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To examine the change in craving following high frequency rTMS stimulation of the right dorsolateral prefrontal cortex (DLPFC) in patients with opioid dependence: A prospective hospital based study

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Abstract
Background: *Opioid craving presents as an irresistible urge to take or as intense thoughts about opioid. The aim of this study to examine the change in craving following high frequency rTMS stimulation of the right dorsolateral prefrontal cortex (DLPFC) in patients with opioid dependence.*
Material & 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 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.*
Results: *The active group consists of 30 patients in the age range of 25.06(5.55) years while the sham control group had 10 patients with age range of 26.40(7.87) years. The comparison of mean scores of Temperament and character dimensions between active and sham group, there was significant difference found in harm avoidance (p 0.50) between active compared to sham groups with no other dimensions showing significant difference seen. The comparison of mean scores of active and sham with ASI Subscales, no significant difference was observed between the two groups on all the dimensions.*
Conclusion: *We concluded that High frequency right prefrontal rTMS was found to have short-term anti-craving effects and trend towards sustaining the effects in opioid dependent patients.*
Keywords: *Opioid craving, rTMS, dorsolateral prefrontal cortex, ASI, OCDUS.*

Introduction

Opioid addiction is one of the most prevalent neuropsychiatric disorders, which results from a complex interplay between genetic and environmental factors, resulting in deleterious consequences to the physical and psychological

health of the individual, along with significant impairment in social and occupational domains of functioning. Addictive behaviour associated with opioid is characterized by craving for opioid, loss of control over consumption, and the development of tolerance and dependence for the substance.[1]

Opioid craving presents as an irresistible urge to take or as intense thoughts about opioid. This construct also subsumes the intent to use opioid, anticipation of positive outcome, anticipation of relief from withdrawal symptoms & negative affect, lack of control over use and cue-induced autonomic response.[2] Craving is associated with the ―brain reward centre situated in medial forebrain bundle comprising the meso-cortico limbic dopamine pathway.[3] These dopaminergic neurons arise from the ventral tegmental area of the brainstem and projects to the nucleus accumbens in the ventral striatum and the prefrontal cortex. The dorsolateral prefrontal cortex (DLPFC) is related to craving through the mesofrontolimbic connections.[4] The development of craving plays an important role in the development of opioid dependence, maintenance of the opioid taking behavior and has been implicated in relapse.[5] Hence, the strategies to reduce craving plays a pivotal role in the management of opioid related disorders.

Transcranial magnetic stimulation (TMS) is a noninvasive and relatively painless tool which was introduced into neurosciences by Barker *et al* in 1986.[6] If TMS pulses are delivered repetitively and rhythmically, it is called repetitive TMS (rTMS; Wassermann et al, 1996)[7]. rTMS has been used to inhibit or activate discrete cortical areas; low-frequency rTMS (when frequency of stimulation is <1Hz) induces a decrease in cortical excitability resulting in an inhibitory effect (Wasserman et al, 1996)[7], whereas high-frequency rTMS (when frequency of stimulation is >1Hz) may lead to activation of cortical areas.[8]

Several open label, randomized sham controlled studies and cross over designs have demonstrated the efficacy of high frequency rTMS of the left DLPFC in reducing negative symptoms of schizophrenia and producing functional improvement.[9,10] rTMS has been found to be overall active enough in reducing auditory hallucinations (AH) in schizophrenic patients.[11] There has been less data on the effectiveness of rTMS in other psychiatric disorders such as mania[12], OCD[13], panic disorder[14] and posttraumatic stress disorder[15]. The aim of this study to examine the change in craving following high frequency rTMS stimulation of the right dorsolateral prefrontal cortex (DLPFC) in patients with opioid dependence.

Material & 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

Socio-demographic data sheet

A semi-structured pro-forma was used for recording demographic details like age, sex, marital status, religion, education, occupation, socioeconomic status, habitat, and family type, as well as clinical data such as duration of opioid use, age of onset of opioid use, age of regular intake, type of opioid use, amount of daily opioid consumption, last intake, past history of medical or psychiatric illness, treatment history, family history of medical or psychiatric illness and premorbid personality. It also included details of physical examination of all organ systems and mental status examination. Finally, diagnosis of the patient according to ICD-10 DCR and the drugs taken during rTMS sessions were also recorded.

Obsessive Compulsive Drug Use Scale (OCDUS)[16]: The OCDUS is constructed analogue to the Obsessive Compulsive Drinking Scale (OCDS)[17]. 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: The ASI was developed by AT McLellan et al. 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)[18]

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

The active group consists of 30 patients in the age range of 25.06(5.55) years while the sham control group had 10 patients with age range of 26.40(7.87) years. The education varied from 8.80 (4.53) years for the active group and 8.00 (4.48)

years for the sham group. The duration of opiate use is in range of 4.11 (3.72) years for the active group and 7.22 (8.30) years for sham group. The age of onset of opiates use is in range of 21.05 (6.04) years for the active group and 19.20 (5.37) years for sham group. Duration of regular use of opiates is 2.65 (2.24) years for the active group and 6.52 (10.68) years for sham group. No statistical difference was found in between two groups (table 1). There was no significant difference in the active group compared to the sham rTMS, in group interaction craving with treatment over time in OCDUS (table 2).

The comparison of mean scores of Temperament and character dimensions between active and sham group, there was significant difference found in harm avoidance (p 0.50) between active compared to sham groups with no other dimensions showing significant difference seen (table 3).

The comparison of mean scores of active and sham with ASI Subscales, no significant difference was observed between the two groups on all the dimensions (table 4).

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

Variables	Active N=30 Mean (SD)	Sham N=10 Mean (SD)	T	df	p
Age (In years)	25.06(5.55)	26.40(7.87)	0.591	38	0.558
Education	8.80 (4.53)	8.00 (4.48)	0.477	38	0.636
Duration of opiate use (In years)	4.11 (3.72)	7.22 (8.30)	1.642	38	0.109
Age at onset (In years)	21.05 (6.04)	19.20 (5.37)	0.859	38	0.396
Duration of Regular Use (In years)	2.65 (2.24)	6.52 (10.68)	1.874	38	0.069

Table 2: Group*OCDUS score Interaction with Treatment in Between Group

Variables		Active (30) Mean ± SD	Sham (10) Mean ± SD	F	P	Effect Size (Eta squared)
OCDUS	**Baseline**	25.96 (5.31)	28.30 (2.40)	2.299	.115	.111
	After 10 rTMS sessions	4.70 (1.55)	10.50 (1.95)			
	2 weeks post rTMS	1.96 (0.92)	7.90 (1.37)			

Table 3: Comparison of TCI dimensions at baseline between active and sham group

Variables	Active N=30 Mean (SD)	Sham N=10 Mean (SD)	t	df	P
Harm avoidance	11.60 (3.59)	14.30 (3.80)	2.028	38	**.050***
Novelty seeking	15.50 (5.08)	16.80 (4.51)	0.718	38	.477
Reward dependence	15.43 (2.67)	15.50 (2.67)	0.068	38	.946
Persistence	5.86 (1.52)	4.90 (2.02)	1.597	38	.118
Self directedness	24.86 (6.22)	28.30 (6.65)	1.485	38	.146
Cooperativeness	28.00 (4.69)	28.80 (6.69)	0.418	38	.678
Self - transcendence	18.73 (5.00)	18.30 (4.19)	0.246	38	.807

*Significance at p<.05 (2-tailed)

Table 4: Comparison of ASI subscales at baseline between active and sham group

Variables	Active N=30 Mean (SD)	Sham N=10 Mean (SD)	t	df	p
ASI-medical	.17 (.17)	.09 (.18)	1.218	38	.231
ASI-employment	.31 (.21)	.40 (.21)	1.152	38	.256
ASI-drug	.48 (.07)	.46 (.09)	0.919	38	.364
ASI-family	.26 (.15)	.29 (.08)	0.542	38	.591

Discussion

The present study examined the anti-craving efficacy of right prefrontal high frequency rTMS in opioid dependent patients. In our study, the opioid dependent cases were selected using ICD-10 DCR, which is used worldwide for research

purposes. 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. In our study, obsessive compulsive drug use scale (OCDUS)[16] which can measure the multidimensional aspects of craving with high internal consistency and reflect the changes in opioid craving with treatment. OCDUS is a state measure providing an index of acute craving, because the questions relate to the degree to which the respondent is currently experiencing these urges.

Neuroimaging studies have demonstrated DLPFC to be a major component of the neural substrate for craving associated with alcohol 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 massive interconnections in cortex and redundant cortical-subcortical loops (George et al, 2002). In a randomized crossover rTMS study in cocaine dependence, one rTMS session over the right DLPFC, but not left, was found to reduce craving by 19% from baseline[19] and in the rTMS efficacy studies with regard to nicotine and food related craving, the results have not been robust with rTMS application to left DLPFC.[20] 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.[21] Our study involved only right handed individuals, hence right DLPFC was selected as the site for rTMS stimulation.

In the previous study of rTMS in cocaine dependence, 2 sessions of 10 Hz rTMS were administered at 20 trains per session, 10 seconds train duration and 1 minute of intertrain interval amounting to 2000 pulses per session[19] and in alcohol dependence, 10 sessions of 10 Hz rTMS were administered at 20 trains per session, 5 seconds train duration and 30 second of intertrain interval amounting to 1000 pulses per session.[22] The rTMS parameters in our study were almost similar (10 Hz, 20 trains per session, train duration of 5 seconds and intertrain interval of 30 seconds, 1000 pulses per session and 10 sessions were given over a period of 2 weeks). The train duration was 5 seconds as administered in the study by Eichhammer et al (2003)[20] with the idea to reduce unwanted side effects like headache and scalp pain. The intertrain interval was shorter (30 seconds) as compared to the previous study by Camprodon et al (2007)[19] in which the intertrain interval was 1 minute. The intertrain interval was the property of the Magstim Rapid device that was used in the present study. In the study by Camprodon et al (2007)[19] the total number of pulses that patients received was 2000/day, but only two rTMS sessions were given (Total number of pulses administered=4000), which led to transient reduction in craving by 19% from baseline, which disappeared after 4 hours. Longer-lasting clinical effects are the result of multiple daily sessions of rTMS which are usually given over a period of several weeks. Hence, in our study, 10 rTMS sessions were administered (Number of pulses administered=1000/day; Total=10,000 pulses), with the view to sustain the possible anti-craving effects of rTMS. The power level of 110% of motor threshold (MT) was used for the present study, which was well within the safety guidelines proposed by Wassermann (1997), as compared to the previous study (Camprodon et al, 2007)[19] which had used a power level of 90% of MT. The coil used in the present study was of figure-of-eight shape which has the advantage of producing more focal stimulation as compared to the circular coils used in previous studies (Eichhammer et al, 2003)[20].

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)[20] and 6 (Camprodone et al, 2007)[19] respectively. But in a recent rTMS study on alcohol dependence, sample size wass 45 (Mishra et al, 2010)[22]. 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.

The patients who received active rTMS were similar to the sham group with respect to age, education, marital status, religion, occupation, habitat and family type. The mean age of patients was 25.06 ± 5.55 years in the active group and 26.40 ±7.87 years in the sham group, which is greater than that of Camprodon et al (2007)[19] (age range=19-23 years) but lesser than Mishra et al (2010)[22] (mean age active=39.36 ± 8.93 and sham =38.20 ± 6.85 years). No significant group difference was noted in socio-demographic variables between the active and sham group, but in both the groups more than 60% of the patients were from middle and upper socioeconomic status and urban background. Both the groups had similar duration of opioid use, age of onset of opioid use, years of opioid dependence. The mean age of onset of opioid use was 25.06 (5.55) years for the active group and 26.40 (7.87) years for the sham group. The amount of opioid was difficult to compare in view of the varying opioid content of different types of preparations consumed in this Catchment area and lack of standardization. More than 80% of the patients in both the groups were consuming capsule spasmo proxyvon and heroin, although no significant group difference was observed in terms of the type of opioid consumption; the reasons being the easy availability in this catchment area. There was no significant difference between group difference in terms of past and family history of any psychiatric or any major medical illness, treatment history.

All the patients were abstinent for more than 10 days before the beginning of rTMS session. The rTMS session was started 3 days after the completion of detoxification (duration=7-10 days) with the idea to prevent the interference of Lorazepam in determination of motor threshold (MT) if given. The abstinence period was minimized in our study so as to complete the rTMS sessions (duration=2 weeks) and 2weeks post rTMS assessment during the stay.

In our study, OCDUS was used in view of its ability to measure multidimensional aspects of craving with high internal consistency and reflect the changes in opioid craving with rTMS treatment. The baseline (Pre-rTMS) mean OCDUS total score was similar in both the groups, being 25.97 (5.31) in the active group and 28.3. (2.40) in the sham group. There was no significant group differences in the Pre-rTMS OCDUS Total score. There was significantly higher reduction in mean OCDUS Total score after 10 rTMS sessions in patients receiving active rTMS (4.70 ± 155) than sham rTMS (10.50 ± 1.95) ($p<0.001$). The significant reduction in OCDUS scores in all the parameters following rTMS application in the active group reveals the short-term anti-craving efficacy of high frequency rTMS in opioid dependence. Increased activity in the mesolimbic dopaminergic pathway has been implicated in craving associated with opioid dependence.[23] The application of rTMS to the DLPFC could have modulated the altered activity in the mesolimbic pathway through the mesofrontolimbic connections. It has been hypothesized that high frequency rTMS application to the right DLPFC possibly leads to a transynaptic suppression of the left DLPFC (i.e. the dominant hemisphere in right handed persons) via transcallosal connections[21], which could be a possible mechanism in reduction of opioid craving in our patients.

The difference in craving scores after the last rTMS session between both the two groups were not sustained in the subsequent 2weeks post rTMS assessment. In the one month Post-rTMS total OCDUS score, lower craving was observed in the active group (1.96± 0.92) as compared to the sham group (7.90 ± 1.37), with a trend towards significance between the group difference ($p=0.111$). Previous rTMS studies in nicotine and cocaine dependence were able to establish its short-term anti-craving effects only.[19,20] The possible sustained anti-craving effects of rTMS could be due to the extended number of rTMS sessions employed in our study. The duration of anti-craving effect of rTMS could be possibly

increased by extending the number of sessions and increasing the interval between the sessions.

Conclusion

We concluded that High frequency right prefrontal rTMS was found to have short-term anti-craving effects and trend towards sustaining the effects in opioid dependent patients.

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