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Original Article

Evaluation of neurological symptoms of acute tramadol poisoning and its relationship with laboratory findings

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Abstract

Introduction: Tramadol is a unique opioid and the most prescribed opioid worldwide. Tramadol-related overdose and death have been increased in several countries. Due to the high level of tramadol use, misuse, and overdose in Iran, and considering the cost and time spent doing laboratory tests for all patients, this study aimed to investigate the possible relationship between changes in laboratory findings of patients poisoned by tramadol and their neurological manifestations to evaluate the need for these tests.

Methods: This was a cross-sectional descriptive study of patients with acute tramadol poisoning who were referred to the Emergency department of Sina hospital, Tabriz, Iran from March 2020 to March 2021. Lab tests taken from the patient in the emergency department were recorded. Meanwhile, the patients' neurological symptoms were noted. And demographic information of patients was collected in a predesigned checklist and was analyzed by IBM® SPSS® 20.0 release software.

Results: A total of 95 patients including 76.8% male and 23.2% female with an average age of 28.26 ± 10.57 were admitted to the emergency department. The most common symptoms of neurological impairment experienced by patients were seizure (32.6%) and decreased level of consciousness (38.8%). There was no relationship between the neurological symptoms of tramadol poisoning with neither arterial blood gas characteristics nor hematological factors ($P > 0.05$).

Conclusion: The neurological manifestations of tramadol poisoning were not related to arterial blood gas characteristics such as PH, PCO2, PO2, and $HCO3^-$. Also, there was no relationship between hematological factors including white blood cell (WBC), red cell distribution width (RDW), platelets (Plt), sodium (Na), potassium (K) and blood sugar (BS), and neurological symptoms caused by acute tramadol poisoning. Therefore, requesting these tests during tramadol poisoning should be reconsidered.

Introduction

Opioids are a set of natural and chemical analgesic substances similar to morphine that attach to opioid neurotransmitters in synapses.[1] They have been used for thousands of years to reduce pain. Tramadol is an atypical and unique opioid, which is used as an analgesic for moderate to severe pain, but also, it is useful in the treatment of opioid withdrawal.[2] In the last decade, it seems that tramadol-related overdose and death have been increased in several countries.[3] The most common adverse effects of tramadol are nausea, vomiting, dry mouth, constipation, vertigo, drowsiness, and increased sweating.[4,5] Tramadol poisoning can affect multiple organ systems.[6] Decrease in the level of consciousness, seizures, and respiratory depression are the most severe complications of tramadol overdose.

Seizures due to tramadol poisoning are not a dose-dependent complication, and they occur in different doses.[7] Seizures in tramadol poisoning are more common than with other opioids.[8] Tramadol use, misuse, and overdose in Iran are significantly high.[9-11]

For most patients who refer to the emergency department, basic tests are requested regardless of their chief complaint, while their diagnostic value is unclear. due to the high cost and time consuming of laboratory tests for all patients, this study aimed to evaluate the diagnostic value of performing these tests on the relationship between neurological symptoms in patients with definite diagnosis of tramadol poisoning and laboratory findings.

Methods

This study was a cross-sectional descriptive study.

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We included all the patients who have been referred to the emergency department of Toxicology center in Sina hospital, Tabriz, Iran due to poisoning; whether accidentally or intentionally. Patients with unreliable history, a history of drug use or primary toxicology screening for opioids and buprenorphine, a history of chronic tramadol use due to underlying disease and, patients whose records were incomplete or had left the hospital before the end of 24 hours under observation, were excluded from the study. Lab test reports including arterial blood gas (ABG) characteristics such as PH, PCO2, PO2, and *HCO3*$^{-}$, hematological factors such as white blood cell (WBC), red cell distribution width (RDW), platelets (Plt), blood sugar (BS), sodium (Na), potassium (K) and the patient's 24-hour clinical course based on the presence or absence of neurological findings were recorded. Eventually, patients with neurological disorders during the poisoning, whether at home, in the emergency department, or the toxicology ward, were compared in terms of demographics, hematological and biochemical findings, and arterial blood gases; to patients who have spent 24 hours with no complications and had been discharged.

Statistical analysis

The data collection tool was a checklist with demographic information of the patients included in the study, which recorded all the variables of age and sex and laboratory findings of patients. All collected demographic information and studied data were analyzed by IBM® SPSS® 20.0 release software. For descriptive statistical studies of the population, mean, standard deviation, median, mode, interval, frequency statistics, frequency percentage, cumulative frequency, frequency distribution table, and pie charts and histograms of data were calculated. T-test was used to compare quantitative data between the two groups and chi-square was used for qualitative data. Spearman correlation was used to evaluate the possible relationship between the studied factors.

Results

A total of 95 patients including 76.8% male and 23.2% female with an average age of 28.26 ± 10.57 were admitted to the emergency department of Sina hospital as a toxicology center from March 2020 to 2021. Age did not obey normal distribution. Interquartile range (IQR) of the population was between 21-32 years old.

The most common symptoms of neurological impairment experienced by patients were seizure (32.6%) and decreased level of consciousness (38.8%). In the case of other symptoms, balance and gait disorders were more common.

The IQR and the median of hematological, biochemical and ABG factors of the patients are shown in Table 1.

Seizure had no relation with PH, PCO2, PO2, and *HCO3*$^{-}$ (*P* value of these data were 0.850, 0.869, 0.362, and 0.828, respectively). Decreased level of conciseness had no relation with PH, PCO2, PO2, and *HCO3*$^{-}$ (*P* values of 0.657, 0.350, 0.739, and 0.741, respectively). Hemiparesis also had no relation with PH, PCO2, PO2, and *HCO3*$^{-}$ (*P* values of 0.276, 0.210, 0.480, and 0.353, respectively).

No relationship was between neurological findings of tramadol intoxicated patients with hematological factors. Related data are summarized in Table 2.

There was a significant relationship between seizures and platelets, this relationship was very weak and was not clinically significant. (Correlation Coefficient = 0.216)

Discussion

Tramadol use, abuse, and related problems have increased in Iran and other countries. In this study we investigated the relation between laboratory finding of patients poisoned with tramadol and their neurological manifestations. Our study involved 95 people; including young people in the community. The male to female ratio was approximately 3:1. Seizure and decreased level of consciousness were the most common symptoms among tramadol-intoxicated patients which are in agreement with previous reports.

In the study done by Habibollahi et al about tramadol use and abuse, most patients were in their early twenties, with men having a higher percentage of the population.

Table 1. Median and IQR of hematological, biochemical and ABG factors of patients

	Median	IQR
Hematological and biochemical factors		
WBC	9300	7100-12100
RDW	12	12-13
Platelets	229000	182000-269000
Blood sugar	100	95-104
Blood sodium	140	138-141
Blood potassium	4	3-4
Blood-Arterial gases coordinates		
PH	7.36	7.32-7.40
PCO_2	46	42-52
PO_2	48	41-58
HCO_3^-	25	23-27

ABG, arterial blood gas; WBC, white blood cells; RDW, red cell distribution width.

Table 2. P values of relationship between neurological symptoms and patient's hematological findings with Spearman test

	WBC	RDW	Plt	BS	Na	K
Seizure	0.934	0.259	0.036	0.675	0.205	0.064
Decreased level of conciseness	0.439	0.336	0.424	0.224	0.737	0.582
Hemiparesis	0.458	0.820	0.514	0.624	0.411	0.651
others	0.026	0.120	0.341	0.711	0.668	0.426

WBC: white blood cell; RDW: red cell distribution width; Plt: platelets; BS: blood sugar; Na: sodium; K: potassium.

One-third of the patients used safe doses of tramadol as a medication but still, it led to seizures.[12] In another study done by Habibollahi et al, they determined tramadol in human plasma samples via the C capillary electrophoretic method with ultra violet-detection which was suitable for clinical applications and could detect tramadol poisoning easily.[13]

Rahimi et al study declared that seizures were the most common symptom in patients with tramadol poisoning, most of who were young men. In the laboratory findings Na and k level were in their normal range but pco2 level was raised.[14]

A study conducted by Zaare Nahandi et al, on the factors affecting seizure caused by tramadol poisoning, reported that there was no relation between patient's demographic data including sex, age, and history of previous tramadol use with seizures due to tramadol poisoning; but the higher the dose of tramadol, the later the seizure occurs.[15]

According to Beilin et al, increasing doses of tramadol did not affect the incubation of peripheral white blood cells' ability of phagocytosis, nor their phagocytic index.[16]

In the present study, there was no relationship between the neurological effects of tramadol poisoning with ABG characteristics such as PH, PCO2, PO2, and $HCO3^{-}$.

Also, there was no relationship between hematological factors considered in this study, which included WBC, RDW, Plt, Na, K, and BS with neurological symptoms caused by tramadol poisoning.

A study done by Kolski et al showed that calcium and sodium levels in rabbits increased in response to tramadol administration. Serum electrolyte levels: (Na+), (K+), (Ca2+) may be affected by tissue damage due to hypoxia.[17]

Contrary to the findings of our study, Elyazji et al stated that oral administration of tramadol to rabbits resulted in hematologic changes such as increased WBC and MCV levels, while hematocrit, hemoglobin, RBC, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and Plt counts were significantly decreased. Tramadol seems to affect the defense mechanism and immune system of rabbits in long-term use.[18]

Limitations of the study

In the future, conducting a study with a larger sample size will surely achieve more reliable results. A prospective study design is recommended for a better and more complete collection of hematological and biochemical characteristics.

Conclusion

Based on this study, no relationship was between the neurological manifestations of tramadol poisoning with ABG characteristics such as PH, PCO2, PO2, and HCO3-. Also, there was no relationship between hematological factors including WBC, RDW, Plt, Na, K, BS, and neurological symptoms caused by acute tramadol poisoning. There was a significant relationship between seizures and platelets, but this relationship was very weak and was not clinically significant. Therefore, our study has shown that all laboratory tests are not required for all patients with tramadol poisoning and it can be cost and time-consuming.

Study Highlights

What is current knowledge?

- In tramadol toxicity may be some laboratory findings change, then we can predict symptoms or signs.

What is new here?

- The neurological manifestations of tramadol poisoning were not related to any laboratory findings

Authors' Contribution
Conceptualization: Paria Habibollahi.
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Formal Analysis: Masoumeh Poureskandari.
Methodology: Hasan Amiri.
Project administration: Paria Habibollahi.
Supervision: Orhan Delice.
Validation: Orhan Delice.
Writing – original draft: Mahsa Makouei.
Writing – review & editing: Masoumeh Poureskandari.

Competing Interests
The authors declare that there is not any conflict of interest.

Ethical Approval
This research was approved by the regional ethics committee of Tabriz University of Medical Science's emergency department with registry no IR.IAU.TABRIZ.REC.1399.161.

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