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Review Article

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Risk of tramadol induces seizure following naloxone therapy: Systematic review and meta-analysis

Shahin Shadnia[a], Mitra Rahimi[a], Babak Mostafazadeh[a], Peyman Erfan Talab Evini[a], Mohammad Meshkini[a], Leila Simani[b], Arezou Mahdavinejad[a], Helia Sedaghatmonfared[a], Ehsan Razeghi[a], Mahsa Daneshmand[c], Sayed Masoud Hosseini[a,*]

[a] *Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[b] *Cognitive Neuroscience Division, Department of Neurology, Columbia University Irving Medical Center, New York, USA.*
[c] *Department of comparative bioscience, faculty of veterinary medicine, university of Tehran, Tehran Iran.*

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Abstract

Tramadol overdose is a significant global health issue with a rising prevalence. Several studies have highlighted a notable occurrence of seizures in individuals experiencing tramadol overdose. The incidence of seizures following the administration of naloxone in patients with tramadol overdose remains a topic of debate. This systematic review and meta-analysis assessed the incidence of tramadol-induced seizures after the administration of naloxone in individuals who had overdosed on tramadol. Our study conducted a comprehensive search across multiple medical databases to identify articles reporting tramadol-induced seizures following naloxone therapy. The search encompassed Cochrane Central Register of Controlled Trials, MEDLINE-PubMed, Scopus, Ovid, Embase, Springer, Web of Sciences, Science Direct, and PubMed, with all searches completed by November 30, 2023. Additionally, the search encompassed reference lists of included studies and gray literature sources such as dissertations, organizational publications, and websites to gather supplementary data. The analysis involved calculating pooled odds ratio for seizure incidence between groups based on subgroups related to tramadol abuse history, seizure history, and intubation needs using fixed-effect models and odds ratios for gender distribution using random-effect models, all with 95% confidence intervals (CI).

The results indicate a marginally elevated seizure risk in the naloxone group versus controls; however, this difference did not reach statistical significance (OR: 0.91, 95% CI: 0.63–1.31; p=0.62). Subgroup analyses based on previous seizure history and tramadol abuse revealed slight differences between the naloxone and control groups in these subgroups, leading to an overall odds ratio of 0.89, 95% CI: 0.64, 1.23, with a P-value of 0.48. Further subgroup analysis indicated no significant disparity between the two groups concerning the need for intubation (p=0.13) and male gender distribution (p=0.49).

In conclusion, the study suggests that the use of naloxone in patients with tramadol toxicity does not independently trigger seizures. Naloxone administration was not associated with an increased risk of intubation or seizures. However, the lack of randomized clinical trials in this area necessitates more robust investigations to draw definitive conclusions.

Keywords: Tramadol; Naloxone; Seizure; Overdose; Poisoning.

*** Corresponding Author**:
Sayed Masoud Hosseini, , Ph.D., Toxicological Research Center, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.. E-mail: hoseinim902@gmail.com.

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The administration of tramadol and the morbidity associated with its overdose have increased in recent years [1, 2]. As reported by the Centers for Disease Control and Prevention (CDC), the age-adjusted rate of deaths due to overdose of synthetic opioids such as tramadol increased significantly since 2013 [3]. Especially following the reclassification of hydrocodone as a Schedule II controlled substance by the Drug Enforcement Administration (DEA) in the United States and the deregistration of propoxyphene-containing medications, there has been a significant rise in the prescription of tramadol for the management of chronic noncancer pain. Meanwhile, tramadol has become a commonly prescribed opioid analgesic for the management of moderate to severe pain [4, 5]. Although tramadol overdose is not typically associated with life-threatening consequences, it has the potential to induce seizures, which may subsequently elevate the risk of mortality [6].

The specific mechanism through which tramadol induces seizures remains unknown. Studies have indicated that tramadol inhibits gamma-aminobutyric acid (GABA) receptors at higher dosages [6]. The interaction between opioid function and seizure occurrence is intricate and is thought to be influenced by the distinct actions of the opioid receptors (i.e., κ, δ, and μ). The κ-receptors, predominantly on glutamatergic neurons, produce an overall inhibitory impact. In contrast, δ- and μ-receptors are typically positioned on nerve cells that impose an inhibitory effect on glutamatergic neurons, leading to an overall disinhibitory effect upon their activation [7].

Tramadol overdoses have been linked to complications such as seizures, serotonin syndrome, and central nervous system (CNS) depression. A comprehensive meta-analysis comprising 51 studies and 101,770 patients revealed that seizures are a significant complication of tramadol overdose, with an aggregated occurrence rate of 38% in cases of tramadol overdose, 37% in instances of tramadol abuse, and 3% in situations of tramadol ingestion at recommended therapeutic levels [1]. The likelihood of experiencing seizures as a result of tramadol overdose has been extensively documented. Studies have indicated that 7% of individuals who were intoxicated with tramadol experienced repeated episodes of seizures [8]. From 1997 to 2017, the Food and Drug Administration received reports of 2019 cases involving seizures related to tramadol. Among these cases, 145 were fatal [9]. Therefore, it is crucial to manage the tramadol-induced seizures effectively. The potential occurrence of a seizure and the probability of experiencing repeated seizures in cases of tramadol overdose could have notable implications for treatment strategies [8].

Management of tramadol-induced seizures mainly involves the use of a benzodiazepine such as lorazepam, supportive measures to prevent harm, and cessation of tramadol and other medications potentiating seizure [9]. Administering activated charcoal within 1-2 hours of tramadol ingestion can be beneficial for detoxification. Naloxone, an opioid antagonist routinely used for opioid overdoses, has been mainly used to manage respiratory depression in patients with tramadol overdose. However, the prescription of naloxone in tramadol overdose is controversial [10, 11]. Some studies reported no association between naloxone and tramadol-induced seizure [7, 12]. Some other studies showed that naloxone may trigger seizure occurrence in tramadol overdose patients [13-15]. These conflicting findings highlight a significant research gap regarding the appropriateness of naloxone as a treatment for tramadol toxicity.

The primary objective of the present meta-analysis is to assess the risk of seizures induced by tramadol following the administration of naloxone in tramadol overdose. A prior systematic review and meta-analysis indicated that naloxone administration did not elevate the risk of seizures in individuals with tramadol overdose [16]. This study aims to evaluate the existing studies by synthesizing data from original research published up to November 30, 2023.

2. Materials and Methods

The research protocol was approved by the Ethics Review Committee within the Research Deputy Department of Shahid Beheshti University of Medical Sciences in Tehran, Iran, under the REC code IR.SBMU.RETECH.REC.1402.449. The study methods were predetermined and recorded in a protocol officially registered with PROSPERO under the registration number CRD42023493854.

2.1. Participants, interventions, and outcomes

The present meta-analysis and systematic review follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PICO terms utilized for the research question were as follows: tramadol overdose patients who received naloxone (P); tramadol overdose patients who did not receive naloxone (C); administration of any dose of naloxone (I); occurrence of seizure following naloxone administration (O).

Seizure occurrences were documented based on specific definitions outlined in the study, and they had to be reported by the investigators, events confirmed by clinical tests, hospital admission, or documented in the electronic medical/health records. Self-reported seizures were not considered. Additionally, the study also documented the prior history of tramadol abuse and seizure.

2.2. Data sources and search strategy

PICO terms and their corresponding synonyms were derived from the MeSH database and integrated into the search syntax. Multiple databases, including the MEDLINE-PubMed, Cochrane Central Register of Controlled Trials, Embase, Scopus, and Web of Science, were searched using advanced search techniques to guarantee the thorough retrieval of relevant primary sources. The above-mentioned databases were searched up to November 30, 2023. The MeSH terms corresponding to the PICO components were retrieved from the MeSH database on the PubMed website and utilized to construct the search syntax. The search was not restricted by date or language. The detailed search syntax for each of the aforementioned databases is provided in the supplementary information (Table 1). To identify additional relevant studies, both published and unpublished (gray literature), the following methods were also employed: the reference lists of pertinent articles and textbooks were reviewed; authors of relevant studies were contacted if additional data was needed; trial registries like the International Clinical Trials Registry Platform of WHO and the ClinicalTrials.gov were searched; ProQuest Dissertations and Theses database was searched for relevant dissertation; and Google hand search was conducted.

2.3. Data collection and data analysis

2.3.1. Selection of studies

There was one interventional study (RCT) investigating the incidence of seizure after naloxone administration in patients with tramadol overdose. Besides, observational prospective or retrospective studies (e.g., cross-sectional and cohort) that investigated the incidence of seizure after naloxone administration in patients with tramadol overdose were included. After performing the search strategy, duplicates were removed. Each identified study underwent a comprehensive screening to determine whether it presented relevant data of interest. Three review authors independently screened the titles and abstracts of all retrieved studies during the literature searches and excluded studies that did not fulfill the established inclusion criteria. Subsequently, the full texts of the remaining studies were examined. Any discrepancies during the study selection process were addressed through discussion or, if required, with the assistance of a fourth review author. Case reports, case series, in vivo and in vitro studies, reviews, letters, conferences, correspondence, recommendations, and guidelines were excluded. The flowchart illustrating the process of study selection is presented in **Figure 1**.

2.3.2. Data extraction and management

A standardized data abstraction form was created to extract information from the studies included in the analysis. Two reviewers independently extracted participant's baseline characteristics data, including sample size, age, gender, country ethnicity, type of tramadol exposure, and underlying disease. Additional data included study type (e.g., cross-sectional, cohort, RCT) and publication year, pharmacological exposures and interventions (which include descriptions of the pharmacological intervention, dosage, and frequency of administration), and outcome events (e.g., seizure occurrence, seizure frequency, need for intubation, ICU admission, duration of hospitalization, mortality). Any discrepancies during the data extraction process were addressed through discussion or consultation with another reviewer if necessary. Subsequently, the extracted data was entered into the Revman® v.5.4.1 software for meta-analysis.

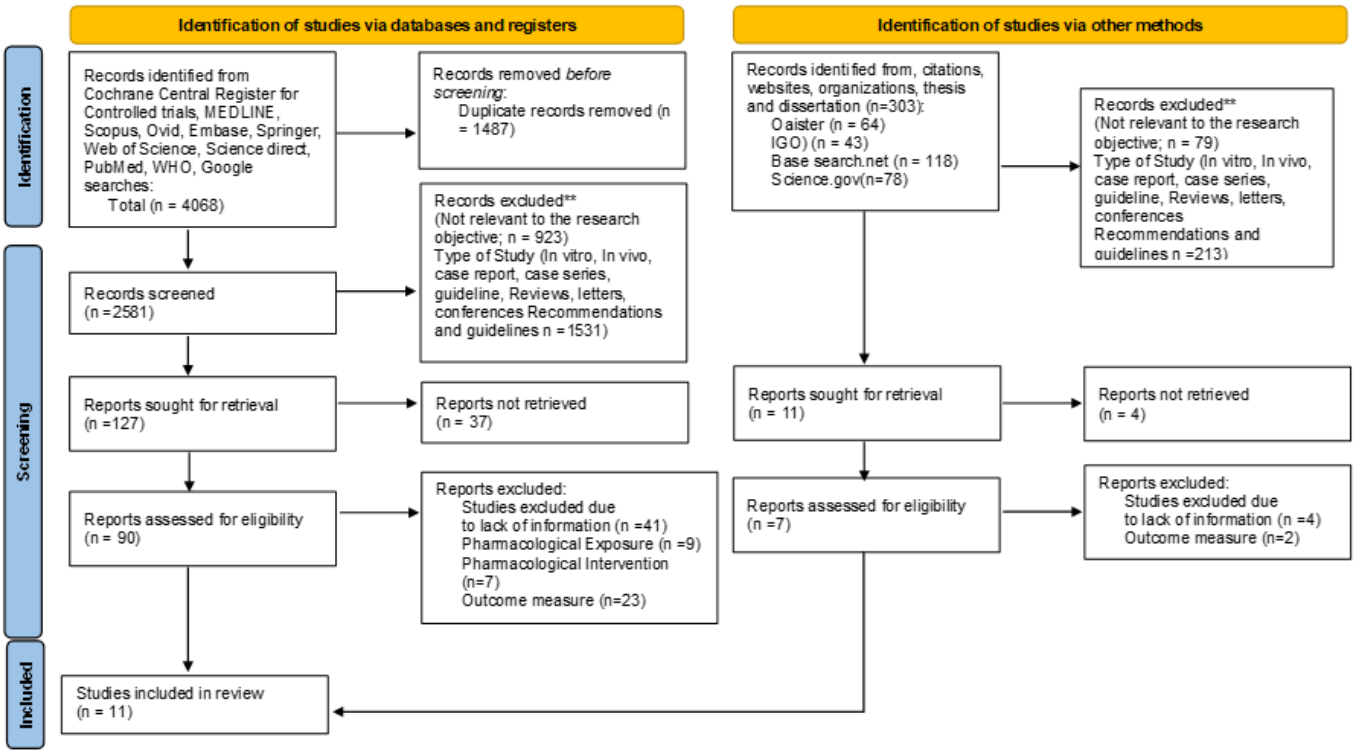

Figure 1. Flowchart of primary study selection process

2.4. Risk of bias assessment (ROB)

The quality of one randomized controlled trial (RCT) was assessed using the Cochrane Risk of Bias (RoB) tool, including assessments of random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting. For the included cohort and cross-sectional studies, bias was evaluated by BM and PETE using the Newcastle-Ottawa quality assessment scale. This scale evaluates the criteria for selecting study groups, their comparability, and the determination of outcomes in cross-sectional and cohort studies. While both cohort and cross-sectional studies are vulnerable to various biases, the NOS assessment scale has effectively assessed potential biases in observational studies. In cases where additional information was required, the authors of the articles were contacted. Two independent authors scored the quality of the studies. Discussions were conducted to resolve any disagreements that arose during the ROB, and when deemed necessary, consultation with the third author was sought.

2.5. Dealing with missing data

The researchers tried to reach out to the authors of the articles to acquire any missing data. If some authors were uncooperative, the data from their articles were not included in the study. However, there has been a debate concerning the potential impact of these omitted data on the systematic review results.

2.6. Assessment of heterogeneity

Heterogeneity was evaluated using the I^2 statistic, with interpretation guided by the thresholds recommended in the Cochrane Handbook for Systematic Reviews of Interventions to assess variability in intervention effects across studies. According to these thresholds, heterogeneity might not be important if the I^2 value falls between 0% and 40%, may represent moderate heterogeneity if it ranges from 30% to 60%, may indicate substantial heterogeneity if it lies between 50% and 90%, and may reflect considerable heterogeneity if it is within 75% to 100%.

2.7. Data synthesis

Data synthesis was done using Cochrane Revman v.5.4.1 for meta-analysis of the data. LibreOffice Calc v.7.0.4.2 analyzed the central variables. The study employed fixed- and random-effects models to calculate the odds ratio (OR) and their corresponding 95% confidence intervals (CIs) for the specified outcome. Meta-analysis was performed on continuous and categorical variables from the included studies, with a minimum of three studies analyzing the same data type. Single-study findings were excluded from the meta-analyses and were instead described qualitatively. The choice between fixed and random-effects models depended on significant heterogeneity. Specifically, a fixed-effects model is applied when heterogeneity is absent, whereas a random-effect model is employed when heterogeneity is present. Subgroup analyses were conducted to assess the incidence of seizures after naloxone treatment in individuals with tramadol overdose to investigate potential variations in outcomes based on the male gender and intubation requirement.

3. Results and Discussion

3.1. Search results and Characteristics of included studies

The pre-established search methodology returned 4371 publications, with 303 sourced from gray literature, as depicted in **Figure 1**. After eliminating duplicate entries, 2884 records were available for initial screening. Subsequently, 2873 publications were excluded based on predetermined inclusion criteria, leaving 90 publications for comprehensive text evaluation. Ultimately, 11 studies met the criteria for data extraction.

3.2. Study characteristics

The eleven studies incorporated in this analysis comprised one randomized controlled trial, three prospective cohort studies, and seven cross-sectional studies, all published from 1997 to 2019. These studies investigated adults (n=10) and children (n=1). The characteristics of the included studies are presented in **Table 1**. The Mean age of patients who received naloxone was 23.4 years old, while the mean age of those in the control group who did not receive naloxone was 26 years. All studies accounted for both genders in their analyses. The sample size varied from 19 to 742, with a total sample size of 1798.

The ingested dose of tramadol in the control group ranged from 6.45 mg/kg to 2000 mg, and in the naloxone-received group ranged from 8.8 mg/kg to 3200 mg. The most frequent reasons for overdose were suicide, abuse, and accidental exposure, respectively. All 11 studies included in the meta-analysis provided information on the seizure occurrences in both naloxone and control groups.

Table1. Demographics and clinical characteristics of included studies.

First author	Year of publication	Country	Type of study	total cases (n)	Naloxone group (n)	control group (n)	seizure in control group	seizure after naloxone	ROB
Spiller HA, [28]	1997	USA	Prospective cohort study	87	8	79	6	1	***
Farzaneh S, [27]	2012	Iran	Cross-sectional study	122	60	62	7	16	***
Farzaneh ES, [21]	2012	Iran	Randomized controlled trial	124	62	62	6	15	High ROB
Hossein Hassanian-Moghaddam, [29]	2015	Iran	Cross-sectional study	20	17	3	0	0	***
Rania Hussein, [17]	2017	Egypt	Prospective cohort study	60	30	30	15	2	****
Kathy A Marquardt, [30]	2005	USA	Cross-sectional study	190	11	179	26	0	***
Neeraj Chhabra, [31]	2017	USA	Cross-sectional study	742	93	649	41	7	**
Brian Patrick Murray, [7]	2019	USA	Cross-sectional study	80	11	69	39	3	******
Nastaran Eizadi-Mood, [18]	2013	Iran	Cross-sectional study	104	19	85	12	1	****
Arash Okazi, [32]	2018	Iran	Prospective cohort study	250	27	223	71	7	*****
Hossein Hassanian-Moghaddam, [33]	2012	Iran	Cross-sectional study	19	3	16	5	1	**

However, only two studies reported a previous history of seizures in these groups, and two reported the need for intubation in patients. Tramadol abuse was mentioned in only two studies. Most studies had low quality and a high risk of bias. A detailed risk of bias assessment was presented in the supplementary material (**Figures 2**, **3**, and **4**).

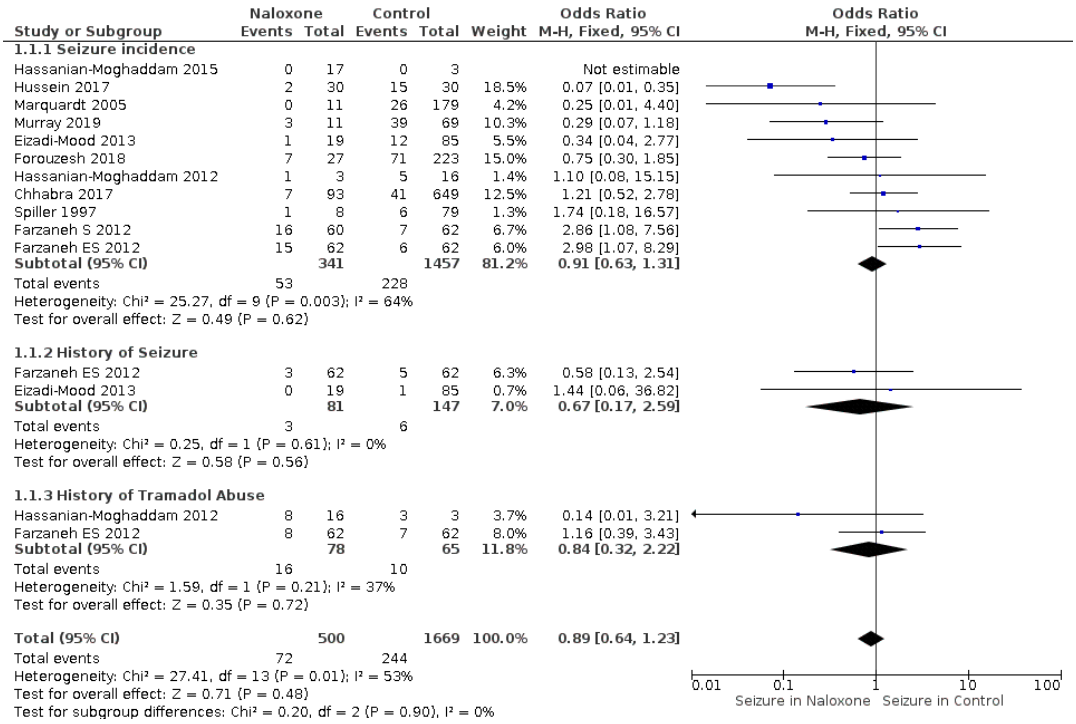

Figure 2. Forest plot for the odds ratio of seizure incidence in the naloxone-receiving group versus the control group. Subgroup analysis was conducted on the history of seizures and the history of tramadol abuse in patients. Weights are from fixed-effects analysis.

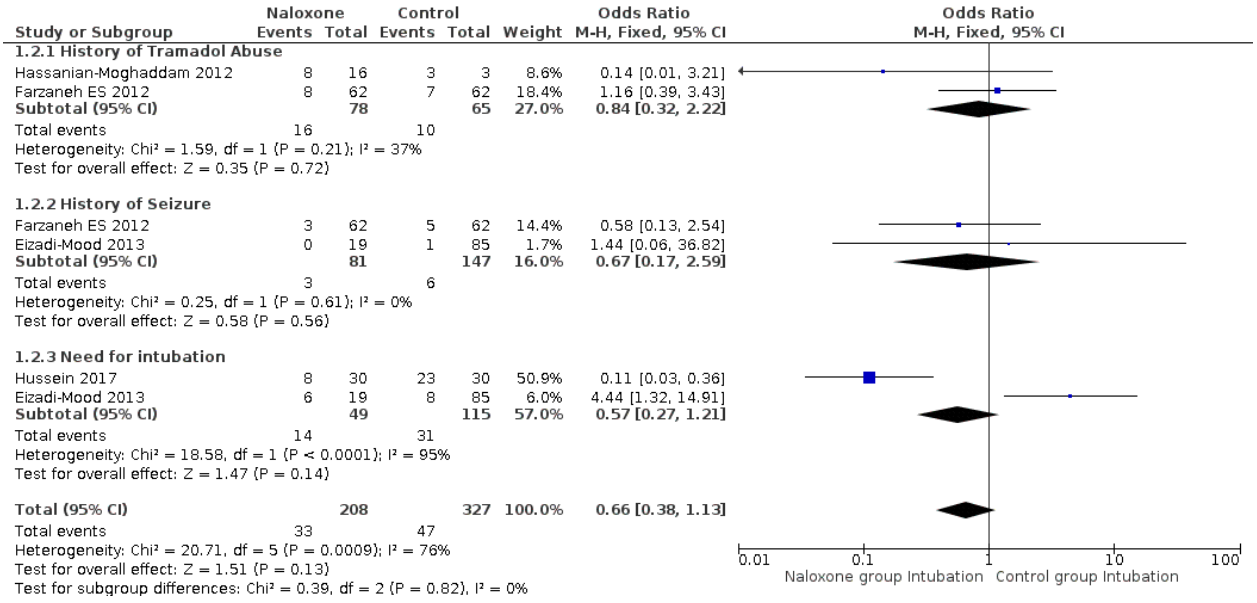

Figure 3. Forest plot for the odds ratio of intubation requirement in the naloxone-receiving group versus the control group. Subgroup analysis was conducted on the history of seizures and the history of tramadol abuse in patients. Weights are from fixed-effects analysis.

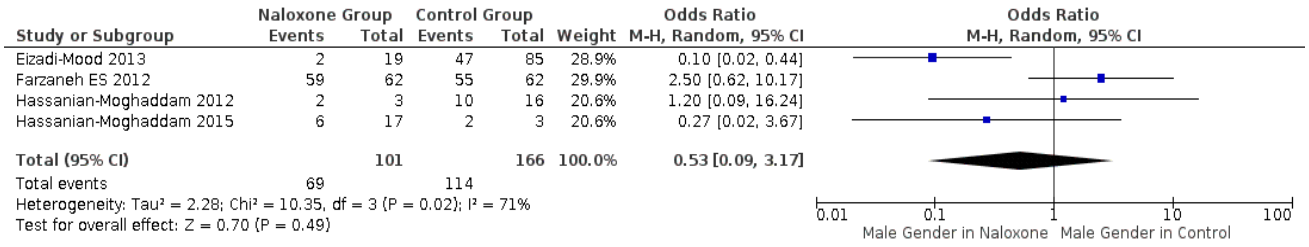

Figure 4. Forest plot for the odds ratio of male gender distribution in the naloxone-receiving group versus the control group. Weights are from random-effects analysis.

3.3. Meta-analysis

Figure 2 presents the comparison of seizure incidence between the naloxone and control group. The odds of seizures appeared slightly higher in the naloxone group, but compared with the control group, the observed difference was not statistically significant (odds ratio: 0.91 [0.63, 1.31], P value = 0.62). When incorporating the subgroup analyses of previous seizure history and tramadol abuse, slight differences between the naloxone and control groups emerged in these specific analyses. The overall analysis yielded an odds ratio of 0.89 [0.64, 1.23] with a P-value of 0.48. However, the studies exhibited a high level of heterogeneity (53%), which limited the ability to establish a definitive relationship between naloxone use and seizure incidence in patients.

The analysis of the need for intubation, depicted in Figure 3, also showed significant heterogeneity among the studies. The data indicated an increased requirement for intubation in the naloxone group relative to the control group; however, this difference did not reach statistical significance (odds ratio: 0.57 [0.27, 1.21], P value=0.14). Including tramadol abuse history and previous seizure history in the analysis did not significantly alter the need for intubation in patients (odd ratio: 0.66 [0.38, 1.13], P value=0.13).

The analysis of male gender distribution between the study groups, as presented in Figure 4, revealed no significant differences between the naloxone and control group patients (approximately 68.31% vs. 68.68%, respectively, P value 0.49). Similarly, the analysis of mean age in patients from four studies did not show significant differences between the naloxone and control group (23.38 vs. 26 years old, respectively).

Overall, patients across various studies used tramadol doses ranging from 500 to 10,000mg in both the naloxone and control groups. However, due to the heterogeneity of the studies, no definitive relationship could be established between the dose of naloxone used and the incidence of seizures. This limitation also applied to the analysis of hospital admissions and time of arrival at the hospital, as reported in the studies.

3.4. Discussion

The primary objective of the present study was to review the scientific literature concerning seizures induced by tramadol overdose following the administration of naloxone. Our results found no significant association between the occurrence of tramadol-induced seizure and the administration of naloxone. Even adjusting the analysis for the history of seizure and history of tramadol abuse did not alter the results. Furthermore, the analysis of male gender distribution and mean age between the study groups showed no significant differences between the naloxone and control group patients. Our findings are consistent with those of Eizadi-Mood et al. (2019), who reported no significant difference in tramadol-induced seizures between patients who received naloxone and those who did not [16].

Prior review study [16] aligning with the conclusions drawn by Murray et al. in their 2019 study [7] have also indicated that the administration of naloxone did not show any correlation with the incidence of seizures in individuals with tramadol toxicity. Furthermore, in the study by Hussien and colleagues [17], a significantly higher likelihood of seizures in the control group (patients not administered naloxone) compared to the case group (patients receiving naloxone) was observed. However, the presence of methodological constraints prevents the ability to ascertain conclusions within this study definitively. This discrepancy may be linked to the

historical context of the control group in the above-mentioned study [17]. The control group in Hussien et al.'s study was drawn from a period during the Egyptian revolution on July 25, 2011, characterized by economic and political crises, potentially contributing to lower medical standards and a higher incidence of seizures in the control group. In a study by Eizadi-Mood et al. [18], the control group included patients admitted with seizures accompanied by respiratory depression requiring tracheal intubation.

In contrast, the intervention group comprised individuals with apnea or respiratory depression (respiratory rate <12) who were administered supplemental oxygen via mask or nasal cannula. The reduced incidence of seizures observed in the naloxone-treated group might reflect their less severe clinical presentation (managed non-invasively with oxygen support) compared to the control group, who had a history of seizures and underwent intubation, indicating more critical conditions. Furthermore, several studies have reported that opioid receptor antagonists such as Antanal-1 and Antanal-2 can elevate the seizure threshold, supporting the notion that naloxone—as an opioid antagonist—may not increase seizure risk [19]. Similarly, preclinical studies have demonstrated that naltrexone, another opioid antagonist, reduces seizure-like activity [20].

In contrast, studies are reporting that naloxone may induce seizures in individuals experiencing tramadol overdose [21, 22]. However, in research studies where a higher incidence of seizures was observed in the group administered naloxone, definitive conclusions are also hindered by methodological limitations. For example, in the study by Farzaneh et al. [21], significant differences existed among patients in the control and case groups in terms of ingested dose of tramadol and time elapsed before hospital admission, potentially contributing to the increased occurrence of seizures in the naloxone-receiving group. Similarly, in the study by Eizadi-mood et al. [18], the patient groups were not adequately matched regarding consciousness levels, thereby preventing a conclusive determination of naloxone's impact on tramadol-induced seizures. Overall, the included studies have not precisely examined tramadol-induced seizures in the groups receiving naloxone and the control group separately. Given these methodological shortcomings in the primary studies and the absence of randomized clinical trials, a research gap exists in exploring the association between naloxone and tramadol-induced seizures. The specific pharmacological factors contributing to tramadol-induced seizure remain uncertain, given that most patients exhibit normal results on EEG and brain CT scans. Additional investigation is required to elucidate the underlying mechanism of tramadol-induced seizures comprehensively. There is ongoing research regarding the impact of the co-administration of benzodiazepines (BZD) and naloxone on tramadol-induced seizures. While the evidence does not strongly support the protective effects of naloxone in tramadol-induced seizures, there have been experimental reports of seizures being induced by naloxone at higher doses of tramadol. This phenomenon may be attributed to an impact on the (-) enantiomer that exceeded the counteracting effect observed on the (+) enantiomer [23].

Additionally, the seizure event observed after administering naloxone could be attributed to naloxone. The precise mechanisms through which naloxone might trigger seizures remain unclear. However, previous studies suggest a receptor-independent antagonism of γ-aminobutyric acid (GABA) is the most probable explanation [24, 25].

In this research, the impact of two specific sub-groups was also taken into account: individuals with a history of tramadol abuse and those with a history of seizures. This consideration led to a slight divergence between the two groups, suggesting a slight bias towards the naloxone group in the outcomes. Previous research has indicated that a history of tramadol misuse may result in oxidative stress, inflammatory reactions, and disturbances in the GABA neurotransmitter system, potentially increasing the risk of tramadol-induced seizures [26]. This result is consistent with the findings of Farzaneh et al. in 2012 [21] and 2011 [27], which reported that the administration of tramadol increased the likelihood of tramadol-induced seizure. Furthermore, consistent with the study by Eizadi-Mood et al. (2019), when administering naloxone to tramadol-poisoned patients, risk factors such as a prior history of seizures and tramadol misuse should be taken into consideration. Therefore, these variables may have introduced a small confounding effect in the analysis. Unfortunately, due to

insufficient data regarding the history of tramadol abuse and the history of seizure in study subjects (only two studies reported these variables data), the adjusted analysis was not rigorous enough. Thus, the interpretation regarding the confounding effect of these two variables is not assertive.

One of the notable strengths of this study was the thorough survey of scientific databases and relevant grey literature, resulting in the inclusion of a large number of articles in the analysis. Furthermore, the research aimed to distinguish between tramadol overdose patients who underwent naloxone administration and those who did not, establishing case and control groups, respectively. Subsequent subgroup analysis was carried out to enable a more thorough exploration of the potential influence of other variables on the relationship between naloxone administration and the occurrence of tramadol-related seizures. However, this study is constrained by certain limitations. A significant drawback of this systematic review and meta-analysis is the varying quality and substantial heterogeneity among the primary studies included in the review. The lack of RCTs investigating the effects of naloxone on tramadol-induced seizures resulted in incomplete data for secondary objectives.

Conclusion

In our comprehensive review and meta-analysis of existing data, it appears that there is no statistically significant association between the administration of naloxone and the occurrence of seizures in patients with tramadol overdose. Additionally, there is no clear association between the requirement for intubation and the use of naloxone in these patients. By adjusting the analysis for the history of tramadol abuse and prior seizure episodes, a slight increase in the odds of seizure incidence was observed in the naloxone-treated group. However, the observed difference was not statistically significant. The history of seizure and the history of tramadol abuse may act as confounding variables, resulting in a biased increase in tramadol-induced seizure in the control group. Age and gender do not appear to influence the incidence of seizures, intubation requirements, or length of hospital stay. Naloxone should not be withheld in tramadol overdose due to seizure risk, but further robust cohort, prospective case-control, and RCT studies are needed to confirm these findings. The presence of methodological limitations in the original research studies has created a gap in the literature regarding the investigation of the relationship between naloxone and the incidence of tramadol-induced seizures.

Conflict of interest

The authors declare no competing interests.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Authors Contributions

Conceptualization and Methodology: S.S. and S.M.H.; Literature Search: L.S. and A.M.; Screening and Selection of Studies: H.S. and E.R.; Data Extraction: S.M.H. and M.R.; Quality Assessment: B.M. and P.E.T.E.; Analysis and visualization: M.M.; Writing – Original Draft: M.D.; Writing – Review and Editing: S.M.H.

Authors Orcid numbers:

Shahin Shadnia: 0000-0002-9401-0781
Mitra Rahimi: 0000-0002-8785-8207
Babak Mostafazadeh: 0000-0003-4872-9610
Peyman Erfan Talab Evini: 0000-0002-0995-4973
Mohammad Meshkini: 0000-0001-6547-140X
Leila Simani: 0000-0002-1349-4252
Arezou Mahdavinejad: 0000-0001-9604-2018
Helia Sedaghatmonfared: 0009-0005-3060-9989
Ehsan Razeghi: 0000-0001-5480-802X
Mahsa Daneshmand: 0000-0002-8152-0117
Sayed Masoud Hosseini: 0000-0002-2046-1272

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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