Acute Tramadol Poisoning; Evaluating the Risk Factors of Seizures and Finding a Correlation with Tramadol Blood Level

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KEYWORDS
Tramadol poisoning,
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Tramadol dose,
Tramadol blood level.

ABSTRACT

Tramadol-induced seizures (TIS) are reported to occur in 15%–35% of tramadol poisoned cases. The present study aimed to evaluate the risk factors of TIS and to find out if there is a correlation between TIS and the ingested dose and the blood level of tramadol. This study included cases of both genders with acute tramadol poisoning admitted to Tanta University Poison Control Center from January 2019 to December 2019. Each case was subjected to history taking, clinical and laboratory evaluation including tramadol urine screen, and tramadol blood level estimation at admission. Sixty-two cases were enrolled in the study. Their mean age was 28.3 ± 9.6 years, 85.5% of them were males; addiction was the most common mood of poisoning. The seizure was recorded in 40.4% of the cases. There was a significant statistical difference between non- seizing and seizing groups regarding ingested tramadol dose and tramadol blood level. Furthermore, there was a strong significant positive correlation between ingested tramadol dose, tramadol blood level and occurrence of seizures. Receiver operating curve analysis revealed that ingested tramadol dose and tramadol blood level had an excellent discriminatory power in predicting seizure occurrence, but tramadol blood level had a better area under the curve. It was concluded that acute tramadol poisoning is associated with an increased risk of developing seizures. The ingested tramadol dose and the tramadol blood level could be used as excellent predictors of seizures in cases of tramadol overdoses.

Introduction

Tramadol is a centrally acting analgesic used to treat mild to severe pain of different sources. Based on the literature, this analgesic is one of the most prescribed opioids in the world (Sweileh, et al., 2016; Subedi, et al., 2019). Tramadol is a less potent μ-agonist than morphine and is a "safer" opioid alternative (Hassamal, et al., 2018).

Although the mechanism of action of tramadol is via stimulation of μ-opioid receptors, in addition to, inhibition of serotonin and noradrenaline reuptake, its analgesic effect is mainly secondary to its non-opioid properties and via activation of central monoaminergic pathways (Taghaddosinejad, et al., 2011; Majidi and Fard, 2014).

Acute tramadol toxicity is presented with nausea, vomiting, and constipation. It can also be manifested by seizures, central

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nervous system (CNS) depression, respiratory depression, and serotonin syndrome including altered mental status, neuromuscular and autonomic hyperactivity (Sansone and Sansone, 2009; Boostani and Derakhshan, 2012; Rahimi, et al., 2014). Seizures are reported to occur in 15% – 35% of tramadol poisoned cases. They can occur even with therapeutic doses (Boostani and Derakhshan, 2012; Eizadi-Mood, et al., 2014).

The exact mechanism of the tramadol-induced seizure (TIS) is still incompletely understood. However, it may be due to its inhibitory effects on gamma-aminobutyric acid (GABA) receptors together with its opioid receptor agonist activity (Rehni, et al., 2008; Baldo, 2018).

Some studies have revealed associations between TIS and some risk factors. These risk factors included opioid dependence, gender, age, tramadol dose, tramadol blood level, and delay time. However, the effects of these factors are still under debate and other risk factors have remained unclear (Ahmadimanesh, et al., 2018; Bazmi, et al., 2020). Likewise, the risk of TIS is higher with larger doses of tramadol but it does not appear to be dose-dependent (Talaie, et al., 2009; Hassamal, et al., 2018). In addition, the minimum stimulant dose of tramadol and its blood concentrations that induce seizures remain unknown (Dadpour, et al., 2020). Thus, the current study aimed to evaluate the risk factors of TIS and to find out if there is a correlation between TIS and the ingested dose and the blood level of tramadol.

Patients and Methods:

Study design and setting:

This prospective, cohort study was carried out from the start of January 2019 to the end of December 2019 on sixty-two cases of acute tramadol poisoning admitted to Tanta University Poison Control Center (TUPCC).

Ethical considerations

The study was conducted after approval of the Local Research Ethical Committee, Quality Assurance Unit, Faculty of Medicine, Tanta University (approval code: 34074/8/20). Informed written consent was obtained from the adult conscious patient or his/her legal guardian (if the patient was unable to participate in the consent process) after receiving detailed information about the study. The confidentiality of data was maintained by making a code number for each patient. All data were anonymously analyzed and the results of this research were used only for scientific purposes.

Inclusion criteria:

This study included all cases older than 18 years old, of both genders, diagnosed as isolated acute tramadol poisoning and admitted to TUPCC during the study period. Diagnosis of acute tramadol poisoning was based on the history of tramadol ingestion, clinical manifestations of acute tramadol overdose, and positive urine tramadol screen test.

Exclusion criteria:

Cases younger than 18 years old, asymptomatic cases, cases with negative urine tramadol screen, and cases with a history of epilepsy, structural brain lesion, head trauma, systemic comorbidities were excluded. Moreover, cases with exposure to other substances in addition to tramadol and cases that received any treatment before admission to TUPCC were also excluded.

Methods:

All cases were subjected to:

- History taking:
  - Personal history with an emphasis on age and gender.

- Toxicological history including the route of exposure, mode of poisoning, the dose of tramadol, and time elapsed between exposure and admission to the hospital (delay time).

- Clinical examination:
  - Vital signs (pulse, blood pressure, respiratory rate, and temperature)
  - Consciousness level by Glasgow Coma Scale (GCS).
- General clinical examination
- Laboratory investigation:
  - Routine laboratory investigations including liver enzymes, urea, creatinine, random blood glucose level, electrolytes; sodium (Na) and potassium (K) levels, and complete blood count (CBC) were performed for each case at admission to exclude the cases who did not fulfill the criteria of the study.
  - Arterial blood gases (ABG) analysis: 1 milliliter (ml) arterial blood sample was taken on a heparinized tube for its estimation.
  - Detection of tramadol in urine: 20 ml urine sample was obtained from each case immediately on admission and before receiving any treatment in clean dry sterile plastic containers labeled with his/ her name, serial number, and date of collection to be used for a drug urine screen. Each sample was subjected to rapid qualitative screening for tramadol by an enzyme immunoassay (Acro Rapid Test Diagnostic).
- Tramadol blood level: 3 ml venous blood samples were collected immediately on admission in heparinized tubes. The samples were centrifuged at 4000 rpm for 10 minutes. Then, plasma was separated and deeply stored at -70 ºC until analysis. Quantification of tramadol blood level was done by gas chromatography.
- Treatment: all cases received routine treatment including standard emergency and supportive care, decontamination, and administration of specific antidote (naloxone) when indicated. The administered naloxone dose, the need for intubation and mechanical ventilation (MV), and the hospitalization period were recorded.

Statistical analysis:

Statistical analysis was performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015). For quantitative data, the Shapiro-Wilk test for normality was performed besides visual assessment of graphs. For normally distributed data, variables were summarized as mean ± standard deviation (SD), and comparison between two groups was carried out using independent samples t-test. For abnormally distributed data, the variables were summarized as the median and interquartile range (IQR, expressed as 25^{th} – 75^{th} percentiles), and comparison between two groups was carried out using the Mann-Whitney test. Correlations were performed using Spearman's rank-order correlation. Analysis of receiver operating characteristic (ROC) curve was done to assess the relation between true-positive results and false-positive results for each measurement (DeLong, et al., 1988). The area under ROC curve was graded as follows: 0.90-1 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; and 0.60-0.70 = poor. Sensitivity and specificity were calculated. Sensitivity is the proportion of those whom the test indicated having seizures among those who already had seizures. Specificity is the percentage of those the test judged not having seizures out of those who already did not develop seizures. A

p- value ≤ 0.05 was adopted for the interpretation of statistical tests.

Results:

Throughout the study period, 78 cases of acute tramadol poisoning were admitted to TUPCC. Out of them, 62 cases fulfilled the inclusion criteria and were accepted to participate in this study. Demographic and toxicological findings of the studied cases were illustrated in table (1). Their mean age was 28.3 ± 9.6 years and most of them (85.5%) were males.

The study revealed that tramadol abuse was the most common cause of poisoning (75.8%). In addition, the route of exposure was oral in all cases participated in this study. The median delay time was 4 hours. The ingested tramadol dose in the studied cases ranged from 125 to 4500 mg with a median of 1000 mg (Table 1).

The study declared that 37 cases (59.6%) did not suffer from seizures (non-seizing group), while seizures were reported in 25 cases (40.4%; seizing group). Twenty-one cases (84%) of the seizing group experienced a single seizure attack, while 4 cases (16%) had recurrent attacks. Seizures in all cases were generalized tonic-clonic and developed within the first 24-hours after tramadol ingestion. There was a significant statistical difference between the non- seizing group and the seizing group regarding ingested tramadol dose ($p < 0.001$). However, no significant differences were detected between the two groups as regards age, gender, mode of poisoning, and delay time (Table 1).

Table (1): Demographic and toxicological findings of the studied cases with acute tramadol poisoning (n=62)

Variables		Non-seizing group (n = 37)	Seizing group (n = 25)	Total studied patients (n = 62)	Test statistic	p
Age (years)	Mean ± SD	27.7 ± 8.8	29.1 ± 10.8	28.3 ± 9.6	0.578 [a]	0.565
	Range	18.0 - 55.0	18.0 - 59.0	(18.0 - 59.0)		
Gender n (%)	Male	31 (83.8%)	22 (88.0%)	53 (85.5%)	FE	0.728
	Female	6 (16.2%)	3 (12.0%)	9 (14.5%)		
Mode of poisoning n (%)	Addiction	28 (75.7%)	19 (76.0%)	47 (75.8%)	4.762 [b]	0.069
	Accidental	4 (10.8%)	6 (24.0%)	5 (8.1%)		
	Suicidal	5 (13.5%)	0 (0.0%)	10 (16.1%)		
Delay time (h)	Range	0.5 - 12.0	0.5 - 15.0	0.5 - 15.0	0.282 [c]	0.778
	Median	4.0	4.0	4.0		
	IQR	2.0 - 6.0	3.0 - 7.0	3.0 - 6.5		
Ingested tramadol dose (mg)	Range	125.0 - 1250.0	675.0 - 4500.0	125.0 - 4500.0	5.995 [c]	<0.001*
	Median	450.0	1575.0	1000.0		
	IQR	340.0 - 1000.0	1300.0 - 3375.0	450.0 - 1500.0		

[a]: Independent samples t-test; [b]: Fisher-Freeman-Halton exact test; [c]: Mann-Whitney test; FE: Fisher's exact test; IQR: interquartile range; SD: standard deviation; n: number; h: hour; mg: milligram; * significant at p≤ 0.05.

Table (2) demonstrated that GCS ranged between 3 and 15 with a median of 13. The blood pressure, temperature, and respiratory rate were within the normal range in more than half of the studied cases. On the other hand, tachycardia was detected in most cases (79.0%). The mean oxygen (O_2) saturation was 92.9 ± 6.6. Additionally, table (2) showed the incidence of clinical symptoms and signs of tramadol overdose. No significant statistical differences were detected between the two groups as regards all clinical findings.

Table (2): Clinical findings of the studied cases with acute tramadol poisoning (n=62)

Variables		Non-seizing group (n = 37)	Seizing group (n = 25)	Total studied patients (n = 62)	Test statistic	p
Glasgow Coma Score (GCS)	**Range**	3.0 - 15.0	3.0 - 15.0	3.0 - 15.0	0.726 [a]	0.468
	Median	13.0	12.0	13.0		
	IQR	9.0 - 14.0	4.0 - 14.0	6.0 - 14.0		
GCS n (%)	**13 - 15**	22 (59.5%)	11 (44.0%)	33 (53.2%)	1.491 [b]	0.475
	9 - 12	6 (16.2%)	5 (20.0%)	11 (17.7%)		
	3 - 8	9 (24.3%)	9 (36.0%)	18 (29.0%)		
Pulse Beats/minute n (%)	**Normal**	9 (24.3%)	3 (12.0%)	12 (19.4%)	2.126 [c]	0.403
	Tachycardia	27 (73.0%)	22 (88.0%)	49 (79.0%)		
	Bradycardia	1 (2.7%)	0 (0.0%)	1 (1.6%)		
Blood pressure mmHg n (%)	**Normal**	22 (59.5%)	18 (72.0%)	40 (64.5%)	2.755 [c]	0.255
	Hypertension	11 (29.7%)	7 (28.0%)	18 (29.0%)		
	Hypotension	4 (10.8%)	0 (0.0%)	4 (6.5%)		
Temperature °C n (%)	**Normal**	30 (81.1%)	19 (76.0%)	49 (79.0%)	0.232 [b]	0.630
	Increased	7 (18.9%)	6 (24.0%)	13 (21.0%)		
Respiratory rate Cycles/minute n (%)	**Normal**	26 (70.3%)	12 (48.0%)	38 (61.3%)	3.201 [c]	0.209
	Tachypnea	8 (21.6%)	9 (36.0%)	17 (27.4%)		
	Bradypnea	3 (8.1%)	4 (16.0%)	7 (11.3%)		
O_2 saturation (%)	**Mean ± SD**	93.6 ± 6.5	91.9 ± 6.9	92.9 ± 6.6	0.956 [d]	0.343
	Range	79.0 - 100.0	79.0 - 100.0	79.0 - 100.0		
Headache n (%)	**Absent**	23 (62.2%)	15 (60.0%)	38 (61.3%)	0.029 [b]	0.864
	Present	14 (37.8%)	10 (40.0%)	24 (38.7%)		
Vomiting n (%)	**Absent**	24 (64.9%)	15 (60.0%)	39 (62.9%)	0.151 [b]	0.697
	Present	13 (35.1%)	10 (40.0%)	23 (37.1%)		
Agitation n (%)	**Absent**	22 (59.5%)	19 (76.0%)	41 (66.1%)	1.822 [b]	0.177
	Present	15 (40.5%)	6 (24.0%)	21 (33.9%)		
Hyperreflexia n (%)	**Absent**	26 (70.3%)	14 (56.0%)	40 (64.5%)	1.327 [b]	0.249
	Present	11 (29.7%)	11 (44.0%)	22 (35.5%)		
Pupil n (%)	**RRR**	25 (67.6%)	11 (44.0%)	36 (58.1%)	3.635 [c]	0.118
	Constricted	11 (29.7%)	13 (52.0%)	24 (38.7%)		
	Dilated	1 (2.7%)	1 (4.0%)	2 (3.2%)		

[a]: Mann-Whitney test; [b]: Pearson's Chi -square test for independence; [c]: Fisher-Freeman-Halton exact test; [d]: Independent samples t-test; IQR: interquartile range; SD: standard deviation; n: number; *: significant at $p \leq 0.05$.

Table (3) showed that a normal acid-base state was recorded in 61.3% of cases, the remaining cases suffered from acid- base disturbances. The most common acid- base disturbance was respiratory acidosis (16.1% of all cases). Tramadol blood level ranged from 100 to 1500 ng/ml with a median of 550 ng/ml. The median tramadol blood level was significantly higher in seizing group than non-seizing group (1100 vs 300 ng/ml; $p < 0.001$), but no significant differences were detected between both groups as regards the acid base disturbances.

Table (3): Laboratory findings of the studied cases with acute tramadol poisoning (n=62)

Variables		Non-seizing group (n = 37)	Seizing group (n = 25)	Total studied patients (n = 62)	Test statistic	p
Acid-base status	Normal	23 (62.2%)	15 (60.0%)	38 (61.3%)	4.422 [a]	0.347
	Met. acidosis	4 (10.8%)	1 (4.0%)	5 (8.1%)		
	Met. alkalosis	2 (5.4%)	0 (0.0%)	2 (3.2%)		
	Resp. acidosis	6 (16.2%)	4 (16.0%)	10 (16.1%)		
	Resp. alkalosis	2 (5.4%)	5 (20.0%)	7 (11.3%)		
Tramadol blood level (ng/ml)	Range	100.0 - 710.0	600.0 - 1500.0	100.0 - 1500.0	6.553 [b]	<0.001*
	Median	300.0	1100.0	550.0		
	IQR	130.0 - 400.0	950.0 - 1300.0	225.0 - 1000.0		

[a]: Fisher-Freeman-Halton exact test; [b]: Mann-Whitney test; IQR: interquartile range; SD: standard deviation; n: number; ng: nanogram; ml: milliliter; *: significant at $p \leq 0.05$.

Table (4) revealed that the median administered dose of naloxone was 1.4 mg. Intubation and mechanical ventilation (MV) was indicated in 14 cases (22.6%). Moreover, the median duration of hospital stay was 7 hours. There were no significant statistical differences between the two groups regarding the administered dose of naloxone, the need for intubation and MV, and the duration of hospital stay.

Table (4): Administered dose of naloxone and duration of hospital stay of the studied cases with acute tramadol poisoning (n=62)

Variables		Non-seizing group (n = 37)	Seizing group (n = 25)	Total studied patients (n = 62)	Test statistic	p
Administered naloxone dose (mg)	Range	0.0 - 10.0	0.0 - 10.8	0.0 - 10.8	1.814 [a]	0.070
	Median	0.0	2.8	1.4		
	IQR	0.0 – 4.4	0.0 – 8.8	0.0 – 6.0		
Intubation and MV n (%)	No	31 (83.8%)	17 (68.0%)	48 (77.4%)	2.126 [b]	0.145
	Yes	6 (16.2%)	8 (32.0%)	14 (22.6%)		
Duration of hospital stay (h)	Range	1.0 - 36.0	1.0 - 60.0	1.0 - 60.0	0.476 [a]	0.634
	Median	7.0	7.0	7.0		
	IQR	3.0 - 11.0	5.0 - 10.0	4.0 - 11.0		

[a]: Mann-Whitney test; [b]: Pearson's Chi- square test for independence; IQR: interquartile range; MV: mechanical ventilation; n: number; mg: milligram; h: hour; *: significant at $p \leq 0.05$.

The study revealed significant strong positive correlations between the occurrence of seizures and both the ingested tramadol dose and the tramadol blood level. However, no significant correlations could be detected between the occurrence of seizures and the other variables demonstrated in table (5).

Table (5): Spearman's correlation between seizures and some variables

Variables		Frequency of seizures
Age (years)	r_s	0.025
	p	0.847
Delay time (h)	r_s	0.050
	p	0.700
Dose of tramadol (mg)	r_s	0.753
	p	<0.001*
Tramadol blood level (ng/ml)	r_s	0.837
	p	<0.001*
GCS	r_s	-0.069
	p	0.597
O_2 saturation (%)	r_s	-0.089
	p	0.492
Dose of naloxone	r_s	0.205
	p	0.111
Duration of hospital stay (h)	r_s	0.055
	p	0.672

r_s: Correlation coefficient; h: hour; * significant at $p \leq 0.05$

Analysis of receiver operating characteristics (ROC) curve of ingested tramadol dose and tramadol blood level for predicting seizure occurrence in acute tramadol poisoning was demonstrated in table (6) and figure (1). The tramadol blood level had a better AUC than the ingested tramadol dose (AUC= 0.993, 95% CI= 0.929 – 1.000 vs AUC= 0.951, 95% CI= 0.864 – 0.990 respectively). There was no significant statistical difference between the AUC of both variables.

Table (6): Comparison between ingested tramadol dose (mg) and tramadol blood level (ng /ml) for predicting the occurrence of seizure using ROC curve analysis

Parameters	Tramadol dose (mg)	Tramadol level (ng/ml)
AUC (95% CI)	0.951 (0.864 – 0.990)	0.993 (0.929 – 1.000)
p – value (null hypothesis: AUC=0.5)	<0.001*	<0.001*
Best cut off value	>1100	>710
Sensitivity (%)	88.0	92.0
Specificity (%)	89.2	100.0
p-value from Pairwise comparisons of AUCs		
p	0.051	

AUC: area under the curve; CI: confidence interval; *significant at $p \leq 0.05$.

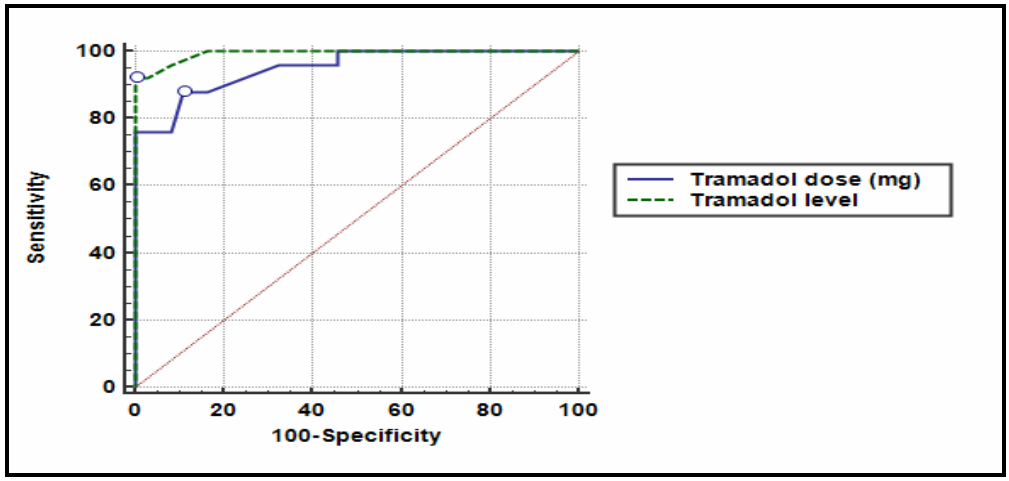

Fig. (1): ROC curve analysis of tramadol blood level and ingested tramadol dose as predictors of the occurrence of seizures.

Discussion:

Tramadol is widely used as a safe centrally acting analgesic. However, the occurrence of seizures after its therapeutic use or overdose is a well-known and documented phenomenon (Ryan and Isbister, 2015). The present study aimed to evaluate the risk factors of TIS and to find out if there is a correlation between TIS and the ingested dose and the blood level of tramadol among cases with acute tramadol poisoning admitted to TUPCC.

The age of the studied cases ranged from 18 to 59 years old with a mean age of 28.3 ± 9.6 years. This finding is in agreement with the findings reported by some studies where mean ages were; 28.4 years in Iran in Boostani and Derakhshan (2012) study, 29.63 and 29.7 in Egypt in Hussien and Elguindy (2017) and Shamloul et al. (2020) studies respectively. However, younger mean ages were reported by other studies in Egypt (Ismail et al., 2018) and in Iran (Bazmi et al., 2020; Soroosh et al., 2020).

Male predominance was recorded among cases of the current study (85.5%). This result supports the results of other studies in Egypt (Enaba et al., 2015; Shamloul et al., 2020) and in Iran (Babahajian et al., 2019; Bazmi et al., 2020). On the other hand, some studies in the USA reported that women had been poisoned with tramadol more than men. This could be attributed to the cultural differences between Arabic and Islamic countries and the USA (Spiller et al., 1997; Marquardt et al., 2005).

Many factors could contribute to the increased incidence of tramadol use among Egyptian middle-aged men including its effect in increasing sexual pleasure and delaying ejaculation. In addition, it is an available strong pain killer that has antidepressant-like properties through its serotonin and norepinephrine reuptake inhibitory effect. Thus, tramadol is widely used to overcome the stresses of life in the Egyptian community including financial and social problems (Salem et al., 2008; Fawzi 2011; Rahimi et al., 2014; Shamloul et al., 2020).

The current study revealed that the most common cause of tramadol poisoning is addiction followed by suicidal attempts then accidental poisoning. These results are in agreement with the results reported by other

Egyptian studies (Adree et al., 2018; Shamloul et al., 2020; Tawfik and Abd El Wahab, 2020). This demonstrates the magnitude of the problem as tramadol is considered one of the most common drugs of abuse in Egypt.

This study demonstrated that all cases were intoxicated orally. This is similar to the findings reported by some studies in Egypt (Fouad et al., 2015; Rizk et al., 2016; Nasr et al., 2018). They explained this by the availability of oral forms of tramadol in the Egyptian market.

The delay time ranged from 5 to 15 hours with a median of 4 hours which is in the same line with the findings reported by Ismail et al. (2018), Babahajian et al. (2019) and Bazmi et al. (2020). However, Tawfik and Abd El Wahab (2020) reported a longer mean delay time (6.3±3.3 hours). The relatively short delay time recorded in this study could be explained by the existence of TUPCC in the middle of the Delta region with easy transportation facilities.

The ingested tramadol dose in the studied cases ranged from 125 to 4500 mg with a median of 1000 mg. This result is relatively similar to the results of Shadnia et al. (2012) and Babahajian, et al., (2019) who reported mean and median ingested doses of 1164 ± 985.2 mg and 1200 mg respectively. Ismail et al. (2018) and Tawfik and Abd El Wahab (2020) reported higher mean ingested doses (1660 ± 0.39 and 1400 ± 0.7 mg respectively).

Seizures were reported in 25 cases (40.4%) of the present study. This is in partial agreement with the results of other studies. The incidence of seizures was 46.2% in Talaie et al. (2009), 48% in Taghaddosinejad et al. (2011), and 46% in Nasr et al. (2018). Nevertheless, different seizure rates were reported by other studies. Some studies recorded higher percentages (Babahajian et al., 2019; Bazmi et al., 2020). On the other hand, other studies reported lower percentages (Ryan and Isbister, 2015; Tawfik and Abd El Wahab, 2020).

This wide range of seizure frequency could be attributed to differences in study methods, study populations, socioeconomic status, sample sizes, pattern, and dose of tramadol consumption. Moreover, tramadol is metabolized in the liver through cytochrome P-450 (mainly CYP2D6) to its active metabolite (O-dimethyl tramadol) that has serotonergic activity. Hence, genetic CYP polymorphism and racial differences play a role in tramadol-induced seizures (El-Mansoury et al., 2016; Nakhaee et al., 2019).

The type of seizures encountered in all seizing cases in this study was generalized tonic-clonic. Seizures developed within 24-hours after tramadol ingestion. Twenty-one of seizing cases (84%) had a single seizure attack. While 4 cases (16%) had recurrent attacks. Enaba et al. (2015) reported generalized tonic-clonic seizures in all their cases but the attacks were recurrent in 81% of cases. Babahajian et al. (2019) recorded generalized tonic-clonic seizures in 93.8% of their study cases and 80.4% of the cases had single seizure attacks.

No significant differences were detected between the non- seizing and seizing groups as regards age, gender, the mood of poisoning, and delay time. Similar results were reported by Rahimi et al. (2014). A significant difference was present between the two groups regarding the ingested dose of tramadol. The median ingested dose in non-seizing and seizing cases were 450mg and 1575mg respectively. Different studies reported higher doses of tramadol intake in the seizing group with significant differences between both groups (Abuelfadl et al., 2016; Rizk et al., 2016; Adree et al., 2018). Other studies reported higher doses but with non-

significant differences between both groups (Enaba et al., 2015; Babahajian et al., 2019).

The minimum ingested tramadol dose in the seizing group recorded in this study was 675 mg, which partially agrees with El-Hadidy and El-Gilany (2016) who reported 550 mg as a minimum tramadol dose inducing seizures. In contrast, other studies reported lower minimum tramadol doses able to induce seizures, 100 mg, 225 mg, and 300 mg in Talaie et al. (2009), El-Mansoury et al. (2016) and Adree et al. (2018) studies respectively. Nevertheless, the lowest recorded tramadol dose that can induce seizures was 50 mg (Pedramfar and Haghighi, 2010; Asadi et al., 2015).

In the present study, GCS ranged between 3 and 15 with a median of 13. Cases with GCS ranging between 13 and 15 accounted for 53.2% of the studied cases. This result is more or less similar to the result of Taghaddosinejad et al. (2011) who found that the mean GCS was 14 (range: 7- 15) and that most of their cases (56.3%) had a GCS of 15. No significant statistical differences were found between both groups as regards the median GCS and the severity of disturbed consciousness.

Tachycardia, hypertension, tachypnea, and fever were recorded in 79 %, 29%, 27.4%, and 21% of the studied cases. Mean O_2 saturation was 92.9 ± 6.6. No significant statistical differences were found between non- seizing and seizing cases regarding the vital signs and O_2 saturation. These findings could be attributed to catecholamines and serotonin reuptake inhibitory effects of tramadol rather than to the opioid effects of the drug (Marquardt et al., 2005; Soroosh et al., 2020).

The clinical manifestations of tramadol toxicity in the present study included headache (38.7%), vomiting (37.1%), coma (29%), agitation (33.9%), hyperreflexia (35.5%), the constricted pupil (38.7%), and respiratory distress. However, this study showed no significant statistical differences between cases with or without seizures regarding all these findings. Different studies showed the variable incidence of tramadol overdose manifestations (Ahmadimanesh et al., 2018; Murray et al., 2019; Soroosh, et al., 2020). The manifestations of tramadol poisoning vary according to several factors including ingested tramadol dose, tramadol consumption with or without other substances, and differences in pharmacokinetics and pharmacodynamics characteristics (Fouad, et al., 2015).

The normal acid-base state was recorded in 61.3% of the studied cases. Meanwhile, respiratory acidosis was the most common acid-base disturbance (16.1% of cases). These results are nearly similar to the results of Ismail, et al., (2018) who reported that a normal acid-base state was present in 58% of their cases and that respiratory acidosis was the most common acid-base disturbance they recorded (28%). On the other hand, Tawfik and Abd El Wahab, (2020) reported that a normal acid-base state was present in 43% of their cases. Additionally, they reported a higher incidence of respiratory acidosis (33%) which was also the most common acid-base disturbance. Respiratory acidosis could be attributed to reduced medullary chemo-receptors sensitivity to hypercapnia caused by opioid agonists that leads to diminished ventilation. Furthermore, opioids also decrease the ventilatory response to hypoxia. The combined loss of both hypercarbic and hypoxic drives leaves no stimulus to breathe and apnea may follow (Nelson and Olsen, 2015).

The median tramadol blood level in the present study was 550 ng/ml. In addition, the median tramadol blood level was significantly higher in the seizing group than the non-seizing group (1100 vs 300 ng/ml). These

results partially coincide with the results of Abuelfadl, et al., (2016) who reported a mean tramadol blood level of 661ng/ ml with a significantly higher mean blood level in the seizing group. Nasr et al. (2018) reported a mean tramadol blood level of 614ng/ ml but with no significant difference between seizing and non- seizing groups. A higher mean tramadol blood level of 2950 ng/ ml was reported by Ahmadimanesh, et al., (2018) with a significant difference between both groups. Furthermore, Tawfik and Abd El Wahab, (2020) reported a high mean tramadol blood level (1800ng/ ml) but with no significant difference between both groups.

The administered dose of naloxone ranged between 0 and 10.8 mg with a median of 1.4 mg. The seizing group received a higher median dose of naloxone than the non-seizing group, but the difference was statistically non-significant. While El-Sarnagawy and El-Gharbawy (2016) reported that the median administered dose of naloxone was 2.4 mg and that the seizing group received a significantly higher dose than the non- seizing group. Naloxone is a pure competitive opioid antagonist without any agonist effects. It is indicated in cases of opioid overdose accompanied by CNS depression or respiratory depression (Nelson and Howland, 2015). The seizureogenic effect of naloxone in cases of tramadol overdose is controversial. Farzaneh et al. (2012a) and Farzaneh et al. (2012b) concluded that naloxone use in the management of tramadol overdose can increase the risk of seizure occurrence. On the other hand, Eizadi-Mood et al. (2014) and Hussien and Elguindy (2017) reported that naloxone reduced the incidence of seizures in tramadol overdosed cases.

Intubation and MV was indicated in 22.6% of the studied cases. This is similar to the results of Tawfik and Abd El Wahab (2020) who reported that 20% of their study cases needed to be intubated and mechanically ventilated. Meanwhile Adree, et al. (2018) reported a lower incidence of the need for intubation and MV (13.7%). Non-significant statistical difference was found between both groups as regards the need for intubation and MV

The duration of hospital stay in this study ranged from 1 to 60 hours with a median of 7 hours. This result partially agrees with the results of Ismail et al. (2018). But this duration was shorter than the mean hospitalization period reported by Ghasempouri et al. (2014). Also, no significant difference was found between both groups regarding the hospitalization period and this is by Shadnia et al. (2012).

A check for the correlations between the occurrence of seizures and different variables was done. It revealed that only the ingested tramadol dose and the tramadol blood level had a significant strong positive correlation with the occurrence of seizures. In the same line with these results El-Mansoury et al. (2016) detected a significant positive correlation between seizure occurrence and the tramadol dose but this correlation was moderate. On the other hand, Abd-Elwahab (2012) found no significant correlation between tramadol blood level and seizure occurrence.

Analysis of ROC curve showed excellent discriminatory power of ingested tramadol dose for predicting seizure occurrence in acute tramadol poisoning (AUC =0.951), at cut-off value >1100 mg, 88.00% sensitivity, and 89.20% specificity. These results are supported by some studies (Sun et al., 2007; Babahajian et al., 2019; Soroosh et al., 2020). These studies revealed an increased frequency of seizures with higher tramadol doses and suggested that seizures are dose-dependent in tramadol overdose. On the contrary, other studies reported that seizures are unlikely to be dosedependent in tramadol

overdose (Talaie et al., 2009; Habibollahi et al., 2019). The reason for this discrepancy could be attributed to drug dependence and tolerance. Also, the purity and concentration of active ingredients in various tramadol formulations cause differences in pharmacokinetics and pharmacodynamics properties (Vazzana et al., 2015; Bazmi et al., 2020).

Analysis of ROC curve of tramadol blood level for predicting seizure occurrence in acute tramadol poisoning demonstrated that tramadol blood level had excellent AUC =0.993 with 92.00% sensitivity and 100.00% specificity at cut-off value > 710 ng/ml. In the study done by Abuelfadl et al., (2016), the analysis of the ROC curve of blood tramadol level for prediction of seizures revealed a fair AUC of 0.738 at a cut off value >600 ng/ml, with sensitivity of 73.91% and a specificity of 74.91%. The discriminatory power of tramadol blood level is better than that of the ingested tramadol dose but there is no significant statistical difference between their AUCs.

Conclusion and recommendations:

Based on the findings of the current study, acute tramadol poisoning is associated with an increased risk of developing seizures. The ingested tramadol dose and the tramadol blood level have significant strong positive correlations with seizure occurrence. In addition, both have an excellent discriminatory power for the prediction of seizures, but that of tramadol blood level is better. Each one of them has good and bad criteria. The ingested tramadol dose is easy to be calculated and does not cost any money but is not reliable as it is based on the history reported by the patient or his/ her proxy. On the other hand, the tramadol blood level costs time and money but it is reliable. Hence, we recommend using either of them in the prediction of TIS according to the situation and each case circumstances. In addition, it is recommended to increase social awareness about the dangers of tramadol abuse particularly among youth and athletes in gyms.

Limitations:

One of the limitations of the current study could be related to the small sample size as per being a single-center study. Hence, we suggest future larger multicenter studies. Another limitation was the estimation of ingested tramadol dose, which was determined based on patient self-reporting, which is subjective and unreliable.

Conflict of interest:

The authors declare that they have no conflict of interest.

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التسمم الحاد بالترامادول؛ تقييم عوامل الخطر التي تهيئ لنوبات التشنج وإيجاد علاقة مع مستوى الترامادول بالدم

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يذكر ان نوبات التشنج تحدث في ١٥٪ -٣٥٪ من حالات التسمم بالترامادول. تهدف الدراسة الحالية إلى تقييم عوامل الخطر لنوبات التشنج الناتجة عن الترامادول ومعرفة ما إذا كان هناك ارتباط بينها وبين الجرعة المتعاطاة وبينها وبين مستوى الترامادول في الدم وقد تضمنت هذه الدراسة حالات من كلا الجنسين مصابين بتسمم حاد بالترامادول تم إدخالهم إلى مركز طنطا الجامعي لعلاج حالات التسمم في الفترة من يناير ٢٠١٩ إلى ديسمبر ٢٠١٩. وقد خضعت كل حالة لأخذ التاريخ والتقييم السريري والمختبري بما في ذلك فحص البول للكشف عن وجود الترامادول وتقدير مستوى الترامادول في الدم عند الدخول. تم تسجيل اثنين وستين حالة في الدراسة. كان متوسط أعمارهم ٢٨,٣± ٩,٦ عام، ٨٥,٥٪ منهم من الذكور، وكان الإدمان هو الطريقة الأكثر شيوعًا للتسمم. تم تسجيل نوبات التشنج في ٤٠,٤٪ من الحالات. كان هناك فارق ذو دلالة إحصائية بين المجموعة التي لم يحدث بها نوبات تشنج والمجموعة التي حدث بها نوبات تشنج فيما يتعلق بجرعة الترامادول المتعاطاة ومستوى الترامادول في الدم. علاوة على ذلك، كان هناك ارتباط إيجابي قوي ذو دلالة إحصائية بين جرعة الترامادول المتعاطاة ومستوى الترامادول في الدم وبين حدوث نوبات التشنج. كشف تحليل منحنى روك أن كلاهما يتمتع بقوة تمييزية ممتازة في التنبؤ بحدوث النوبات، لكن مستوى الترامادول في الدم كان له معدل انحدار لوجيستي أفضل. وقد استنتج ان التسمم الحاد بالترامادول يرتبط بزيادة خطر الإصابة بنوبات التشنج. ويمكن استخدام جرعة الترامادول المتعاطاة ومستوى الترامادول في الدم كمتنبئين ممتازين لنوبات التشنج في حالات الجرعات الزائدة من الترامادول.