**ORIGINAL ARTICLE**

# Tramadol Overdose Induced Transient Paresthesia and Decreased Muscle Strength: A Case Series

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## Abstract

*Background:* Tramadol overdose is relatively common in Iran. A series of tramadol poisoned patients with paresthesia and decreased muscle strength are described.
*Methods:* In this prospective cross-sectional study, all referred cases to Mashhad Medical Toxicology Center with suspected tramadol poisoning between 1st July 2010 and 1st September 2012 were included. Patients with mixed overdose, history of neurologic and musculoskeletal disorders including primary seizure, and history of addiction were excluded. Patients were visited on admission, 6 and 12 hours later. All cases underwent complete neurologic examination. Muscle strength was assessed with manual muscle testing.
*Results:* Tramadol overdose accounted for 1026 cases during the study period. Eight hundred eighty nine cases were excluded and finally 137 cases were tramadol only overdose. Most patients (92%) were men. Mean (SD, min-max) age was 24.5 (6.9, 10-42) years. The strength of upper and lower limbs symmetrically declined in the first visit and increased gradually in 6 and 12 hours post-admission, but the strength of lower limbs was more significantly affected on admission and after 6 hours ($P < 0.001$) compared to upper limbs. Paresthesia happened in 64%, 9% and 0% in upper limbs and 86%, 35% and 3% in lower limbs on admission, and after 6 and 12 hours. No spasticity and flaccidity were observed. On admission, pupils were symmetrically reactive and 6.7 (2.3, 1-11) mm wide. Pupil size significantly declined to 5.6 (2.1, 1.3-9.0) mm 6 hours later ($P < 0.001$).
*Conclusion:* Transient paresthesia and transient symmetrical decline in muscle strength of upper and lower limbs are potential neurologic complications following tramadol abuse and overdose. Further studies are needed to fully clarify the pathogenesis and mechanism of these complications following tramadol overdose.

**Keywords:** Muscle Strength; Paresthesia; Seizure; Substance-Related Disorders; Tramadol

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## INTRODUCTION

Opioid abuse is common in Iran and its pattern is rapidly changing (1,2). In recent years, opioid abusers were more tended towards newer, low-cost and more available compounds including tramadol (1-3). Although tramadol is not an over-the-counter medication, some abusers can find it illegally from dealers and irresponsible medicine retailers. Hence, it is plausible that the abuse and overdose of tramadol is increasing. Management of tramadol poisoning can be different with regards to its various adverse effects (4).

Tramadol, a synthetic opioid, is prescribed for its analgesic effects especially in post-surgery setting (4), renal colic and premature ejaculation (5). However, it is abused as an illicit opioid to induce euphoria as well as improving leisure sexual activity (5,6).

Tramadol acts via opioid and non-opioid receptors (7). The mechanisms of action include inhibition of serotonin reuptake, stimulation serotonin release and inhibition of norepinephrine reuptake (8). Activation of opioid and serotonin-mediated pathways may lead to desirable effects (8). In case of overdose, tramadol may lead to various adverse effects especially on central nervous system causing loss of consciousness, seizure and serotonin syndrome (4,9-11). It can also induce CPK increase and acute renal failure (11).

Tramadol overdose is relatively common in our setting - Mashhad Medical Toxicology Centre (MTC) (2). We have frequently encountered tramadol poisoned patients with paresthesia and decrease of muscle strength. In this study, we investigated development of paresthesia and decrease of muscle strength following tramadol overdose.

## METHODS

*Inclusion and exclusion criteria*

In this prospective cross-sectional study, all referred cases to MTC with suspected tramadol poisoning between 1st July 2010 and 1st September 2012 were included. MTC in Imam

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Reza Hospital is a 42 bed toxicology ward with around 8,000 admitted poisoned cases each year (12). The diagnosis was made based on history from the patients or their relatives as well as clinical manifestations confirmed primarily with tramadol urinary test and secondarily by measurement of serum tramadol level.

Exclusion criteria comprised of history of mixed overdose, history of neurologic and musculoskeletal disorders including primary seizure, history of addiction, history of chronic diseases, electrolyte imbalances, and cases with positive methadone, morphine, amphetamine, methamphetamine, phencyclidine, benzodiazepines, barbiturates, cocaine, tricyclic antidepressants and phenothiazine in urine or serum.

*Data collection*

Demographic characteristics of patients, history, clinical and laboratory findings were entered into a predesigned checklist. All patients were examined by a clinical toxicologist on their arrival, and 6 and 12 hours later. In all 3 visits, history and clinical findings were completely repeated and any potential discrepancies in history were further evaluated. Seizure episode was confirmed if it happened within triage under the supervision of physician or nurses or if the second author (HK) was convinced of an episode of seizure based on history and explanations by the patient's relatives. Urinary screening tests were performed using urine rapid tests (ACON Laboratories, Inc., San Diego, CA, USA).

Dose of ingested tramadol (number of ingested tablets) in each patient was asked through history taking. Paresthesia was evaluated based on asking patients about sensation of tingling, pricking or burning. In addition, all cases underwent complete neurologic physical examination including sensory examination (light touch, pinprick and temperature sensation), motor examination (muscle tone, muscle strength, deep tendon reflexes (DTR)) and cerebellar tests. Muscle strength was assessed with manual muscle testing based on the Medical Research Council scale from 0 (no visible or palpable contraction) to 5 (normal muscle strength, full range of motion against gravity, maximal resistance) (13). Pupil size was also measured using a pupilometer.

*Ethics and statistical analysis*

Ethics approval was obtained from ethics committee of the Mashhad University of Medical Sciences (MUMS/89/1876). Informed consent was obtained from all patients prior to enrollment. Treatment of patients was not influenced within process of data collecting. Statistical analysis including Student's t-test and chi-square tests were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). In all calculations, two tailed tests with P values of less than 0.05 were considered to be statistically significant.

## RESULTS

*Socio-demographic characteristics*

Tramadol overdose accounted for 1026 cases (5.9% of all poisoning cases) admitted to MTC during the study period. Among them, 889 cases excluded (421 cases due to co-ingestion, 16 cases due to history of primary seizure, 365 cases due to positive urinary immunoassay for other drugs, 3 cases with chronic diseases, 84 cases that abandoned treatment for personal reasons, 1 case with electrolyte imbalance and 3 cases with history of musculoskeletal diseases). One hundred thirty seven cases were included that majority of them were men (92%). Mean (standard deviation (SD), min-max) age was 24.5 (6.9, 10-42) years.

Mean (SD, min-max) dose of tramadol ingested was 1481 mg (630, 200-2100 mg). Seizure developed in 16 patients

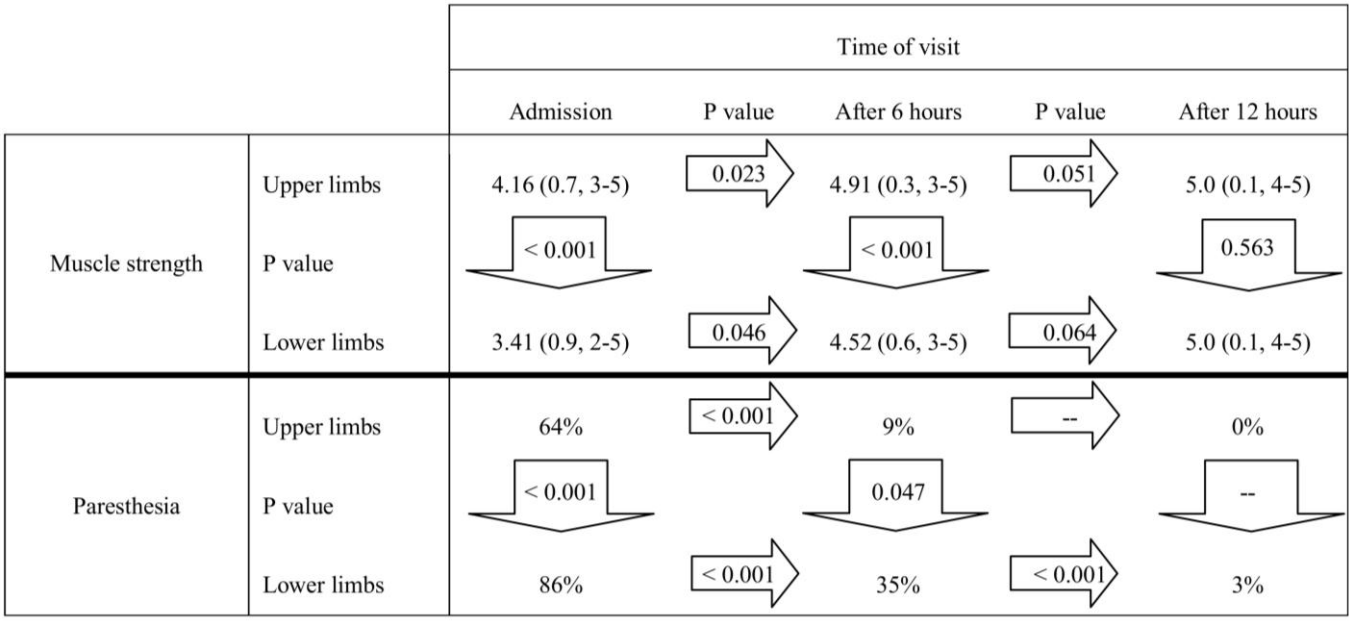


**Figure 1.** Score of muscle strength (presented with mean (SD, min-max)) and presence of paresthesia (presented with frequency (%)) on admission, 6 and 12 hours after admission (P values shows the level of sginificance of comparig each visit with next visit and comparing upper limbs with lower limbs)

(12%). The mean (SD) dose in patients with seizure (1287 (1413) mg) was not significantly different from patients without seizure (1531 (1180) mg). Mean age and duration of admission, and gender distribution were not significantly different between patients with and without seizure.

*Muscle strength*

On admission, mean (SD) muscle strength score of upper limbs symmetrically decreased to 4.16 (0.7) and increased to 4.91 (0.3) and 5.0 (0.1) in 6 and 12 hours post-admission respectively (Figure 1). Strength of lower limbs symmetrically declined to 3.41 (0.9) in the first visit and increased to 4.52 (0.6) and 5.0 (0.1) in 6 and 12 hours post-admission, respectively. The means of muscle strength in upper and lower limbs in 6 hours post-admission were significantly different from the first visit on admission (P = 0.023, 0.046 respectively). Comparison of means of muscle strength in upper and lower limbs in 12 hours post-admission to 6 hours post-admission showed no significant difference but approached the significance (Figure 1).

Mean muscle strength of lower or upper limbs was not significantly different between patients with and without seizure in each visit (Table 1).

Comparison of mean strength between upper and lower limbs revealed that strength of lower limbs were more seriously decreased on admission and 6 hours post-admission (P < 0.001), but not after 12 hours (P = 0.563).

*Paresthesia*

Paresthesia happened in 64%, 9% and 0% in upper limbs and 86%, 35% and 3% in lower limbs on admission, 6 and 12 hours post-admission, respectively. The presence of paresthesia in upper and lower limbs significantly reduced in each visit (P < 0.001). Comparison of presence of paresthesia in upper and lower limbs revealed that it was more frequent in lower limbs on admission and 6 hours post-admission (P < 0.001, 0.047, respectively). This comparison was not done for 12 hours post-admission time-point due to statistical reasons (Figure 1).

*Tone and DTRs*

In all 137 cases no spasticity and flaccidity were observed. Tone was not affected. DTRs were normal in majority of cases (92.5%) on admission and all cases after 6 and 12 hours (Figure 2).

*Pupils*

On admission, pupils were symmetrically reactive and 6.7 (2.3) mm wide on average. Pupil size significantly declined to 5.6 (2.1) mm 6 hours later (P < 0.001) (Table 1). Mean pupil size was not significantly different between patients with and without seizure on admission (P = 0.074) and 6 hours later (P=0.940) but 4 patients with miosis developed apnea on admission.

*Heat rate*

On admission, the mean (SD) heart rate was 91 (14) bpm (Table 1). Heart rate was significantly higher in patients who developed seizure (P < 0.001) (Table 1).

*Associations*

Patients without paresthesia had significantly wider pupils on admission (mean (SD) difference: 1.1 (0.59 - 1.52), P < 0.001). Paresthesia was not associated with seizure as well as muscle strength in upper and lower extremities. Increased DTRs were significantly correlated with declined strength of upper (P = 0.001) and lower limbs (P < 0.001) on admission. Exaggerated DTRs were not statistically related to seizure, heart rate, size of pupils, and presence of paresthesia.

*Treatments and outcome*

Patients were treated conservatively and symptomatically. They mainly received fluids and benzodiazepines if seizure occurred. Patients were hospitalized for a mean (SD) of 1.24 (0.1) days ranging from less than 24 hours to 5 days. One hundred and two cases (74%) were discharged in the first 24 hours. One subject died in the intensive care unit 43 hours after exposure due to ventricular tachycardia.

**Table 1.** Compression of muscle strength, pupil size and heart rate of patients with and without seizure (n = 137)

| | All cases* | Seizure (-) | Seizure (+) | P Value |
|---|---|---|---|---|
| Variables** | | | | |
| SUL-0 | 4.16 (0.7) | 4.19 (0.06) | 4.06 (0.13) | 0.333 |
| SUL-6 | 4.91(0.3) | 4.91 (0.32) | 4.91 (0.29) | 0.944 |
| SUL-12 | 5.00 (0.1) | 4.99 (0.1) | 5.00 (0.00) | 0.575 |
| SLL-0 | 3.41 (0.9) | 3.42 (0.9) | 3.36 (0.9) | 0.752 |
| SLL-6 | 4.52 (0.6) | 4.56 (0.5) | 4.39 (0.7) | 0.151 |
| SLL-12 | 5.00 (0.1) | 5.00 (0.0) | 4.94 (0.2) | 0.160 |
| Pupil-0 (mm) | 6.70 (2.3) | 6.50 (2.34) | 7.33 (2.23) | 0.074 |
| Pupil-6 (mm) | 5.60 (1.3) | 5.59 (1.29) | 5.61 (1.32) | 0.940 |
| HR (bpm) | 91 (14) | 78 (13) | 104 (12) | < 0.001 |
| Chronic | 10.2 (3.0-33.8) | <0.001 | 2.3 (0.6-8.4) | 0.21 |

* Results are presented as mean (SD).

** SUL-0: Strength of upper limbs on admission, SUL-6: Strength of upper limbs 6 hours post-admission, SUL-12: Strength of upper limbs 12 hours post-admission, SLL-0: Strength of lower limbs on admission, SLL-6: Strength of lower limbs 6 hours post-admission, SLL-12: Strength of lower limbs 12 hours post-admission, Pupil-0: Size of pupils (mm) on admission, Pupil-6: Size of pupils (mm) 6 hours post-admission, HR: Heart rate (bpm)

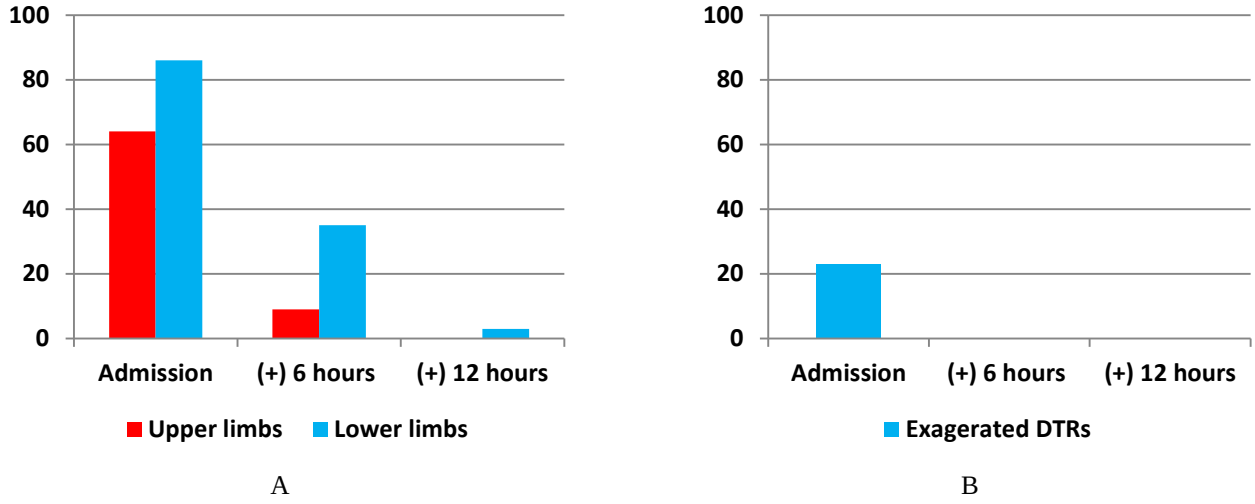


**Figure 2.** Frequency of paresthesia (A) and exaggerated deep tendon reflexes (B) during admission (n = 137)

## DISCUSSION

During the two-year study period, 1026 patients with tramadol overdose were admitted to MTC. This number is higher than reported rate of tramadol overdose in other countries (2,7,14-16). This is probably due to easy availability and low cost of tramadol in Iran. In addition, the method of sampling is different in other studies as in current study, all patients admitted to a hospital were included but in some studies, the data were collected via a poison center (14,15).

The rate of tramadol overdose induced seizure was 12% in our study; however, different rates of this complication (1-35%) have been reported in the literature (14,17). The ingested dose of the drug might possess a role on this disparity. In one multi-center study, Grond and Sablotzki claimed that 500 mg tramadol was the lowest dose associated with seizure (16). However, Talaie et al. showed that seizure due to tramadol overdose is not dose-dependent (18). In current study, seizure occurred even with ingestion of 200 mg tramadol, which is within therapeutic dose of the drug. In this respect, there was no significant difference in ingested dose between patients with and without seizure.

In the present study, we found no significant difference in pupil size on admission between patients with and without seizure (despite the P value was close the level of significance (P = 0.074)), unlike a recent study that showed patients with mydriasis are more vulnerable to seizure (2). Nevertheless, similar to the study by Tashakori and Afshari, heart rate was significantly higher in patients with seizure compared to those without (2).

In this study, a transient decline of muscle strength in both upper and lower limbs was observed. The possible mechanism for the effect of tramadol on the muscle strength can be related to its effect on calcium channels. Medei et al. demonstrated that 200 µM tramadol can inhibit L-type calcium current (ICa-L) in cardiac myocytes of rats (19). In this regard, tramadol was shown to reduce the peak amplitude of ICa-L and to shift the steady- state inactivation of ICa-L to more negative membrane potentials (19). The pattern of muscle strength decrease was transient in this study that might be due to short elimination half-life of tramadol which is about 5.1 to 6 hours (16,20).

In the present study, paresthesia was observed in both upper and lower limbs in a remarkable proportion of patients, and it was similarly transient. Tramadol can inhibit serotonin reuptake and increase serotonin serum level. Serotonin excess may lead to neurologic effects including paresthesia. Praharaj et al. explained serotonin reuptake inhibitors can induce sensory disturbances, which are one of the unusual adverse effects (21). Vetrugno et al. showed that long-term tramadol treatment can induce diurnal sensory symptoms and restless legs syndrome (22). These further confirm the potential neurotoxicitic effects of tramadol.

In several studies, critical adverse effects of tramadol use and overdose have been reported that greatly affects its safety for outpatient prescription and use. In many European countries, dextroproxyphene (an opioid derivative) has been banned from the market due to various complications (23). A similar preventive measure should be taken against tramadol prescription in Iran.

## LIMITATIONS

We could not examine electromyography/nerve conduction velocity (EMG/NCV) in the patients studied. We could not measure serum tramadol level and thus the correlation of serum level of tramadol and severity of muscle strength decrease could not be analyzed. It is necessary to assess serum tramadol level and EMG/NCV in future studies to find out the pathogenesis of tramadol neurotoxicity.

## CONCLUSION

Transient paresthesia, transient symmetrical decline in muscle strength of upper and lower limbs and seizure are

potential neurologic complications following tramadol abuse and overdose. Development of paresthesia was not correlated to seizure. Further studies are needed to fully clarify the pathogenesis and mechanism of these complications following tramadol overdose.

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