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Original Article

Assessment of brain structural changes in patients with opium dependence disorder on methadone maintenance treatment, opium tincture treatment and healthy individuals

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Abstract

Introduction: Methadone maintenance and opium tincture treatments has been recommended as harm reduction strategies for opioid-dependent patients in Iran. However, the effects of long-term administration of methadone and opium tincture on the brain are not fully understood. In this study we investigated the effects of methadone and opium tincture maintenance treatments on the brain volumes of former opium addicts by magnetic resonance imaging (MRI) volumetry of brain compared to healthy participants.

Materials and Methods: The present case-control study was performed in Mashhad, Iran in 2015-2017. Via con venient sampling method, 36 participants were selected and allocated in 3 equal groups (methadone maintenance treatment, opium tincture treatment, and normal control). The volumes of gray matter, frontal lobe, temporal lob e, cingulate gyrus, limbic system, amygdala, and hippocampus of all participants were assessed using MRI volu metry. Data analyzed by ANOVA, using SPSS software (ver. 16).

Results: There were no significant statistical differences between mean volumes of any assessed region of the br ain among three groups (P>0.05).

Conclusion: Methadone maintenance treatment and opium tincture treatment have no hazardous effects on the v olumes of gray matter, frontal lobe, temporal lobe, cingulate gyrus, limbic system, amygdala, and hippocampus o f former opium addicts.

Keywords: Brain, Dependence, Magnetic Resonance Imaging, Methadone, Opium.

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Introduction

Opioid dependency is one of the prominent health problems in the world (1). As Iran is located near the sites of cultivation and production of opium, opioids, and opium, in particular, are the most common illicit drugs of abuse (2). The high prevalence of using the opium is one of the major differences in the pattern of recreational opioid abuse between Iran and western societies, where heroin or therapeutic opioids are the main opioids of abuse (3). There is an association between the regional brain volumes and the numbers of neurons in different parts of the brain (4).

Changes in the regional or whole-brain volumes may reflect the changes in brain-specific functions, such as what is observed in dementia (5). Ventricular enlargement has repeatedly been reported in substance-related disorders like alcohol and cocaine dependence for more than two decades as a result of substance dependence disorder (6,7). There are some reports about possible cortical volume loss of the brain in opioid-dependent patients, even with the prescribed opioids in therapeutic dosages, too (8,9). Long-term use of synthetic opioid receptor agonists such as methadone has been accepted as a harm reduction strategy in the treatment of heroin dependence disorder (10). Considering the high prevalence of abuse of opium compared to heroin in Iran, local studies conducted in Iran have argued that the opium dependent patients should not directly undergo MMT unless under particular circumstances, such as repeated failure to maintain abstinence or some psychiatric disorders comorbidities (11). On the other hand, since 2010 the Ministry of Health and Medical Education of Iran introduced a new protocol of harm reduction strategy for patients who have failed to complete outpatient maintenance treatments or residential approaches by replacing opium tincture instead of illegal opiates (12).

However, despite the significant attention toward recommending MMT and opium tincture treatment (OPT) in Iran, their long-term effects on the brain of former opium addicts are not fully understood (9).

Therefore, we decided to study the effects of these two treatment protocols on brain volumes of former opium addicts and compare the results to healthy individuals as the control group, by using magnetic resonance imaging (MRI) volumetry.

Materials and Methods

The present case-control study performed in Mashhad, Northeast of Iran in 2015-2017. Participants in the case group were selected by convenient sampling method from the patients who were referred to outpatient addiction clinic of Ibn-e-Sina psychiatric hospital, the main psychiatric hospital of Mashhad. According to the fact that there was no published study which compares brain structural changes in patients with opium dependence disorder on MMT with patients on OPT and healthy subjects, this pilot study was carried out with a sample size of 36 participants in three equal groups.

Safety of electromagnetic waves used in MRI up to 8 Tesla, for human subjects, has discussed repeatedly and no danger has found (13). So, all participants were studied by brain MRI without contrast, and their brain volumes were calculated using volumetric MRI techniques. Brain MRI performed in the department of radiology of Ghaem hospital of Mashhad.

Outpatient addiction clinic of Ibn-e-Sina hospital offered different therapeutic services for patients suffering from substance abuse disorders, including opium abuse disorder. Patients diagnosed with having opium abuse disorder could benefit from abstinence and harm reduction strategies, including methadone maintenance treatment or opium tincture maintenance treatment. Twenty four participants of the present study were former opium addicts, who were under maintenance treatment in this clinic. Twelve of them were selected from a group of 350 patients who were under MMT and 12 were selected from a group of 300 patients who were under OPT. The third group consisted of 12 healthy participants as the control group. A trained resident of psychiatry interviewed all participants under the supervision of a board-certified psychiatrist based on DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision) to meet the inclusion criteria of the study.

The inclusion criteria for the MMT group was having DSM-IV-TR criteria of opium dependence disorder, regular consumption of opium for at least five years before the beginning of MMT, consuming a stable dosage of methadone for at least 12 consecutive months without any discontinuing of treatment. Patients with any history of neurological disease, any history of psychiatric illnesses other than opium dependence disorder, any history of being treated by psychiatric

medications, any history of drug abuse except for opium, nicotine and alcohol on an ongoing basis, positive HIV test, history of head trauma, disorders causing chronic pain which made the patient use analgesics, having a piece of metal in the body or claustrophobia which interfered with performing brain MRI were not entered in to the study, as well. As the study has no specific intervention and follow-up phase, there were no specific exclusion criteria except refusing to perform MRI after accepting to participate in the survey which did not happen throughout the study. A group of 12 patients under OPT was enrolled in the study after being matched for age and sex with MMT participants. The same person interviewed them to meet the inclusion criteria, which was the same as the MMT group, except that they should not receive methadone or another opioid receptor agonists but opium tincture in their medical history. Exclusion criteria in the OPT group were similar to the MMT group.Due to the absence of standard brain volume data in the general population, a group of 12 age/sex-matched healthy participants were enrolled in the study, too. MRI performed in gray matter, frontal lobe, temporal lobe, cingulate gyrus, limbic system, amygdala, and hippocampus. A trained resident of radiology evaluated MRI images quality and collaborated in data analysis, which was mainly conducted by a Ph.D. of Medical Physics.

Due to ethical considerations, MRI images were reported by a board-certified radiologist and the resident of radiology, who was in charge of the study, was responsible for making participants informed of any possible pathology of the CNS. However, no pathological finding was reported in MRI images. Source images acquired with a high-resolution 1.5 Tesla MRI system in the sagittal plane. Figure 1 shows an example of source images of the brain. For image analysis, Statistical Parametric Mapping (SPM) method used for volumetry (14) using SPM software version 8.0 (15). We also used options available in the toolbox SPM included WFU_Pick Atlas software version 3.0 and Easy Volume software (16,17). This method is based on comparing voxel to voxel brain images and examines the differences in brain structural and functional images. By using this method, we can study the effect of a particular factor (e.g., using a chemical substance in this study) on brain tissue that includes gray matter, white matter, and cerebrospinal fluid. As all variables have normal distribution, they were analyzed by ANOVA, using SPSS software (ver. 16). P value less than 0.05 was considered as significant.

Results

In the present study, 36 participants, aged 30-50 year-old, underwent brain MRI. All participants were male. Twelve of them were former opium addicts on MMT at the time of the study, 12 of them were former opium addicts on OPT at the time of the study, and 12 of them were a healthy population.

Table 1 shows the mean volume ratio of brain gray matter, frontal lobe, temporal lobe, cingulate gyrus, limbic system, amygdala, and hippocampus.

As the mean volume of the amygdala of the participants in the MMT group was the smallest mean volume acquired in the study, we reported the mean volume ratio of other parts of the brain in all participants compared to the mean volume of the amygdala of the MMT group. As it can be seen, there were no significant statistical differences between means of any of the assessed volumes of brain. Figure 1 shows sagittal high resolution T1 images.

Table 1. Mean volume ratio of different brain regions in participants on MMT, participants on OPT and normal participants based on the mean volume of the amygdala of the MMT group

Groups	Gray matter	Frontal lobe	Temporal lobe	Cingulate gyrus	Limbic system	Amygdala	Hippocampus
Normal	157.15	54.04	23.07	17.56	42.59	1.04	4.48
MMT	152.04	52.67	22.26	17.22	41.44	1	4.33
OPT	159.67	55.70	23.63	17.30	42.00	1.04	4.41
P-value*	0.25**	0.21**	0.07**	0.82**	0.71**	0.50**	0.61**

*significant at P<0.05 **Using ANOVA

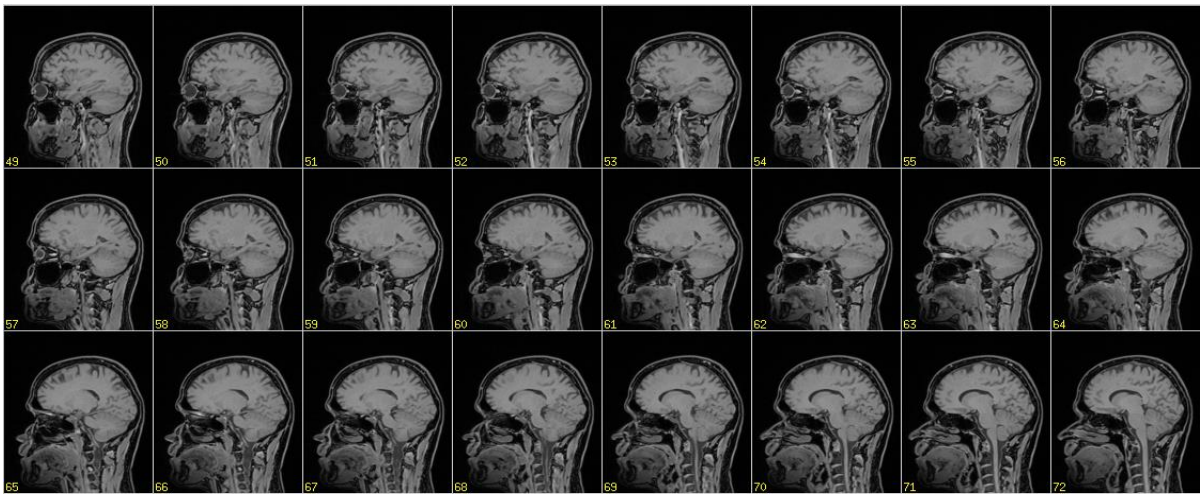

Figure 1. Source image of the brain. Sagittal high resolution T1 images are acquired

Discussion

Methadone and opium tincture are full opioid agonists available for harm reduction strategies in Iran. Since large numbers of different opioid receptors are in the brain, the brain is the target organ for the effects of opioid agonists (18,19). In the present study, we compared the effects of MMT and OPT on brain volumes of former opium addicts compared with healthy individuals by the harmless and non-invasive method of MRI volumetry of the brain. Based on the results of our study, there were no significant statistical differences between mean brain volumes of gray matter, frontal lobe, temporal lobe, cingulate gyrus, limbic system, amygdala, and hippocampus between three groups of participants of the study.

In 1998, Pezawas and his colleagues reported a significant cortical volume loss of the brain in opioid-dependent patients (20). One decade later, Tanabe et al. reported lower gray matter volume in the right and left medial orbitofrontal cortices of substance-dependent individuals compared to control group. Since participants were dependent on 2 or more substances, so the authors could not specify the types of drugs that were responsible for the observed changes (21). Overall, some authors concluded that although the etiology of volume loss in opioid-dependent patients is unclear, long-term opiate use produces obvious structural changes in the brain (20). They hypothesize that reduction in size and shape of dopaminergic neurons of mesolimbic pathways after prolonged administration of any opiates, even morphine, and the changes in neurofilament and glial fibrillary acidic proteins in the brain may lead to ventricular enlargement (22,23).

On the other hand, there is some other evidence about the effects of opiates on the brain volume, which are not consistent with the results of the previous studies. The effect of morphine on the cerebella cortex volume of the rats was studied by Ghasemi et al. Results indicated no significant differences in morphine injected rats compared to controls (24). In another study, brain volume changes were examined in the adult male rats after administration of methadone and buprenorphine. No difference was observed in gray matter, white matter, and total brain volume compared to the control group (25).

As we focused on the treatment outcome of patients with opium dependence disorder, and comparing different treatment outcomes, disagreement about how abusing different opiates could affect the brain has little impact on the results of our study. According to inclusion criteria of our study, only patients who were dependent on opium (no other opiates) could participate in the study; so, we could eliminate the confounding effects of consuming different substances on the brain of participants in the period they did not seek any treatments. Furthermore, using three groups of participants provided the chance to compare the effects of MMT and OPT with each other and with a healthy group.

We could not find any differences between the mean volumes of the regions we assessed in the brain. It seems that, aside from likely baseline changes of the brain in former opium dependent individuals, methadone maintenance treatment or OPT has not brought visible negative changes in the brain after 12 months. Even, it could be suggested that 12 months treatment on

these protocols may reverse the probable adverse effects of opium on the brain, too.

However, even though morphine is the main alkaloid of opium tincture, considering the above findings as the effects of methadone or morphine could be misleading.

Methadone maintenance and opium tincture treatments are therapeutic packages; therefore, patients under these treatment protocols frequently receive other non-pharmacological interventions such as individual or group psychotherapy, family interventions especially for their dysfunctional interpersonal relationships, psychoeducation about the concept of addiction and strategies of treatment, improving life skills, participation in behavioral modification activities (11,12).

Because these interventions could affect brain function (26), it could be concluded that the findings of the present study should be attributed to the treatment packages, not only the medications. Therefore, they could not distinguish the probable effects of methadone from morphine on the morphology of the brain.

Allocating participants in 3 groups and homogeneity of our sample in the history of the substance of abuse (dependency in opium) strengthen the design of our study. While, different doses of opium which consumed by patients and the variety in the duration of abuse, probably diet interactions and nutritional deficiencies in participants, limited sample size and the accuracy of the device (MRI device) are the most critical limitations of the study.

Conclusion

We concluded that methadone maintenance and opium tincture treatments, as packages of treatments, have no adverse effects on the brain volumes in gray matter, frontal lobe, temporal lobe, cingulate gyrus, limbic system, amygdala, and hippocampus in patients with opium dependence disorder.

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