Journal of Clinical Toxicology
ISSN: 2161-0495

Fouad et al., J Clin Toxicol 2015, 5:3
DOI: 10.4172/2161-0495.1000249

Research Article Open Access

Critical Score as a Predictor for Progression of Tramadol Intoxication

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Received date: 9 April, 2015; **Accepted date:** 14 May, 2015; **Published date:** 20 May, 2015

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Abstract

The rate of tramadol abuse in Egypt is becoming disastrous in spite of adding it to the narcotics list by the Egyptian government in the recent years. This study aims to construct a predictive model for acute tramadol intoxicated cases. This study was conducted on tramadol intoxicated patients attending the emergency department of the Poison Control Center (PCC), Ain Shams University hospitals during the period from 1/10/2010 to 30/9/2011. All the patients were subjected to history taking, clinical examination, laboratory investigations, electrocardiography (ECG) and calculation of the APACHE II score. The current study constructs and assesses a new score for prediction of prognosis of tramadol intoxicated patients from clinical and laboratory results obtained from the most predictive parameters affecting the APACHE II score and the most important variables that differentiate best between the studied groups. The area under the ROC curve for the predictive score was 0.996, the best cut-off point was 26 with a sensitivity of 98.46% and specificity of 95.62%.Conclusion: patients with predictive score >26 on admission considered as mild cases while patients with predictive score<26 on admission considered as moderate or severe cases.

Keywords: Critical; Score; Predictor; Progression; Tramadol; Intoxication

Introduction

Tramadol is a widely used, synthetic centrally acting opioid analgesic for the treatment of moderate to severe pain. It has a weak μ-receptor agonist activity that blocks the pain pathways as well as the inhibition of the reuptake of the biogenic amines especially serotonin and norepinephrine in central nervous system [1]. It was approved for marketing as a non controlled analgesic in 1995 under the trade name of Ultram® [2]. Although tramadol was generally considered to be devoid of any serious adverse effects of traditional opioid receptor agonists, such as respiratory depression and drug dependence; recently, abuse and dependence as well as toxicity and deaths have been increasingly reported as it is the only clinically available nonscheduled opioid in most countries [3-5]. Tramadol overdose became one of the most common causes of drug poisoning in the recent years, especially in male young adults with history of substance abuse [6]. Oral route is the most common route of toxicity due to its availability in pharmacies. Toxicity can happen to those who take therapeutic doses of the drug as well as those who abuse it [7,8]. Several deaths have been reported when tramadol was ingested alone in overdose or with others drugs, particularly the central nervous system (CNS) depressants like benzodiazepine and also in ultrarapid metabolizers. The usual causes of death related to tramadol ingestion include cardiorespiratory depression, refractory shock, asystole and even severe hepatic failure [9-11]. The clinical manifestations of tramadol toxicity can vary from person to person. It depends on many factors including how an individual's body responds to the drug, how much was taken and whether it was taken in combination with any other substances or not [12]. The main signs of tramadol intoxication include seizures which may be followed by extreme drowsiness progressing to coma with respiratory depression, cold clammy skin, cardiac arrest and death [8]. The recently published data have shown an important increase in tramadol poisoning which is still constitutes a major challenge for hospitals and poisoning centers [13]. Standardized diagnostic pathways may be helpful in reducing the risk of false or delayed admissions to the ICU in tramadol intoxicated patients [14].The overall prognosis of patients admitted to ICU directly from emergency departments is better than the prognosis for those admitted to the ICU from general wards and the delayed recognition of critically ill patients increases the risk of cardiopulmonary arrests and death in the intensive care unit (ICU) [15,16]. Patients with intoxication are seen first in the emergency departments (ED) so evaluation of these patients and assessment of their status are mandatory and this needs a good scoring system for analyzing patient status to be beneficial in predicting their prognosis [13].

	Group I (n=73)	Group II (n=64)	Group IIIa (n=56)	Group IIIb (n=9)	F-value	p-value
	M ± SD	M ± SD	M ± SD	M ± SD		
Delay time (hr)	3.44 ± 1.96[a]	3.72 ± 2.18[a]	4.69 ± 0.54[ab]	6.00 ± 1.67[b]	3.115	0.027[*]

Dosage (mg)	837.67 ± 568.35[a]	1350.78 ± 954.97[a]	1439.29 ± 804.49[a]	2856.25 ± 826.23[b]	10.88	0.000*
Systolic blood pressure (mmHg)	142.05 ± 22.91[b]	134.22 ± 29.64[b]	130.89 ± 31.23[b]	92.50 ± 13.72[a]	7.93	0.000*
Diastolic blood pressure (mmHg)	92.6 ± 14.72[b]	88.13 ± 19.75[b]	86.43 ± 19.39[b]	57.50 ± 9.59[a]	9.07	0.000*
Mean artereial pressure (mmHg)	109.05 ± 17.27[b]	104.16 ± 22.55[b]	101.20 ± 22.95[b]	69.78 ± 23.45[a]	9.24	0.000*
Respiratory rate (breath/minute)	16.74 ± 1.99[b]	17.33 ± 1.92[b]	11.71 ± 5.60[a]	32.11 ± 2.14[c]	49.236	0.000*
Temperature (°C)	37.32 ± 0.29[a]	37.37 ± 0.35[a]	37.34 ± 0.837[a]	38.56 ± 1.45[b]	11.27	0.000*

M: Mean; SD: Standard Deviation

*There is a significant difference by using One Way ANOVA at p<0.05

The same letter means that there is no significant difference between the two groups by using Duncan multiple comparison test at p<0.05

The different letters mean that there is a significant difference between the two groups by using Duncan multiple comparison test at p<0.05

Group I: Patients in Emergency Room (ER) and discharged

Group II: Patients admitted to inpatient unit

Group IIIa: Patients admitted to intensive care unit (ICU) and survived

Group IIIb: Patients admitted to intensive care unit (ICU) and died

Table 1: Comparison between studied groups as regards delay time (hours), dosage of tramadol taken (mg) and vital data.

Material and Methods

This prospective study was conducted on tramadol intoxicated patients attending the emergency department of the Poison Control Center (PCC), Ain Shams University hospitals during the period from 1/10/2010 to 30/9/2011.An informed consent was obtained from each patient or from his/her relatives for inclusion in the study.

ABG	Group I (n=73)	Group II (n=64)	Group IIIa (n=56)	Group IIIb (n=9)	F-value	p-value
	M ± SD	M ± SD	M ± SD	M ± SD		
pH	7.39 ± 0.03[d]	7.29 ± 0.06[c]	7.19 ± 0.19[b]	7.11 ± 0.20[a]	40.59	0.000*
$PaCO_2$ (mmHg)	38.69±0.04[a]	40.9 ± 10.14[a]	44.20 ± 13.69[a]	57.00 ± 12.93[b]	10.45	0.000*
HCO_3^- (mmol/L)	23.13 ± 1.68[c]	19.68 ± 5.18[b]	16.41 ± 7.62[a]	16.72 ± 7.25[a]	18.47	0.000*
Glucose (mg/dl)	89.10 ± 18.89[a]	86.19 ± 26.77[a]	142.86 ± 68.8[b]	159.00 ± 35.08[b]	19.38	0.000*
Na (meq/l)	137.34 ± 3.72[a]	138.39 ± 26.50[a]	138.20 ± 5.78[a]	135.78 ± 12.90[a]	0.80	0.495
K (meq/l)	3.66 ± 0.30[b]	3.53 ± 0.39[b]	2.97 ± 0.24[a]	4.42 ± 1.75[c]	37.158	0.000*
Aspartate Aminotransferase (AST) (U/l)	20.38 ± 6.87[a]	21.83 ± 8.26[a]	36.09 ±10.97[b]	86.22 ± 29.45[c]	76.56	0.000*

Alanine transaminase (ALT) (U/l)	9.37 ± 4.50[a]	10.63 ± 5.54[a]	24.11 ± 9.54[b]	72.56 ± 23.43[c]	104.12	0.000*
Bilirubin (mg/dL)	0.78 ± 0.86[a]	0.66 ± 0.15[a]	0.68 ± 0.25[a]	0.82 ± 0.46[a]	0.69	0.554
Urea (mg/dL)	27.42 ± 7.21[a]	28.63 ± 7.66[a]	31.59 ±12.68[a]	92.78 ± 27.35[b]	105.23	0.000*
Creatinine (mg/dl)	0.73 ± 0.27[a]	0.76 ± 0.26[a]	0.91 ± 0.25[b]	2.11 ± 0.43[c]	71.22	0.000*
Creatine phosphokinase (CPK) (IU/L)	59.88 ± 4.98[a]	58.95 ± 5.91[a]	130.91 ± 10.41[b]	525.33 ± 186.72[c]	142.29	0.000*
Creatine kinase MB (CK-MB) (U/L)	16.46 ± 7.86[a]	13.94 ±7.51[a]	31.00 ± 10.85[b]	123.56 ± 10.40[c]	440.366	0.000*
Hematocrit value (%)	38.23 ± 2.77[a]	39.978 ± 5.10[ab]	42.06± 5.64[b]	48.06 ± 9.57[b]	14.63	0.000*
Total leucocyte count (10^3/mm)	8.593 ± 2.96[a]	9.283 ± 3.55[a]	16.25 ± 6.54[b]	17.58 ± 4.07[b]	44.30	0.000*

Table 2: Laboratory parameters of studied groups.

Exclusion criteria: Age under 15 years of both sexes was excluded as APACHE II has not been validated for use in children or young people aged under 15 due to difference in its parameters. Patients with renal, hepatic, cardiovascular or respiratory diseases were excluded from the study to avoid the effect of these diseases on the results obtained. This was known from detailed history obtained from patients and was confirmed by clinical examination. The patients with history of epilepsy were also excluded. Co-administration of benzodiazepines, barbiturates, alcohol, cannabis or opiates with tramadol was excluded from the study. Pregnant females were also excluded to avoid the effect of pregnancy on the laboratory parameters obtained.

Groups	**Group I (n=73)**	**Group II (n=64)**	**Group IIIa (n=58)**	**Group IIIb (n=9)**	**F-value**	**p-value**
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**		
APACHE II Score	3.38 ± 1.32[a]	8.06 ± 1.78[b]	16.23 ± 3.99[c]	35.67 ± 6.1[d]	498.51	0.000*

M: Mean; SD: Standard Deviation

*There is a significant difference by using One Way ANOVA at p<0.05

The same letter means that there is no significant difference between the two groups by using Duncan multiple comparison test at p<0.05

The different letters means that there is a significant difference between the two groups by using Duncan multiple comparison test at p<0.05

Group I: Patients in Emergency Room (ER) and discharged

Group II: Patients admitted to inpatient unit

Group IIIa: Patients admitted to intensive care unit (ICU) and survived

Group IIIb: Patients admitted to intensive care unit (ICU) and died

Table 3: Comparison between studied groups as regards the APACHE II score.

The patients were classified according to their pattern of management in the Poison Control Center (PCC) of Ain Shams University Hospital into three groups: Group I (Emergency department cases): Patients discharged from the hospital after clinical assessment and observation for 4-6 hours. Group II (Inpatient cases): Patients admitted to the inpatient unit. Group III {Intensive Care Unit (ICU) cases}: this group represents patients admitted to the Intensive Care Unit. Patients of this group are subdivided according to their outcome into two subgroups: Group IIIa: Patients admitted to Intensive Care Unit (ICU) and survived. Group IIIb: Patients admitted to Intensive Care Unit (ICU) and died.

Independent variables	Coeffecients B	Std.Error	T-test		F-test		R^2%
			Value	p-value	Value	P value	
Constant	9.930	17.948	0.553	0.581	211.198	0.000*	88.50
Mean arterial pressure	0.023	0.007	3.217	0.002			
Glascow coma score (GCS)	-1.481	0.093	-15.942	0.000			
pH	-5.802	2.206	-2.630	0.009			
Serum creatinine	2.977	0.574	5.185	0.000			
Total leukocyte count	0.118	0.044	2.660	0.008			
*p<0.05							

Table 4: The multiple linear regression model for the dependent variable (APACHE II score) with different independent variables.

Every selected patient was subjected to the following: a) History taking including personal history. b) Clinical examination including general and systemic examination. c) Investigations include Electrocardiography (ECG), arterial blood gases (pH, $HCO3^-$, PaO2 and PaCO2), routine investigations (Serum glucose, Na, K), renal profile (BUN, serum creatinine), hepatic profile {Aspartate Aminotransferase (AST), Alanine transaminase (ALT) and serum bilirubin}, CBC {white blood cells (WBCs), hematocrit value}, Creatine phosphokinase (CPK) and Creatine kinase MB (CK-MB) levels. d) Calculation of APACHE II score for all patients was done.

	Eigenvalue	% of Variance	Canonical Correlation	Wilks' Lambda	Chi-square	df	P-value
Function	35.648	71.9	0.986	0.188	1469.50	39	0.000

Table 5: Summary of canonical discriminant function.

Statistical analysis: Data were collected, checked, revised and analyzed by SPSS statistical package version 19. Excel computer program was used to tabulate the results, and represent it graphically. One Way ANOVA was used to declare the significant difference between groups at $p<0.05$ for the quantitative variables. Variables required for calculating the APACHE II score were collected for each patient and entered into a computer program designed to provide an estimate. Qualitative variables were expressed as count and percentages. Chi-square test for distribution was used to show the significant difference between study groups at $p<0.05$. Multiple linear Regression was used for getting the most predictive parameters affecting the APACHE II score. Discriminant analysis was done to identify the variables (clinical and laboratory) in tramadol intoxication that best discriminate patients in ER, patients in inpatient unit and patients in ICU (survived and none survived).A new score for prediction of prognosis of tramadol intoxicated patients was constructed from clinical and laboratory results obtained from the most predictive parameters affecting the APACHE II score by the multiple linear regression in addition to the most important variables that differentiate best between the studied groups obtained from the discriminant analysis. The ability and the accuracy of this score to predict the prognosis of tramadol intoxicated patients was assessed and evaluated by the ROC curve analysis.

Results

In this prospective study, a total of 202 patients met our inclusion criteria and were enrolled into the study. Group I (Emergency department cases) was 73 patients who were assessed clinically and observed for 4-6 hours then discharged from the hospital. Group II (Inpatient cases) was 64 patients. Group III {Intensive Care Unit (ICU) cases} consisted of 65 patients who were subdivided according to their outcome into two subgroups: Group IIIa (56 patients): Patients admitted to Intensive Care Unit (ICU) and survived. Group IIIb (9 patients): Patients admitted to Intensive Care Unit (ICU) and died.

Age and sex

Age of the patients ranged from 16 to 69 years with mean age between 28.84 and 34.97 years with non-significant difference between studied groups. Males represented the majority of cases (78.7%) while females represented (21.3%).

Delay time, dosage taken, manner of poisoning and vital data

Table (1) shows that the mean delay time for reaching hospital was between 3.44 hours and 3.72 hours in group I and II while it was between 4.69 hours and 6.00 hours in group IIIa and IIIb. The mean dosage of tramadol taken ranged between 837.67 mg (group I) and 2856.25 mg (group IIIb). The majority of patients (81.7%) were addict

on tramadol and showed accidental toxicity, 15.8% attempted suicide and only 2.5% due to iatrogenic manner. Duration of hospitalization of patients ranged between 1 to 6 days with most of them discharged within 1-2 days. Regarding vital data, almost all studied patients had tachycardia. There was non-significant difference between group I, II and IIIa regarding systolic and diastolic blood pressure as well as the mean arterial pressure while there was significant decrease in group IIIb. Respiratory rate was within normal range in patients of group I and II while it was decreased in patients of group IIIa and increased in patients of group IIIb. Group IIIb showed significant increase in body temperature when compared with group I, II and IIIa.

	Group I	Group II	Group IIIa	Group IIIb
	(n=73)	(n=64)	(n=58)	(n=9)
Manner of poisoning	16.339	19.601	17.892	19.493
Respiratory rate	1.326	1.22	-1.846	-2.275
Cyanosis	-2.088	2.461	34.335	37.338
Respiratory Failure	76.065	83.579	158.732	172.147
Pulmonary oedema	-17.5	-21.211	-12.361	-21.351
Shock	-13.609	-10.278	2.873	27.773
Cardiac arrest	141.146	132.046	127.259	233.208
Seizure	-49.094	-19.704	-12.998	-16.039
Coma	-11.506	-2.573	8.586	6.653
ST segment changes	49.829	66.426	87.721	121.984
pH	623.242	607.869	606.527	608.071
$HCO3^{-}$	0.235	-0.031	0.321	0.668
K	25.061	23.154	18.848	25.04
Alanine transaminase (ALT)	-0.174	-0.136	-0.127	0.279
Creatine kinase MB (CKMB)	-1.1	-1.159	-0.897	0.145
(Constant)	-2367.5	-2275.8	-2305.2	-2541.7

Table 6: Classification function coefficients of discriminant analysis.

General manifestations

As regards skin examination, sweating was found in more than half of patients of group I (54.8%), 46.9% of group II and most of patients of group IIIa and IIIb (75% and 66.7% respectively). Cyanosis was seen in about all patients of group IIIa and IIIb while it was not observed in any patient of group I or II. Regarding the pupil size, miosis was observed in most of patients of group IIIa and IIIb while mydriasis was observed in less than half of patients of group II (45.3%) and IIIb (44.4%).

Systemic manifestations

Examination of the respiratory system revealed respiratory failure which occurs in most of patients of group III a (94.6%) and all patients of group IIIb (100%). Pulmonary oedema was observed in all patients of group IIIb (100%) and 21.4% of group IIIa. Regarding the cardiovascular system, most of the studied patients had minor cardiovascular effects such as palpitation which occurred in 47.94% of patients of group I, 75% of group II and 41.1% of group IIIa. On the other hand, severe cardiovascular effects such as shock and cardiac arrest occurred in patients of group IIIa and IIIb as 7.1% of group IIIa and 77.8% of group IIIb suffered shock while 33.3% of patients of group IIIb presented with cardiac arrest.

Concerning the gastrointestinal manifestations, almost all cases of group I, II and about half of cases of group IIIa suffered nausea. Vomiting occurred in all patients of group II and most of patients of group I, IIIa and IIIb. Regarding the neurological manifestations, headache occurred in near half of patients of group I, II and IIIa. Dizziness was observed in 24.7% of group I and 45.3% of group II. Agitation was noticed in most of patients of group I, II and about half of group IIIa. All patients of group II (100%), 85.7% of group IIIa and 44.4% of group IIIb had seizures. As regards coma, none of patients of group I presented with it which was seen in more than half of patients of group II and all patients of group IIIa and IIIb and it was commonly grade I. The mean glascow coma score (GSC) was between 13.91 and 14.95 in group I and II while it was between 3.00 and 8.76 in group IIIa and IIIb.

Parameter	Score
Manner of poisoning	
Therapeutic error	3
Addiction	2
Suicidal	1
Blood pressure	
Normal (110-135/65-85 mmHg)	3
Hypertension (>140/90 mmHg)	2
Hypotension (BP<90/60 mmHg)	1
Respiratory rate	2

Normal (12-24breath/min)	
Bradypnea (<12 breath/min) or Tachypnea>24 breath/min)	1
Cyanosis	
Absent	2
Present	1
CNS manifestations	
a)Seizure	
Absent	2
Present	1
b)Coma	2
Absent	
Present	1
Cardiovascular complications	
a)Shock	
Absent	2
Present	1
b)Cardiac arrest	
Absent	2
Present	1
Pulmonary complications	
a)Respiratory failure	
Absent	2
Present	1
b) Pulmonary edema	
Absent	2
Present	1
Ischemic changes	
Absent	2
Present(elevated or depressed ST segment, flat or inverted T wave, deep Q)	1
pH	
7.35-7.45	3
7.23-7.34	2
<7.23	1
$HCO3^{-}$	
22-24 mmol/l	3
15-21.9 mmol/l	2

<15 mmol/l	1
Serum K	
3.5-5 meq/l	2
<3.5 meq/l or >5 meq/ l	1
Serum createnine	
0.6-1.4 mg/dl	2
>1.4 mg/dl	1
Alanine Aminotransferase (ALT)	
5-56 U/L	2
>56 U/L	1
White blood cell count	
4,500 - 10,000 mm3	2
>10000 mm3	1
Creatine kinase MB (CK-MB)	
Up to 24 U/L	2
>24 U/L	1
Total Maximum	**40**
Minimum	**18**

Table 7: predictive Score for progression of tramadol intoxication.

Laboratory parameters

Table (2) shows the values of laboratory parameters of studied groups. Arterial blood gas analysis (ABG) revealed metabolic acidosis in patients of group I and II while mixed metabolic and respiratory acidosis was observed in severe cases (group IIIa and IIIb).Serum glucose was within the normal range for patients of group I and group II while it was slightly increased in patients of group IIIa and IIIb where half of studied patients (50%) had normal glucose level, 31.2% had hyperglycemia and only 18.8% of patients had hypoglycemia. As regards serum Na, it was within the normal range in almost all studied patients. On the other hand, serum potassium was within the normal range in patients of group I and II while it was decreased in patients of group IIIa and increased in patients of group IIIb. As regards liver function tests, Aspartate Aminotransferase (AST) and Alanine transaminase (ALT) were within the normal range for patients of group I and II while they were increased in patients of group IIIa and IIIb. Regarding kidney function tests, serum urea was within the normal range for patients of group I, II and IIIa while it was increased in patients of group IIIb. Serum creatinine was within the normal range for patients of group I and II while it was increased in patients of group IIIa and IIIb. Creatine phosphokinase (CPK) and Creatine kinase MB (CK-MB) levels were within normal levels in patients of group I and II while they were slightly increased in patients of group IIIa and markedly increased in group IIIb. The total leukocyte count was within the normal range for patients of group I and II while it was increased in patients of group IIIa and IIIb. The hematocrit value was within normal value in patients of group I and II while it was slightly increased in patients of group IIIa and IIIb.

Electrocardiographic changes (ECG)

Most of patients had sinus tachycardia (56.9%), 37.1% had prolonged QTc, 1.5% had elevated ST segment, 3% had depressed ST segment and 3% of patients had inverted T wave.

APACHE II score: It was calculated to all studied patients as an emergency score. Table (3) shows the APACHE II score of studied groups. Group IIIb showed statistically significant nadir score (recorded to be 35.67) when compared with group I, II and IIIa.

Multiple linear Regression analysis: Multiple linear Regression analysis was used for getting the most predictive parameters affecting the APACHE II score. Table (4) shows that out of the 14 parameters which constituted the APACHE II score, mean arterial pressure, serum creatinine, pH, total leukocyte count and glascow coma score (GSC) were more often disturbed in patients who had a complicated outcome by multiple linear regression statistical analysis.

Discriminant Analysis: It determines which variables (clinical and laboratory) discriminate best between the studied groups. Table (5) shows the summary of the discriminant function. The discriminant function has Eigenvalue of 35.648 and accounts for 71.9 percent of the variance. The Wilks' Lambda which evaluates the statistical significance of the discriminatory power of the discriminant function was 0.188 with canonical correlation of 0.986, Chi-square of 1469.50 and degree of freedom (df) of 39. The discriminant function is

statistically significant in differentiating between the four studied groups.

Table (6) shows that by using discriminant analysis, the current study has discovered 15 variables, which best discriminate between the four studied groups. These variables are manner of poisoning, respiratory rate, cyanosis, respiratory failure, pulmonary oedema, shock, cardiac arrest, seizures, coma, ST segment changes, pH, $HCO3^-$, K, Alanine transaminase (ALT) and Creatine kinase MB (CK-MB).

Construction of a predictive score: The current study constructs and assesses a new score for prediction of prognosis of tramadol intoxicated patients from clinical and laboratory results obtained from the most predictive parameters affecting the APACHE II score by the multiple linear regression and the most important variables that differentiate best between the studied groups obtained from the discriminant analysis.

Table (7) shows The predictive score which depends on manner of poisoning, blood pressure, respiratory rate, skin manifestations (cyanosis), CNS manifestations (coma and seizures), cardiovascular manifestations (shock and cardiac arrest), pulmonary manifestations (respiratory failure and pulmonary edema) and ECG findings (ischemic changes as elevated or depressed ST segment, flat or inverted T wave, deep Q). In addition to investigational parameters which are simple, routine and readily available in most hospitals {pH, HCO^{3-}, serum K, createnine, Alanine transaminase (ALT), total leukocyte count and Creatine kinase MB (CK-MB)}.

The ability and the accuracy of this score to predict the prognosis of tramadol intoxicated patients was assessed and evaluated by the ROC curve analysis. The area under the ROC curve for the predictive score was 0.996, the best cut-off point was 26 with a sensitivity of 98.46% and specificity of 95.62%. It means that if the patient has score <26, the patient condition is moderate or severe and if it was ≥26, the patient condition is mild.

Discussion

Tramadol abuse became a disastrous problem in the Egyptian community in spite of adding it to the narcotics list by the Egyptian government. This problem is increasing due to its lower price, illegal transactions and availability without prescription either with fake prescriptions from pharmacies or on the black market [10,17]. Several fatal incidents have drawn attention toward its underestimated toxicity despite of the general attitude about its safety [18].

According to records from the Poison Control Center of Ain Shams University Hospitals (PCC) of Egypt; 190, 376 and 691cases of tramadol toxicity were admitted in the years 2008, 2009 and 2010 respectively. This crescendo highlights the rising of this type of toxicity (records from PCC).The incidence of tramadol poisoning has over increased during the time of the current study. In the period between October 2010 and September 201, 1020 patients presented to PCC with tramadol intoxication of which 202 cases met our inclusion criteria were enrolled in the study [19-24].

As regards the results of the current study, the mean APACHE II Score in group III b showed statistically significant highest worse score (recorded to be 35.67) when compared with group I, II and III a. This significantly higher mean APACHE II score with 100% deaths agrees with Abbott et al., 1991; Chen et al., 1993; Chiavone & Sens, 2003 and Gupta& Arora, 2004; as these studies reported nonavailability of survivors above APACHE II score of 40 and patients with APACHE II scores of 35 or higher in ICUs had a 100% hospital mortality rate. A study by Chen et al., 2007 found that the post-ICU non survivors had greater severity of illness on admission with a mean admission APACHE II score of 22.9 ± 5.5, compared to 18.6 ± 6.1 for post-ICU survivors. Haidri et al., 2011 demonstrated that the mean APACHE II score of patients who were successfully discharged from ICU has lower score as compared to patients who died.

Out of the 14 parameters which constituted the APACHE II score, mean arterial pressure, serum createnine, pH, total leukocytic count and Glascow coma score were more often disturbed in patients who had a complicated outcome. The Glasgow coma score and serum createnine had the maximum significance clearly indicating that glascow coma score (GCS) and serum createnine played an important role in mortality prediction for the patients in this study.

The severity scoring systems are needed to assess quality of care, treatment efficacy, reducing health care cost, providing better care, and improving outcomes. The prediction of patient outcome was useful in prognosis, decision making for treatment withdrawal, cost benefit analysis, comparison between different centers, monitoring and assessment of new therapies [15,25,26]. A major limitation of scoring system is their dependence on sophisticated investigations. Such investigations may not be easily available in any hospital therefore there is a need for a simple prognostic scoring system which can be used easily for patients with tramadol intoxication [27].

From the current study, it could be noticed that the clinical course of tramadol intoxication may vary from a mild self-limiting to a life-threatening. Patients whose condition progresses to severe may require intensive therapy and such treatment may require admission to ICU. Therefore determination of the severity for patients with acute tramadol intoxication is critical. Previous clinical approaches to this problem have required the collection of a large amount of clinical and laboratory data to derive prognostic scores such as the APACHE II score. Such a system would require the collection and storage of a large number of data points, which might limit its practical use. Recent modifications to the scoring systems have explored approaches in which fewer data points are used [16].

It is necessary for every intensive care unit to have a prediction system which is validated for its specific kind of patients because of the differences between intensive care unit patients [21].

The aim of the present study is to construct a score able to accurately predict a severe outcome in tramadol intoxicated patients on admission (in the Emergency Department), using routine and easily measured parameters which are available in any hospital. This score can be a useful tool to select on admission the patients with a high risk of developing severe manifestations and who need to be hospitalized in the Intensive Care Unit (ICU). The current study constructs and assesses a new score for prediction of prognosis of tramadol intoxicated patients from clinical and laboratory results obtained from the most predictive parameters affecting the APACHE II score by the multiple linear regression and the most important variables that differentiate best between the studied groups obtained from the discriminant analysis.

This predictive score depends on manner of poisoning, blood pressure, respiratory rate, skin manifestations (cyanosis), CNS manifestations (coma and seizures), cardiovascular manifestations (shock and cardiac arrest), pulmonary manifestations (respiratory failure and pulmonary edema) and ECG findings (ischemic changes as

elevated or depressed ST segment, flat or inverted T wave, deep Q). In addition to investigational parameters which are simple, routine and readily available in most hospitals {pH, $HCO3^-$, serum K, createnine, Alanine transaminase (ALT), total leukocyte count and Creatine kinase MB (CK-MB)}.The area under the ROC curve for the predictive score was 0.996, the best cut-off point was 26 with a sensitivity of 98.46% and specificity of 95.62%.

Conclusion

The predictive score of the present study is considered to be specific and sensitive and it can be used for prediction of outcome and rapid initiation of appropriate therapy in the emergency department for lowering hospital morbidity and mortality in tramadol intoxicated patients and it may be helpful in reducing the risk of false or delayed admissions to the ICU in these patients. It can be assessed soon at emergency department, is quick and easy to use and applicable even in small hospitals.

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