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To Examine the Amendment in Desire Following High Frequency rTMS Stimulation of the Correct Dorsolateral Anteriorcortex (DLPFC) in Patients with Opioid Dependence as Compared to Sham Stimulation: A Comparative Hospital Based Study

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Abstract

Background: Opioid abuse is a worldwide problem causing serious physical, psychological, social and economic consequences. The aim of this study to assess the change in craving parameters following high frequency rTMS stimulation of the right DLPFC in patients with opioid dependence as compared to sham stimulation. **Subjects and Methods:** This is a prospective, hospital-based, randomized, sham-controlled transcranial magnetic stimulation study conducted at the Centre of Cognitive Neurosciences Department of Central Institute of Psychiatry (C.I.P.), Ranchi, India. The hospital has bed strength of 673 with more than 53,500 patients attending the outpatient clinic every year. The data was analyzed using the computer software program, Statistical Package for Social Sciences-version 10.0 (SPSS-10.0) for Windows®, with different parametric and nonparametric tests, as indicated. The level of significance was taken as $p < 0.05$ (two tailed). **Results:** Our study showed that the socio demographic and clinical variables (categorical) between the active and sham groups. Also there was no significant difference in type of opiates and family psychiatric history between the two groups. There was positive correlation between persistence and OCDUS with significant ($p<.05$) in one week & TCI dimension with OCDUS with significant ($p<.05$) at 4 weeks. There was no significant correlation between ASI and OCDUS with significant ($p<.05$). **Conclusion:** We concluded that neurophysiological variables such as quantitative EEG, evoked potentials, frontal activation tasks should be measured along with rTMS in opioid dependence for more comprehensive assessment of the treatment effect.

Keywords: Opiod Abuse, rTMS, DLPFC, ASI.

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Introduction

Opioid abuse is a worldwide problem causing serious physical, psychological, social and economic consequences. Opioid abuse and dependence are major public health problems around the world. It is estimated that 15.6 million people, including 11 million heroin users, take opioids. People who are opioid dependent have a higher frequency of antisocial personality disorders than individuals in the general population.[1] It has been shown that more than half of the patients seeking treatment of opioid dependency have coexisting psychiatric conditions.[2]

Opioid stimulation can proportionately affect the magnitude of a reward by potentiating the release of neurotransmitters.[3] Some receptor activation can produce effects through negative feedback too. Opioid agonists inhibit the activity of the locus coeruleus. The opioid withdrawal syndrome is believed to be largely because of hyperactivity in the locus coeruleus once this inhibition is discontinued Changes in G protein–coupled receptors, variations in transcription and translation, and increased activity of cyclic adenosine monophosphate second messenger channels also contribute to withdrawal and tolerance.

Studies have reported reduction in craving in cocaine and nicotine dependence after rTMS application. One recent study has revealed the efficacy of transcranial direct current stimulation (tDCS) in reducing craving in alcoholism. To the best of our knowledge, there are no studies on the anticraving efficacy of rTMS in opioid dependence. Neuroimaging studies have demonstrated DLPFC to be a major component of the neural substrate for craving associated with opioid and other psychoactive substances.[4] Although, the depth of penetration of rTMS is limited, the

deeper brain substrates for craving can be influenced by cortical rTMS because of the cortex's massive interconnections and redundant cortical- subcortical loops.[5] Various rTMS efficacy studies with regard to substance related craving have revealed that rTMS application to the right DLPFC produces significant reduction in craving, whereas on application to left DLPFC the results have not been robust. It was hypothesized that high frequency rTMS to the right DLPFC leads to a transynaptic suppression of the left DLPFC (i.e. the dominant hemisphere in right handed persons) via transcallosal connections.[6] The aim of this study to assess the change in craving parameters following high frequency rTMS stimulation of the right DLPFC in patients with opioid dependence as compared to sham stimulation.

Subjects and Methods

This is a prospective, hospital-based, randomized, sham-controlled transcranial magnetic stimulation study conducted at the Centre of Cognitive Neurosciences Department of Central Institute of Psychiatry (C.I.P.), Ranchi, India. The hospital has bed strength of 673 with more than 53,500 patients attending the outpatient clinic every year.

In this study 45 patients with a diagnosis of Opioid dependence syndrome fulfilling the inclusion and exclusion criteria were taken, but 5 of them dropped out of the study. Two patients discharge against medical advice, before completing study. Rest 3 patients the rTMS sessions had to be terminated prematurely because of technical problems with the rTMS machine. The selected 40 patients were divided into active and sham group by purposive sampling. Written informed consent was obtained from the patient prior to the study after explaining the procedure in detail.

Inclusion criteria

1. Diagnosis of opioid dependence syndrome according to Diagnostic Criteria for Research (DCR) of International Classification of Diseases - tenth edition (ICD-10; WHO, 1992).
2. Male patients aged between 18-60 years.
3. Patients with OOWS scores ≤3
4. Right handed, normotensive patients.
5. Patients giving written informed consent.

Exclusion criteria

1. Co-morbid psychiatric, major medical or neurological disorders.
2. History of seizures or significant head injury.
3. Subjects with pacemaker or metal in any part of the body excluding the mouth

Obsessive Compulsive Drug Use Scale (OCDUS)[7]: The OCDUS is constructed analogue to the Obsessive Compulsive Drinking Scale (OCDS).[8] Similar to the OCDS, the OCDUS consists of two subscales: The obsessive subscale (OB), which measures the obsessive thoughts about drug, and the compulsive subscale (CP), which measures the compulsive drive to use drug and the experienced control over drug use. The sum of both scales results in a total score (TOT). All questions of the OCDUS refer to the last week. All items have a 5-point Likert scale (0-4) and the total score ranges from 0 to 40. The internal consistency is seen to be 0.91. All factors of the scale show significant correlations between test and retest data.

Addiction Severity Index: It is a very widely used scale to provide information about the areas of an individual's life that may contribute to his or her substance use disorder. The ASI evaluates seven functional life areas including medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. Each area is examined separately to identify problem symptoms. The ASI provides a 10-point interviewer-determined severity rating of lifetime problems. Internal consistency and test-retest reliability coefficient, range from .96-.97 and .85-.95 respectively in various samples.

Temperament and Character Inventory (TCI)[9]: The TCI contains 240 items is a battery of tests designed to assess differences between people in seven basic dimensions of temperament and character. Temperament refers to automatic emotional responses to experience that are moderately heritable and stable throughout life; the four measured temperament dimensions are Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence. In contrast character refers to self concept and individual differences in goals and values, which influence voluntary choices, intentions, and the meaning of what is experienced in life. Differences in character are moderately influenced by sociocultural learning and mature in progressive steps throughout life. The three measured character dimensions are Self-Directedness, Cooperativeness and Self-Transcendence. With the exception of the Persistence scale, the main scales have a total score of three to five subscales. In total the TCI consists of 7 main scales and 25 subscales. The TCI can be filled in by persons from 15 years of age. The 240 questions of the TCI are answered with "CORRECT" or "INCORRECT". The TCI can be filled in in approximately in 40 minutes.

Statistical Analysis

The data was analyzed using the computer software program, Statistical Package for Social Sciences-version 10.0 (SPSS-10.0) for Windows®, with different parametric and nonparametric tests, as indicated. The level of significance was taken as $p < 0.05$ (two tailed).

Results

Our study showed that the socio demographic and clinical variables (categorical) between the active and sham groups. Both groups with greater proportion being employed, belonging to middle and upper socio-economic status, predominantly being unmarried, from Hindu background and urban background showed no significant difference in

any of the variables. Also there was no significant difference in type of opiates and family psychiatric history between the two groups [Table 1]. There was positive correlation between persistence and OCDUS with significant (p<.05) in one week & TCI dimension with OCDUS with significant (p<.05) at 4 weeks [Table 2 & 3]. There was no significant correlation between ASI and OCDUS with significant (p<.05) [Table 4].

Table 1: Comparison of Socio-demographic and clinical variables (categorical) between active and sham groups.

Variable		Active N=30 n (%)	Sham N=10 n (%)	X2	df	P
Marital status	Married	9(30)	5(50)	1.319	1	.446
	Unmarried	21(70)	5 (50)			
Religion	Hindu	20(67)	5(50)	0.889	1	.457
	Other	10(33)	5(50)			
Occupation	Unemployed	5(16)	3(30)	0.833	1	.653
	Employed	25(84)	7 (70)			
Socioeconomic Status	Lower	7(23)	4(40)	1.045	1	.418
	Middle and Upper	23(77)	6 (60)			
Habitat	Rural	5(16)	2 (20)	0.058	1	1.000
	Suburban	25 (84)	8 (80)			
Family	Nuclear	10(33)	4 (40)	.147	1	1.000
	Joint	20 (67)	6 (60)			
Type of Opiate	Spasmoproxyvon	11(37)	4 (40)	3.740	-	.470
	Heroin and Brownsugar	16(53)	4 (40)			
	Fortwin (pentazocine)	2 (7)	1 (10)			
	Syrup corex	1 (3)	0 (0)			
	Opium dodapost	0 (0)	1 (10)			
Family psychiatric history	No	24 (80)	8 (80)	.000	1	1.000
	Yes	6 (20)	2 (20)			

Table 2: Correlation between TCI dimensions and baseline OCDUS in active group.

Variables	OCDUS-1	P
Harm avoidance	.205	.278
Novelty seeking	.049	.797
Reward dependence	.358	.052
Persistence	.370	.044*
Self directedness	.093	.626
Cooperativeness	.032	.867
Self – transcendence	.110	.563

Table 3: Correlation between TCI dimensions and OCDUS 4 week in active group.

Variables	OCDUS-4 week	P
Harm avoidance	0.172	0.365
Novelty seeking	0.062	0.744
Reward dependence	-0.119	0.531
Persistence	0.094	0.620
Self directedness	-0.043	0.823
Cooperativeness	-0.111	0.560
Self - transcendence	0.095	0.619

Table 4: Correlation between ASI dimensions and baseline OCDUS in active group (N-30)

Variables	OCDUS-1	P
ASI-medical	.079	.678
ASI-employment	.307	.099
ASI-drug	.207	.272
ASI-family	.358	.052

Discussion

In this study 45 patients with a diagnosis of Opioid dependence syndrome fulfilling the inclusion and exclusion criteria were taken, but 5 of them dropped out of the study. Two patients were discharged against medical advice, before completing study. In rest 3 patients the rTMS sessions had to be terminated prematurely because of technical problems with the rTMS machine. Hence the final sample size, with which study was completed, consists of 40 subjects. Out of total sample, active rTMS was administered to 30 patients and 10 patients received sham stimulation. Previous rTMS studies on nicotine and cocaine related craving had a relatively smaller sample size i.e. 14 (Eichhammer et al, 2003) and 6 (Camprodone et al, 2007) respectively.[10,11] But in a recent rTMS study on alcohol dependence, sample size wass 45 (Mishra et al, 2010).[12] Only male patients were selected in our study because majority of the patients coming to our institute for deaddiction are males, with significant underrepresentation of female patients. In our study, the dropout rate was significantly high (11.11%) which was comparable to the previous rTMS studies in other psychiatric illness (11% in Grisaru et al, 1998; 24% in Kaptsan et al, 2003).[13,14] The common reason for dropout cited in the literature is change in diagnosis, withdrawal of informed consent due to adverse events or physical illness unrelated to the study (Grisaru et al, 1998; Kaptsan et al, 2003).[13,14] The major drop out in our study was rather due to technical problems with the rTMS unit. All the 40 selected patients cooperated for both pre- and post-rTMS examination. OOWS, ASI, TCI and OCDUS a baseline rating was could be administered on all the selected subjects. OCDUS after 10 sessions of rTMS and 2weeks post rTMS was administered on all the selected subjects.

In the present study, there is positive correlation between persistence and craving, at baseline and till 2nd week of rTMS. Persistence is an eagerness of efforts in response to signals of anticipated rewards. Individuals with high

persistence work harder even in response to mild punishment and tend to overachieve despite frustration. High persistence is an adaptive behavioral strategy when rewards are intermittent but the contingencies remain stable, however when contingencies change rapidly this persistence tend to become maladaptive (Cloninger, 1994).[15]

Canon et al (1997),[16] hypothesized that individual with high persistence are able to sustain their motivation to stop using substance and are more tenacious about participating in aftercare. Negative affect is a common antecedent of lapse and relapse of substance use. In our study we also found there is high harm avoidance in opioid users. Again harm avoidance is associated with negative emotionality (Cloninger et al, 1994).[15] Studies suggest that affect is implicated in a range of concept relevant to substance use including positive and negative reinforcement, behavioral motivation and regulation of cognition and mood (Quirk,2001).[17] Individuals who experience greater level of negative affect are at high risk of using drugs as coping mechanism (to improve mood/ distract from unpleasant feeling) (Strong et al, 2012).[18] Harm avoidant individuals tend to be cautious, fearful, tensed, pessimistic and negativistic than other people. Hence they tend to experience stressful, humiliating and embarrassing event and then have tendency to lapse (Cheetham et al, 2010).[19]

On correlating addiction severity index and baseline OCDUS in active group, no significant correlation were found however there were trends toward significance ($p < .051$) between baseline OCDUS and employment and family. In our study the severity of OCDUS baseline score showed trend toward significance of positive correlation with employment status, which can be interpreted, hence patients who were employed were more likely to be using opioids more. In an Indian study by Kumar et al. (2011),[20] who studied the comparison of socio demographic parameters between alcohol dependent subjects and opioid dependent subjects, found that opioid group needed more employment support than alcoholic group ($p = 0.01$). The second finding of a trends toward positive correlation between ASI family and OCDUS baseline suggest that where there were more family conflict the score toward higher, there by indicating more severe dependence in opioid. This in turn may be reason for patients impaired family function and his employment which is reflected in our study finding of trends toward significance ($p < .051$) between baseline OCDUS and employment and family.

The result of our study suggests no correlation with regard to legal history. This was in contrast to the finding of Gilligan et al.[21] (1988) who suggested subject had higher behaviour problems and more legal history. The Indian study by Kumar et al (2011),[20] also had finding that subjects with opioid dependence needed more support for their legal problems compared to alcohol dependence subjects. In our study the legal history was obtained from the patient verbally during interview and no external validation of this information was done, hence the possibility of underreporting of the legal complication cannot be ruled out.

As we know temperament is stable and enduring pattern, it does not change easily with environmental stimulation. High harm avoidance acts sometimes as a moderating factor in substance use especially when there are stressful events and lack of coping resources which consequently fails to offer rewards at regular intervals. This makes the contingencies to become stable and contributing to maladaptive pattern of persistence. As a whole, high negative emotionality and stressors increases the likelihood of lapse and relapse and maladaptive persistence tends to contribute to this vicious cycle of craving and subsequent use of substance.

Conclusion

We concluded that more number of studies using double-blind sham-controlled design should be carried out to minimize rater bias and to establish the anti- craving efficacy of rapid rTMS in opioid dependence. Neurophysiological variables such as quantitative EEG, evoked potentials, frontal activation tasks should be measured along with rTMS in opioid dependence for more comprehensive assessment of the treatment effect.

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