Does Naloxone Prevent Seizure in Tramadol Intoxicated Patients?

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ABSTRACT

Background: Tramadol poisoning has increased in recent years. Seizure is one of the side-effects of tramadol toxicity. There is a controversy about possible preventive effect of naloxone in tramadol poisoning induced seizure. Therefore, this study was performed to compare seizure incidence in tramadol poisoning patients who received and did not receive naloxone, as an opioid antagonist.

Methods: This study involved prospective data collection followed by retrospective analysis on 104 tramadol poisoning patients who were admitted in a referral poisoning center. The incidences of seizure were compared between patients received naloxone and those did not. Outcome was considered as survived without or with complications and death. Logistic Regression analysis was used to determine the effects of different variables on seizure incidence.

Results: 70 (67.3%) of the patients were men. The mean age of the patients was 26.3 ± 9 years old. 18.3% of the patients received naloxone in their treatment period. Seizure incidence was significantly higher among tramadol poisoning patients who did not receive naloxone compare with those received naloxone (14.1% vs. 5.1%). Among different variable studied, age had a significant effect on predicting of seizure (odds ratio = 2.09; 95% of confidence interval: 1.82-2.26; *P* value, 0.004).

Conclusions: Although the seizure incidence was lower in patients with tramadol poisoning who received naloxone, the logistic regression did not support the preventive effect of naloxone on seizure in tramadol poisoning cases.

Keywords: Naloxone, poisoning, seizure, tramadol

INTRODUCTION

Now-a-days opioids use and its related mortality and morbidity are one of the major concerns world-wide.[1-3] Recently the trend of opioids use has changed because synthetic opioids such as tramadol are available too. Tramadol related deaths in 2008 reported 32.5 times more than in 2005.[4] Tramadol has mild

to moderate analgesic effect due to inhibition of reuptake of both norepinephrine and serotonine.[5] Nausea, vomiting, restlessness, headache, seizure and low consciousness are the symptoms of tramadol poisoning.[6,7] Tramadol induced seizure may be dose independent. Seizure incidence was estimated about 15-35% in tramadol poisoning, but it could occur even in therapeutic ranges.[5,8-10]

Although tramadol poisoning may be non-life-threatening but, if accompanied by seizures it has been associated with reports of increased mortality and morbidity, including hypoxia, trauma, muscular damage and rhabdomyolysis, which may cause hospitalization of patients in the intensive care unit.[4,11-13] The seizure may be controlled with benzodiazepines, although benzodiazepines, even at therapeutic doses, may increase the morbidity and possible lethality of tramadol poisoning.[14]

A study by Rehni *et al*. suggested that tramadol exerts its seizurogenic effect on mice possibly via an opioid-dependent gamma-aminobutyric acid inhibitory pathway.[15] Furthermore, Tramadol exerts its seizurogenic effect on mice through an H_1 receptor activation linked pathway possibly through an opioid receptor dependent release of histamine from the mast cells.[16]

Shafaroodi *et al*. in their study have reported that the effects linked to mechanisms including coupling to Gi proteins and increasing GABAergic transmission and this mechanism may explain the blockade or reverse of the anticonvulsant effect by naltrexone.[17]

Naloxone - as an opioid antagonist - is used to reverse of synthetic and non-synthetic opiate induced respiratory depression. There are some controversies studies about the naloxone and inducing seizure in tramadol poisoning.[15-27] In animal studies, naloxone reduced the seizure related some opiate like drugs.[19] Furthermore, there has been an improvement in abnormal brain waves in 91% of tramadol poisoned patients after naloxone injection.[20] However, other studies indicate that naloxone markedly increased colonic seizure[21] and even some of them showed that naloxone did not modify the reaction of tramadol seizurogenic effects.[22] Patients will be at risk of seizure as an adverse effect itself[23] and Naloxane seizurogenic effect could put them in a worse condition.[18]

Since tramadol poisoning has become prevalent in recent years in Iran due its simple availability and due to the controversies about the role of naloxone on seizure activity as an epileptogenic,[24,25] or preventive as anticonvulsive effects[26,27] in tramadol poisoning cases; we evaluated seizure incidence in tramadol poisoned patients who received or did not receive naloxone.

METHODS

This study involved prospective data collection followed by retrospective analysis and was conducted by the Clinical Toxicology Department, Isfahan University of Medical Sciences (IUMS) over a 12-month period from September 2010 to September 2011 in the poisoning referral center, Noor hospital, IUMS. The protocol was reviewed and approved by the Institutional Ethics Committee of the IUMS (The Research Project Number 389278).

Diagnosis of tramadol poisoning was based on clinical evaluation of the patient by the clinical toxicologists and if needed urine test by gas chromatography/mass spectrometry or high-performance liquid chromatography.

For patients with coma who didn't have a gag reflex on admission, gastric lavage and activated charcoal was administrated after tracheal intubation.

For those patients who had a seizure with respiratory depression on admission, midazolam (0.1 mg/kg) intravenously and tracheal intubation plus mechanical ventilation were performed. Therefore these patients did not receive naloxone for respiratory depression; and followed for possible re-current seizure during their hospitalization.

Patients with apnea or respiratory depression (respiratory rate <12) received the supplemental oxygen by mask or nasal cannula as well as intravenous naloxone (starting 0.01 mg in addict patients and 0.4 mg in non-addict patients). Naloxone intravenously was administered until the oxygen saturation of above 95% and respiratory rate above 12 was achieved. All these patients were also followed for the presence of seizure during hospitalization.

Therefore, the patients were divided in to 2 groups (those received naloxone and not received naloxone). The qualification for exclusion from the study included:

- The patients who were discharged before complete remission by personal willing
- The patients who had a past medical history of epilepsy, seizure or were transferred to the other parts because of neurologic or internal problems
- The patients who also ingested anti convulsants, monoamine oxidase inhibitor drugs, tricyclic antidepressant, selective serotonine reuptake inhibitor and etc.

The diagnosis of seizure was based on jerky movements of the whole body, tonic and colonic spasms and convulsions. The check list included age, sex, appearing seizure, tramadol dose, time between tramadol ingestion and hospital admission, time between hospital admission and naloxone administration and outcome in different groups.

SPSS version 18 was used to analysis data. Data are presented as mean ± SD or *n* (%) where appropriated. We used Chi-square test, Mantel Hansel and student *t*-test to compare variables. Logistic regression analysis was used to determine the effects of different variables on seizure incidence. $P < 0.05$ was considered as significant.

RESULTS

The study involved 104 patients (age range: 15-85 years). The mean age of patients was 26.3 ± 9 years old and 67.3% were male. The results regarding the different variables including demographic patients in two studied groups has been shown in Table 1.

In all patients symptoms on admission were: Nausea (14.4%), vomiting (16.3%), loss of consciousness (25%), confusion (29.8%), coma 1%, hypotension 4%, tachycardia 4%, hyperventilation 2% and apnea 2%. Loss of consciousness and the temperature on admission were significantly different between the two studied groups ($P < 0.05$) [Table 2].

The results regarding paraclinical tests have been shown in Table 3. Although there were some significance different in some parameters; all of them were within the normal values.

Table 1: Comparison of different variables in two groups (received or not received naloxone)

Parameter	Patients who did not receive naloxone 85 (81.7%) (%)	Patients who received naloxone 19 (18.3%) (%)	*P* value
Age (year)	25±0.83	32.7±3.5	0.04
Male	57 (54.8)	13 (12.5)	0.90
Female	28 (26.9)	6 (5.8)	0.90
Tramadol dose (mg)	1571.16±1312.47 (minimum 100 mg and maximum 10 g)	1562.04±1329.44 (minimum, 100 mg and maximum 7 g)	0.009
Time between tramadol ingestion and hospital admission (h)	3.87±0.38	3.5±1.07	0.71

The results are presented as number (%) or mean±standard error where appropriate

Table 2: Comparison of clinical manifestation between the two studied groups (*N*=104)

Parameter	Patients who did not receive naloxone 85 (81.7%) (%)	Patients who received naloxone 19 (18.3%) (%)	*P* value
Nausea	12 (14.1)	3 (15.8)	NS
Vomiting	15 (17.6)	2 (10.5)	NS
Seizure	12 (14.1)	1 (5.3)	<0.05
Loss of consciousness	17 (20)	9 (47.4)	<0.05
Temperature (°C)	37±0.3	38.3±1.2	NS
Pulse rate (number/min)	81±1	80±2	NS
Respiratory rate (number/min)	18±4	18±5	NS
Systolic blood pressure (mmHg)	107.67±1.73	112.88±2.88	NS
Diastolic blood pressure (mmHg)	69.07±1.01	69.85±2.87	NS

Data are persecuted as *n* (%) or mean±standard error whole appropriated. NS=Non-significant

Table 3: Comparison of paraclinical manifestation between the two studied groups (*N*=104)

Parameter	Patients who did not receive naloxone	Patients who received naloxone	*P* value
WBC (×10³)	5.3±4.33	10.8±1.2	1.20
RBC (×10⁶)	4.8±0.09	4.5±0.15	0.02
Hb (g/dl)	15.5±1.3	13.1±0.4	0.38
Na (meq/l)	133±4	132±8	0.80
K (meq/l)	6.5±2.5	6.7±2.6	0.98
BUN (mg/dl)	13±0.7	17±3.5	0.01
Cr (mg/dl)	1.02±0.12	1.1±0.15	0.95
BS (mg/dl)	95±8	119±12	0.18
PTT	33±2	32±2	0.51
PT	13±0.1	13.6±0.3	0.002
INR	1.03±0.02	1.2±0.12	0.09
AST	25±4.6	33.5±10.7	0.05
ALT	19.5±3.7	33.5±10.7	0.03

Data are persecuted as mean±standard error. WBC=White blood cell, RBC=Red blood cell, Na=Sodium, K=Potassium, BUN=Blood urea nitrogen, Cr=Creatinine, BS=Blood sugar, PTT=Partial thromboplastin time, PT=Prothrombin time, INR=International normalized ratio, AST=Aspartate aminotransferase, ALT=Alanine transaminase, Hb=Hemoglobin

The average time between hospital admission and naloxone administration was 0.48 ± 0.15 (range: 0-11.30) h.

The past history of seizure was unknown in 2 patients which were excluded. And only one patient had a past history of seizure because of previous tramadol ingestion.

Clinical outcomes between two groups were followed during the hospitalization period. In the naloxone group, incidence of the need to intubation was significantly higher than the other group (P <0.05) [Table 4].

Based on binary backward stepwise logistic analysis, among different variable studied, age had the significant effect on predicting of seizure (odds ratio [OR] =2.09; 95% confidence interval [CI]: 1.82-2.26; P value, 0.004). None of the patients died.

DISCUSSION

In this study, we compared the incidence of seizure and outcomes of patients with tramadol poisoning who received or not received naloxone during the treatment period.

Table 4: Comparison of outcome between the two studied groups (*N*=104)

Complication	Patients who did not receive naloxone 85 (81.7%) (%)	Patients who received naloxone 19 (18.3%) (%)	*P* value
Aspiration pneumonia	2 (2.4)	2 (10.5)	0.15
Need to intubation	8 (9.4)	6 (31.6)	0.01
Renal failure	3 (3/6)	0	<0.001

The results showed most of the patients were male. In the study by Rehni *et al*. seizure following tramadol poisoning was also mostly observed in men that were acceptable due to abundance of men in this study.[15]

Most of the patients had symptoms such as nausea, vomiting and decrease consciousness. This finding is consistent with other studies and might be attributed to inhibiting effects of tramodol on monoamines reuptake.[11,15]

Our study showed that the seizure was lower in patients who received naloxone. It was consistent with other studies which showed naloxone prevented seizure in tramadol or opioid poisoned patients.[15,19,20] In a study about management of post-seizure complaints of tramadol intoxicated patients, naloxone was effective in the management of post-seizure complaints of tramadol poisoning.[20] However in a case-control study naloxone induced a seizurogenic effect in patients with tramadol overdose.[5]

Some studies also indicated the administration of naloxone markedly attenuate the tramadol-induced potentiating of seizurogenic activity.[28] Naloxone has been found to exert therapeutic effects in animal models of ischemic and traumatic brain diseases.[29] Although the exact mechanism is poorly understood, the antagonistic property of naloxone for opioid receptors is stereospecific studies demonstrated that naloxone was capable of reducing lipopolysaccharide and beta amyloid peptide induced morphologic changes of microglia, decreasing production of cytokines and protecting neurons.[30] Furthermore, the neuroprotective effect of naloxone has been confirmed in a mouse alphavirus encephalomyelitis model and light induced photoreceptor degeneration model through attenuating microglial activation,[31]

Yang *et al*. proved that continuous administration of naloxone after life-threatening neurologic emergency could inhibit glial activation and lower the brain's vulnerability to a second hit in later life. Naloxone treatment immediately could reduce cytokine production, glial activation and further lower the vulnerability of immature brains in adulthood.[28]

In this study, the minimum and maximum dose of tramadol which caused seizure was 100 mg and 4 g, but in other studies this minimum and maximum dosage was 200 mg[20] and 500 mg,[11] whereas seizure happens with therapeutic dosage of tramadol.[9-15,32] Although in patients who received naloxone the incidence of seizure was lower, the dosage of tramadol ingestion in this group was significantly higher than those patients not received naloxone. On previous studies, generalized tonic colonic seizure was seen in severe poisoning or high dosage of Tramadol at first 24 h of poisoning.[9,32,33]

The seizure happened only once in our patients and controlled with benzodiazepine. In another study also the recurrent seizure was rare.[34]

Need for intubation and aspiration pneumonia was higher in patients who received naloxone. The ingested dose and loss of consciousness was also higher in these patients as well.

An effect of naloxone on respiratory failure has been also presented in other studies.[18,28]

In this study, renal failure developed in 3 patients. Two case reports has been reported renal failure as well. In one study renal failure occurred with 6 grs tramadol[13] and in the other it was happened with 4 grs tramadol ingestion.[35] There was no mortality in our cases during the study period, however tramadol-related fatalities has been reported in Iran especially among substance abusers.[4]

CONCLUSIONS

Although the seizure incidence was lower in patients with tramadol poisoning who received naloxone, the logistic regression did not support the preventive effect of naloxone on seizure in tramadol poisoning cases. Most guidelines recommend naloxone as the first step of treatment in opioid overdose, there are some controversies between studies regarding using naloxone in tramadol poisoning due to possible risk factor for seizure.

Limitations of the study

- This study involved prospective data collection followed by retrospective analysis which was performed over 1 year. Further clinical trial study is needed to provide sufficient evidence for supporting naloxone administration in tramadol poisoning
- The incidence of seizure was lower in our study compare to others[5,8-10] which could be due to the small number of sample size evaluated in our 1 year study.

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