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Research Paper: Occurrence and Recurrence of Seizures and Related Factors in Patients With Tramadol Ingestion

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ABSTRACT

Background: Rate of tramadol poisoning and seizure and its complications is high in Iran. We investigated the occurrence and recurrence of tramadol-induced seizures and related factors in patients with tramadol poisoning.

Methods: This was a descriptive longitudinal study conducted in a poisoning referral hospital in Tehran, Iran. During April to June 2017, adult patients (≥16 years) with tramadol ingestion and poisoning admitted to hospital were selected by convenience sampling method. We studied the rate of seizure occurrence and recurrence among them. Also, the association between seizure occurrence and recurrence and patients' demographic characteristics and poisoning-related factors were investigated. Data were analyzed by SPSS 16 and significant level was set at <0.05.

Results: In total, 250 patients participated in the study. Their mean age was 26.39 years and 214 (85.6%) of them were male. Of all, 159 (63.6%) were single, 106 (42.4%) were unemployed and 24 (9.6%) were students. Main reason of tramadol consumption was suicide. Co-administration of drugs was reported in 83 (33.2%) cases. Incidence of seizure occurrence and recurrence were 31% and 38.5%, respectively. There was no statistically significant relationship between the occurrence and recurrence of seizures and patients' age, gender, marital status, occupation, reason for tramadol consumption, co-administration of drugs and naloxone administration. Probability of seizure occurrence and recurrence raised with increased tramadol dose (P<0.001 and P<0.01, respectively). Seizure recurrence led to longer hospital stay (P<0.001).

Conclusion: Rate of the occurrence and recurrence of tramadol-induced seizure seems clinically significant, but the prognosis is generally good in cases with seizure. Greater ingested dose and late hospital admission were associated with higher probability of seizure occurrence and recurrence. Further studies are required to investigate the risk factors of tramadol-induced seizure.

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1. Introduction

Tramadol is an opioid-like analgesic that directly affects central nervous system [1, 2]. This drug was first introduced in European countries about 4 decades ago and soon became popular worldwide, because it was perceived to have less side effects and dependency, compared to opioids, but recent studies have demonstrated drug dependence and potential abuse of tramadol [1, 3-5]. Tramadol was licensed for prescription in Iran in 2002 [1]. Official statistics have shown rapid increase in tramadol consumption in Iran which is due to excessive prescriptions and also its easy and uncontrolled availability in the country [5]. Many young people consume tramadol for its euphoric effects and this drug is illegally distributed and smuggled in Iran [6].

Seizure is a common neurological side effect of tramadol that may occur even at therapeutic doses [5]. Tramadol poisoning is the leading cause of drug-induced seizures in Iran [1]. Despite self-limiting nature of these seizures, they can lead to mortality and morbidity [7-10]. Another concern for patients with tramadol poisoning is unpredictable recurrence of seizures [8]. Risk factors of seizures due to tramadol intoxication are still unknown, but reports have accounted patients' age and gender, ingested dose of tramadol and co-ingestion of other drugs, as risk factors [6, 11-14].

Tramadol poisoning is a common emergency in poisoning wards of Iran and rate of seizure due to tramadol is greater than other countries [1, 7]. Regarding high seizure incidence in cases with tramadol ingestion and the unavailability of guidelines for the management of these cases, recognition of high-risk patients for seizure is of great value in clinical settings. This study investigated incidence of the occurrence and recurrence of tramadol-induced seizures. We also studied the association between tramadol-induced seizures and demographic characteristics as well as poisoning-related factors. Results will assist in better management of patients with tramadol poisoning and preventing seizure and further complications in these cases.

2. Materials and Methods

This descriptive longitudinal study was conducted in Baharloo Hospital (a poisoning referral center) in Tehran, Iran. Adult patients (≥16 years) with tramadol ingestion who were admitted during April to June 2017 were selected by convenience sampling method. Tramadol consumption was confirmed by laboratory tests in all study participants. There is no quantitative measurement of the ingested tramadol dose in this hospital and given that seizure can occur in any ingested dose, we did not set any inclusion criteria for consumed dose. However, to record the consumed dose of tramadol we used the reports of patients or their relatives.

Patients with the history of neurologic disorders and active seizure at admission, as well as those with seizure due to electrolyte and metabolic imbalances or glucose deficiency were excluded from the study. Written informed consent was obtained from all patients or their guardians. Study participants were monitored during hospital stay and the occurrence and recurrence of seizure among them were recorded. Patients' data were recorded in study checklists by codes to respect their confidentiality. Association between seizure occurrence and recurrence and patients' demographic characteristics and poisoning-related factors were investigated. The Chi-squared test, t test, Mann-Whitney U test and Spearman's rank correlation coefficient were used for data analysis. Distribution of quantitative data are presented as Mean±SD or median (Interquartile Range [IQR]) according to the distribution of the variables. Statistically significant level was considered at <0.05.

3. Results

In total, 250 patients were included in the study. Mean±SD age of study participants was 26.39±7.39 years and they were in the age range of 16-52 years. Of all, 214 (85.6%) were male. Mean±SD age was 26.9±7.4 years in males and 21.1±5 years in females (P<0.001). Educational attainment was ≤high-school certificate in 227 (90.8%) cases. According to patients' self-report, 120 (48%) were employed, 106 (42.4%) were unemployed and 24 (9.6%) were students. Housewives were considered unemployed in this study. The reason of tramadol ingestion was suicide in 173 (69.2%) cases, abuse/dependency in 47 (16.8%) and recreational drug abuse in 30 (12%) cases. There were no cases with accidental poisoning. Co-ingestion of other drugs was reported in 83 (33.2%) patients. Main co-ingested drugs were benzodiazepines and methadone consumed in 25 (30%) and 19 (23%) patients, respectively.

First time seizure occurred in 78 (31%) patients. Twenty-seven (11%) patients received naloxone immediately after admission. The association between seizure occurrence and patients' demographic characteristics and poisoning-related factors are summarized in Table 1. Recurrence of seizure occurred in 30 (38.5%) of 78 patients who developed first seizure. Frequency of seizure recur-

Table 1. Comparison of patients' characteristics and poisoning-related factors according to seizure occurrence

Variables		Seizure Occurrence		P
		Yes	No	
Age, y	Mean±SD	25.27±6.36	26.89±7.87	0.1
Gender No. (%)	Male	65(30.37)	149(69.63)	0.5
	Female	13(36)	23(64)	
Marital Status No. (%)	Single	48(29.27)	116(70.73)	0.3
	Married	30(34.88)	56(65.12)	
Educational attainment No. (%)	<High-school	36(30)	84(70)	0.9
	≥High-school	42(32.3)	88(67.7)	
Occupation No. (%)	Unemployed	25(23.6)	81(76.4)	0.08
	Employed	45(37.5)	75(62.5)	
	Student	8(33.3)	16(66.7)	
Reason of tramadol ingestion No. (%)	Suicide	53(30.6)	120(69.4)	0.6
	Addiction	13(41.9)	18(58.1)	
	Recreational	12(40)	18(60)	
Co-ingestion of other drugs No. (%)	Yes	21(27)	57(73)	0.15
	No	62(36)	110(64)	
Tramadol dose (mg)	Median (IQR)	1600(600-2000)	500(300-1000)	<0.001
Duration from drug ingestion to hospitalization (h)	Median (IQR)	3(2-5)	2(1-3)	<0.001
Hospitalization duration (d)	Median (IQR)	1(1-2)	1(1-1.75)	0.1
Naloxone prescription No. (%)	Yes	7(26)	20(74)	0.5
	No	71(31.8)	152(68.2)	

Abbreviations: SD=Standard Deviation, N=Number, IQR=Interquartile Range

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rence was twice in 19 (63.3%), 3 times in 10 (33.3%) and 6 times in 1 (3.3%) patient. Seizure episodes were short with median (IQR) of 30 (20-60) seconds and the longest duration episode lasted 180 seconds. Median (IQR) duration between seizure recurrences was 30 (20-60) minutes and this duration ranged from 3 to 360 minutes. The association between seizure recurrence and patients' demographic characteristics and poisoning-related factors are summarized in Table 2.

There was a correlation between tramadol ingested dose and delayed time from drug ingestion to hospital admission (r=0.7, P<0.001). All seizures were generalized tonic-clonic and there was no ICU admission or mortality. Regardless of seizures, all patients were discharged in good condition.

4. Discussion

This study investigated the incidence and risk factors of tramadol-induced seizure in Iranian adults. We found seizure incidence of 31% in cases with tramadol ingestion which is similar to the rate of 30.2% in another study conducted in the same center [14]. Incidence of tramadol-induced seizure varies between different countries and even regions within a country. Sparse reports in different centers of Iran have shown an incidence rate of 15% to even 69% [15-18]. The rate of seizure in tramadol poisoning have been 8% and 14% in USA [19,

Table 2. Comparison of patients' characteristics and poisoning-related factors according to seizure recurrence

Variables		Seizure Frequency		P
		Once	More Than Once	
Age, y	Mean±SD	24.8±5.62	26±7.42	0.4
Gender No. (%)	Male	40(61.5)	25(38.5)	>0.9
	Female	8(61.5)	5(38.5)	
Marital status No. (%)	Single	15(50)	15(50)	0.1
	Married	33(68.75)	15(31.25)	
Educational attainment No. (%)	<High-school	20(55.6)	16(44.4)	0.3
	≥High-school	28(77.8)	14(22.2)	
Occupation No. (%)	Unemployed	15(0.6)	10(0.4)	0.5
	Employed	29(64.4)	16(35.6)	
	Student	4(50)	4(50)	
Reason of tramadol ingestion No. (%)	Suicide	10(77)	3(23)	0.4
	Addiction	30(56.7)	23(43.3)	
	Recreational	8(66.7)	4(33.3)	
Co-ingestion of other drugs No. (%)	Yes	13(62)	8(38)	0.9
	No	35(61.4)	22(38.6)	
Tramadol dose (mg)	Median (IQR)	1000(425-2000)	2000(1200-4000)	0.01
Hospitalization duration (Days)	Median (IQR)	1(1-1)	2(1-2)	0.01
Naloxone prescription No. (%)	Yes	4(57)	3(43)	0.9
	No	44(62)	27(38)	

Abbreviations: SD=Standard Deviation, N=Number, IQR=Interquartile Range

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20], 54.4% in Serbia [11] and 61% in Egypt [12]. Seizure recurrence incidence was 38.5% in this study. This rate also varies in different studies of Iran: the rates of 2% [21], 7% [8] or even 50% [22] have been reported. In comparing seizure incidence rates in populations with tramadol ingestion, differences in the study methods and participants, sample sizes and tramadol consumption patterns should be considered.

Genetic differences in drug metabolism can be the reason of varieties in the rate of tramadol complications. Generally, Iranians and people of the Middle East are at high risk for tramadol-induced seizures [7]. The results show that more than one-third of patients with tramadol use are prone to seizure or its recurrence. This pattern is of clinical importance and calls for specific measures in the management of tramadol ingested patients in Iran. Fortunately, seizures were short and self-limiting even when they recurred among our study participants. Overall, the prognosis of patients was good and just those with recurrent seizures had median of one-day longer hospitalization. These findings are in line with other studies in Iran and foreign countries [11, 12, 18, 20, 22, 23] and are promising for physicians providing care to poisoned patients.

The mean age of patients was 26.39 years and the majority of them were male. Poisoning with tramadol and other drugs usually happens in people younger than 30 in Iran [6, 11, 14, 21-23]. The majority of tramadol intoxications also happen among men, worldwide [11, 14, 16, 18, 23, 24]. We did not find any relationships

between patients' age and gender and the occurrence or recurrence of seizures. While old age is commonly considered a risk factor for tramadol-induced seizures [25], studies show no association between age and seizure incidence [11, 15, 18, 26]. We did not find any relationship between gender and tramadol induced-seizure either, which is in line with another study in Iran [26]. Studies on the association between gender and tramadol-related seizure are usually descriptive and further investigations are required in this regard.

Of all participants, 64% were single and more than 90% were with high-school or lower educational attainment. We did not find any association between seizure occurrence and marital status, education and occupation of participants. Studies in Iran [6, 24] and Nigeria [27] have shown that tramadol poisoning is more prevalent among singles, compared to married people. It has been proposed that marriage is a protecting factor for tramadol-related seizures but further studies are needed to confirm this idea. Several descriptive studies have demonstrated that most patients with tramadol poisoning are with low educational attainment but this relationship needs further analytical studies [27].

Study of our participants' occupation was with limitations because classification of different jobs in broad categories is not so precise and we also used self-report about the occupational status. Rate of students with tramadol poisoning is considerable in this study and declares the need of preventive interventions in this group. Further studies on the relationship between socioeconomic status of people and tramadol consumption patterns and related complications are recommended.

The main reason of tramadol ingestion was suicide in our patients that is consistent with other Iranian reports [6, 18, 24]. Reason of tramadol ingestion was not associated with seizure occurrence but we found a relationship between tramadol ingested dose and the occurrence and recurrence of seizures. Consistent with our findings, several studies have found that greater ingested dose of tramadol can increase the probability of seizure [8, 12, 13, 22, 13, 28]. However, some studies show no relationship between tramadol dose and seizure occurrence [15, 16, 18]. Seizures can occur at the lowest therapeutic dose and none of patients with tramadol ingestion are free of seizure risk. Despite the ubiquitous belief that co-ingestion of drugs rises the probability of tramadol-related seizure [28], we did not find such association. Confirmation of this association needs further well-designed studies.

We observed that increased time from tramadol consumption to hospitalization raised the risk of occurrence and recurrence of seizures. Another study in Tehran also showed a relationship between seizures and late hospital admission [17]. There is no study to explain this association but early admission after tramadol ingestion and hospital care may decrease the rate of seizure as a complication of tramadol consumption. Measuring time from drug ingestion to hospital admission was with high probability of bias and error, because we only used patients' report which may have confounded our findings.

The opiate antidote naloxone is prescribed for tramadol poisoning in some centers [29]. Studies have demonstrated that naloxone is not effective in reversal of tramadol toxic effects and it may even increase the probability of tramadol-induced seizures [12, 24, 29]. Only 27 study patients received naloxone and there was no association between its prescription and seizures. We also found another study conducted in Iran that showed no association between naloxone administration and seizures in tramadol poisoned patients [15]. Considering the good prognosis of our patients and the mentioned risks of naloxone, its prescription in tramadol intoxicated patients should be with caution and definite indication.

This is a cross-sectional study with convenience sampling method and limited sample size that restricts its generalization. Information about several variables such as occupation, time of hospitalization and tramadol dose were obtained by self-report that provokes the risk of bias and error. We also did not separate patients according to ingested dose: many recognize 400 mg of tramadol as poisoning, but we did not have required laboratory equipment for the quantitative measurement of tramadol dose and many patients also developed symptoms at lower doses. Therefore, we included any patient with tramadol ingestion, even in lack of symptoms. Despite all limitations, this study was of numerous studies that focused on recurrence of seizure and its relationship with demographic factors. Future studies on risk factors for seizure in tramadol poisoning are strongly recommended.

5. Conclusion

The rates of seizure occurrence and recurrence in our study were considerably high; although, they were self-limiting and with good prognosis. Higher dose of ingested tramadol and delayed time from ingestion to hospitalization were associated with the elevated risk for seizure occurrence and recurrence. This study shows good prognosis of patients with tramadol ingestion even after

several seizure episodes. Further studies are required for understanding of tramadol-induced seizure risk factors.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: IR.Tums.MEDICINE.REC.1396.2785).

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Conflict of interests

The authors certify that they have no affiliation with or involvement in any organization or entity with any financial interest, or non- financial interest in the subject matter or materials dismissed in this manuscript.

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