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ORIGINAL RESEARCH

Demographic and Clinical Characteristics of 907 Cases with Naltrexone Intoxication; a 14-Year Cross-Sectional Study

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Abstract: **Introduction:** Opioids have been the leading cause of death from poisoning in Iran for several years. This study aimed to evaluate the clinical and para-clinical presentations of naltrexone intoxication, its toxic dose, and its epidemiological properties. **Methods:** This retrospective cross-sectional study was conducted on medical records of patients presenting to Toxicology Department of Loghman Hakim Hospital, Tehran, Iran, following naltrexone intoxication, from 2002 to 2016. Patients' demographic and laboratory data, clinical signs, supposed ingested dose, and intent of naltrexone consumption were collected, analyzed, and then interpreted. **Results:** 907 patients with the mean age of 36.6 ±11.7 years were evaluated (94.3% male). The mean amount of naltrexone consumed by the intoxicated patients reported in the medical records was 105.8 ± 267.8 mg. One hundred thirty patients (14.3%) used naltrexone to treat substance use disorder. Two hundred eighty-seven poisoned patients (31.6%) were current opium users who intentionally or unintentionally used naltrexone concomitantly. The most common symptoms observed in these patients were agitation (41.8%), vomiting (16.4%), and nausea (14.8%). Among patients with naltrexone poisoning, 25 patients were intubated (2.8%), and three passed away. Aspartate aminotransferase (AST) levels were significantly higher in patients intoxicated with naltrexone who needed intubation (p = 0.02). **Conclusion:** The probability of intubation of cases with naltrexone intoxication was associated with AST elevation. It seems that, the number of intensive care unit (ICU) admissions and mortality rates are not high among these patients.

Keywords: Naltrexone; poisoning; aspartate aminotransferases; cross-sectional studies; retrospective studies

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1. Introduction

Naltrexone is a long-acting, pure opioid antagonist that blocks mu-receptors and is used in various disorders such as opioid and alcohol use disorder (1). Iran is among the countries with the highest prevalence of opioid use disorder, and opium is the most common substance among these patients (2). Afghanistan is the number one producer of opiates globally, which might lead to Iran's highest number of seized opiates in 2018. In addition, opioids have been the leading cause of death from poisoning in Iran for several years (3-5). Consequently, many opioids and naltrexone poisoning cases are referred to Loghman Hakim Hospital, the most crowded referral poisoning center globally (6).

The reduced opioid tolerance caused by naltrexone makes patients vulnerable to opioid overdose after missed doses or discontinuation of treatment (7). Three possible causes of death related to naltrexone have been suggested: Opioid

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overdose during naltrexone treatment, opioid overdose after naltrexone treatment discontinuation, and intoxication with naltrexone in patients with opioid use disorder (8).

The most common side effects of naltrexone are gastrointestinal (GI) complaints such as diarrhea and abdominal cramping. These adverse effects are analogous to the symptoms of opioid withdrawal, as the mu receptor blockade will increase GI motility. Naltrexone has been reported to cause liver damage (when given at doses higher than recommended). It carries an FDA boxed warning for this rare side effect.

Naltrexone may induce a withdrawal syndrome lasting up to 72 hours. It is recommended that the patients spend a period of seven to ten days of opioid abstinence before naltrexone treatment to avoid withdrawal symptoms, such as agitation and restlessness, altered level of consciousness, nausea and vomiting, abdominal pain, diarrhea, myalgia, tachycardia, and dilated pupils (9).

This retrospective cross-sectional study aimed to evaluate the clinical and para-clinical presentations of naltrexone intoxication during 14 years in Loghman Hakim Hospital.

2. Methods

2.1. Study design and setting

This research is a retrospective cross-sectional study on medical records of 907 patients with naltrexone intoxication from April 2002 to March 2016 in Loghman Hakim Hospital, in which trained clinical toxicologists record patients' history and trend of management, as well as their vital signs.

This study has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics Code: IR.SBMU.REC.1394.149). All patients' data were anonymous and identified by the file numbers to preserve patients' confidentiality.

2.2. Participants

All the patients who referred to Loghman Hakim Hospital with naltrexone poisoning, both opioid dependent and non-dependent, and also all patients with intentional or accidental poisoning were included in this study. All cases of multiple drug toxicity were excluded. Since there is no laboratory method in the world to confirm the use of naltrexone, we also relied on the patient's history of using this drug.

2.3. Data gathering

Demographic data were collected, including age, sex, history and type of drug use disorder, and history of alcohol use disorder. Other background data included the amount of naltrexone consumed, clinical characteristics, and lab data. In addition, withdrawal symptoms, electrocardiograms (ECG), arterial blood gases (ABG), venous blood gases (VBG), blood electrolytes, and liver and kidney function tests were evaluated. Mortality rate, cause of death, and duration of intensive care unit (ICU) admission were also analyzed.

Moreover, the effect of each variable, including demographic and other background data, on need for intubation and duration of hospitalization was assessed.

2.4. Statistical analysis

The present study used SPSS 26.0 for Windows for data analysis. Normality was then examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In addition, quantitative variables were reported as median and interquartile range (IQR). Qualitative variables were also presented as frequency (percentage). Additionally, Mann-Whitney U test and Kruskal-Wallis test were used to evaluate data with non-normal distribution, and Chi-square test was used to compare categorical variables. The relationship between the duration of hospitalization and other independent quantitative variables was analyzed using Spearman correlation analysis. P-values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

Medical records of 907 patients with the diagnosis of naltrexone intoxication were studied. The majority of cases were male (855 cases, 94.3%) with a mean age of 36.6 ±11.7 years. The mean amount of naltrexone consumed by the intoxicated patients reported in the medical records was 105.8 ± 267.8 mg. One hundred thirty patients (14.3%) used naltrexone to treat substance use disorder. Two hundred eighty-seven poisoned patients (31.6%) were current opium users who intentionally or unintentionally used naltrexone concomitantly. The most common symptoms observed in these patients were agitation (41.8%), vomiting (16.4%), and nausea (14.8%). Baseline characteristics of patients are presented in Table 1. Table 2 summarizes the laboratory finding of patients.

3.2. ECG findings

Among 612 patients whose ECG was examined, 523 patients had normal ECG, 27 patients had right axis deviation, 37 patients had left axis deviation, and one patient experienced ST depression. One patient experienced ST elevation. Two patients had T-flat, and two patients experienced T-invert.

3.3. Outcomes

Among the 907 patients with naltrexone intoxication, evaluated in this study, 759 (83.7%) patients were discharged after completion of the treatment course, 145 (16.0%) patients were discharged against medical advice. Three patients were

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Table 1: Baseline characteristics of patients with naltrexone intoxication

Variable	N	Values
Age (year)	878	36.64 ± 11.75
Sex		
Male	907	855 (94.3)
Female		52 (5.7)
Intoxication characteristics		
Naltrexone Dosage (mg)	710	105.83 ± 267.77
Time elapsed to presentation	706	4.82 ± 6.31
Vital signs		
Temperature (c)	483	36.93 ± 0.3
Pulse rate (beats/minute)	839	81.84 ± 11.93
Diastolic blood pressure (mmHg)	842	75.64 ± 10.2
Systolic blood pressure (mmHg)	852	117.9 ± 15.8
Oxygen Saturation (%)	26	93.95 ± 7.9
Glasgow coma scale	96	13.08 ± 1.92
Presenting symptoms		
Vomiting	907	149 (16.4)
Nausea		134 (14.8)
Diarrhea		70 (7.7)
Agitation		379 (41.8)
Seizure		24 (2.6)
Outcome		
Intubation	907	25 (2.8)
Hospitalization (hour)		27.88 ± 28.8
ICU admission		56 (6.2)
ICU Stay (hour)		4.82 ± 2.8
Mortality		3 (0.3)

Data are presented as mean ± standard deviation or frequency (%). ICU: intensive care unit. N: number of data available regarding that variable on the patients' profile.

deceased (one patient died because of cardiopulmonary arrest, one due to acute tubular necrosis (ATN), and the third patient died due to coagulation disorder).

There was a significant difference between patients who needed intubation and those who did not in terms of age range (mean rank; 560.58 vs 432.99; p = 0.014), aspartate aminotransferase (AST) level (mean rank; 129.39 vs 96.51; p = 0.02), atrial HCO3 (mean rank; 36.5 vs 24; p = 0.049), dose of drug used (less than 100mg vs more than 100 mg; Pearson Chi-Square: 14.5; p = 0.021), and intention of naltrexone use (suicide vs other; Pearson Chi-Square: 4.72; p = 0.03). The duration of hospitalization in patients who consumed more than 100 mg naltrexone was significantly higher than patients who consumed less than 100 mg naltrexone (p = 0.001).

4. Discussion

In this study, it was shown that naltrexone poisoning was not associated with serious adverse events or high mortality rate, contrary to previous assumptions.

Naltrexone is a pure competitive opioid antagonist at the mu (μ), kappa (K), and delta (δ) receptors. Naltrexone is used orally for patients following opioid detoxification to maintain opioid abstinence and as an adjunct to achieve ethanol abstinence. However, naltrexone should not be administered to an opioid-tolerant patient (10). Naltrexone may induce a withdrawal syndrome lasting up to 72 hours (11).

Hassanian et al. conducted a study from December 2007 to March 2008 in Loghman-Hakim Hospital. Among 132 patients who were evaluated, agitation was the most prominent presentation with 96.2% prevalence, followed by altered level of consciousness, nausea, vomiting, abdominal pain, diarrhea, bone and muscle pain, tachycardia, and dilated pupils. Except for agitation, no relationship was found between the presence of these symptoms and the dose of naltrexone used (9).

Furthermore, another cross-sectional study was performed on patients hospitalized with a history of naltrexone use coinciding with opioid substances at Razi Hospital, Rasht, Iran, during 2007- 2008. The collected data were demographic information, drug use disorder information, clinical signs and symptoms, laboratory findings, and the therapeutic measures taken. The mean age of the patients was 33.7 ± 10.2

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Table 2: Laboratory findings of patients with naltrexone intoxication

Variable	N	Values
Arterial blood gas analysis		
PH	56	7.41 ± 0.11
PCO2 (mmHg)	51	39.65 ± 34.61
PO2 (mmHg)	49	93.69 ± 112.19
HCO3 (mEq/L)	50	24.14 ± 10.7
Base excess (mEq/L)	51	0.98 ± 5.47
Venous blood gas analysis		
PH	214	7.3938 ± 0.23
PCO2 (mmHg)	214	40.709 ± 27.7
PO2 (mmHg)	202	41.000 ± 21.38
HCO3 (mEq/L)	215	24.714 ± 4.57
Base excess (mEq/L)	203	2.073 ± 6.55
Other laboratory data		
Sodium (mEq/L)	763	141.1 ± 4.5
Potassium (mEq/L)	756	4.2 ± 0.6
Blood Sugar (mg/dL)	773	108 ± 36.6
Hemoglobin (g/dL)	706	13.9 ± 1.7
Blood urea nitrogen (mg/dL)	757	30 ± 10.8
Creatinine (mg/dL)	758	1 ± 0.4
Aspartate Transaminase (IU/L)	199	36.2 ± 37.3
Alanine Transaminase (IU/L)	197	27.1 ± 22
Alkaline Phosphatase (IU/L)	205	211.7 ± 82.5
Creatine phosphokinase (IU/L)	142	767.3 ± 1571.6
Lactate dehydrogenase (IU/L)	143	653.7 ± 488.8

Data are presented as mean ± standard deviation. PCO2: Partial Pressure of Carbon Dioxide; pH: Potential of Hydrogen; PO2: Partial Pressure of Oxygen.

years. The majority of the cases were male (95.6%) and urban (96.7%). The leading cause of withdrawal symptoms in 91.1% of the patients was inappropriate naltrexone usage. In 80% of the cases, the only poisoning agent consumed was naltrexone. The major clinical features were nausea, vomiting, and agitation. In addition, the primary therapeutic measures were supportive intravenous fluids and methadone administration. The mean hospitalization period was 21.8 ± 18 hours (12).

The current study was consistent with the previous studies in terms of general characteristics. The median age of patients was 35, and the male was the dominant sex among patients with naltrexone intoxication. Contrary to the primary hypothesis, there was no significant difference between the various age groups regarding clinical consequences. This is probably due to the high prevalence of addiction among this population (13). In accordance with the previous studies, the main clinical presentations among the studied population were agitation, vomiting, nausea, and diarrhea. Some cases experienced seizures. These manifestations were mainly due to the withdrawal syndrome caused by naltrexone exposure in opioid-tolerant patients.

In another study conducted in Australia from 2000 to 2003, the severity and duration of withdrawal symptoms due to accidental or intentional naltrexone abuse were suggested to be variable and unpredictable. Oral naltrexone was estimated to have a mortality rate four times greater than methadone in treating patients with opioid use disorder (8). In this study, results revealed that the risk of intubation in patients who were intoxicated with naltrexone with suicidal intention was significantly higher than the patients who were intoxicated due to other reasons (accidental or to quit addiction). Analysis revealed that patients who consumed more than 100 mg naltrexone were those who committed suicide. In other words, patients with naltrexone intoxication and suicidal intention were more likely to consume naltrexone more than 100 mg (Pearson Chi-square=4.5; p<0.03). Thus, increased odds of intubation in patients with suicidal intention are probably due to the higher dose of naltrexone exposure in these patients.

There are contradictions about naltrexone hepatotoxicity and it does not appear to increase hepatic enzymes at therapeutic doses (14-17). Some studies have shown that high doses of naltrexone (up to 400 mg/day) do not affect liver enzyme levels (17). On the contrary, other studies have shown that naltrexone may increase hepatic transaminases at a 300 mg/day dose (18, 19).

The present study shows that high levels of AST were asso-

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ciated with greater need for intubation and more extended hospital stays among patients with naltrexone poisoning. It is recommended to pay more attention to the relationship between elevated AST and the clinical consequences of naltrexone poisoning in future studies.

Considering that Loghman Hakim Hospital is the scientific center of clinical toxicology and the referral center in Iran, so the findings of the study can be generalized, at least, to Iran. For future studies, we recommend a prospective study with pre-designed forms to facilitate data entry and prevent missing data in order to aid in preparing a comprehensive and practical protocol for management of naltrexone intoxication.

5. Limitations

Due to the type of research, this study has poor internal validity, which may be negligible due to the importance of the subject and the number of cases studied. Moreover, as mentioned above, several cases had missing information regarding the doses of naltrexone, patients' ages, and their intention for consuming naltrexone.

6. Conclusion

This study showed that there are many cases of poisoning with naltrexone in Iran. The probability of intubation was associated with AST elevation, which may be due to liver damage caused by high doses of naltrexone. It seems that, the number of ICU admissions and mortality rates are not high among patients with naltrexone intoxication.

7. Declarations

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7.2. Authors' contributions

Each author's contribution is in the analytical search for scientific publications, writing the article, and approving the content.

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7.4. Conflict of interest

The authors declare that they have no competing interests.

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