

Risk of Seizure after Naloxone Therapy in Acute Tramadol Poisoning: A Systematic Review with Meta-Analysis

Abstract

Background: Many studies have focused on the relationship between naloxone and seizure in tramadol poisoning but the results are in conflict. We performed a meta-analysis study to see whether naloxone prevents or increase the risk of seizure in tramadol poisoning. **Methods:** Bibliographic literature searches were conducted in the ISI Web of Science, Excerpta Medica Database (EMBASE), PubMed, and Cochrane from January 1990 to December 2017 for relevant articles. Pooled data were analyzed by calculating odds ratios (ORs) with 95% confidence intervals (CIs). The outcome includes seizure. To investigate the publication bias, Begg's and Egger's tests were used along with funnel plot as a graphical test. **Results:** Seven studies met the inclusion criteria. The meta-analysis showed I^2 , 27%, (P value, 0.23) indicating no significant heterogeneity. As a result, using the fixed effect, the OR was 1.14 (95% CI = 0.60–2.18, P value, 0.69) which was not significant, means naloxone did not increase the risk of seizure. **Conclusions:** Naloxone therapy did not increase the risk of seizure significantly in the treatment of acute tramadol poisoning. We suggest considering the risk/benefit when administration naloxone, especially for the seizure risk factors including previous history of seizure, tramadol misuse, and co-ingestion.

Keywords: Meta-analysis, naloxone therapy, poisoning, review, tramadol overdose

Introduction

Poisoning is one of the most common medical emergencies. Early diagnosis of poisoning and appropriate management can be vital. The general pattern of poisoning is different in any geographic region.^[1-3] Tramadol is one of the most commonly prescribed opioid drugs throughout the world to control moderate-to-severe pains.^[4,5] The association between tramadol use and fatal poisoning or history of drug misuse has been reported in previous studies.^[6-12]

One of the important clinical manifestations of tramadol is seizure,^[13-16] occurring in <1% of the usual dose of tramadol users,^[17] but it is also observed due to tramadol poisoning.^[18-23] Naloxone is an opioid antagonist used to restore the respiratory depression caused by natural and synthetic opiates.^[24,25] The efficiency of naloxone for reversing central nervous system toxicity of tramadol has been questioning.^[26,27]

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Many studies have focused on the relationship between naloxone and seizure in tramadol poisoning but the results are in conflict. Some animal studies reported naloxone reduced the seizure activity of opioid and tramadol.^[28-31] However some studies did not support naloxone therapy for the treatment of tramadol overdose due to potentiality seizure episode occurrence.^[32,33] The highest prevalence of seizures induced by naloxone was in the first 2 h after injection in tramadol poisoning.^[33]

As tramadol overdose and misuse is common in many emergency departments; and because of different reported effects of naloxone to show whether naloxone prevents or induce a seizure episode in patients with tramadol poisoning, we performed a systematic review and meta-analysis on human studies to see the relationship between naloxone and seizure in tramadol poisoning.

Materials and Methods

The project was approved by the Institutional Ethics Committee of the

How to cite this article: Eizadi-Mood N, Ghandehari M, Mansourian M, Sabzghabae AM, Samasamshariat S, Sadeghi E. Risk of seizure after naloxone therapy in acute tramadol poisoning: A systematic review with meta-analysis. *Int J Prev Med* 2019;10:183.

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Access this article online

Website:
www.ijpvmjournal.net/www.ijpvm.ir

DOI:
10.4103/ijpvm.IJPVM_268_18

Quick Response Code:



Isfahan University of Medical Science with a grant number of 393904.

Data sources

Bibliographic literature searches were conducted in the ISI Web of Science, Excerpta Medica Database (EMBASE), PubMed, and Cochrane from January 1990 to December 2017 for relevant articles. References lists of the selected articles were also searched.

Search strategy

We searched all four databases using keyword search techniques for relevant studies according to the search tools of each database. The selected keywords were as follows: (Naloxone OR Naloxon) AND (Poisoning OR Toxicity OR Tramadol OR "Tramadol Poisoning" OR "Tramadol Toxicity" OR "Tramadol Intoxication" OR "Drug overdose") (seizures OR seizure) in Title and MESH/subject and in Abstract.

Inclusion and exclusion criteria

Studies included in the meta-analysis had to meet the following criteria: (i) addressing about naloxone and tramadol; (ii) original studies. All types of clinical trials, historical cohort, case control, and cross-sectional studies with the main outcome of seizures that happened one and half hours after naloxone injection in the course of acute tramadol poisoning were included and analyzed. Articles related to animal studies, non-English articles, case reports, and review articles were excluded.

Screening and Selection

At the first screening stage, two reviewers independently screened title and abstract of retrieved documents to determine those which met the eligibility criteria. Primary selection of studies was based on the inclusion criteria. The duplicated publications were excluded. Full citations of those documents considered eligible at least by one reviewer were imported into an EndNote database. In the next stage, the full text of the imported papers was provided and reviewed for subject relevancy individually by each of the two reviewers. A critical appraisal checklist was used to evaluate the validity of the selected studies and to criticize them. Finally, the two researchers made a face-to-face meeting, discussing on articles selections. Discrepancies were resolved through discussion. In the cases, where consensus did not happen, a third researcher made the final decision on the eligibility of a particular article. Consequently, those studies, which have been considered as valid by both researchers, selected for data extraction.

Data extraction

A list of eligible studies was produced. Also, a specific checklist for data extraction was designed for recording

data from the selected studies. The extracted data were the author's name, country, year of publication, type of study, age, gender, naloxone administration, presence of seizure, past history of seizure, history of tramadol misuse, co-ingestion, tramadol dose, time between ingestion and admission, number of seizure, exclusion criteria, other seizure risk factors outcome, and length of hospital stay in selected studies.

Synthesis

We calculated the odds ratio (OR) as the summary effect and the corresponded 95% confidence interval (CI) for each study. Heterogeneity among the studies was assessed by the Chi-square test of heterogeneity and I^2 statistic and also by the Forest Plot. If no strong evidence of heterogeneity were seen across the studies, fixed-effect model and Mantel-Haenszel method were used to pool the ORs. To investigate the publication bias due to small studies, Begg's and Egger's tests were used along with funnel plot as a graphical test.

Results

Study selection

The search strategy has been shown in Figure 1. A total of 907 articles from four databases were searched by two researchers. With the elimination of repetitive articles and considering the inclusion and exclusion criteria, 64 articles were examined and their full text was extracted for further investigation. In the end, seven articles complied with the criteria and enter the meta-analysis.

The information regarding these seven articles has been shown in Table 1. The total number of patients

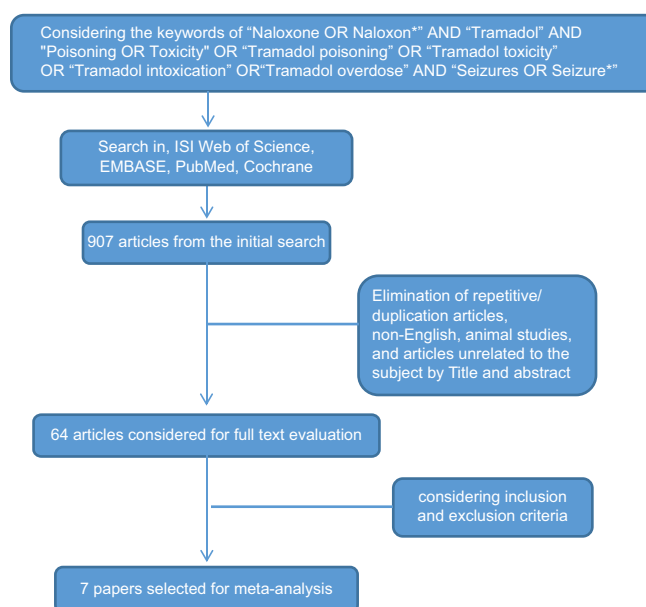


Figure 1: Flow chart of the literature search for performing the meta-analysis

Table 1: Brief details of the included published articles used for the meta-analysis

First author/area	Type of study/year	Age (years) (mean±SD) (case/control)	Sex (F/M) (case/control)	Tramadol dose (mean±SD) (case/control)	History of tramadol abuse (number) (case/control)	Past history of seizure (number) (case/control)	Co-ingestion (case/control)	Presence of factor (low blood glucose, low calcium)	Time between ingestion and admission (h) (case/control)	Outcome (case/control)	Hospital stay (h) (mean±SD) (case/control)
Farzaneh E/Iran	Case-control (RCT)/2012	27±3 26.33/29.46	10/114 case 3/59 control 7/55	NM	15 8/7	8 3/5	Co-ingestion cases were excluded	Considered as exclusion criteria	NM	Seizure 15/6 apnea 6/4 loss of consciousness 12/4. No serotonin syndrome and no mortality	7
Hassanian-Moghaddam H/Iran	Observational, retrospective/2015	3.7±2.9 range; 9 months to 10 years	9/11	13.1±19.4 mg/kg	NM	NM	Children with multiple drug exposures other than tramadol were excluded	NM	4.7±2.9 h (range: 1-10.5 h)	No complications	49.5±48.1
Marquardt K.A/USA	Retrospective chart review/2005	26.2±20.0 ranged from 9 months to 80 years	105/85	Ranged from a taste amount to 5000 mg	NM	NM	Cases with co-ingestion or unknown outcomes were eliminated	NM	NM	No effect (36.3%), minor effects (43.7%), moderate effects (19.5%) major effects (0.5%) CNS depression (n=52), coma (n=3) respiratory depression (n=1) No death, no serotonin toxicity. One case developed pneumonia	NM
Ryan N.M/Australia	Observational cases series/2015	Median age, 41 (IQR: 28-47 years, range: 17-69 years)	43/28	Median dose: 1000 (IQR: 800-2000 mg, range: 450-6000 mg)	NM	One patient	Co-ingestion cases were included	NM	NM		NM
Spiller H.A/USA	Prospective case series/1997	26.8±17.2 ranged from 1 to 86	51/36	NM	NM	NM	NM	NM	NM		15.2±15.8 (range 2-96 h)

Contd...

Table 1: Contd...

First author/area	Type of study/year	Age (years) (mean±SD) (case/control)	Sex (F/M) (case/control)	Tramadol dose (mean±SD) (case/control)	History of tramadol abuse (number) (case/control)	Past history of seizure (number) (case/control)	Co-ingestion (case/control)	Presence of seizure risk factor (low blood glucose, low calcium)	Time between ingestion and admission (h) (case/control)	Outcome (case/control)	Hospital stay (h) (mean±SD) (case/control)
Hassanian-Moghaddam H/Iran	Retrospective/2013	22.8±6.9 range, 3-72	157/368	Apnea patients 2184.2±1371 mg. Other patients 1358.4±1071.8 mg	204 (38.9%) data were not recorded in 21 (4%) patients	NM	Patients with co-ingestants were excluded	NM	50.3% (within 1-3 h) 31.4% (3-6 h post-ingestion)	One death in case/one death in control	NM
Eizadi-Mood N/Iran	Prospective data collection followed by retrospective analysis/2014	26.3±9 32.7±3.5/25±0.83	34/70 Case 6/13 Control 28/57	1562.04±1329.44 mg /1571.16±1312.47 mg	NM	One patient had a past history of seizure	NM	NM	3.5±1.07 /3.87±0.38	Aspiration pneumonia in 4 cases (2/2). Need to intubation in 14 cases (6/8). Renal failure in 3 cases (0/3). No mortality	NM

NM=Not mentioned in the article, Patients received naloxone (case) and those did not receive naloxane (control)

in these seven studies was 1101. The meta-analysis showed I^2 , 27%, (P -value, 0.23) indicating no significant heterogeneity. Naloxone did not significantly increase the risk of seizure although patients received naloxone had 1.14 chance of seizure compared to the control group (OR, 1.14; 95% CI, 0.60–2.18) (Z value, 0.40; P value, 0.69). Egger's ($P = 0.017$) test result also showed publication bias exists [Figures 2 and 3].

The squares indicate ORs for the primary studies and the size of the square reflect the statistical weight of each study. The horizontal lines also represent the estimated CIs (95%) for the odds of naloxone on the incidence of seizure. The diamond indicates overall OR and the corresponded 95% CI. The vertical line shows the line of no effect (OR = 1). The I^2 statistic gives information on how consistent results of the primary studies are (i.e., value >50% suggesting inconsistency among studies).

Discussion

We performed a meta-analysis about the relationship between naloxone administration and seizure in tramadol poisoning. Our meta-analysis showed I^2 was <50% indicating no significant heterogeneity. As a result, using the fixed effect, the OR was 1.14 (95% CI = 0.60–2.18, P value, 0.69) which was not significant, means naloxone did not increase the risk of seizure.

We included seven articles in this meta-analysis. One study performed by Hassanian-Moghaddam *et al.* was not estimable in the meta-analysis as seizure did not occur in any groups.^[34]

Two articles of this meta-analysis showed naloxone increased the risk of seizure. In a study by Spiller *et al.*, all exposure reported to seven poison centers were evaluated. The seizure was more in patients received naloxone compared to control group. From 87 tramadol cases, 8 patients received naloxone

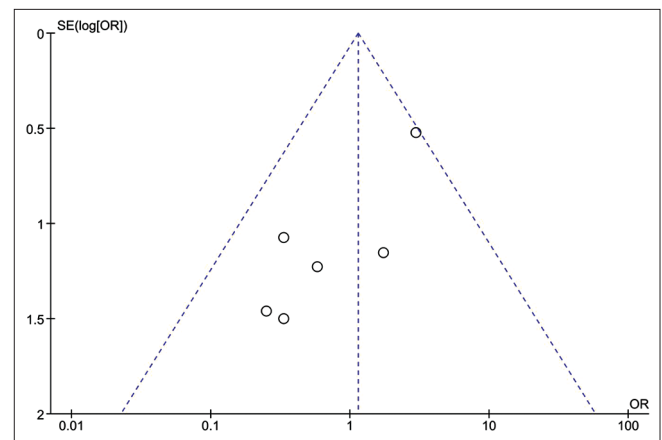


Figure 2: Funnel plot of articles about the relationship between naloxone administration and seizure in tramadol toxicity

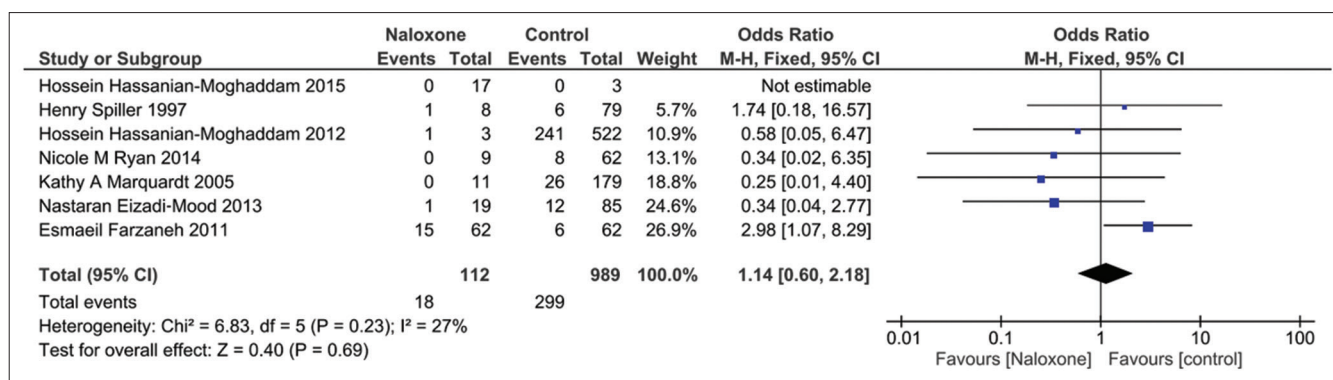


Figure 3: Forest plot of relationship between naloxone administration and seizure in tramadol

in which 1 case experienced seizure immediately after naloxone administration.^[35] However, the seizure risk factors such as a previous history of tramadol misuse, seizure, and blood glucose level had not been reported in their study which may be limiting factors. Also, urine drug screen had not been reported in 68 from 87 cases for possible co-ingestion to show the effect of drug-induced seizure. In the second study, Farzaneh *et al.* evaluated 124 patients with tramadol poisoning and randomized them into two groups, those with conservative management and those received 0.8 mg naloxone. A seizure episode had been observed more in patients received naloxone (24% versus 9%) which was significant.^[36] Although patients with co-ingestion and some predisposing factor for seizure including low blood glucose, abnormal renal function, electrolyte abnormality had been excluded in their study. However, 4.8% of patients receiving naloxone had a previous history of seizure, and 12.9% cases with seizure had a history of tramadol misuse.^[36]

Four studies included in the meta-analysis showed different results and naloxone reduced the risk of seizure.^[7,31,37,38] In a retrospective review by Marquardt *et al.* on 190 tramadol exposures and seizure did not happen in patients received naloxone. Co-ingestion as a possible risk factor for seizure had been considered as an exclusion criterion in their study.^[7] The frequency of seizure in patients received naloxone was less (5.1%) compared to control group (14.1%) in a study by Eizadi -Mood, on 104 cases of tramadol poisoning, although the rate of seizure in the naloxone group was lower, logistic regression did not support the protective effect of naloxone on seizure induced by tramadol exposure. Patients with past history of seizure or epilepsy and co-ingestion with drugs induced seizure had been excluded.^[31] Hassanian-Moghaddam *et al.* evaluated the prevalence and predisposing factors of apnea in tramadol poisoning. A seizure episode happened in one of the patients received naloxone who was also tramadol misuser.^[37] Ryan and Isbister investigated the effects of tramadol overdose. Nine patients received naloxone and

no seizure was observed. Past history of seizure, tramadol misuse, co-ingestion had not been mentioned in the group received naloxone which may be a limitation of their study.^[38]

One of the major limitations of our meta-analysis is the quality of studies. Only one randomized-controlled trial (RCT) article had our inclusion criteria for this meta-analysis. Also as the publication bias has existed in the studies included in our meta-analysis, more researches need to confirm that naloxone increases the risk of seizure. Considering of ethical guidelines, many researchers may not conduct RCT research. Secondly, due to the limited resources, we could get only articles in English.

In conclusion, Naloxone therapy did not increase the risk of seizure significantly in the treatment of acute tramadol poisoning. We suggest considering the risk/benefit when administration naloxone, especially for the seizure risk factors including previous history of seizure, tramadol misuse, and co-ingestion. Also, it might be suggested to perform an RCT study using a combination of diazepam/naloxone for tramadol overdose toxicity which has shown the beneficial effect in an animal study performed by Lagard *et al.*^[32]

Acknowledgements

We would like to thank the Isfahan Clinical Toxicology Research Center and Isfahan University of Medical Sciences. Also the authors would like to thank the staffs of the Khorshid hospital library for their great cooperation.

Authors contribution

Nastaran Eizadi-Mood, Maliheh Ghandehari, and Ali Mohammad Sabzghabae were involved in concept and design of the study. Maliheh Ghandehari, Shiva Samasamshariat, and Erfan Sadeghi did acquisition of data. Marjan Mansourian analyzed and interpreted the data. All authors contribute in drafting the article or revising it critically. Final version of the articles was approved for publishing by all authors. The manuscript has been read and approved by all the authors.

Financial support and sponsorship

The project was approved by the Institutional Ethics Committee of Isfahan University of Medical Sciences with a grant number of 393904.

Conflicts of interest

There are no conflicts of interest.

Received: 14 Jul 18 **Accepted:** 07 Oct 18

Published: 09 Oct 19

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