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Selected Topics: Toxicology

Effects of Intravenous Lipid Emulsion Administration in Acute Tramadol Poisoning: A Randomized Controlled Trial

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□ **Abstract—Background: As the prevalence of tramadol toxicity is increasing, managing these patients with the aim of treatment and complete recovery has become a major challenge for health care professionals. Objective: This study evaluated the short-term effects of IV lipid emulsion (ILE) administration in cases of tramadol poisoning. Methods: In this double-blind, randomized controlled trial, 120 patients with pure tramadol poisoning and a Glasgow Coma (GCS) score ≤ 12 referred to a poisoning center in Tehran, Iran were selected and randomly assigned 1:1 to receive ILE 20% (intervention) or 0.9% saline (control) after admission and primary stabilization. The patient's vital signs, GCS score, hospitalization duration, and rate of seizure occurrence were recorded and compared between the two groups. Results: Mean (SD) age of participants was 25.3 (5.4) years and 84 (70%) were male. Mean (SD) ingested dose of tramadol was 3118 (244) mg, which was not different between the groups. Compared with controls, the ILE group had a higher level of consciousness after treatment (median [interquartile range] GCS score 12 [10–13] vs. 10 [8–12]; $p = 0.03$). In addition, length of hospitalization (median [interquartile range] (2 [1–3] days vs. 4 [4–6] days; $p < 0.01$) and rate of seizure occurrence were lower in the intervention group (16/60 vs. 30/60; $p < 0.01$). Conclusions: In the setting of tramadol poisoning with a decreased level of consciousness and based on our study's findings, administration of ILE is suggested to help manage patients in hospital emergency departments. However, larger trials might be needed to confirm these findings before entering the guidelines. © 2023 Elsevier Inc. All rights reserved.**

□ **Keywords—IV lipid emulsion; poisoning; tramadol; randomized controlled trial**

Introduction

Tramadol is a synthetic analgesic with a direct effect on the central nervous system (CNS). Although it is considered an opioid due to its active metabolite O-desmethyl-tramadol, which is the mu receptor agonist, it is commonly prescribed for moderate to severe pain relief, as it is considered safer than other opioids because of its low probability of respiratory depression and low potential for dependence and abuse (1,2). Some reported adverse effects of tramadol include tachycardia, hypertension, seizure, respiratory depression, agitation, CNS depression, and serotonin syndrome (3–7). The maximum recommended dose of tramadol is 400 mg daily,

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but some of its complications, such as seizures, can occur even at the therapeutic dose (1,2,8). The high availability of tramadol in the Middle East has contributed to its growing use in this region (1,9). In Iran, tramadol poisoning or abuse is a very common scenario among patients in poisoning emergencies, with a prevalence of 13.1% among all patients with drug poisoning, in addition to seizure and mortality rates of 34.6% and 0.7%, respectively (10). The liver metabolizes tramadol via N- and O-demethylation–mediated cytochrome P450 pathways (particularly CYP2D6) and is primarily excreted through the kidneys (6). The frequency of rapid metabolizers in Iran varies from 12% (reported in the Eastern Mediterranean area) to 21% (reported in Saudi Arabia), depending on their geographical origin, due to genetic differences (11).

IV lipid emulsions (ILEs), initially developed for parenteral nutrition, have indicated effectiveness in the treatment of local anesthetic systemic toxicity (LAST) (12–14). The evidence supports the use of ILEs in LAST resuscitation, to the extent that the American Society of Regional Anesthesia and Pain Medicine advised ILE for local anesthetic–induced cardiotoxicity (15). The role of ILEs in reversing the adverse effects of poisoning with various systemic drugs has been an issue of interest in clinical toxicology. Although many studies have investigated the role of ILE in several drugs and substances such as cocaine, calcium channel blockers, β-blockers, organophosphates, digoxin, non–local anesthetics drugs, and psychotropic agents, one randomized controlled trial (RCT) and an animal investigation found ILE reduced seizure and mortality from acute tramadol toxicity, respectively (16–21). Administration of ILE has gained interest in recent years in clinical settings as well. In terms of antipsychotic drugs, ILE had a positive impact on patients' Glasgow Coma Scale (GCS) score and length of stay after clozapine poisoning (22). Consistent with this, an RCT reported the safety and efficacy of ILE administration in antipsychotic-related poisoning (23). In line, another randomized trial evaluated the effect of ILE in non–local anesthetic drug poisoning, which found an association between ILE and increased GCS score (24). In addition, the positive impacts of ILE administration in metoprolol were reported in a human experimental model (25). ILE has also been trialed in patients with aluminum phosphide poisoning (18,26). Finally, concerning organophosphate poisoning, two studies were performed and found conflicting results (27,28).

However, there is still a lack of high-quality evidence to support using ILEs to treat systemic drug poisoning, especially tramadol. In this study, we sought to examine the short-term effects of ILE administration in managing tramadol-intoxicated patients with decreased levels of consciousness.

Materials and Methods

Study Design, Study Setting, and Population

This RCT included patients with tramadol poisoning who were admitted to the emergency department of a university-affiliated referral poisoning center in Tehran, Iran, from April 2019 to February 2021. Patients aged from 16 to 65 years, with a positive history of $\geq$ 400-mg tramadol ingestion, a positive urine screen test, clinical manifestation of tramadol poisoning, and GCS score $\leq$ 12 (scale of 3–15) were included in this study. The urine screen test qualitatively assessed the presence of tramadol and several other drugs, stimulants, and opioids separately (including tramadol, methadone, morphine, amphetamine, methamphetamine, tricyclic antidepressants, cocaine, cannabis, buprenorphine, and benzodiazepine). Patients were only included if they had pure tramadol toxicity without any other positive test. Dosing of the tramadol ingested was determined via statements from bystanders, companions, or family members; empty blister packs of tramadol tablets found with the patient; or statements from the emergency medical services team. This was double-checked with the patient after gaining full consciousness. Those for whom dosing could not be determined were excluded.

Patients with respiratory depression were administered naloxone at a starting dose of 0.05 mg every 1–2 min. Patients with an improved level of consciousness and respiratory depression after naloxone administration; positive drug tests other than tramadol; medical disorders (e.g., diabetes; renal, hepatic, or cardiac diseases; cancer; or AIDS), other conditions requiring particular nutrition regimens that might interfere with body metabolism and hence affecting ILE metabolism, and pregnant and lactating women were excluded from the study. Any patients deemed high risk for ILE infusion (assessed on the basis of medical history of hyperlipidemia and cerebrovascular or coronary diseases) were excluded. Finally, patients diagnosed with epilepsy or any other medical condition causing seizures were excluded from our trial.

Ethical Considerations

The Research Ethics Committee of Tehran University of Medical Sciences approved this study. Obtaining informed consent from the patients was not possible due to their decreased level of consciousness; written informed consent was obtained from representatives of the patients after a brief explanation before participation in the study.

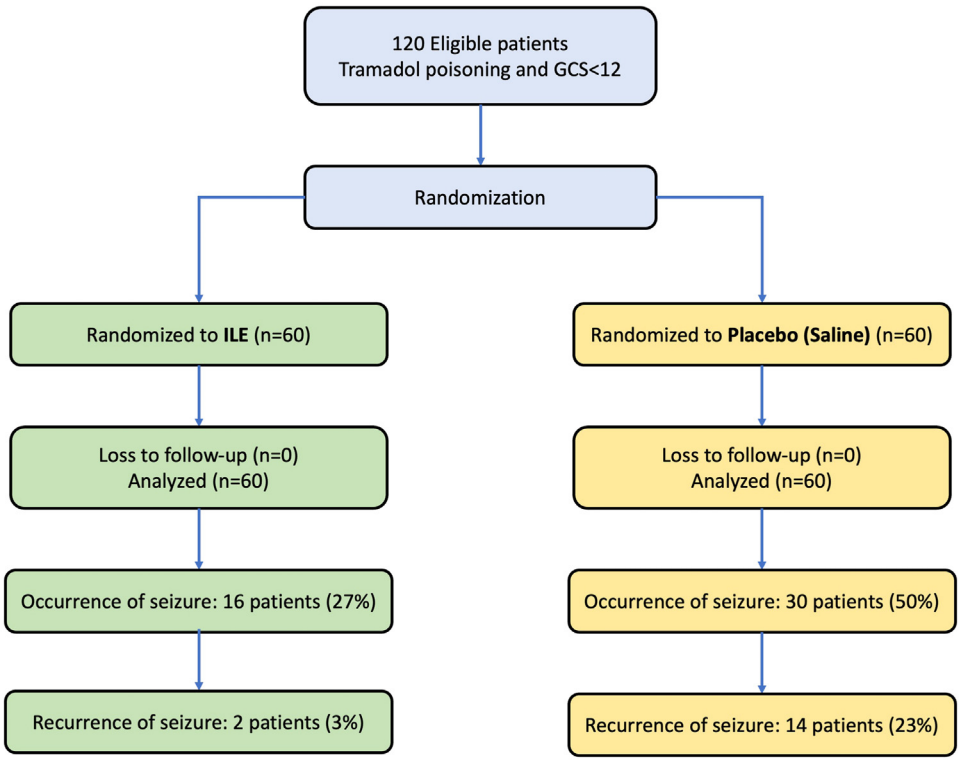

Figure 1. Study enrollment, distribution of studied patients, and seizure occurrence during hospital stay. GCS = Glasgow Coma Scale; ILE = IV lipid emulsion.

Method of Determining the Sample Size

We calculated the sample size using G * Power software, version 3.1.9.2, considering α equal to 0.05 and study power 0.8 for each group for the occurrence of seizure outcome, and considering possible sources of reduction in the number of patients in each group. A prior study found a seizure frequency of 35% in patients with tramadol poisoning (10). Using Russ Lenth's power tool with an α of 0.05 and power of 80%, an absolute reduction of 25% was calculated.

Randomization and Allocation Concealment

In this study, 120 patients with pure tramadol poisoning and decreased level of consciousness were ultimately studied. We performed randomization using computer-generated random numbers. They were then randomly allocated into the intervention or control groups (60 patients in each group) by applying the sequentially numbered, opaque, sealed envelopes method (29). Demographic characteristics, the ingested dose of tramadol, and vital signs were recorded using a checklist at the time of admission.

Intervention and Control Groups

In the intervention group, patients received 100 mL ILE 20% infusion (SMOFlipid 20%, each 1000 mL containing soybean oil, refined 60 g; triglycerides, medium-chain 60 g; olive oil, refined 50 g; fish oil rich in omega-3 fatty acids 30 g; glycerol 25 g; purified egg phospholipids 12 g; all-rac-α-tocopherol 163–225 mg; sodium hydroxide to adjust pH at 8; sodium oleate 0.3 g; water for injection to 1000 mL) as a bolus and a maximum of 250 mL in the following 15 min, in addition to routine supportive care (such as mechanical ventilation, cardiac monitoring, volume expansion, administration of benzodiazepine drugs, and sodium bicarbonate), if needed (18,30). The control group received 0.9% saline. All patients were blinded in their grouping because they were not completely conscious at the time of ILE infusion. In addition, the site study staff, investigators, and clinical providers were all blinded to the allocated treatments. To ensure the blinding of the health care team, a colored sleeve was placed over the infusion bags for both ILE serum and saline.

Outcome Measurement

In this study, vital signs such as systolic and diastolic blood pressure (SBP and DBP), pulse rate, respiratory

depression (respiratory rate < 10 breaths/min or oxygen saturation < 90%), body temperature, and GCS score of the patients were recorded three times: at the time of admission and at 12 and 24 h after admission in two groups (31). These were measured by the physician. Patients in both groups were evaluated for clinical and laboratory signs of hyperlipidemia (especially triglyceride levels > 400 mg/dL) for potential complications. In both groups, the length of hospital stay, occurrence of seizure or its recurrence, and other complications during hospital stay were also reported. Seizure occurrence was assessed by a bedside researcher who was an observer in the ward. Length of hospital stay was obtained from electronic health records of the hospital. Rhabdomyolysis was determined on the basis of serum creatine kinase levels, as the most sensitive indicator of myocyte injury (32). Pneumonia was defined on the basis of radiologic findings and clinical signs and symptoms.

Statistical Analysis

The intention-to-treat method was used for analysis, however, there was no crossover between the groups and there were no missing data. Statistical analysis was performed using SPSS software, version 22 (IBM Corp). Data are presented as mean (SD) for normally distributed variables or median (interquartile range [IQR]) for categorical and skewed variables. The χ^2 test and Fisher exact test were used to analyze the qualitative variables. The *t* test and Mann-Whitney *U* test (according to the distribution of the quantitative variables) were also used for the data analysis. For nonparametric variables (GCS and hospitalization duration) Kruskal-Wallis H test was used. The level of statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

As depicted in Figure 1, all 60 patients randomized to ILE or saline were analyzed. Mean (SD) age of all participants was 25.3 (5.4) years, without any significant difference between intervention and control groups (23.2 [6.7] vs. 27.5 [4.0] years; $p = 0.17$). In the intervention group, 40 were male; in the control group, 44 of the 60 patients were men ($p = 0.42$). The mean (SD) dose of ingested tramadol was 3118 (244) mg (range 400–10,000 mg) and was not significantly different between groups. In addition, the median GCS scores were 10 and 9.5 in the intervention and control groups, respectively. Moreover, baseline body temperature, SBP, DBP, and pulse rate were similar in the groups. There was no difference in the occurrence of seizures before randomization (26/60 in the ILE group and 18/60 in the control group; $p = 0.13$). Details of the baseline characteristics of patients are presented in Table 1.

Study Outcomes

Table 2 compares vital signs, GCS, length of hospital stay, and rates of complications between the intervention and control groups at 12 and 24 h after admission. In-hospital seizure occurred in 16 of the ILE patients during or after treatment, and in the control group, 30 patients had seizures ($p = 0.04$). Moreover, the recurrence of seizures was reported in 2 of the patients allocated to ILE compared with 14 patients in the control group ($p < 0.01$) (Figure 1).

The level of consciousness (based on GCS score) was higher in patients receiving ILE 12 h after admission (median [IQR] 12 [10–13] vs. 10 [8–12]; $p = 0.03$). In addition, patients randomized to ILE had significantly lower mean SBP ($p = 0.04$). One day after admission, ILE patients had a higher GCS score (median [IQR] 14 [11–15] vs. 12 [9–14]; $p = 0.02$). Similarly, SBP and DBP were both lower in the ILE group. No significant difference was observed in pulse rate and respiratory depression after 12 or 24 h. ILE administration was associated with a shorter length of hospital stay compared with controls (median [IQR] 2 [1–3] days vs. 4 [4–6] days; $p < 0.01$).

Outcomes in Patients Experiencing Seizures Before Admission

A comparison of patients experiencing seizures before admission is presented in Table 3. There was no difference between the ILE group and controls in GCS and SBP after 12 h of admission. However, the length of stay was significantly lower in the ILE group (median [IQR] 3 [2–5] days vs. 5 [4–7] days; $p = 0.02$).

Patients with respiratory depression at admission were analyzed for assessment of hospitalization duration (28/60 in ILE and 34/60 in the control group; $p = 0.44$). In the subgroup of patients having respiratory depression, patients receiving ILE had a significantly lower duration of hospitalization compared with the control group (3 [2–5] days vs 7 [6–8] days; $p = 0.01$).

All patients made a full recovery at discharge. No blood lipid abnormality was reported for any of the patients.

Discussion

We investigated the effect of ILE administration in patients with acute tramadol poisoning. Tramadol intoxi-

Table 1. Comparison of Patients' Characteristics Between the Intervention and Control Groups at the Time of Admission

Variable	Intervention Group (n = 60)	Control Group (n = 60)	*p* Value
Gender, n (%)			0.42
Male	40 (33)	44 (37)	
Female	20 (17)	16 (13)	
Age (years), mean (SD)	23.2 (6.7)	27.5 (4.0)	0.17
Delay from drug consumption to admission (h), mean (SD)	4.7 (1.3)	4.3 (1.2)	0.12
Dose of ingested tramadol (mg), mean (SD)	2840 (216)	3397 (269)	0.37
Glasgow Coma Scale score, median (IQR)	10 (8–10)	9.5 (7–10)	0.51
Body temperature (°C), mean (SD)	37.1 (0.44)	37.3 (0.44)	0.11
Respiratory depression, n (%)	28 (46.7)	34 (56.7)	0.27
Occurrence of seizure before randomization, n (%)	26 (43)	18 (30)	0.13
Systolic blood pressure (mm Hg), mean (SD)	129.7 (19.9)	127.7 (18.8)	0.68
Diastolic blood pressure (mm Hg), mean (SD)	80.5 (2.0)	83.2 (1.1)	0.83
Pulse rate (beats/min), mean (SD)	105.2 (10.2)	102.1 (8.7)	0.64

IQR = interquartile range.

Table 2. Comparison of Vital Signs, Glasgow Coma Scale, Duration of Hospitalization, and Rate of Complications Between the Intervention and Control Groups 12 and 24 h after Admission

Variable	Intervention Group (n = 60)	Control Group (n = 60)	*p* Value
12 h after admission			
GCS score, median (IQR)	12 (10–13)	10 (8–12)	0.03
SBP (mm Hg), mean (SD)	120.8 (10.2)	129.9 (14.1)	0.04
DBP (mm Hg), mean (SD)	77.1 (15.2)	82.4 (9.6)	0.58
PR (beats/min), mean (SD)	108.3 (15.5)	102.2 (22.8)	0.13
Respiratory depression, n (%)	6 (10)	10 (16)	0.28
24 h after admission			
GCS score, median (IQR)	14 (11–15)	12 (9–14)	0.02
SBP (mm Hg), mean (SD)	123.4 (11.0)	131.0 (9.6)	0.03
DBP (mm Hg), mean (SD)	78.9 (8.9)	85.4 (6.2)	0.04
PR (beats/min), mean (SD)	119.6 (19.9)	115.1 (75.8)	0.21
Respiratory depression, n (%)	2 (3.3)	6 (10)	0.14
Duration of hospitalization (days), median (IQR)	2 (1–3)	4 (4–6)	< 0.01
Occurrence of seizure, n (%)	16 (27)	30 (50)	< 0.01
Recurrence of seizure, n (%)	2 (3)	14 (23)	< 0.01
Pneumonia, n (%)	8 (13)	14 (23)	0.16
Rhabdomyolysis, n (%)	2 (3)	10 (17)	0.01

DBP = diastolic blood pressure; GCS = Glasgow Coma Score; IQR = interquartile range; PR = pulse rate; SBP = systolic blood pressure.

Table 3. Comparison of Variables After 12 h in the Intervention and Control Groups in Patients with Seizure

Variable	Intervention Group (n = 26)	Control Group (n = 18)	*p* Value
12 h after admission			
Glasgow Coma Scale score, median (IQR)	9 (8–11)	8.5 (8–11)	0.67
Systolic blood pressure (mm Hg), mean (SD)	128.0 (19.7)	131.9 (13.4)	0.34
Diastolic blood pressure (mm Hg), mean (SD)	70.9 (15.2)	78.9 (9.9)	0.02
Pulse rate (beats/min), mean (SD)	112.3 (12.8)	98.3 (22.9)	0.28
Respiratory rate (breaths/min), mean (SD)	11.4 (2.4)	10.8 (4.0)	0.32
Body temperature (°C), mean (SD)	37.2 (0.4)	37.4 (0.5)	0.14
Duration of hospitalization (days), median (IQR)	3 (2–5)	5 (4–7)	0.02

IQR = interquartile range.

cation can affect several organ systems, including gastrointestinal, central nervous, cardiovascular, respiratory, renal, and endocrine systems, in addition to causing serotonin syndrome and rhabdomyolysis (33). Recently, tramadol poisoning has been a significant cause of drug toxicity in Iran, and the most frequent complications of tramadol toxicity include seizure, respiratory depression, and tachycardia (34–36).

Seizure is considered one of the most serious adverse effects of tramadol overdose and is often tonic–clonic and self-limiting (37). However, there were reports of recurrent seizures after tramadol poisoning, which led to long-term use of anticonvulsant medications (8). Moreover, each seizure episode is accompanied by an increase in the risk of trauma and neurologic sequelae. Hence, and due to the need for cost reductions concerning the length of hospital stay in developing countries with resource constraints, seizure prevention in tramadol-intoxicated patients is of high importance. Some animal studies have reported the effectiveness of ILE in preventing seizures and lowering the mean DBP in tramadol-injected rabbits, and have reported promising effects of ILE in hemodynamic stabilization and seizure prevention in adult male albino rats, consistent with our present findings (20,38). Nevertheless, use of ILE in the treatment of poisoning had been studied in only a few scenarios, which were based mainly on low-quality clinical evidence and cost-effectiveness (39). There was only one human RCT investigating the role of ILE in acute tramadol poisoning management (21). This study found a significantly lower incidence of seizures and a shorter stay in the ILE-receiving group, which aligned with our findings. However, some differences should be noted. First, patients in this study had a relatively lower ingested tramadol dosage compared with ours. Accordingly, seizure occurrence was also lower in the previous study, attributable to the lower dosage. Our study might be able to differentiate the groups in more detail.

Previous studies in nonpoisoned patients have shown that ILE administration increases diastolic blood pressure by enhancing α1-mediated vasoconstriction and decreasing endothelium-mediated vasodilation (40,41). The rise in blood pressure might be an adverse effect of tramadol poisoning, although this was not seen in our study and all patients were normotensive at admission (42). The difference in blood pressure at 12 and 24 h was statistically significant in our study, but not clinically significant. Indeed, this should not be considered among the main prominent findings of our study, and further high-quality studies are required on the effects of tramadol intoxication and ILE administration on blood pressure among intoxicated patients.

The Lipid Injection for the Purpose of Antidotal Effect in Lipophilic Medicine Intoxication (LIPAEMIC) report presents the results of a 3-year study of the effects of ILEs on various systemic toxicities (43). No intoxications with tramadol have been included in the LIPEAMIC report. This report found that drug-induced loss of consciousness response to ILE begins immediately after infusion. The median GCS score increased from 4 to 8 after ILE administration in drug-induced obtundation, however, one serious and two minor adverse effects of ILE were reported in a total of 48 cases. These adverse effects included bronchospastic reaction, hyperamylasemia, and interference with laboratory analysis. Our trial found no adverse effect in patients, consistent with case reports, case series, and systematic reviews (44).

Patients receiving ILE had significantly higher GCS score after 12 and 24 h of admission. Although GCS score elevation may result from the time passed from ingesting tramadol, it should be noted that prolonged low consciousness can cause complications, such as aspiration and respiratory depression. The need for clinical contextualization should be considered, as GCS score might not be a practically useful tool in poisoned patients (45).

The effect of ILE on seizure due to tramadol toxicity can also be attributed to the lipid sink theory, as ILE administration removes tramadol from the tissues to prevent it from coupling to its receptors (19). However, the "lipid sink" theory may have some limitations in justifying our findings due to the short half-life of ILE. A novel term introduced recently—*lipid shuttle*—may provide better evidence and be more important in explaining the physiology behind ILE effects (46). This mechanism represents increased blood carriage, "shuttling" drugs from vital target organs, such as the brain and heart, to other organs for storage or detoxification.

In this study, all of the patients survived and were discharged in good condition, but those treated with ILE regained consciousness earlier, and their length of hospital stay and rate of complications were lower than the control group. In addition, the frequency of rhabdomyolysis was higher in the controls, which might have led to longer hospitalization in this group.

The frequency of in-hospital seizure occurrence in our study was 38.5% in patients with acute tramadol poisoning. Noteworthy, our study was well-suited for the study of seizure frequency, given the young mean age of our population (25 years) and the previously observed increased frequency of tramadol-induced seizure in younger patients (47).

Limitation

There are several limitations that should be mentioned. First, as our study had a relatively low sample size, it should be treated as a pilot trial. The second limitation was the precise determination of the consumed dose of tablets. The patients were selected from those who had ingested $\geq$ 400 mg of tramadol to fulfill the tramadol intoxication criteria. Although we tried to assess exactly based on available data, there was no definitive measurement of the ingested dose. Thus, the probability of bias remains considerable. However, according to inclusion criteria, consumption dose or drug serum level dose did not influence the criteria for choosing the patients. Third, the lack of sufficient information regarding patients' history of other drug uses and their potentially related seizures may have influenced the study results. Fourth, despite our best efforts, the blinding of the health care workers might have been affected by several factors, such as the unclear status of IV cannula flushing after the intervention. Fifth, the lack of data for consciousness and respiratory rate for early hours after randomization could be another limitation of our study. Finally, the lack of data regarding seizure control with benzodiazepines in those randomized to the ILE vs. control group highlights the need for further evaluation of this in future studies. The short-term follow-up of the patients after ILE administration and the single-center nature of the study were other limitations of this research. Multicenter RCTs with larger sample sizes should be conducted to better evaluate the effect of various ILE regimens on acute tramadol poisoning.

Conclusions

This study found short-term benefits of ILE infusion in patients with tramadol intoxication and loss of consciousness who were admitted to the emergency department. Although ILE could reduce hospitalization time and seizure rate, these results are not definitive and this study is hypothesis-generating for future studies. With the support of future larger clinical trials, ILE can be a suitable potential candidate for use in the acute setting for patients referred for tramadol poisoning.

Declaration of competing interest

None.

References

1. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg 2017;124:44–51.
2. Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry (Edgmont) 2009;6(4):17–21.
3. Spiller HA, Gorman SE, Villalobos D, et al. Prospective multicenter evaluation of tramadol exposure. J Toxicol Clin Toxicol 1997;35:361–4.
4. Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. Am J Health Syst Pharm 1997;54:643–52.
5. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol 2008;27:201–5.
6. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 2015;18:395–400.
7. Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clin Toxicol (Phila) 2015;53:545–50.
8. Shadnia S, Brent J, Mousavi-Fatemi K, Hafezi P, Soltaninejad K. Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. Basic Clin Pharmacol Toxicol 2012;112:133–6.
9. Bigdeli I, Corazza O, Aslanpour Z, Schifano F. Novel psychoactive substances (NPS): a study on Persian language websites. Iran J Public Health 2013;42:511–15.
10. Rostam-Abadi Y, Gholami J, Amin-Esmaeili M, et al. Tramadol use and public health consequences in Iran: a systematic review and meta-analysis. Addiction 2020;115:2213–42.
11. Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Trends Pharmacol Sci 1999;20:342–9.
12. Raman M, Almutairdi A, Mulesa L, Alberda C, Beattie C, Gramlich L. Parenteral nutrition and lipids. Nutrients 2017;9:388.

13. Ciechanowicz S, Patil V. Lipid emulsion for local anesthetic systemic toxicity. Anesthesiol Res Pract 2012;2012.
14. Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity. Reg Anesth Pain Med 2018;43:113–23.
15. Neal JM, Bernards CM, Butterworth 4th JF, et al. ASRA practice advisory on local anesthetic systemic toxicity. Reg Anesth Pain Med 2010;35:152–61.
16. Arora NP, Berk WA, Aaron CK, Williams KA. Usefulness of intravenous lipid emulsion for cardiac toxicity from cocaine overdose. Am J Cardiol 2013;111:445–7.
17. Sebe A, Dişel NR, Açıkalın Akpınar A, Karakoç E. Role of intravenous lipid emulsions in the management of calcium channel blocker and β-blocker overdose: 3 years experience of a university hospital. Postgrad Med 2015;127:119–24.
18. ELabdeen SMZ, Saad K, Oreby MM, Elgazza FM. Assessment of intravenous lipid emulsion as an adjuvant therapy in acute aluminum phosphide poisoning: a randomized controlled trial. Ain Shams J Forensic Med Clin Toxicol 2020;34:51–68.
19. Levine M, Hoffman RS, Lavergne V, et al. Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity. Clin Toxicol (Phila) 2016;54:194–221.
20. Vahabzadeh M, Moshiri M, Mohammadpour AH, Hosseinzadeh H. Promising effects of intravenous lipid emulsion as an antidote in acute tramadol poisoning. Reg Anesth Pain Med 2013;38:425–30.
21. Kazemifar AM, Yazdi Z, Bedram A, Mahmoudi J, Ziaee M. Effects of intravenous lipid emulsion on tramadol-induced seizure; a randomized clinical trial. Arch Acad Emerg Med 2021;9(1):e20.
22. Elgazzar FM, Elgohary MS, Basiouny SM, Lashin HI. Intravenous lipid emulsion as an adjuvant therapy of acute clozapine poisoning. Hum Exp Toxicol 2021;40:1053–63.
23. Basiouny S, Elgohary M, Elgazzar F, Lashin H. Intravenous lipid emulsion as an adjuvant therapy of acute antipsychotic poisoning: a randomized controlled trial. Ain Shams J Forensic Med Clin Toxicol 2022;38:19–32.
24. Taftachi F, Sanaei-Zadeh H, Sepehrian B, Zamani N. Lipid emulsion improves Glasgow Coma Scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning–a randomized controlled trial. Eur Rev Med Pharmacol Sci 2012;16(suppl 1):38–42.
25. Petersen KM, Bøgevig S, Petersen TS, et al. Hemodynamic effects of intravenous, high-dose lipid emulsion with and without metoprolol infusion in healthy volunteers: a randomized clinical trial. Clin Pharmacol Ther 2019;105:1009–17.
26. Taalab YM, Helmy M, Aba El -Hassan A. Evaluation of the role of intravenous lipid emulsion as a putative treatment for acute aluminum phosphide poisoning. Mansoura J Forensic Med Clin Toxicol 2022;30:71–84.
27. Pannu AK, Garg S, Bhalla A, Dhibar DP, Sharma N. Lipid emulsion for the treatment of acute organophosphate poisoning: an open-label randomized trial. Clin Toxicol (Phila) 2022;60:602–8.
28. Majeed S, Malik AH, Dar B. Evaluation of intravenous lipid emulsion as a novel therapeutic antidote in severe organophosphorous poisoning–a prospective randomized, comparative study. Al Ameen J Med Sci 2019;12:160–5.
29. Clark L, Fairhurst C, Torgerson DJ. Allocation concealment in randomised controlled trials: are we getting better? BMJ 2016;355:i5663.
30. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. Scand J Trauma Resusc Emerg Med 2010;18:51.
31. Gupta K, Prasad A, Nagappa M, Wong J, Abrahamyan L, Chung FF. Risk factors for opioid-induced respiratory depression and failure to rescue: a review. Curr Opin Anaesthesiol 2018;31:110–19.
32. Efstratiadis G, Voulgaridou A, Nikiforou D, Kyventidis A, Kourkouni E, Vergoulas G. Rhabdomyolysis updated. Hippokratia 2007;11:129–37.
33. Nakhaee S, Hoyte C, Dart RC, Askari M, Lamarine RJ, Mehrpour O. A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment. Forensic Toxicol 2021;39:293–310.
34. Bazmi E, Behnoush B, Hashemi Nazari S, Khodakarim S, Behnoush AH, Soori H. Seizure prediction model in acute tramadol poisoning; a derivation and validation study. Arch Acad Emerg Med 2020;8(1):e59.
35. Behnoush B, Bazmi E, Nazari SH, Khodakarim S, Looha MA, Soori H. Machine learning algorithms to predict seizure due to acute tramadol poisoning. Hum Exp Toxicol 2021;40:1225–33.
36. Iravani FS, Akhgari M, Jokar F, Bahmanabadi L. Current trends in tramadol-related fatalities, Tehran, Iran 2005-2008. Subst Use Misuse 2010;45:2162–71.
37. Dasgupta HS, Sahoo DP, Barman B, Brahma D. Low-dose tramadol-induced seizure: a case report. J Pharmacol Pharmacother 2022;13:203–6.
38. El Zahed ES, Khalefa AA, Shalaby N, Ahmed F. The role of lipid emulsion in treatment of acute tramadol toxicity in adult male albino rats. Zagazig J Forensic Med 2018;16:59–75.
39. Gosselin S, Hoegberg LC, Hoffman RS, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol (Phila) 2016;54:899–923.
40. Haastrup AT, Stepniakowski KT, Goodfriend TL, Egan BM. Intralipid enhances alpha1-adrenergic receptor mediated pressor sensitivity. Hypertension 1998;32:693–8.
41. Gosmanov AR, Smiley DD, Peng L, et al. Vascular effects of intravenous intralipid and dextrose infusions in obese subjects. Metabolism 2012;61:1370–6.
42. Lehmann KA, Horrichs G, Hoeckle W. [The significance of tramadol as an intraoperative analgesic. A randomized double-blind study in comparison with placebo]. Der Anaesthesist 1985;34(1):11–19.
43. Cave G, Harvey M, Willers J, et al. LIPAEMIC report: results of clinical use of intravenous lipid emulsion in drug toxicity reported to an online lipid registry. J Med Toxicol 2014;10:133–42.
44. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila) 2010;48:1–27.
45. Fulton JA, Greller HA, Hoffman RS. GCS and AVPU: the alphabet soup doesn't spell "C-O-M-A" in toxicology. Ann Emerg Med 2005;45:224–5 author reply 5.
46. Fettiplace MR, Weinberg G. Lipid emulsion for xenobiotic overdose: PRO. Br J Clin Pharmacol 2023;89:1708–18.
47. Jovanović-Cupić V, Martinović Z, Nesić N. Seizures associated with intoxication and abuse of tramadol. Clin Toxicol (Phila) 2006;44:143–6.

Article Summary

1. Why is this topic important?

As the prevalence of tramadol poisoning is increasing, there is a need for better management and prevention of seizures.

2. What does this study attempt to show?

This study aimed to show the efficacy of intravenous lipid emulsion (ILE) in patients with acute tramadol poisoning using a randomized controlled trial.

3. What are the key findings?

ILE reduced the incidence rate of seizures, decreased the duration of hospital stays, and increased the level of consciousness.

4. How is patient care impacted?

Patient care can be influenced by reduced hospitalization time and better outcomes in the course of hospitalization.