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Original Article

Comparing the frequency tramadol abuse in seizure and non-seizure complaint patients referred to neurology emergency department of a university affiliated hospital

Running Title: Tramadol abuse and seizure

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Abstract

Aim: Due to its similar opioid effects, tramadol is commonly abused worldwide. One of the notable side effects of tramadol is seizure. The present study compares the frequency of tramadol abuse among seizure and non-seizure (other reasons) patients referring to the Neurology Emergency Ward of Ali Ibn Abi Talib Hospital, a referral center affiliated to Rafsanjan University of Medical Sciences, Iran.

Methods: This cross-sectional study reviewed 141 patients referring to the emergency ward of a referral hospital. The data were collected by clinical examination, face-to-face interviews, and a structured self-questionnaire for each client. The data were analyzed using descriptive statistics, non-parametric chi-square, and independent T-test.

Results: In this cross-sectional study, 82 male (58.2%) and 59 female subjects (41.8%) were included. The results revealed the average age of patients being 30.16 ± 9.12. The incidence of tramadol abuse was approximately 36.8% in the total population study. Twenty-five and half percent of the subjects were referred to the neurology emergency ward for seizure while 16.3% of the subjects were referred to other wards for non-seizure complaints. In this study, we no relationship was found between the duration of consumption and the concurrent use of other medications; however, there was a statistically significant correlation between the dose of tramadol and the incidence of seizure.

Conclusion: The result of the present study illustrated a significant incidence of seizure in men with tramadol abuse and a direct correlation with medication dose.

Keywords: Abuse; Medication; Non-seizure; Seizure; Tramadol

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Introduction

Tramadol is a synthetic analog of morphine with central effects most often prescribed for relieving moderate to severe pain. This medication is an agonist for μ-receptors and the adrenergic and serotonergic systems. It increases the release of serotonin and has a half-life of 4-6 hours. The duration of drug administration for analgesic effect is usually less than five days, and the dose must not exceed 50-100 mg per 4-6 hours. This is one of the most common drugs that is abused in most countries (1, 2). Like other opioids, complaints like nausea, dizziness, drowsiness, constipation, dry mouth, hypotension, sweating, and sleep apnea are the common side effects. Besides, the seizure is the most concerning side effect of this medication, with a 13.7% prevalence (1-3). Tramadol consumers maintain the following reasons for taking this medicine: improving sexual dysfunctions (4), storing energy , and overcoming psychological problems, e.g., depression, anxiety, stress, etc. (5). However, some reports have warned against the increase in tramadol drug misuse among the youth (6, 7). Previous studies have indicated that tramadol misuse is common among the high school students (8, 9). Seizure is known to be one of the most destructive and dangerous neurological side effects of tramadol (10). The prevalence of seizure in those experiencing the drug for the first time appears to be 1%, which can increase to 2-6 times when abused with other drugs (11). Stimulating organic brain diseases, including metabolic genetic diseases as well as head trauma can elevate the risk of seizure in individuals who abuse tramadol. Ongoing treatment of tramadol overdose includes supportive therapy and adequate ventilation. Since naloxone only resolves some symptoms while raising the risk of seizure and it has no proven effect in reducing the risk of mortality, it is not recommended in tramadol overdose (11, 12).

The present study aimed to determine the prevalence of tramadol abuse among patients with epileptic and non-seizure complaints who referred to the emergency department of a referral hospital.

Materials and methods

In this cross-sectional study, the information of each patient with seizure or non-seizure was recorded. This investigation was carried out in the Emergency Department of Ali Ibn Abi Talib Hospital, a referral center affiliated to Rafsanjan University of Medical Sciences throughout one year.

A checklist on demographic and clinical findings details of each patient (including drug history, dose, duration of consumption, substance use such as stimulant and cannabis as well as any possible history of seizure) was filled out by the investigator who was most often present in the hospital during one year. The study population included 141 subjects who were divided into two groups; 68 patients were diagnosed with seizure by a neurologist via international League Association Epilepsy (ILAE) criteria, and 73 non-seizure subjects referring to the neurology

emergency ward for reasons other than seizure. All patients who were enrolled in the study had a seizure attack in the previous 6 hours.

Exclusion Criteria

Patients younger than 18 years having a history of brain stroke, brain tumor, central nervous system congenital diseases, brain infections, coma or epilepsy, and consuming antiepileptic medications or other drugs likely inducing a seizure were excluded.

In the present study, the frequency of tramadol abuse among the seizure and non-seizure patients referring to the emergency ward was recorded during a year. Variables such as age, sex, duration of seizure incidence, and consumption of the other medications in 141 patients were studied.

At the end of the study, data were extracted and analyzed using SSPS software version 19. Qualitative variables were reported by frequency and percent, and the results were represented in the graphs and tables for the two groups of study.

Results

Totally, 68 patients with seizure and 73 with problems other than seizure were referred to the hospital; those who failed to complete the study were excluded.

With respect to the age variable, the data were divided into four groups and calculated according to the range formula based on the smallest and largest types. Most subjects were in the age group under 32 years old (67 subjects), but the subjects with tramadol misuse, amounted to 22, were in the age group above 60; we found the increased risk of seizure in patients with tramadol misuse being not significantly different in various age groups and no significant relationship between tramadol misuse and seizure incidence by the age groups (P-value $\geq$ 0.05). However, a higher seizure frequency was observed in patients younger than 32 years old with tramadol abuse (**Table 1**). The mean age of the subjects was 30.16 ± 9.12 years old, with the minimum and maximum of 18 and 76, respectively. In terms of sex, there were 82 males (58.1%) and 59 females (41.9%). The prevalence of tramadol use was 36.8% in the total study population (52 out of 141 subjects) whereas 20.5% of the subjects complained of seizure and 16.3% had other complaints. Totally, 68 patients with seizure were diagnosed among whom 29 were tramadol abusers and 39 had a negative history of tramadol abuse (**Table 2**). A larger portion of patients with seizure who had a history of tramadol misuse were male ($p < 0.05$). About 39.4% of male and 13.9% of female patients referring to the emergency department for complaints other than seizure had tramadol misuse (**Table 3**). In the present study, the dose of tramadol was measured based on the number of consumed tramadol Tablet 100 mg. For a possible relationship between the dose of tramadol and the incidence of seizure this study was carried out. Therefore, patients were divided into five groups. In the non-seizure group, patients took six tablets from time to time at most but not based on a regular pattern. In this group, the number of tramadol consumers of a total of 10-15 pills or above was zero. Besides tramadol dose, the number of consumed tramadol tablets in both seizure and non-seizure groups was also recorded (**Table 1**).

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Table 1. Baseline characteristics of patients

Characteristics No. (%)	Seizure group (N=68)	Non-seizure group (N=73)
Age (year)		
Under 32	38 (56.7%)	29 (43.3%)
32-46	12 (48.0%)	13 (52.0%)
46-60	9 (33.3%)	18 (66.7%)
Over 60	9 (40.9%)	13 (59.1%)
Sex		
Male	43 (52.4%)	39 (47.6%)
Female	25 (42.4%)	34 (57.6%)
Duration of seizure incidence (hour)		
Less than 1	17 (100%)	-
1-3	12 (100%)	-
3-5	2 (100%)	-
Consumption of the other medications		
Alcohol	8 (72.7%)	3 (27.3%)
Tricyclic antidepressants	4 (40%)	6 (60%)
Anti-psychotic drugs	2 (100%)	0 (0.0%)
Lithium	1 (100%)	0 (0.0%)
Drugs	7 (58/3%)	5 (41.7%)
History of tramadol misuse		
Yes	46 (67.6%)	59 (80.8%)
No	22 (32.4%)	14 (19.2%)
Dose based on number of pills (100 mg)		
0	36 (39.1%)	56 (60.9%)
1-5	4 (26.7%)	11 (73.3%)
5-10	13 (68.4%)	6 (31.6%)
10-15	8 (100%)	0 (0.0%)
More than 15	7 (100%)	0 (0.0%)

No: Number

We found a significant relationship between the tramadol dose and the number of tablets used in terms of the occurrence of seizure ($p<0.05$). Majority of the seizures occurred within the first hour (56.2%) of tramadol consumption whereas 37.5% and 6.2% of the patients had a seizure during 1–3 hours and 3–5 hours of tramadol use, respectively. In other studies, the seizure incidence has not been reported 24 hours following tramadol consumption while in this study failed to observe the frequency of seizure beyond 5 hours after tramadol administration. According to the data represented in **Table 4**, when the time interval of tramadol consumption is longer, the number of seizures also decreases thereby suggesting that this rate is related mainly to the tramadol dose. In a different analysis, the coincident effect of tramadol dose and the interval between tramadol intake and incidence of seizure in both seizure and non-seizure clients were addressed. In so doing, the subjects were classified into four subgroups based on the number of consumed pills. Most subjects affected with seizure had taken 5–10 pills (40.6%). The subjects were also divided into three subgroups based on the consumption period; less than 1 hour, 1–3 hours, and 3–5 hours. The results indicated that in majority of the cases (56.2%), the seizure had occurred in less than 1 hour. As illustrated in **Table 4**, a significant correlation was discerned between the interval of tramadol consumption and seizure incidence as well as

Table 2. Distribution of frequency of tramadol misuse in patients with seizure referred to the emergency

	Tramadol misuse	
Age, year	**[Yes]**	**[No]**
Under 32	24 (63.2%)	14 (36.8%)
32-46	4 (33.3%)	8 (66.7%)
46-60	0 (0.0%)	9 (100%)
Over 60	1 (11.1%)	8 (88.9%)
Total	29 (42.6%)	39 (57.4%)

Table 3. Distribution of frequency of tramadol misuse in patients with complaints except seizure referring to the emergency department

	Tramadol abuse	
Age, y	**[Yes]**	**[No]**
Male	16 (39.4%)	23 (60.6%)
Female	5 (13.9%)	29 (86.1%)
Total	21 (28.8%)	52 (71.2%)

tramadol dose and the number of pills. One hundred and forty-one patients were evaluated for the impact of co-consumption of tramadol and alcohol and known medications associated with seizure. Among them, 105 patients never consumed or abused other drugs or alcohol. Out of 12 patients who had co-consumed tramadol with illicit drugs, seizure occurred in 7 subjects. Alcohol had the highest frequency in referred patients with seizure after tramadol abuse. In all the patients referring to the emergency department, only 5.6% of them had co-abused tramadol with alcohol. Of those patients who had referred due to other reasons than seizure, 41.8% had a history of permanent or occasional tramadol use. The detail of the frequency of co-consumption of tramadol with other medications is represented in **Table 1**. Eventually, the results of the present study indicated a significant difference in co-consumption of alcohol and other medications (e.g. tricyclic antidepressants and antipsychotics) in all the patients referring with seizure. The description of coincident tramadol or non-tramadol abuse with other drugs in patients is set out in **Table 1.**

Table 4. Distribution of tramadol misuse in the patients based on the time of the seizure and the dosage of tramadol (in terms of the number of pills)

Dose based on number of pills, No. (%)	<1 hour	1-3 hours	3-5 hours	Total
Less than 5	1 (25%)	3 (75%)	0 (0.0%)	4 (100%)
5-10	8 (61.5%)	4 (30.8%)	1 (7/7%)	13 (100%)
10-15	4 (50%)	3 (37.5%)	1 (12/5%)	8 (100%)
More than 15	5 (71.4%)	2 (28.6%)	0 (0.0%)	7 (100%)
Total	18 (56.2%)	12 (37.5%)	2 (6.2%)	32 (100%)

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Discussion

Due to the ever-increasing prevalence of drug abuse especially tramadol in recent years and the importance of the prevention of such social incidents and their complications, the issue is considered a health priority. In a study by Taghadosinejad et al., it was reported that tramadol is one of the five common medications that is misused during the past five years in Iran (13). In another study by Pedramfar et al., it was stated that around 1% of the tramadol abusers suffer from tonic-clonic seizures without connection with the first dose of tramadol use (2). According to the previous investigations, the number of tramadol abusers has been increasing in recent years, especially in Middle East countries (14, 15).

In this study, the prevalence of tramadol users in seizure and non-seizure patients referring to the emergency department was reported to be 36.8% in the total population (52 of 141 patients) 20.5% of whom presented with seizure and 16.3% with non-seizure complaints. It seems these differences are more related to the population variations and the small sample size in this specific group. In several similar studies conducted in other cities of Iran, the prevalence of tramadol abuse appeared to be, for example, 50-180 cases per year in Mashhad and 2.17% in Ardabil (2).

The result of this research indicated no difference between the two groups of the study based on the variables of age and simultaneous use of other medications and alcohol. However, a significant relationship was observed between the dose of tramadol and incidence of seizure. In line with this study, some researchers insist on seizure occurrence at higher doses of tramadol (3) so that particularly in doses higher than 500mg, the incidence of seizure increases substantially (12). However, another research by Talaei and et al. concluded that seizure, as a side effect of tramadol use, is not dose-dependent. We also found the prevalence of seizure being significantly higher in male tramadol abusers, which is in agreement with Talaie's study conducted on 215 cases (10). Nevertheless, other pertinent studies failed to find a relationship between gender and the occurrence of seizure in tramadol users (3, 13). A higher than 500mg tramadol dose can increase the incidence of seizure in this drug overdose (10, 12). On the other hand, co-administration of antipsychotic, tricyclic antidepressant medications, and alcohol may induce seizure in even therapeutic doses of tramadol (16- 18). In the literature, the seizure incidence has been reported at the first 24 hours following the administration of tramadol (10) whereas in our study, no seizure was recorded after 5 hours. The major limitation of this study was population differences and the small sample size. These findings need to be confirmed in a larger group of patients with tramadol use and seizure.

Conclusion

The results suggest that the risk of seizure incidence is higher in male tramadol misusers. Furthermore, a direct relationship was identified between the tramadol dose, and the occurrence of seizure.

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