

# Assessment of the Role of Naloxone in the Prognosis of Tramadol Intoxicated Patients

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Received date: September 25, 2017; Accepted date: November 03, 2017; Published date: November 10, 2017

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## Abstract

**Background:** Tramadol is opioid analgesic which acts on the central nervous system. Most of clinicians may not routinely consider naloxone for tramadol cases because of risks of inducing seizures.

This study aims to evaluate the effect of naloxone in the prognosis of patients with tramadol intoxication and its role in inducing seizures.

**Methods:** This study included both prospective and retrospective studies. The prospective study involved 30 patients with tramadol intoxication admitted to the poison control center during the year of 2015 who received naloxone while the retrospective study involved 30 patients with tramadol intoxication admitted to the poison control center during the years of 2011-2012 who didn't receive naloxone.

**Results:** The studied patients were in the age 16-60 years range with male predominance (75%). Most of patients (65%) were tramadol addict. The mean delay time was  $3.32 \pm 1.50$  hours while the dose of ingested tramadol among studied patients was  $1439.29 \pm 804.49$  mg. The most common symptom on admission among studied patients was sweating (66.7%), cyanosis (61.7%) and bradypnea (60%). The seizure was significantly lower in naloxone group (6.6%) when compared with the non naloxone group (50%). Death occurred in 23.3% of the non naloxone group and only 3.3% of naloxone group.

**Conclusion:** The incidence of seizure was lower in patients with tramadol toxicity who given naloxone which means that naloxone not precipitate seizure in patients with tramadol toxicity as what was thought by the majority of previous studies.

**Keywords:** Tramadol; Intoxication; Prognosis; Naloxone; Seizure

## Introduction

Tramadol is an opioid analgesic acts directly on the central nervous system. It has dual action; acts on the  $\mu$ - opioid receptors and both serotonergic and noradrenergic nociception enhancing their effects [1]. Tramadol abuse has been increased in Egypt in the last few years due to social and economic instability [2]. Tramadol is considered by many physicians as weak opioid missing the usual serious side effects of other opioids but actually it has the risks of overdose as with morphine [2-4]. The most dangerous effect of tramadol poisoning is seizures which may be associated with fatal consequences such as hypoxia, trauma and rhabdomyolysis [5,6]. Tramadol is the cause of many deaths either when ingested alone or with alcohol or other drugs, especially the central nervous system (CNS) depressants as benzodiazepine [7-9]. Naloxone is a pure opioid antagonist competitively blocks the effects of opioids without any agonist effects. It is indicated if tramadol overdose is accompanied with CNS depression or respiratory depression with no effect on its serotonin or norepinephrine action [10,11]. Several data revealed serious adverse effects following its administration such as seizures [12-14]. Precipitation of seizures in tramadol intoxicated patients following low

dose of naloxone is rare, but in patients who are in risk of seizures it could increase the mortality rate [5]. Most of clinicians may not routinely consider naloxone for tramadol cases because of risks of inducing seizures or are unclear of its efficacy so this study aims to evaluate the effect of naloxone in the prognosis of patients with tramadol intoxication and its role in inducing seizures.

## Materials and Methods

This study included both prospective and retrospective studies. The prospective study involved 30 patients with tramadol intoxication admitted to the poison control center during the year of 2015 who received naloxone while the retrospective study involved 30 patients with tramadol intoxication admitted to the poison control center during the years of 2011-2012 who didn't not receive naloxone (naloxone was not available in our PCC as well as all over Egypt during this period after 25th January 2011 revolution due to political and economic instabilities as there was drug shortage problem [15].

**Exclusion criteria:** Age below 16 years old, patients with chronic diseases, such as, heart or respiratory diseases, kidney or liver failure and epilepsy and patients who ingested other drugs of abuse with

tramadol such as benzodiazepines, barbiturates, alcohol, cannabis or opiates.

The patients were divided into two equal groups; those who didn't not receive naloxone (group I) and those who received naloxone (group II). Patients with tramadol intoxication were diagnosed depending on history of ingestion, clinical assessment and performing urine test by immunoassay (Preliminary drug screen test was performed by "Abon Biopharm Tramadol Screen Kits, China" then confirmed by ARCHITECT immunoassay analyzing system).

The check list involved age, sex, having seizures, dosage of tramadol taken, manner of poisoning, delay time, in addition to clinical data which include, general (vital signs, skin and eye examination), neurological, cardiovascular system (CVS) and respiratory examinations in addition to the outcome in the two groups.

Group II received supportive care and naloxone while group I received just supportive care. On admission, gastric lavage was done and activated charcoal was administrated after tracheal intubation for comatose patients while patients who had seizures with respiratory depression, midazolam (0.1 mg/kg) was given intravenously in addition to performing tracheal intubation and mechanical ventilation. Patients who presented with respiratory center depression (respiratory rate <12) given oxygen as well as naloxone intravenous (group II). All these patients were followed during the period of hospitalization for occurrence of seizures. Prognosis and outcome were compared between patients of both groups. Outcome was considered in patients as survived or not.

### Ethical considerations

Informed consent was obtained from the patients or their relatives before enrolment in the prospective study. In the retrospective study, all of the required measures were taken to keep the patient's information confidential. Approval of Institutional Review Board (IRB) of Ain Shams University was taken.

### Statistical analysis

Data will be collected, checked, revised, entered the computer and analyzed by SPSS statistical package version 20. Excel computer program will be used to tabulate the results, and represent it graphically. One Way ANOVA will be used to declare the significant difference between groups at  $p < 0.05$  for the quantitative variables which are normally distributed. Chi-square test for distribution will be

used to show the significant difference between study groups at  $p < 0.05$ . The results of statistical analysis will be represented in tables, pie charts and histograms for interpretation and discussion.

### Results

The studied patients were in the age 16-60 years range. The mean age was  $29.63 \pm 8.97$  years with majority of them was at the age group of 21- 40 years accounting for (70%) of cases followed by the age groups 16-20 (18.3%) and >40 years (11.7%) with male predominance 75%.

Most of patients (65%) were tramadol addict and 27% took tramadol accidentally and attempted suicide in (8%) of the cases.

The mean delay time and dosage of tramadol taken among studied patients was  $3.32 \pm 1.50$  hours and  $1439.29 \pm 804.49$  mg, respectively.

Statistical analysis by using student t test revealed that there was a significant difference between the two studied groups regarding pulse but no significant differences as regards the other vital data such as systolic, diastolic blood pressure, respiratory rate and temperature (Table 1).

The most common clinical manifestation of tramadol intoxicated patients on admission was sweating (66.7%), cyanosis (61.7%), bradypnea (60%), coma (55%), miosis (50%), tachycardia (46.7%), hyperthermia (41.7%), dizziness and hypotension (35%), nausea & vomiting (31.7%), agitation (26.7%), hypertension (21.7%), cardiac arrest (13.3%), bradycardia (11.7%), seizures (10.2%) and mydriasis (8.3%) (Table 2).

The seizure was significantly lower in naloxone group (6.6%) after naloxone administration when compared with the non naloxone group (50%) (Table 3).

We follow the outcome among patients in the two groups during the period of hospitalization. The incidence of intubation was significantly higher in the non naloxone group than the other group ( $P < 0.05$ ). Patients of non naloxone group needed mechanical ventilation (40%) more than patients of naloxone group (13.3%). Death occurred in (23.3%) of the non naloxone group and only (3.3%) of naloxone group (Table 3).

The length of hospital stay in non-naloxone group (group I) was significantly higher ( $2.03 \pm 1.47$ ) than naloxone group (group II) ( $1 \pm 0$  days) (Table 3).

Vital data	Group I (M $\pm$ SD)	Group II (M $\pm$ SD)	t	P value
Pulse (beats/ minute)	92.10 $\pm$ 31.08	108.79 $\pm$ 29.56	3.093	0.002*
Systolic blood pressure (mmHg)	110.33 $\pm$ 36	111.50 $\pm$ 47.29	0.136	0.44
Diastolic blood pressure (mmHg)	67.33 $\pm$ 18.37	68.00 $\pm$ 27.71	0.132	0.44
Respiratory rate (breath/minute)	14.87 $\pm$ 12.06	14.67 $\pm$ 13.76	0.08	0.53
Temperature ( $^{\circ}$ C)	37.30 $\pm$ 0.75	37.37 $\pm$ 0.72	0.53	0.29

M:Mean SD: Standard Deviation  
\* = There is a significant difference by using student t test at  $p < 0.05$   
Group I: Patients didn't receive naloxone

Group II: Patients received naloxone

**Table 1:** Comparison between studied groups as regards the vital data.

Symptoms	Number	%
Sweating	40	66.7
Cyanosis	37	61.7
Bradypnea	36	60
Coma	33	55
Miosis	30	50
Tachycardia	28	46.7
Hyperthermia	25	41.7
Dizziness	21	35
Hypotension	21	35
Nausea & vomiting	19	31.7
Agitation	16	26.7
Tachypnea	16	26.7
Hypertension	13	21.7
Cardiac arrest	8	13.3
Bradycardia	7	11.7
Seizures	17	10.2
Mydriasis	5	8.3

females were only (25%). It means that tramadol use is common in young adult male, which agrees with other studies in different countries such as Shadnia et al., Talaie et al., Taghaddosinejad et al. and Elmanama et al. [16-19]. Elmanama et al. [19] contribute the use of tramadol by young adults to the absence of awareness of its harmful effects and its easy accessibility while Salem et al. [20] explained it by its alleged usages as a medication for premature ejaculation, extended orgasm and increase sexual pleasure as promoted in many online drug stores and media.

The majority of studied patients (65%) were addict on tramadol indicating its potential abuse. Rafati et al. [21] and Tjaderborn et al. [4] reported that tramadol is associated with the development of physical dependence with greater abuse potential and a severe withdrawal syndrome. On the other hand, Clarot et al. [22], Marquardt et al. [23] and McDiarmid et al. [24] stated that tramadol has low risk for abuse and dependence and considering it as an unattractive substance of abuse and its abuse is not clinically relevant.

The mean delay time was  $3.32 \pm 1.50$  h. These findings agree with Hassanian-Moghaddam et al. [25] who observed that 50.3% of the studied patients presented within 3 h of tramadol ingestion.

Regarding the pulse, near half of studied patients (46.7%) had tachycardia. This is in accordance with Marquardt et al. [23] and Tashakori and Afshari [26] who observed tachycardia in most of their patients and considered it as the main signs of tramadol toxicity and relating it to the enhancing action of tramadol on both serotonin and norepinephrine.

As regards the blood pressure, hypotension was observed in (35%) of studied patients while hypertension was observed in 21.7%. Kaya et al. [27], Daubin et al. [8], Pothiwala and Ponampalam [9] explained hypotension by two different mechanisms; first tramadol central effect on the opioid receptors causing inhibition of the vasomotor center and the second is its direct effect on the vessels by inducing vasodilatation through activation of nitric oxide production. While Mehrpour et al. [28] attributed hypertension to the inhibitory effect of tramadol on serotonin and norepinephrine reuptake. In contrast to these studies, Grond and Sablotzki [29] reported that tramadol had no effects on hemodynamics, except in case of ingestion of large dose.

In this study, sweating was the commonest symptom in patients with tramadol intoxication (66.7%). This result is in agreement with Shadnia et al. [16] who observed sweating in most of his studied patients and attributed it to the monoaminergic effects of tramadol. Marechal et al. [30] considered sweating as a sign of autonomic hyperactivity of serotonin syndrome possibly occurs with tramadol overdose. In contrast to this finding, Persson and Sjöberg [31] observed sweating in small number of his studied patients and considered it as one of the less common clinical manifestations of tramadol toxicity.

The rate of other clinical manifestations such as cyanosis, bradypnea, coma, miosis, seizures and tachycardia in this study was different from the previous studies [23,32].

The seizure was seen only in (50%) of patients of the non naloxone group and managed with benzodiazepine while it happened in one

**Table 2:** Clinical effects seen with tramadol intoxication

	Group I (n=30)	Group II (n=30)	P value
Seizures	15 (50%)	2 (6.6%)	0.000**
Intubation	23 (76.7%)	8 (26.7%)	0.000**
Mechanical ventilation	12 (40%)	4 (13.3%)	0.020*
Death	7 (23.3%)	1 (3.3%)	0.023*
Duration of hospital stay (days)	2.03 ± 1.47	1 ± 0	0.000**

\*= There is a significant difference by using student t test at  $p < 0.05$   
 Group I: Patients didn't not receive naloxone  
 Group II: Patients received naloxone  
 n: number

**Table 3:** Comparison of seizures, the outcome and the duration of hospital stay between the two studied groups.

## Discussion

In this study, most of studied patients were at the age group of 21-40years. Males represented most of studied patients (75%) while

patient only of the naloxone group. This is in agreement with Saidi et al. [11] and Eizadi-Mood et al. [5] who found decrease in the occurrence of seizures among patients who given naloxone and reported that naloxone prevented the incidence of seizures in patients with tramadol intoxication. Liu and Hong [33] and Prow and Irani [34] demonstrated that naloxone decreases the lipopolysaccharide stimulated production of cytokines and nitric oxide in glial cultures as naloxone might be neuroprotective in the neurodegenerative diseases which are inflammatory mediated. Saidi et al. [11] reported that naloxone was effective in the treatment of postictal symptoms of tramadol intoxications.

However Farzaneh et al. [13] and Taghaddosinejad et al. [18] found that incidence of seizures was highly significant among patients in the naloxone group and reported that naloxone induced seizures in patients with tramadol intoxication. Also other studies Farzane et al. [13], Omrani et al. [35] and Sansone and Sansone [36] reported that naloxone highly increased occurrence of seizures and it was not effective in modification of tramadol induced seizurogenic effects. Wermeling et al. [37] explained naloxone precipitating seizures by the sudden reversal of opioid depression after using naloxone.

The Clinical outcomes between two groups were followed during the hospitalization period. In the non naloxone group, incidence of the need for intubation was significantly higher than the other group ( $P < 0.05$ ). Patients of group I needed mechanical ventilation (40%) more than patients of group II (13.3%). Mirmoghtadaee et al. [38] found that the need for intubation and mechanical ventilation were more needed in oral opioid users and abusers (20.3%). On the other hand, this study disagrees with Mood et al. [5] who found that intubation was higher in his patients who given naloxone and explained it by increase the ingested dose of tramadol and loss of consciousness in these patients. Death occurred in (23.3%) of the non naloxone group and only (3.3%) of the naloxone group (Table 3) which means that naloxone improved the outcome in tramadol intoxicated patients. This is in agreement with Saidi et al. [11].

Naloxone shortens the duration of hospitalization among tramadol intoxicated patients. The length of hospital stay in non-naloxone group (group I) was significantly higher ( $2.03 \pm 1.47$ ) than naloxone group (group II) ( $1 \pm 0$  days) (Table 3). This is in agreement with Mood et al. [5].

This is in contrast with Moghaddam et al. [38,39] who suggested that the use of naloxone increase the period of hospitalization due to the need for gradually decreasing the dose instead of sudden cessation.

## Conclusion

It may be concluded that naloxone not precipitate seizures in tramadol intoxicated patients as what was thought by most of the previous studies. Naloxone could improve the outcome of patients with tramadol intoxication as documented by decrease the need for intubation and mechanical ventilation and also the mortality rate in patients who given naloxone in the current study. Naloxone decreases the length of hospital stay so it could reduce the health care costs, decreases patient suffering, and also increases long-term survival among tramadol intoxicated patients.

## Limitations and Recommendations

The small sample size might limit the generalizability of the findings so further studies with more sample sizes are needed to provide

evidence to support routine use of naloxone in tramadol poisoning. Although tramadol poisoning was confirmed by immunoassay, we could not measure the exact tramadol level. Doses of tramadol were measured depending on the history which was taken from patients and/or their relatives and may not be accurate.

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