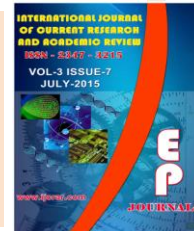




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### Clinical and paraclinical finding in patients Tramadol intoxication with seizure referred to emergency department of Sina hospital

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#### KEYWORDS

Seizure,  
Tramadol,  
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#### A B S T R A C T

Tramadol is an opium-like sedative and is considered an opioid. This drug is used to relieve mild to severe pains and according to the reports it sometimes causes seizure. This study was conducted since no documented study was carried out in Tabriz on the clinical and paraclinic findings about seizure patients intoxicated with tramadol. In a descriptive analytical study that was conducted in the Internal Medicine Department and Emergency Medicine Department of Tabriz University of Medical Sciences on patients intoxicated with tramadol, the clinical and paraclinic findings about seizure patients intoxicated with tramadol were examined. Most of the seizures were identified as pre-hospital seizures. Moreover, 82.2% of the seizures occurred before arriving at the emergency center and 17.8% were in-hospital seizures. Only 6 patients demonstrated trauma during the seizures (5.9%). In most cases tramadol had been consumed all at once. In 78 cases (77.2%) tramadol was consumed all at once and in 23 patients it was consumed gradually. According to the results, tramadol-induced seizures mostly occur before arriving at the hospital and most patients are men who are referred to the emergency centers in confusion.

#### Introduction

Tramadol is an opium-like sedative and a form of opioid. It is an agonist for  $\mu$  receptors, the noradrenergic and serotonergic systems. It also increases the release of serotonin.

Tramadol is highly vulnerable to  $\mu$  receptors. Tramadol inhibits the reabsorption of adrenaline and the increased release of serotonin. It also increases the concentration of adrenaline and serotonin in

synapses. As opposed to morphine, the property of anti-depressants and consciousness are resulted from the consumption of this drug which makes the consumer more active (1).

Consumption of 100 mg of tramadol maximizes the blood level of the drug in 2 hours. In addition, 30% is excreted intact and 60% is excreted through the urine in the form of metabolites broken down in the liver. The halftime life of the drug is between 4 and 6 hours (1).

Consumption of tramadol causes a mental and physical addiction similar to the addiction to opium. By suddenly stopping the consumption of the drug signs such as anxiety, sweating, insomnia, nausea, shivering, diarrhea, muscle aches, RLS, fear, restlessness, hot flashes, and tingling at the endings are demonstrated. Tramadol causes tipsiness and highness and acts as an anti-depressant. Therefore, it is abused commonly and it is usually not known correctly by the youth and therefore is not considered to be addictive by the youth. Tramadol can be obtained with a general physician's prescription and the laws on drugs do not apply to this medicine. However, its addiction is not less than other opioids. It is also reported that this drug is used eagerly (2).

Other side effects of opium-like drugs are seen with tramadol but the possibility of incidence of respiratory depression (as the most lethal side effect of these drugs) with oral tramadol is less than morphine.

Consumption of this drug increases the level of serotonin and therefore it causes nausea more than other opioids. This drug also causes insomnia. Consumption of more than 400 mg of tramadol is dangerous for people who lack the physical resistance to opioids (2).

One of the rare side effects of tramadol is seizure. Seizure is usually caused by the excessive intake of this drug or by the consumption of this drug by epileptic patients, patients with brain injury, patients with liver and renal problems, and alcoholics (3).

This study was conducted since no documented study was carried out in Tabriz on the clinical and paraclinic findings about seizure patients intoxicated with tramadol. The objective of this study was to examine the clinical and paraclinic findings about seizure patients who were intoxicated with tramadol and visited Sina Hospital.

### **Materials and Methods**

In a descriptive analytical study that was conducted in the Internal Medicine Department and Emergency Medicine Department of Tabriz University of Medical Sciences on patients intoxicated with tramadol, the clinical and paraclinic findings about seizure patients intoxicated with tramadol were examined.

All of the seizure patients who were intoxicated with tramadol and who visited the emergency department in 2014 were studied.

All of the patients who were intoxicated with tramadol and were diagnosed with pre-hospital or in-hospital seizure in 2014 were included in the study.

### **Inclusion Criteria**

All of the patients who experienced seizure as a result of tramadol intake

### **Exclusion Criteria**

Cases in which the patient or his/her companions were not ready to cooperate.

- Cases with history of seizure

### **Ethical Considerations**

Considering the type of the study, which was a retrospective study, there was no need for formal consent of the patients and all of the required measures were taken to keep the patients' information confidential.

### **Statistical Analysis**

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean  $\pm$  SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value  $\leq 0.05$  was considered statistically significant.

### **Possible Limitations and Problems**

- Failure of timely attendance by patients in subsequent treatment session
- Patients leaving the study on their own

### **Result and Discussion**

This study was carried out on patients with tramadol toxicity who were diagnosed with seizure in 2014. Analysis of the clinical and paraclinic findings about patients with tramadol toxicity and seizure revealed the following results:

The average age of patients in the study was  $27.80 \pm 8.78$  years and ranged from 15 to 66 years.

81 of the patients (80.2%) were male and 20 (19.8%) were female. 68 patients (67.3%) were transferred to the center by personal cars and 33 (32.7%) were transferred by EMS. In addition, 8 (7.9%), 34 (33.7%), 31

(30.7%) and 46 (45.5%) of the patients showed a history of cardiac diseases, hospitalization, addiction, and drug toxicity. Most of the seizures were pre-hospital seizures and occurred in 83 (82.2%) of the patients before arriving at the hospital. In 18 cases (17.8%) the seizures were in hospital seizure and seizure-induced trauma was seen only in 6 cases (5.9%).

No exact information was obtained concerning the amount of drug used by patients or their companions. However, tramadol was consumed all at once in 78% (77.2%) of the patients and 23 (22.8%) of the cases consumed tramadol gradually within several hours.

Moreover, 80 (79.2%), 12 (11.9%), and 9 (8.9%) of the patients were found in the confusion state, full consciousness, and lethargic states.

Of the 101 patients, CT scan was asked for 92 patients. The results of CT scan were normal for 88 patients (87.1%), and 3 cases showed brain edema. One case also showed SAH.

In addition, 76 patients (75.2%) were released with full personal consent and 25 patients (24.8%) were hospitalized.

In the present study, of 101 studied patients, convulsions had occurred in 83 patients (82.2%) before arriving at the emergency center, and the convulsion had occurred inside the hospital in 18 cases (17.8%). In a study performed at Mashhad University on 158 patients arriving with tramadol intoxication, it was demonstrated that naloxone does not have effect on tramadol-induced convulsion, a finding similar to the results of our study also demonstrating that most of the convulsions have occurred before arriving at the emergency (4).

Saidi and colleagues' study in Tehran demonstrated that complications resulting from tramadol intoxication lead to occurrence of abnormal brain waves after injection (5).

In another study of tramadol-induced convulsion and effect of naloxone on rats conducted in the United States of America by Stone and Raffa, they demonstrated that naloxone injection leads to dominance of negative enantiomer and increase in convulsion (6).

In another study performed by Manson and colleagues on symptoms resulting from tramadol intoxication, naloxone eliminated symptoms resulting from tramadol intoxication to some extent, but this increased convulsion risk (7). In another study, it was reported that tramadol-induced convulsion had been induced by naloxone (8).

In other studies performed in India by Rehni and colleagues on rats undergoing PTZ-induced convulsion, tramadol injection led to decrease in convulsion start time as compared to PTZ, and use of naloxone in tramadol-induced convulsion led to decrease in convulsion; although these studies were performed on animals, they did not confirm ours (9-10).

This study did not demonstrate a relationship between the gender and incidence of convulsion. Marquardt and colleagues demonstrated in their study in USA that there is a relationship between the male gender and tramadol-induced convulsion, which did not confirm our study (11).

In the present study, the mean age of patients was reported as  $27.80 \pm 8.78$  years in the 15-66 range, and 81 patients (80.2%) were men and 20 (19.8%) were women.

In a study performed by Taghaddosi Nezhad and colleagues at Tehran University, there was no relationship between convulsion incidence and age (12), which was in accordance with the present study.

Taghaddosi Nezhad and colleagues' study demonstrated that convulsion is related to high-dosage tramadol, and the mean dosage used was  $115112 \pm 1353$  milligrams in this study (12).

Marquardt and colleagues' study demonstrated that there is a relationship between the dosage of tramadol used and convulsion (11). Most of the tramadol was used at once; in 78 cases (77.2%), tramadol was used at once, and in 23 cases (22.8%), it was used gradually within a few hours. In the present study, no significant relationship was found between the number of tablets taken and convulsion in the study, which did not confirm the mentioned studies.

In Tashakkori and Afshari's study, there was not a relationship between the dosage used and convulsion (4), which confirmed the present study.

In the present study, there was no convulsion with treatment doses. In a study conducted in Iran by Mehrpur, two cases of convulsion were reported with a treatment dosage of 100 milligrams, and they concluded that tramadol administration, particularly with treatment doses, can cause convulsion (13), which our study did not confirm.

In studies conducted in the United States by Spiller and colleagues (14) and Marquardt and colleagues (11), the lowest dosages related to convulsion were 500 and 200 milligrams, respectively (14). In the 2 mentioned studies, too, convulsion occurred with treatment doses. The results of our study did not confirm them.

In the present research, no significant relationship was found between age and convulsion. The studies conducted by Taghaddosi Nezhad and colleagues in Tehran (12) and Tashakkori and Afshari in Mashhad (4) concluded that convulsion incidence was not related to age, which is in accordance with the findings of the present research. In Marquardt and colleagues' study, convulsion was related to low age (11), which our study did not confirm. In this study, 8 patients (7.9%) stated disease history.

Moreover, 34 patients (33.7%) had hospitalization history. Addiction history was also examined in these patients, where 31 of the studied population of 101 patients (30.7%) had addiction history. As for drug toxicity history, 46 patients (45.5%) had drug toxicity history.

In Taghaddosi Nezhad and colleagues' study (12) in Tehran and Tashakkori and Afshari's in Mashhad (10), addiction history was not related to convulsion, which confirmed our findings in this study.

Results of other studies by Jovanovic-Cupic and colleagues (15) and Marquardt and colleagues (11) demonstrated that the amount of tramadol and drug addiction was related to the amount of convulsion. Their findings were contradictory to those of this study. The limitation of this research was that some patients' cases were incomplete.

## **Conclusion**

In view of the results obtained from this study, it can be said that most convulsions due to use of tramadol occur before arriving at the hospital, and most of the group constitutes men having visited emergency centers in confusion state.

Use of tramadol was mostly reported to be due to family problems and friends' advice.

## **Suggestions**

In view of the results obtained from this study in regard to reasons for use of tramadol, it is undeniably important to seek to enhance juveniles' awareness levels of tramadol use, methods for prevention of suicide, and restriction of its availability and distribution, particularly at low ages. The results of this study can provide valuable decisions for development of strategies concerning tramadol use through awareness increase around the society as well as skill-based education on for physicians and authorities in charge of provision of tramadol medication and presentation of care services to patients intoxicated with this medication.

The point to be noted in this study is that there was no information on patients' psychiatric history, and the most common reason for intoxication was reported to be family problems. Therefore, investigation of patients' mental, behavioral, and social damages is of importance in future studies.

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