

Effect of Repetitive Transcranial Magnetic Stimulation (rTMS) on the Drug Use Craving in Patients with Methamphetamine Dependency During Withdrawal Phase: A Sham Controlled Randomized Clinical Trial

Mahtab Motavaselian¹, Atefeh Ghanbari Jolfaei^{1*}, Mohamad Ghadiri Vasfi¹, Hamid Reza Ahmadkhaniha¹, Mehrdad Eftekhari Ardebili², Kaveh Alavi² and Maryam Soltani Ramezanzadeh³

1. Research Center for Addiction and Risky Behaviors (ReCARB), Iran Psychiatric Center, Iran University of Medical Sciences, Tehran, Iran

2. Mental Health Research Center, Iran University of Medical Sciences, Tehran, Iran

3. Iran University of Medical Sciences, Tehran, Iran

Abstract

Background: Methamphetamine is considered as one of the potent psychological stimuli with high addiction capacity. Drug craving is one of the most critical factors in drug addiction, leading to drug use relapse once withdrawn. The objective of the present research was to evaluate the effect of Transcranial Magnetic Stimulation (rTMS) on the drug craving in patients using methamphetamine.

Methods: This study was conducted in a double-blind sham-controlled design on 31 patients in Summer 2016. The patients were randomly assigned into 3 groups (each group comprising 10 subjects) and rTMS was performed at the left Dorsolateral Prefrontal Cortex (DLPFC) with frequency of 15Hz and the left Orbitofrontal Cortex (OFC) with a frequency of 1 Hz. One day before the onset of the intervention and one week following the completion of it, the subjects were evaluated using Hamilton Rating Scale for Depression (HRSD), The Brief Psychiatric Rating Scale (BPRS), and visual cue-induced craving assessment task. In a 6-month follow up after the completion of the sessions, the patients were asked whether they tended to be hospitalized (psychiatric service, campus) for psychiatry or substance was collected in a self and family report manner by phone call. Two patients in the DLPFC group, 1 in the OFPFC, and 4 patients in the control group were hospitalized. However, these frequencies were not statistically significant ($p=0.343$, $\chi^2=2.139$).

Results: Repetitive magnetic stimulation failed to significantly reduce craving, but in a 6-month follow up, most cases of substance related hospitalization were reported to be in the control group.

Conclusion: rTMS can reduce the complications of using methamphetamine, such as the number of substance related hospitalizations.

Keywords: Amphetamines, Craving, Dorsolateral prefrontal cortex, Orbito frontal lobe, Transcranial magnetic stimulation

* Corresponding author

Atefeh Ghanbari Jolfaei, MD

Research Center for Addiction and Risky Behaviors (ReCARB), Iran University of Medical Sciences, Tehran, Iran

Tel: +98 21 6651 9519

Email: ghanbari.a@iums.ac.ir

Received: Jan 14 2020

Accepted: Mar 20 2020

Citation to this article:

Motavaselian M, Ghanbari Jolfaei A, Ghadiri Vasfi M, Ahmadkhaniha HR, Eftekhari Ardebili M, Alavi K, et al. Effect of Repetitive Transcranial Magnetic Stimulation (rTMS) on the Drug Use Craving in Patients with Methamphetamine Dependency During Withdrawal Phase: A Sham Controlled Randomized Clinical Trial. *J Iran Med Counc.* 2020;3(2):89-98.

Introduction

Psychoactive drugs act on the central nervous system, and recurring drug intoxication can result in addiction, complex disease process of the brain which is highly difficult to treat (1). Addiction can be described as a persistent state in which there is reduced capacity to control compulsive drug-seeking, regardless of whether it involves risk of negative consequences (1,2).

Based on the World Drug Report, stimulants belonging to amphetamines are the most commonly used drugs in the world, following cannabis (3). Methamphetamine is one of the strong psychological stimulants with high addiction. It is a cheap substance and can be constructed easily with lasting effects (4). It stimulates the dopamine system of the brain and creates short-lived flash or rush and a peak of pleasure immediately after using (4). Craving is one of the most striking symptoms of addiction and RD, as emphasized by the composite addiction cycle previously mentioned (5). It has been the subject of growing attention, to the extent that it is listed as one of the diagnostic criteria in the category of addiction and RD (6). Drug use craving is one of the most important factors in drug addiction, leads to drug use relapse once withdrawn. Drug use craving can be viewed as a personal experience and multi-dimensional phenomenon mixed with the desire to gain a pleasant feeling or to overcome an unpleasant feeling (4). To the date, there is not an approved specific treatment for amphetamine craving.

Transcranial Magnetic Stimulation (TMS) is a non-invasive stimulation technique that is proving to be valuable for both its research and therapeutic potential in psychiatry (7). In the target cortical area, the magnetic field generates an electric current which induces depolarization of superficial cortical neurons (8). TMS is able to modulate cortical excitability and it is used to facilitate functional brain mapping of cortical regions (9).

In general, low frequency (≤ 1 Hz) rTMS reduces neuronal activity and cortical excitability, while higher frequency rTMS increases neuronal activity and cortical excitability (9) and increases relative regional cerebral blood flow (8) although there are numerous exceptions, especially in the hemisphere contralateral to the site of rTMS application. Thus, low-frequency and high-frequency rTMS applied to

the same brain site can have very different effects on brain circuits (10).

Wang *et al* showed that low frequency rTMS has an inhibitory effect on motor cortex activity and high frequency rTMS has facilitating effects on motor cortex activity. In the treatment of psychiatric disorders with rTMS, efforts have been made to alter the cortex pathologic excitability, associated with certain disorders. For example, based on several studies, reduced activity in the left DLPFC has physiological association with affective disorders. To correct this, many studies have used high-frequency rTMS, which increases excitability, on the left DLPFC to normalize the activity of this region.

In a study conducted in 2003 by Oliver and Calvo, increasing the visual cortex excitability led to three-day non-use in those using 3,4-Methylenedioxy methamphetamine (MDMA) chronically (11).

There is accumulating evidence that stimulating the Dorsolateral part of the Prefrontal Cortex (DLPFC) may be of use in addiction treatment. DLPFC is involved in the decision-making processes (12) and these processes can be altered by rTMS (7). The DLPFC is critically involved in processing the craving of smoking (13,14) and other drugs such as cocaine (15) and alcohol (16,17).

The study by Mishra *et al* was carried out as a single-blind trial and indicated that real stimulation was superior, with a reduction in craving of alcohol lasting for four weeks after the completion of the active rTMS sessions (18).

Craving is a complex concept, encompassing neurobiological and psychosocial variables. It is defined as the desire for the previously experienced effects of a psychoactive drug, motivated by internal and external cues (19). Repeated and intense firing of dopamine neurons provides the pleasurable sensations associated with substance intake. Although psychoactive substances act through an extremely wide range of active compounds with specific neuropharmacological mechanisms of action (10), an essential pharmacological end point remains dopamine release through the mesocorticolimbic pathways. Frequent use of drugs increases the activity of the dopaminergic pathway and its withdrawal leads to reduced activity of the dopaminergic pathways and drug craving and drug use relapse. Hence, this

research was conducted to evaluate the effect of Transcranial Magnetic Stimulation (rTMS) on the drug use craving in amphetamine-dependent patients after its withdrawal.

Materials and Methods

Design

This study was conducted in a double-blind sham-controlled design and patients were selected from among clients referring to the addiction clinic (MMT) of Iran Psychiatric Hospital and addiction clinic of Faculty of Behavioral Sciences and Mental Health affiliated to an academic center, using convenient sampling method. Participants were randomly categorized into 3 groups (Each comprising 10 patients) and rTMS was performed at the left Dorsolateral Prefrontal Cortex (DLPFC) with frequency of 15Hz and the left Orbitofrontal Cortex (OFC) with a frequency of 1 Hz. The required personal information and the last time of drug abuse, the dose and way of using were asked from the participants before onset of the sessions. They were screened once before the intervention and once during the sessions randomly by urine toxicology test and diagnostic kits. The Hamilton Rating Scale for Depression (HRSD), Brief Psychiatric Rating Scale (BPRS), and visual cue-induced craving assessment task for methamphetamine were performed for patients one day before the intervention. HRSD was performed at the end of the 10 sessions up to one week later. Patients were followed up once completing a 6-month treatment. Then, the information on hospitalization (psychiatric service, campus) or non-hospitalization was collected in a self and family report manner by phone call.

Ethical approval and trial registration

All the procedures conform to Iran University of Medical Sciences and Iranian Registry of Clinical Trials (Ethical code: IR.IUMS.FMD.REC 1396.9311286014 and registration reference is IRCT20180630040291N1). All patients, after being informed about the study's procedure, signed a written informed consent before starting the treatment.

Tools

SCID_I: The semi-structured clinical interview was performed based on DSM IV. This comprehensive

tool, for clinical and research purposes, was developed by the American Psychiatric Association in 1997. The test was performed in one session and lasted 45 to 90 min. In a research conducted by Sharifi *et al* (3), this tool was translated into Persian language and its reliability was then determined. The Kappa coefficient was higher than 0.4 and acceptable in almost all diagnoses. Total Kappa was 0.55 in the study for lifetime diagnosis and 0.52 for current diagnosis. These figures were reported to be 0.68 and 0.61, respectively, in the main research (by SCID developers). In addition, in the research conducted by Amini *et al* (4) in 2007, its validity was examined and the obtained Kappa was higher than 0.4 for all diagnoses, except for anxiety disorders. Both studies revealed the Persian version of the tool being reliable and valid (4).

HRSD: The Hamilton Rating Scale for Depression was introduced by Max Hamilton (20) in mid-1960s to query the severity of depression symptoms. This is one of the first scales developed for depression. This questionnaire measures different dimensions of depression (Behavioral, physical, cognitive, emotional, sense of guilt, hypochondria, sexual issues, work, suicide, and sleep disorders). A score between 17 and 24, between 25 and 30, and above 31 represent mild, moderate and severe cases of depression, respectively. In a study conducted by Hamilton, its reliability was reported 0.90 to 0.94 through the correlation coefficient among the evaluators. The validity of the scale was also reported 0.60 to 0.84 through correlation with other tools, and its internal validity was reported to be 0.84 to 0.90 as well.

Visual cue-induced craving assessment task: Drug use craving is an inappropriate motivational state for drug abuse developed in the addict's cognitive organization and it is the main reason for continued drug use and its relapse after treatment. Developing standardized and normalized tools to assess various dimensions of this phenomenon and its monitoring have been one of the goals of the addiction research in the world in recent years. Ekhtiari *et al* developed visual cue-induced craving assessment task for methamphetamine smokers in different groups of people using opioids in Iran. As images related to drugs and ready-to-use devices are the most effective visual signs for stimulating the drug use craving, the

classification of these signs was performed based on this grouping in this research. Although it is necessary to examine the reliability and validity of any psychological test, it is not feasible to examine the validity of the drug use craving assessment tests using test-retest method. Hence, it is suggested that the reliability of these tests be examined using internal consistency and split-half methods. Evaluation of the drug use craving in different groups of people using opioids by different tools, which represent moderate depression and acceptable reliability and validity, can be a great contribution in reducing the drug use craving by identifying more characteristics of this phenomenon with the help of methods such as brain imaging and assessment before and after the therapeutic courses and determining the success rate of treatment protocols. In addition, the relationship between drug use craving and other symptoms of addiction can be studied by this method (21,22).

BPRS: The Brief Psychiatric Rating Scale (BPRS) is a rating scale which a clinician or researcher may use to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behavior. Each symptom is rated 1-7 and depending on the version between a total of 18-24 symptoms are scored. The scale is one of the oldest, most widely used scales to measure psychotic symptoms and was first published in 1962.

Participants

The biographical data of the participants were collected using a checklist including age, gender, marital status, job status, and education level. The information on the use of methamphetamine including drug abuse or drug dependence, the severity of methamphetamine use disorder based on DSM IV duration of use, dose of use (average use per week), the method of drug use, and history of injection were recorded separately in the checklist.

Quantitative variables were described with mean and standard deviation, and in special cases, the median and range of variations and qualitative variables were described with frequency and percentage of frequency. The variables were compared in three groups through analysis of variance. The post-hoc test was used if a significant difference was among the groups. In case the conditions to use parametric tests were not

provided, nonparametric tests (Kruskal-Wallis and Mann-Whitney test) were used. The alpha was set at 0.05.

Screening

Study researchers screened participants for eligibility. Once eligibility was confirmed, the patient signed an informed consent. The number and reasons for any participants excluded or declined were recorded.

Inclusion criteria

The inclusion criteria included:

- People aged 18 to 60 years having the amphetamines dependence criteria based on DSM IV before and during treatment and people who did not use amphetamine at least for 2 weeks.
- The patients reporting to crave for methamphetamine. A semi-structured clinical interview was performed based on DSM IV by a trained clinician (Psychologist). Major psychiatric disorders were assessed for a case, and people with major psychiatric disorders and the ones who met exclusion criteria were eliminated from the research population.

Exclusion criteria included

- Being psychotic during the visit,
- Changing drugs during the last two weeks,
- Co-dependence on drugs other than nicotine and caffeine based on SCID,
- Contraindications for magnetic stimulation, including presence of metal, shunt or implant in the brain, increased intracranial pressure, pregnancy or having intention to be pregnant, history of convulsion and having heart pacemaker,
- Patients who could not provide written informed consent.

rTMS procedure

A MagPro X100 stimulator (Medtronic, Denmark) connected to a standard figure-of-eight coil with an outer half-radius of 75 mm (MCF-B65 Butterfly Coil) was used. The coil center was placed at the left PMC/DLPFC with the coil handle pointing 45° relative to the midsagittal-line. Patients in this group received 10 sessions of high-frequency rTMS (15 Hz) with a pulse intensity of 90% of the individual's motor

threshold, consisting of 45 pulses per train with an inter-train pause of 15 s in 40 stimulation trains for a total of 2400 pulses in 20 min of stimulation. These parameters were based on a previous study (23) and respected safety guidelines (24). Patients in the second group received 10 sessions of low-frequency rTMS (1 Hz) with a pulse intensity of 90% of their individual rTMS, consisting of 30 trains with an inter-train of 1 s and duration train of 40 s in 20 min and for sham group (Sham coil was not available), a regular TMS coil was used which was tilted so that an edge remained in contact with the head. As a consequence, a sham TMS pulse produced a clicking sound that was very similar to an active TMS pulse (25).

Results

In this research, 10 cases participated in the DLPFC group (10 males), 10 in the OFPFC group (9 males), and 11 in the control group (11 males). The median age of the groups was 35 years (28 to 46 years), 34.5 years (26 to 44 years) and 34 years (26 to 52 years), respectively, indicating no significant difference among the groups in terms of age ($\chi^2=0.995$, $p=0.619$). Other background variables are shown in table 1. Two patients in the control group and one in the DLPFC group were excluded during the treatment due to lack of referring. Patients were followed up

for 6 months after the end of the intervention. Seven patients were re-hospitalized in psychiatric service center or campus and 5 of them belonged to the control group.

At the beginning of the treatment, the severity of depression in the OFPFC group was lower than that of other groups; the difference, however, was not statistically significant ($p=0.122$). After treatment, the severity of depression in this group was also significantly lower than that of other groups ($p=0.003$). However, the raw value of variations in depression severity was statistically significant among the groups ($p=0.662$). The percentage of severity of depression in the OFPFC group was more than that of the two other groups; the differences were not, however, significant ($p=0.097$) (Table 2).

Based on the Brief Psychiatric Rating Scale, the severity of psychological pathology in the control group was higher than that of the two other groups before the intervention; the difference was not statistically significant, however ($p=0.096$). After the intervention, the three groups failed to show any significant difference ($p=0.119$). The raw value of variations in the DLPFC group was lower than that of the two other groups ($p=0.051$), but the percentage of variations in the severity of psychological pathology turned out to be devoid of any significant differences

Table 1: Background variables related to participants of research

Variable		DLPFC group	OFPFC group	Control group	Statistical comparison
Education	Median	13	12/5	12	$\chi^2=1.093$
	range of variations	5-15	10-17	4-18	$p=0.579$
Marital Status (frequency)	Single	4	6	3	$\chi^2=2.634$
	Married	3	2	5	$p=0.621$
	Divorced	3	2	3	
Job status (frequency)	Employed	1	4	4	$\chi^2=2.629$
	Unemployed	9	6	7	$p=0.269$
Days of use	Median	135	21/5	25/5	$\chi^2=2.807$
	the range of variations	7-720	14-720	7-180	$p=0.246$
Duration of use (per month)	Median	60	60	96	$\chi^2=1.810$
	the range of variations	12-120	8-144	12-240	$p=0.405$
Approximate dose of use (gm)	Median	0.5	2/3	0.5	$\chi^2=4.216$
	the range of variations	0.25-15	0.25-14	0.25-5	$p=0.121$

among the three groups ($p=0.350$) (Table 3). Before the intervention, the severity of temptation in the control group was greater than that of the two other groups ($p=0.051$). After the intervention, no significant difference was identified among the three groups in this regard ($p=0.350$). In addition, the raw value of variations in the severity of craving and percentage of its variations failed to be different among the three

groups ($p=0.15$ and $p=0.905$, respectively) (Table 4). During a 6-month follow up, two patients in the DLPFC group, one in the OFPFC and 4 patients in the control group were hospitalized. However, these frequencies were not statistically significant ($p=0.343$, $\chi^2=2.139$). Kruskal-Wallis test was used for ranked variables and Chi-square test was employed for qualitative variables.

Table 2: Severity of depression based on Hamilton Depression Rating Scale and its variations during treatment

	DLPFC group		OFPFC group		Control group		Statistical comparison
	Median	Range of variations	Median	Range of variations	Median	Range of variations	
Before treatment	21	10-40	10.5	4-34	28	6-43	$\chi^2=4.200$ $p=0.122$
After treatment	13.6	4-31	3	1-14	15	3-24	$\chi^2=11.835$ $p=0/003$
Variations in severity	9	(-2)-25.4	7	2-31	13	(-18)-35	$\chi^2=0.936$ $p=0.626$
Percentage of severity variations	51.6	(-10/0)-76	63.6	42.9-96.9	42.4	(-0.300)-89.7	$\chi^2=4.668$ $p=0.097$

Table 3: Psychological pathology severity based on Brief Psychiatric Rating Scale and its variations during treatment

	DLPFC group		OFPFC group		Control group		Statistical comparison
	Median	Range of variations	Median	Range of variations	Median	Range of variations	
Before treatment	39	26-77	30	21-78	50/5	21-76	$\chi^2=4.685$ $p=0.096$
After treatment	31	23-56	25	18-42	32	20-50	$\chi^2=4.258$ $p=0.119$
Variations of severity	14	(-9)-23	5	(-5)-51	18	(-2)-41	$\chi^2=5.959$ $p=0.051$
Percentage of variations in severity	27.3	(-34.6)-42.6	14/3	(-23.8)-65.4	18/0	(-2)-41	$\chi^2=2.099$ $p=0.350$

Table 4: Severity of temptation based on a visual scale and its variations during treatment

	DLPFC group		OFPFC group		Control group		Statistical comparison
	Median	Range of variations	Median	Range of variations	Median	Range of variations	
Before treatment	240	0-715	280	15-910	630	5-920	$\chi^2=5.959$ $p=0.051$
After treatment	140	15-455	22/5	0-395	130	0-500	$\chi^2=2.099$ $p=0.350$
Variations in severity	140	(-140)-535	161	(-5)-535	270	(-35)-630	$\chi^2=4.331$ $p=0.115$
Percentage of variations in severity	59.7	(-0.11)-91.7	63.5	(-33.3)-100	62.8	(-0.700)-100	$\chi^2=0.119$ $p=0.905$

Discussion

New studies have been conducted on the effects of non-invasive interventions such as transcranial magnetic waves of rTMS and transcranial Direct Current Stimulation (tDCS) in different brain regions related to the craving and reward, such as OFC, DLPFC and insula.

In the current research, no significant difference was found in the background variables and there was no significant difference in the main variables of HRSD, BPRS and craving in active and inactive groups. The OFC, DLPFC and the control groups were compared to evaluate the therapeutic effect of the two active groups which was revealed to be significant in this study due to small sample size in each group.

Studies on DLPFC magnetic stimulation for craving are more than OFC studies, and most of the studies have measured left and right sides in preventing craving in different substances. In this research, two different sites involved in the craving were compared, which did not show any significant difference due to small sample size. In this research, the visual cue-induced craving assessment task was used to measure the craving in using drug and was reported in percentage. There was no criterion for rating the craving, drug use or lack of drug use. Craving is a multifactorial variable and its relationship with drug use, depends on various factors. Some patients used drug chronically and some patients did not report the duration and frequency of use. Some patients might be hospitalized in psychiatric hospitals and might have mild cognitive disorder under the influence of prescribed drugs, so they might have answered the questions of craving test and other tests less accurately. In the current research, due to small sample size, the studied variables did not show significant effects, but the number of patients in 6-month follow up after the intervention was more than that of the control group and 1 patient was treated with TMS DLPFC. This patient abandoned the treatment after 5 sessions and was hospitalized after 3 months. It seems reducing the dose of use or lack of drug consumption or frequency of use may clinically be more effective in reducing the cravings for drug.

In this research, variations in the severity of depression and craving in the intervention and control groups did not show any significant difference; this could be due to small sample sizes. However, the rate

of re-hospitalization for amphetamine-related reasons was significantly lower in the intervention group.

Methamphetamine releases dopamine and sometimes serotonin. It also temporarily affects monoamine transmitters, leading to increased extracellular concentration of these neurotransmitters (26).

In addition, the chronic use of METH leads to down-regulation of D2 of the frontal cortex and increases glutamate transfer (27-30). Various studies have reported the role of DLPFC in stimulant substances and their dependence (31).

In addition, a number of studies have reported that stimulation of DLPFC by rTMS reduces the craving for use of stimulant substances (32-34) and its inhibition induces increased craving (35).

The mechanism of action of the DLPFC stimulation by rTMS on reducing amphetamine craving has not been recognized. It may have an effect on the neurotransmitters mentioned above and change DLPFC (36).

Another hypothesis relates its effect to the behavior and improvement of mood which leads to reduction in desire for drug consumption and drug seeking behaviors (37). This study evaluated the severity of depression before and after the intervention. It showed no significant change in the DLPFC group; this could be due to the small sample size.

The next hypothesis suggests that stimulation of DLPFC can contribute to a modulation of the HPA axis and thus decrease stress, resulting in reduced drug use and the desire to use drug as a way to self-treatment (38).

The second group of protocols, which was an inhibitory protocol on OFC, was designed based on the hypothesis that stimulation of the dopaminergic activity of the reward pathway affected by chronic amphetamine use can cause significant changes in the OFC through orbitofrontal axis; various studies have shown that OFC hyper-metabolism is associated with severity of drug use craving (39).

In addition, as OFC is involved in the regulation of the drive and obsessive-compulsive behaviors and drug dependence and drug-seeking behaviors are also a spectrum of these behaviors (39), it seems that neuro-stimulative interventions in this region can provide new horizons in the amphetamine-dependence treatment for therapists. Accordingly, the inhibitory protocol on OFC was designed in the second group, which was not effective in inducing craving for

amphetamine due to the small sample size. However, the results demonstrated that this protocol is effective in reducing the severity of depression, which is consistent with the results of several other studies. It can be considered a new alternative in the treatment of depression (40). This protocol also reduces the drug related hospitalization in patients in the long run. Though there has been no study evaluating the use of similar protocols in drug-dependent patients, some investigations have used this protocol in the treatment of OCD which identified neurobiological relationship with addiction and reported its positive effect (41,42). The limitations of this study were small sample size, re-use of methamphetamine by patients, and the patients who dropped out of the study.

Conclusion

Amphetamine use disorder is a disabling condition which necessitates further improvements in intervention strategies. TMS is a newer modality, possibly being effective in remission of patients from this disorder. As studies are limited in this regard, there is a lot of scope for further research especially regarding the comparison of TMS with pharmacotherapy, and the long-term benefits of this type of therapy. Future studies with larger sample sizes and the optimal protocols with longer length of stimulation and sufficient sessions can be conducted for effective and safe treatment of amphetamine use disorders. Moreover, longer follow up studies need to be attempted as well.

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