

Research Paper: Factors Affecting Tramadol-Associated Seizure



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ABSTRACT

Background: Tramadol is a widely prescribed analgesic and due to its opioid-like effects, the potential for abuse of tramadol is noticeable. Besides, the complications of tramadol abuse have become a public health concern. This study aimed to investigate the affecting factors on the seizure, as one of the most common complications of tramadol consumption.

Methods: A total number of 64 patients from 315 patients who were referred to Sina Hospital, Tabriz, Iran because of tramadol toxicity were included in this 9 months cross-sectional retrospective study.

Results: There were 52 males and 12 females in the study. The seizure happened in 53.1% of the subjects and the Mean±SD time between tramadol consumption and seizure was 5.9±7.36 hours. There was no significant association between seizure and sex, age, the dose of tramadol, and previous tramadol consumption history. A significant association was seen between the dose of tramadol and the time of seizure.

Conclusion: Seizure that happens due to tramadol overdose is not dependent on sex, age, and previous history of tramadol consumption. As the dose of tramadol is higher, the seizure happens later. More research is needed to understand why the seizure occurs later in higher doses.

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1. Introduction

Tramadol is a centrally acting opioid-like analgesic [1] that inhibits serotonin reabsorption and is the most prescribed analgesic worldwide [2]. The main mechanism of tramadol is increasing serotonin perfusion and inhibiting serotonin and norepinephrine reabsorption in neurotransmitter synapse [3, 4]. Tramadol was first introduced to the drug market in Iran in 2002 [5]. Like many other countries, tramadol had been sold over the counter as a nonscheduled opioid for years but it went under the category of “controlled drugs” in Iran since April 2007 as a result of an increase in nonmedical tramadol usage as well as the morbidity and mortality following it [6]. Tramadol overdose has been claimed as one of the most common causes of drug poisoning in recent years in a study that was done in Tehran [5].

Tramadol abuse can be followed by several consequences such as psychiatric dysfunctions, inability in decision making, ataxia, and mouth dryness [7, 8]. There are also more important cranial complications such as seizure, apnea, and coma [3]. Seizure is one of the most important mentioned complications and in the past two decades, several researchers have sought to find which risk factors can affect seizure following tramadol consumption [3, 9-12]. Despite this, some issues are still unclear. Most studies did not find a significant association between seizure and consumed dose [3, 9, 13] while Taghaddosinejad et al. noted that seizure is more common in high dose tramadol consumption [10]. Furthermore, there is still debate about whether the seizure following tramadol poisoning has a relationship with the previous history of tramadol consumption or not.

The daily increase of tramadol abuse in Iran's society has increased the rate of tramadol poisoning and there is an increasing concern about the complications of this poisoning. Considering this concern, this study is going to investigate several important areas in tramadol toxicity and find factors that can affect tramadol-associated seizures.

2. Methods

2.1. Time and place:

Data for this cross-sectional study were retrospectively collected in Sina Hospital, affiliated to Tabriz University of Medical Sciences, Tabriz, Iran from September 22, 2016, to June 21, 2017.

2.2. Ethical codes

Ethical clearance was obtained from the Ethics Committee of Tabriz University of Medical Sciences (Code: 9512.17.83). Also, the patient's information remained confidential in this study.

2.3. Inclusion criteria

All patients who were hospitalized due to tramadol poisoning included in the study (315 patients) and the patients with a history of taking another medicine during the last month, a history of chronic disease, seizure, head trauma following a seizure, and opioid addiction (except occasionally tramadol consumption) were excluded from the study (251 patients).

2.4. Data collection

After excluding some patients, a total number of 64 patients remained in the investigation who were aged between 16 and 40 years. The patients were divided into two groups: patients who had seizures and patients who did not have a seizure. All cases (including patients with or without seizure) were evaluated and necessary information including age, sex, the elapsed time from tramadol consumption to seizure, and history of tramadol consumption was recorded in a predesigned questionnaire.

2.5. Statistical analysis

Data analysis was performed using SPSS version 11.5. The t test and correlation test were used for comparing and analysis of quantitative data and they were expressed as the Mean $\pm$ SD. For qualitative data, the Chi-square test was applied and the results were expressed as frequencies and percentages. Values were considered statically significant when the P value was less than 0.05.

3. Results

3.1. Overall results:

No mortality due to tramadol abuse was detected and all of the patients experienced a complete recovery. All of our patients were referred to the hospital because of oral intake of tramadol and no one had referred to the hospital after an IV injection of tramadol.

Sixty-four patients between 16 and 40 years old were included in this study (52 men, 81.2%, and 12 women, 18.8%). Their Mean $\pm$ SD age was 25.37 $\pm$ 6.03 years and most hospitalized cases were in the age range of 20 to 30 years. Only 34 cases (53.1%) experienced seizures. All

Table 1. Comparison of some characteristics between the two groups

Characteristics		No. (%) / Mean±SD		P
		Patients With Seizure	Patients Without Seizure	
Gender	Male (52 numbers in total)	30 (57.6)	22 (42.4)	0.19
	Female (12 numbers in total)	4 (33.3)	8 (66.7)	
Age (y)		24.85±6.22	25.96±5.86	0.91
Previous history of tramadol consuming	With previous history	17(57)	13(33)	0.62
	Without previous history	17(50)	17(50)	
Hospitalization time, d		2.67±2.33	2.89±2.91	0.35
Consumed dose, g		1.49±2.35	1.6±2.19	0.76

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of them had a single seizure and seizures were generalized tonic-clonic. It took from 1 to 24 hours (Mean±SD: 5.90±7.36 hours) for the seizure to occur after consumption in 32 subjects and this period was not recorded in 2 subjects. Thirty-four cases (53.1%) had consumed tramadol for the first time and 30 cases (46.9%) had a history of frequent consumption.

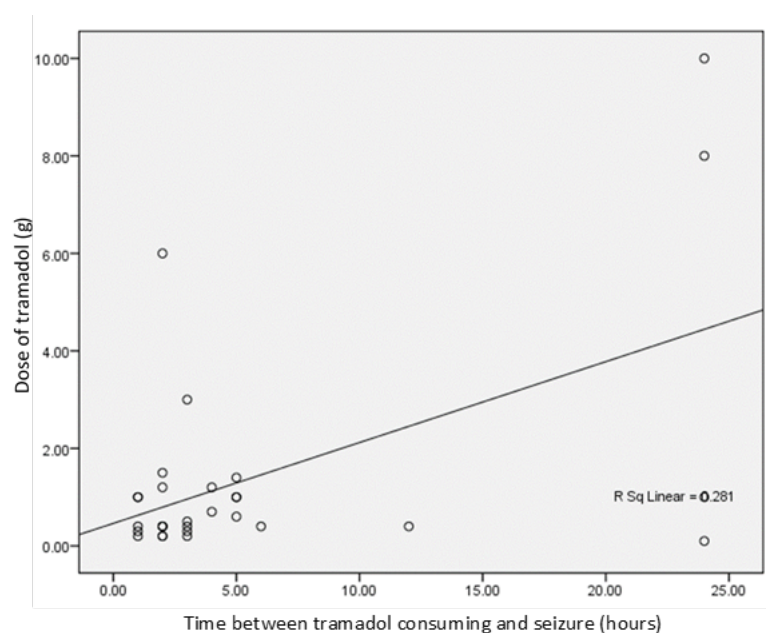
3.2. Results of analysis

There was no significant relationship between seizure and sex ($P=0.19$), seizure and hospitalization time ($P=0.35$) and consumed dose and hospitalization time ($P=0.09$). In cases with a history of frequent use of tra-

madol, more seizures were recorded but no significant relationship was found between the history of frequent tramadol consumption and the occurrence of seizures ($P=0.62$). The results are presented in Table 1. As seen in Table 1, there is no significant difference ($P>0.05$) between the two groups considering the consumed dose.

3.3. Relationship:

The next section of the survey was concerned with the average period from tramadol consumption to seizure occurrence. The analysis determined that no significant relationship exists between age and time-lapse between consumption and seizure occurrence ($P=0.8$) but a signif-

**Figure 1.** Consumed dose in relation to the time of seizure occurrenceInternational Journal of
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icant relation was observed between consumed dose and time-lapse between consumption and seizure occurrence ($P=0.003$). In higher doses, the time between consumption and seizure occurrence increases (Figure 1).

4. Discussion

An initial objective of the project was to identify the association between tramadol consuming history and seizure. We found that seizure caused by tramadol is not dependent on the history of intake and the risk of seizure is the same between subjects with a previous history of consumption and subjects without previous history. This finding is consistent with some other studies [9]. On the other hand, some investigations suggest that there might be a relationship between the risk of seizure and long-time tramadol consumption [14, 15]. Taghaddosinejad et al. in their study mentioned that tramadol should be consumed cautiously in patients who have a previous history of tramadol poisoning [10]. More investigations seem to be needed to show if the previous history of consumption is a risk factor for seizure or not.

Based on our data, there is no significant relationship between consumed dose and seizure occurrence. This finding is approved by other similar articles [3, 9, 13]; however, Taghaddosinejad et al. concluded that the seizure was dose-dependent [10].

One unanticipated finding of this study was that in higher doses of tramadol, the period between consumption and seizure gets longer. This was a surprising outcome for which we could not find a reliable explanation. Taghaddosinejad et al. also evaluated the time of seizure occurrence and showed that the average time of seizure occurrence was 2.6 hours after exposure to tramadol. But, this study did not demonstrate a relation here. Further studies with more focus on this concept are therefore suggested.

Prevalence of seizure was higher in males. This result can be explained by the fact that tramadol consumption is more common in young males thus men have more complications. Lots of other studies have also reported that tramadol overdose is more frequent in males [3, 10, 16, 17].

The results of this study did not show a significant association between age and seizure. This finding is in agreement with previous studies [9, 10].

We observed that the Mean $\pm$ SD time between tramadol consumption and seizure was 5.9 ± 7.36 hours and all of the seizures occurred in the first 24 hours. The mean half-life of tramadol in the blood is about 6 hours

[18-20]. Besides, investigations confirmed that most of the tramadol neurologic side effects appear in the first 6 hours of consumption [21, 22]. This can well explain why seizures mostly occur in about 6 hours and also why seizure occurs later in higher doses. This finding corroborates the ideas of Marquardt et al. [11].

Tramadol-associated seizure is idiosyncratic and it is not dependent on the dose and history of consumption so it should be prescribed carefully even in therapeutic doses.

The findings in this report are subject to at least three limitations. First, the sample size is not large enough; second, the patients may not be honest about their history of tramadol consumption or drug addiction and third, as the study was retrospective we could not get tramadol blood concentration.

Ethical Considerations

Compliance with ethical guidelines

Ethical clearance was obtained from the Ethics Committee of Tabriz University of Medical Sciences (Code: 9512.17.83). Also, the patient's information remained confidential in this study.

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Author's contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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