≤10 (mild withdrawal)                       | 7           | 5            | 12 (20)       |
| 11-≤15 (moderate withdrawal)                | 10          | 12           | 22 (36.67)    |
| >15 (severe withdrawal)                     | 13          | 13           | 26 (43.33)    |
| Family history of alcohol use disorder      |             |              |               |
| Present                                     | 21          | 20           | 41 (68.33)    |
| Absent                                      | 9           | 10           | 19 (31.67)    |
| MCV (fL)                                    |             |              |               |
| ≤85                                         | 3           | 2            | 5 (8.33)      |
| 86-95 (normal range)                        | 17          | 13           | 30 (50)       |
| 96-105                                      | 10          | 15           | 25 (41.67)    |
| AST (U/L)                                   |             |              |               |
| ≤37 (normal range)                          | 6           | 9            | 15 (25)       |
| 38-100                                      | 15          | 11           | 26 (43.33)    |
| ≥100                                        | 9           | 10           | 19 (31.67)    |
| GGT (U/L)                                   |             |              |               |
| ≤85 (normal range)                          | 6           | 12           | 18 (30)       |
| >85-<200                                    | 9           | 9            | 18 (30)       |
| ≥200                                        | 6           | 5            | 11 (18.33)    |
| Lifetime alcohol use in kg                  |             |              |               |
| <50                                         | 8           | 7            | 15 (25)       |
| 50-<100                                     | 11          | 12           | 23 (38.33)    |
| 100-<150                                    | 4           | 5            | 9 (15)        |
| 150-<200                                    | 3           | 3            | 6 (10)        |
| ≥200                                        | 4           | 3            | 7 (11.67)     |
| Age of initial alcohol use (years)          |             |              |               |
| <20                                         | 6           | 10           | 16 (26.67)    |
| 20-<30                                      | 21          | 18           | 39 (65)       |
| ≥30                                         | 3           | 2            | 5 (8.33)      |
| Age of diagnosis of alcohol dependence syndrome (years) | | | |
| 25-<35                                      | 14          | 17           | 31 (51.67)    |
| 35-<45                                      | 9           | 10           | 19 (31.67)    |
| ≥45                                         | 7           | 3            | 10 (16.66)    |
| Duration of dependence in years             |             |              |               |
| <5                                          | 19          | 14           | 33 (55)       |
| 5-<10                                       | 3           | 8            | 11 (18.33)    |
| 10-<15                                      | 5           | 6            | 11 (18.33)    |
| ≥15                                         | 3           | 2            | 5 (8.33)      |
| AUDIT scores                                |             |              |               |
| ≤15 (at risk)                               | 0           | 0            | 0             |
| 16-24 (moderate AUD)                        | 6           | 8            | 14 (23.33)    |
| ≥25 (severe AUD)                            | 24          | 22           | 46 (76.67)    |
| Prior exposure to anticraving medications   |             |              |               |
| Nil                                         | 16          | 19           | 35 (58.33)    |
| Anticraving medication use                   | 14          | 11           | 25 (41.67)    |
| Motor threshold (active)                    |             |              |               |
| ≤40                                         | 2           | 2            | 4 (6.67)      |
| 41-50                                       | 21          | -            | 21 (70)       |
| ≥51                                         | 7           | -            | 7 (11.67)     |

CIWA-Ar - Clinical Institute Withdrawal Assessment of Alcohol revised; MCV - Mean corpuscular volume; AST - Aspartate transaminase; GGT - Gamma-glutamyl transpeptidase; AUDIT - Alcohol use disorder identification test
increased in steps of 5% until approximately 50% of successes are observed in ten consecutive trials. A total of ten sessions (for ten consecutive days) of rTMS (using the STM 9000, ATES MEDICA Device (EBNeuro SpA®, Firenze, Italy) were administered over the left DLPFC (at 120% of the MT determined) with a 70 mm, air-cooled, flat, figure-of-eight coil (maximum machine output 3.2 Tesla), angled tangentially (45°) to the head, with handle aimed posterior, and supported by frame of machine. Earplugs were provided to the patient to reduce auditory distress due to noise of the machine. At left DLPFC, active high-frequency (10 Hz) stimulation was administered for 4 s per train, with inter-train interval of 26 s, and a total of twenty trains per session. Each patient received 800 pulses per day. The sham group was administered rTMS by placing figure of eight coils, tangential to head (similar to active group) without switching it on and no MT was recorded/delivered (no magnetic stimulation by any means was delivered to sham group). However, to provide auditory perception circular coil was switched on and connected to paddle switch. ACQ-NOW was then assessed for both the groups on the last day of completion of rTMS sessions. Study groups received parenteral thiamine supplementation and tablet paracetamol for headache if required. As period of hospitalization was limited all patients underwent group therapy and individual psychotherapy sessions concurrently, 2 days per week for each, respectively, initiated soon after detoxification as per the institutional policy. ACQ-NOW scores were again recorded after 02 weeks from last active or sham rTMS session and following which these patients were started on anticraving medications and discharged from the hospital.

**RESULTS**

All the participants completed the trial. The clinical characteristics of the participants are enumerated in Table 1. Majority of the patients in the trial were advised to seek psychiatric help for alcohol use behavior due to occupational deterioration. The participants all were from the same socioeconomic group. The mean age of participants in this study was 37.13 ± 7.07 years and the mean age at first diagnosis of alcohol dependence syndrome was 36.38 ± 7.15 years. Mean AUDIT scores were 29.03 ± 4.90.

The alcohol use profile between the active and the sham group was comparable [Table 2].

The mean MT in active group was 46.67 ± 5.34. Among the active group, four participants reported headache, four reported drowsiness, and one of scalp discomfort. One patient in the sham group reported of the heaviness of the head. All the above symptoms were short lasting and did not lead to termination of participation.

The repeated measures ANOVA of the ACQ NOW total scores revealed no significant difference between the active and sham groups when measured immediately after rTMS and 2 weeks after the rTMS [Table 3].

**DISCUSSION**

Although high-frequency rTMS have been tried by various researchers in alcohol dependence syndrome, the results have been discordant. In our study, we used a figure of eight coils over the left DLPFC with 10 Hz frequency (4 s per train and twenty trains per session 800 pulses per day) and stimulus intensity of 120% of MT, which was similar to most of the studies as far as parameters of rTMS.
rtMS initially in the sixty male hospitalized patients who were not on any anticraving medications, but effects were not sustained at 2 weeks after therapy. We did not find significant differences in the craving measured by ACQ NOW between the active and sham groups after completion of stimulation therapy and after 2 weeks.

The strengths of our study were the large sample size who did not have a current exposure to an anticraving agent. The randomization was done among the sample population and all of them completed the trial. The mean ages of the patients in our study and those done in the pioneering study by Mishra et al. were comparable. However, he had used rTMS on patients some of whom were already on anticraving medications and in a purposive sampling manner. ACQ NOW in our participants were measured after 2 weeks of treatment in our study unlike Mishra et al. who did the same after 4 weeks.

Hoppner et al. (2011) in their study too did not find a significant reduction of craving measured by the Obsessive Compulsive Drinking Scale (OCDS) after administering high freq (20 Hz) rTMS over left DLPFC. The subsequent study by Herremans et al. (2012) too did not find a significant effect on craving for alcohol as evaluated by OCDS scale. He had used a high frequency of 1560 pulses per session in a randomized cross over trial.[7] However, when he used a H coil TMS of the prefrontal cortex in 18 patients of alcohol use disorder in another study, he reported significant reduction of craving evaluated by a visual analog scale.[14] The H Coil is unique that it delivers deep simultaneous bilateral stimuli when compared to the more focal and shallow stimulation of the cortex by the figure of eight coils used by us.[15]

CONCLUSIONS

To conclude we did not find any significant effect in reduction of craving scores by administration of 10 daily sessions of high frequency rTMS over the left DLPFC in recently detoxified male inpatients with alcohol dependence syndrome.

The limitations of our study are that it was a single-blinded study. The localization of DLPFC was made by 5 cm rule and is a crude way of localization. There is a lack of empirical evidence on hemispheric differences in DLPFC in addiction, but left DLPFC as determined by functional magnetic resonance imaging appeared to play a crucial role in increasing self-control over cravings.[16] Most of the earlier studies too had chosen the left DLPFC. A modification of the orientation of the existing coil rather than a sham coil was used in the study which is also an acceptable method used by other researchers. The assessment of craving by questionnaire method in a hospital setting may be subject to representativeness of the moment, environment, expectancies, subjective mood, and limited by lack of cues of alcohol.[17]

We hope the studies incorporating TMS physiology, frequency, intensity, and rTMS coil orientations relative to cranial anatomy and new pulse sequences that result in long-term neuromodulation will produce more clarity in the therapeutic use of rTMS in alcohol dependence syndrome.

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Conflicts of interest
There are no conflicts of interest.

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