

# Brain MRI Findings in Tramadol Poisoning

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## Abstract

**Background:** Tramadol intoxication and its non-therapeutic abuse have recently become prevalent in Iran. Tramadol overdose cases may be complicated by some neurologic incidences such as seizure. In this study, we aimed to evaluate possible central neural system lesions in patients with tramadol-induced seizure using MRI imaging.

**Methods:** A cross-sectional study was conducted with age- and sex-matched case and control groups. The case group included oral tramadol intoxication cases with loss of consciousness and/or tramadol induced seizure. The control group included patients with seizure without tramadol consumption. The brain MRI was done in the first post-seizure 24-hour. Finally, all data were analyzed using SPSS software.

**Results:** 15 patients (7 females and 8 males) were in the control group and 15 patients (3 females and 12 males) were in the case group with mean age of  $22.27 \pm 6.54$  and  $21.93 \pm 4.57$  years, respectively. 8 patients of case group and 3 patients of control group had abnormal evidence (hyper signal foci in white matter) in brain MRI images; there was no significant difference between the two groups ( $P=0.128$ ). Lesions depth in MRI images of the case group were equally in Subcortical and Deep parts of the white matter (37.5%) and in 2 cases (25%) were observed in both parts. There was no difference between the two groups in this regard ( $P=0.721$ ).

**Conclusion:** In our study, over half of the case group patients had hypersignal but nonspecific evidence in MRI imaging. No significant difference was observed between case and control groups in the lesions pattern.

**Keywords:** Brain; Magnetic Resonance Imaging; Poisoning Tramadol

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## INTRODUCTION

Tramadol is a pure opioid agonist and a synthetic codeine analogue that has been widely used for pain relief. It acts via two different mechanisms and produces its analgesic effects by both opioid pathways and inhibition of reuptake of norepinephrine and serotonin, which are endogenous pain modulating neurotransmitters (1). Tramadol has been used as an analgesic in Iran since 1995. However, it has been legally approved by food and drug administration of Iran (IFDA) in 2003 (2, 3).

There are many studies reporting that tramadol is an addictive drug and can lead to physical and psychological dependency and addiction. Tramadol toxicity might have some early side effects including central nervous system (CNS) depression, tachycardia and cardiac arrest, respiratory depression and arrest, seizure, neuromuscular signs and symptoms, miosis, hypotonicity, and respiratory acidosis. Chronic use of this drug can lead to other side effects including fatigue, dizziness, vertigo, headache, visual disorders, euphoria, dysphoria, and hallucinations. Although it is almost thought to be safe in the therapeutic

doses, there are reports that indicate the probability of seizure induction even within this range of drug doses (4-7).

The peak plasma concentration of tramadol occurs at approximately 1.5 hours after ingestion and its half-life in the plasma is about 6 hours. Tramadol completely penetrates the blood-brain barrier and can increase the risk of brain damages. There are some studies on the neurotoxic effects of tramadol on the brain and CNS, but not many studies have evaluated the alterations in brain imaging of tramadol users or abusers. Moreover, those studies that have assessed brain imaging, have not reported significant findings in most of the cases (4, 8-10).

Tramadol abuse is widespread and rapidly increasing in Iran (3). Seizure and CNS damages are important clinical side effects of this drug that can be evaluated by brain magnetic resonance imaging (MRI). Therefore, the present study aimed to evaluate the alterations in brain MRI of tramadol abusers and compare them with control subjects.

## METHODS

This cross-sectional study was conducted from March

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2016 to March 2017 in the toxicology ward affiliated to Mashhad University of Medical Sciences (MUMS). All participants were aged between 16-66 years. We included patients who had the symptoms of tramadol intoxication including loss of consciousness and/or seizure. The exclusion criteria were: multiple drug consumption, asymptomatic patients, history of epilepsy, mimickers of seizure (e.g. tremor, psychogenic seizure, myoclonus), psychological comorbidities, history of head trauma with more than 30 minutes of unconsciousness, pregnancy and refusing to participate in the study. The control group consisted of 15 patients who were matched according to their age and gender. Multiple urine analysis was performed for all patients to rule out cases with multiple drug intoxication; Brain MRI was performed for all patients and described by a radiologist. MRI is a non-invasive imaging technology that produces three dimensional detailed anatomical images without the use of damaging radiation. MRI provides better soft tissue contrast than CT. It can differentiate between white matter and gray matter, ventricles and other soft tissues better than CT (CT is usually better at imaging bones). These images provide physicians with anatomical and pathological information and can be useful in diagnosis of diseases which cause seizures.

Patients' demographic data including age and sex, dose and duration of tramadol usage, and frequency and route of consumption were obtained and collected. A urine sample was assessed for tramadol and other drugs.

Brain MRI was obtained in the first 24-hour after the seizure. The MRI was performed using Siemens Symphony in standard sagittal section including T1, T2, ADC map and DWI. All images were evaluated by a radiologist and in cases of pathologic findings the patient was referred to a neurologist for further evaluations. Ethics approval was obtained from the ethics committee of Mashhad University of Medical Sciences (No.IR.mums.rec.1394.696). Informed consent was obtained from all patients or their relatives who were legitimately permissive to consent (if the cases were below the age of consent or were unconscious) prior to initiation of the study. We used SPSS 16 for analysis. Kolmogorov-Smirnov test was used for assessment of normal distribution of data. The mean and standard deviation were reported for normal distributed variables, and median and interquartile range (IQR) for non-normally distributed data. According to normal distribution of data, independent samples t-test or Mann-Whitney U test was used for comparison between the two groups. The Fisher's exact test was used to compare the frequencies between the two groups. P value <0.05 was considered as significant.

## RESULTS

A total of 30 subjects, divided into two groups of 15, were included in the study; of which 10 (33.3%) participants were females and 20 (66.6%) were males.

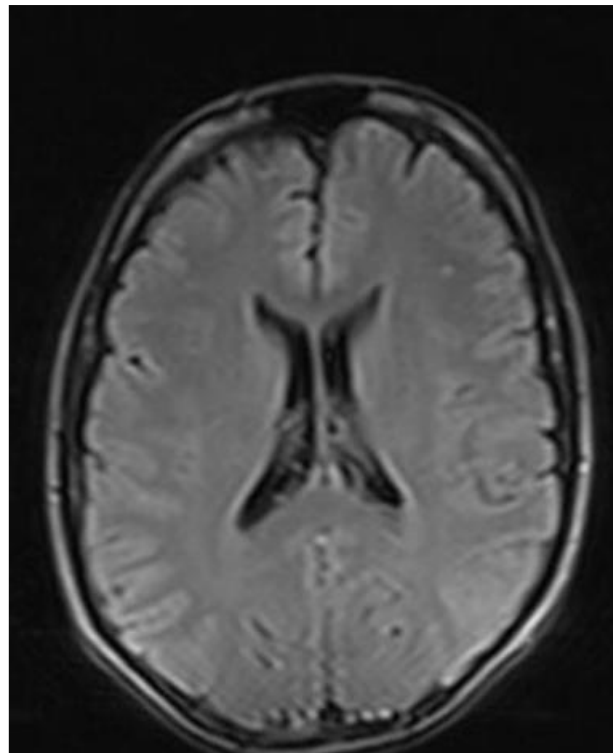
The mean± SD age was 21.93±4.57 years in the case group and 22.27±6.54 years in the control group.

No significant difference was observed between the groups

regarding age and sex. On admission to the emergency department, the most common accompanying symptoms in patients with seizures were nausea and vomiting (100%), followed by tachycardia (40%).

The mean tramadol dose in patients with tramadol-induced seizures was 1320±1081.14 mg, with a minimum (min) of 200 mg and the maximum (max) 4 gr. The mean time from tramadol ingestion to seizure occurrence was 90±67.8 minutes (min=30 and max=300 minutes). Seven patients had tramadol dependency, for whom the mean dependency time for abusers was 33.71±40.11 months, ranging from 2 to 120 months.

In the case group, 8 (53.33%) of the patients had abnormal brain MRI (hypersignal areas), while only three (20%) of the subjects in the control group had hypersignal areas in their brain MRI. The Fisher's exact test showed no significant difference between the two groups (P=0.128). Of the eleven subjects with abnormal brain MRI, four (36.4%) had lesions in subcortical areas, five (45.4%) had lesion in deep areas, and two (18.2%) patients had lesions in both areas. No difference was observed between the case and control groups regarding the depth of the lesions (P=0.721). The brain MRI showed that in most of the cases, the lesion was in the frontal lobe (N=8; 72.7%) (Image 1). 62.5% of the case group and 100% of the control group had lesions in the frontal lobe. The other three patients had lesions in parietal (N=1; 9.1%), fronto-parietal (N=1; 9.1%), and occipital (N=1; 9.1%) lobes. However, there was no significant difference between those with lesion in the frontal lobe and those with lesions in other lobes (P=0.509).



**Image 1.** Axial FLAR brain image shows hyperintense punctate focus in the deep white matter of the left frontal lobe.

One sample Kolmogorov-Smirnov test showed that all variables were normally distributed. There was no significant difference between subjects with abnormal brain MRI and those with normal MRI regarding quantitative variables including the dose of used tramadol, dependency period, time from ingestion to seizure, and age ( $P>0.05$ ). The same finding was observed regarding the qualitative variables such as history of dependency, mydriasis, gender, hypoxia, bradypnea, and tachycardia ( $P>0.05$ ).

## DISCUSSION

In this study, we aimed to evaluate the brain MRI findings of patients with seizure or decreased level of consciousness subsequent to tramadol poisoning.

We found that 8 patients (53.3%) had hypersignal areas in their brain MRI. The hypersignal lesions were equally distributed between the deep and subcortical areas (37.5% for each area) and bilateral lesions found in 2 patients. The results of other literatures are in contrast to ours. In 2012, Bostani et al. (10) evaluated 28 patients with seizure, resulted from tramadol abuse. Only 1 patient was found with hypersignal lesion in the subcortical area. Márquez-Romero et al. (11) reported the MRI findings of a 15-year-old man with generalized tonic clonic seizure after receiving 500mg intravenous tramadol. No lesions were found in MRI and MR-angiography. Likewise, two other case reports found no abnormality in brain MRI of patients with tramadol-related seizures (12, 13). The information about the brain MRI findings in tramadol related seizures is limited to several case-reports, which we believe may be a reason for contradictory results between our study and other reports. Moreover, the studies in this area with larger sample size did not use MRI for evaluating the brain lesions (14, 15).

We showed that lesions are most commonly present in the frontal lobe. The effects of drug abuse on the distribution of the brain lesions have been investigated previously. Alaee et al. (16) evaluated the hyperintensity in the white matter of patients with amphetamine and methamphetamine intoxication. Similar to our results, they showed that 31% of the lesions were located in the frontal lobe and the rest of the lesions were located in temporal, parietal and occipital lobe, respectively. They also reported the same frequency of the lesions in the deep and subcortical area. Lyoo et al. (17) indicated that the frontal and parietal lobe lesions are more frequent in heroin and cocaine dependent individuals compared to the healthy controls. It seems that brain lesions followed by substance abuse do not associate with a specific brain lesion in brain MRI sections.

The mean age of the participants in our study was comparable to other researches in Iran (10, 14). Like previous studies, we found that tramadol intoxication is more common in men.

In our study, patients used 200-2500mg tramadol. Seizures occurred even by using 200mg of tramadol, which is in the therapeutic dosage range of the drug. Previous

investigations reported a seizure after using 50mg of tramadol (18). Some other reports also showed seizure occurrence in more than 50% of the patients, who used tramadol<2500mg (19, 20).

The interval between tramadol consumption and seizure onset was 90 minutes. In one case, seizure was started after 30 minutes. This finding is in accordance with Marquardt et al. (21) that reported 84.6% of seizures occurred in the first 6 hours after tramadol usage. However, some studies reported that less than 50% of the patients had seizure during the first 24 hours of tramadol usage.

According to our observations, it is probable that half of the patients with tramadol-related seizure can have hypersignal areas in their brain MRI. However, it is unclear whether disorders stem from the seizure itself or are caused by tramadol. We recommend applying MRI for all patients with tramadol-related seizures, especially those with the history of alcohol consumption, because even if the CT scan section does not show any abnormality, there may be hypersignal areas in the brain MRI.

## LIMITATIONS

This study had some limitations such as small sample size. However, this was a pilot and first study of its kind. Second, it should be considered that in the cases of illegal drug abuse the drug history is not reliable. Moreover, the recall bias caused by euphoria or post-ictal phase of seizure is inevitable. However, we tried to reduce the risk of recall bias by recording an accurate history from patients' relatives. Third, another source of uncertainty in our findings was that we did not measure the serum level of tramadol. Since tramadol was used orally among the participants of this study, various serum levels of tramadol could be detected.

Our study also had some strength points. Multiple urine analysis was performed for all patients to rule out cases with multiple drug intoxication. This study also benefits from a matched control, so we were able to compare our results with other reasons of seizure.

## CONCLUSION

This study showed that about 50% of subjects with tramadol-related seizures had hypersignal areas in their brain MRI. Frontal lobe was the most common involved lobe. The lesions were equally distributed in the deep and subcortical areas. There was no significant difference between the lesions in the case and control group. This was among the first studies in the field and our results can be used as a baseline for future research.

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