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ORIGINAL RESEARCH

The Effect of Methylphenidate on The Consciousness Level of Intoxicated Patients; a Double-Blind Clinical Trial

Faraz Zandiyeh[1], Maral Ramezani[2,3], Mahdiye Abiyarghamsari[4], Shahin Shadnia[5], Babak Mostafazadeh[5], Peyman Erfan Talab Evini[5], Omid Mehrpour[6], Mitra Rahimi[5]*

1. Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Department of Pharmacology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
3. Traditional and Complementary Medicine Research Center, Arak University of Medical Sciences, Arak, Iran
4. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5. Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
6. Michigan Poison & Drug Information Center, Wayne State University School of Medicine, Detroit, MI, USA.

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Abstract: **Introduction:** Intoxication-related unconsciousness is a frequent and challenging condition in emergency medicine, where rapid interventions are critical to improve patient outcomes. This study aimed to evaluate the efficacy of methylphenidate in improving consciousness levels of intoxicated patients. **Methods:** In this double-blind clinical trial, intoxicated patients over 18 years of age with the Glasgow Coma Score (GCS) 13 and below were studied. 51 people were included in the intervention group and received methylphenidate, while 50 were in the control group and received placebo. Consciousness levels were measured using the Reed score before and at 12, 24, 36, and 48 hours post-intervention and compared between groups using SPSS software version 21. **Results:** 101 patients with the mean age of 34± 14.26 (range: 17-81) years were studied (55.4% male). 74.5% of the people in the intervention group achieved the most alert state (a REED score of zero) after 48 hours, compared to only 32% in the control group. The intervention group had significantly lower average Reed scale (0.33) compared to the control group (0.76) 48 hours after the treatment (p = 0.001). Using Methylphenidate in treatment of intoxicated patients showed effect size of 0.703 (95% confidence interval (CI): 0.299-1.104), number needed to treat of 2.17 (95%CI: 1.48 - 3.34), absolute risk reduction of 46% (95%CI: 0.29 -0.67), and relative risk reduction of 57% (95%CI: 0.37 - 0.72). **Conclusion:** It seems that, the use of methylphenidate in patients with intoxication can reduce the time it takes for their consciousness to return to a normal level. Since benzodiazepines are the leading cause of poisoning, this study suggests that methylphenidate could be beneficial in cases of benzodiazepine poisoning to aid in cognitive recovery.

Keywords: Consciousness; Methylphenidate; Mental Status Schedule; Poisoning

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1. Introduction

Intoxication-related unconsciousness is a frequent and challenging condition in emergency medicine, where rapid interventions are critical to improve patient outcomes. Impaired consciousness poses a diagnostic challenge in the emergency department. Sudden changes in consciousness can be attributed to conditions affecting the brain or heart, including arrhythmias and seizures. Life-threatening infections affecting organs such as the lungs and liver, as well as drug-induced organ dysfunction, may also lead to sudden changes in consciousness (1, 2). Two categories of toxins affect mental status and consciousness in overdose cases. The first category includes stimulants that can lead to confusion, agitation, hallucinations, or seizures. The second category comprises depressants that suppress brain activity, causing reduced consciousness or coma (3).

Unconsciousness caused by various intoxicants, especially depressants like benzodiazepines, opioids, and alcohol, often necessitates prolonged supportive care, particularly when specific antidotes are unavailable or ineffective. Common toxic agents—including barbiturates, baclofen, phencyclidine, carbon monoxide, and organophosphates—can also lead to severe suppression of consciousness, underscoring the need for broadly effective agents that can restore alertness across diverse toxic exposures (4). Dextrose, naloxone,

***Corresponding Author:** Mitra Rahimi; Toxicological Research Center, Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +9821 55419005, Email: mrahimi744@gmail.com, ORCID: https://orcid.org/0000-0002-8785-8207.

and thiamine are prescribed for all patients with reduced consciousness, regardless of the type of drug used, however, they are often ineffective for complex or unidentified toxic exposures, leaving prolonged unconsciousness as a common challenge (5).

Methylphenidate (Ritalin®) is a central nervous system stimulant that primarily acts on dopamine (DAT) and norepinephrine (NET) transporters to inhibit neurotransmitter reuptake, thereby increasing their levels in the synaptic space and stimulating the brain's arousal pathways (6). Studies using functional neuroimaging have indicated that cerebral metabolism can differ across various cortical regions during the conscious resting state, with slightly higher activity observed in the medial parietal, medial occipital, and middorsolateral prefrontal cortices (7). The posteromedial cortex of the parietal lobe, which includes the precuneus, posterior cingulate gyrus, and retrosplenial cortex, is linked to aspects of consciousness involving higher-level cortical and subcortical structures (8, 9).

Improvements in GCS following methylphenidate treatment were significantly linked to increased metabolism in the bilateral precuneus. Methylphenidate is associated with heightened cerebral glucose metabolism in the posteromedial cortex of the parietal lobe, which is part of the neural network responsible for consciousness. This area may be crucial for the pharmacological response to methylphenidate in patients with impaired consciousness (9). Through this mechanism, methylphenidate may counteract sedative-induced unconsciousness by restoring alertness and responsiveness (10). Commonly prescribed as a first-line treatment for attention-deficit/hyperactivity disorder (ADHD) (6, 11), methylphenidate has also shown benefits in improving cognitive function and treatment outcomes in patients with traumatic brain injury (TBI), where it has been associated with faster recovery of consciousness (12-15). Evidence further suggests that methylphenidate can enhance consciousness levels in patients poisoned with benzodiazepines, supporting its potential role in treating intoxication-related unconsciousness (16). Some studies have disputed the positive effects of methylphenidate on enhancing treatment outcomes for patients with TBI (17). Despite these promising findings, there is limited research on its application in unconsciousness due to other types of intoxication. This study aimed to evaluate methylphenidate as a broadly effective consciousness-enhancing agent for intoxicated patients, addressing a significant gap in current treatment options for this condition.

2. Methods

2.1. Study design and setting

This double-blind randomized clinical trial was conducted on over-18-year-old patients with the Glasgow coma scale (GCS) 13 and below, who were hospitalized at intensive care unit of Loghman Hakim Hospital, Tehran, Iran, in 2024, following intoxication. 51 people were included in the group receiving methylphenidate and 50 in the control group, receiving placebo. Consciousness levels were measured using the REED score before and at 12, 24, 36, and 48 hours post-intervention and compared between groups.

Loghman Hakim Hospital is a toxicology referral center, which is equipped with advanced diagnostic and treatment facilities, staffed by highly trained medical professionals specializing in toxicology. The hospital not only provides critical care for poisoning cases but also actively engages in research and education to enhance poison management strategies. Its comprehensive approach has established it as a trusted institution for both patients and healthcare providers across the nation.

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1402.812). The IRCT (IRCT20220305054196N4; date: 2024-03-29) code was also obtained. Before beginning the study treatment, informed consent was obtained from the patient's legal guardian, in addition to deferred consent. The legal guardian completed the consent form and the study items were explained.

2.2. Participants

The inclusion criteria for the study were over 18 years of age, obtaining consent from the patient's legal guardian, experiencing reduced consciousness due to intoxication (GCS 13 and below), and possessing the ability to move for psychomotor testing. It is necessary to measure the level of movement in most consciousness measurement methods. According to this, patients unable to move due to conditions such as cervical spine injury were excluded from the study. The intoxication and its cause were confirmed by medical examinations, patient history, and laboratory tests. There are no limitations on the type of poisoning for inclusion in the study, and the tests serve to confirm the poisoning.

Patients with a history of allergy to methylphenidate, those with unstable vital signs (severe tachycardia, hypotension, hemothorax), oral drug intolerance (If it is not possible to provide the patient with a safe way to administer the drug orally), pregnant and lactating women, individuals who had received an antidote in the current intoxication, those with a history of brain damage, high blood pressure, ischemic heart disease, and epilepsy were excluded from the study. Additionally, patients with mental health issues, blindness, and deafness were also excluded from the study. The reason for excluding these individuals was to prevent errors and correctly assess the state of consciousness.

2.3. Intervention

After inclusion, the patients were randomly allocated to either the control group (placebo) or the group receiving methylphenidate using the Random Number Generator version 1.4, which assigned a number between 1 and 101 to each patient after 48 hours in the ICU. Even numbers assigned pa-

tients to the control group; odd numbers assigned patients to the intervention group. In the intervention group, in addition to the routine care performed in the control group, 5 mg of methylphenidate (Ritalin®, Novartis company) was administered orally twice daily from the second to the fifth day of hospitalization. This dose was selected based on the usual dosing schedule of the methylphenidate. The intervention was discontinued when the patient's level of consciousness reached a GCS of 15 and a REED score of 0. The control group, in addition to the routine care, patients received placebo. The placebo was crafted to mimic methylphenidate in every aspect: shape, size, color, and taste.

We waited for 2 days and then the intervention was started. Because first, we wanted to see if consciousness improved without intervention and if the patient's consciousness improved, the patient was removed from the study; and second, to ensure that the patient did not have any contraindications for the use of methylphenidate, based on tests and examinations. All stages of patient selection and review of inclusion and exclusion criteria were performed by clinical toxicology experts. The number assigned to the patient determined the group. For even-numbered patients, the medicine was given from box 1, and for odd-numbered patients, the medicine was given from box 2. The patients, researcher, data analyzer, and the nurse giving the medicine were blinded to the contents of boxes 1 and 2 and did not know which medicine was the actual treatment and which was the placebo. Drug and placebo boxes were supplied with completely similar appearance and packaging.

2.4. Data gathering

The patient's level of consciousness was checked and recorded using the GCS and REED Score (Table 1) before the intervention and then at 12, 24, 36, and 48 hours after the intervention. In addition, the patient's age, gender, and the type of substance causing intoxication were also recorded. The REED score is easy to use, and in this study, the level of consciousness was measured in a relative manner, evaluating improvement or non-improvement, but it can also be completely measured. The GCS score has been used as well to cover the fog of errors. The data was gathered by researchers using a predesigned checklist.

2.5. Statistical analysis

The sample size needed for each group, with a 95% confidence level, 80% test power, d=0.049, and =0.087 was determined to be 50 individuals for each group using the specified formula. The data was analyzed using SPSS software version 21. The normality of the population was assessed using the Kolmogorov-Smirnov test; parametric data was analyzed using an independent t-test and repeated measure ANOVA with Tukey's posttest, while non-parametric data was analyzed using the chi-square test. The difference between the means of two independent groups, expressed as a standardized effect size, was calculated as the difference between the means divided by the standard deviation (Cohen's d) using independent T-test. The number needed to treat (NNT), absolute risk reduction (ARR), relative risk reduction (RRR), and effect size were calculated and reported with 95% confidence interval (CI). A significance level of $p \leq 0.05$ was used.

3. Results

3.1. Baseline characteristics of studied patients

After randomization, 51 cases were included in the group receiving methylphenidate and 50 in the control group (figure 1). Table 2 compares the baseline characteristics of studied patients between intervention and control groups. The control group had an average age of 33.12 ±12.4 (range: 18 to 73) years, while the methylphenidate group had an average age of 34.84 ± 17.0 (range: 27 to 81) years (P=0.546). The number of men in the methylphenidate and control groups was 36 (70.6%) and 20 (40%), respectively (P=0.002). The average GCS in the methylphenidate and control group was 9.94 ± 2.6 and 10.96 ± 1.9, respectively (P=0.226). The most common cause of poisoning in the control group was benzodiazepines alone (40%), followed by the simultaneous use of benzodiazepines and tramadol (14%). In the methylphenidate group, the most common causes were the use of benzodiazepines (35.3%) and methadone (15.7%) alone (p =0.412) (Figure 2).

3.2. Outcomes

Tables 3 and 4 compare the conciseness level between intervention and control groups based on Reed coma scale and GCS score before and 12, 24, 36, and 48 hours after treatment. No significant difference was observed between groups before and 12, 24, and 36-hour post-intervention (Figure 3). However, at 48 hours, a significant difference emerged, with the methylphenidate group showing significantly lower average scores (0.33 ± 0.6 vs. 0.76 ± 0.6; p = 0.001).

Repeated measures ANOVA for the control group revealed a significant decrease in Reed scale from baseline to 36 hours, baseline to 48 hours, and from 12 hours to 48-hour post-treatment (Table 5).

Based on the cause of intoxication, the change in conciseness level after 48 hours was only significant in cases involving benzodiazepines (p = 0.027) and methadone (p = 0.033) intoxication.

The effect size was 0.703 (95%CI: 0.299-1.104), which indicates that treatment with methylphenidate was effective. NNT, ARR, and RRR were 2.17 (95%CI: 1.48-3.34), 0.46 (95%CI: 0.29-0.67), and 0.57, or 57% (95%CI: 0.37 - 0.72), respectively.

4. Discussion

This study aimed to assess the effectiveness of methylphenidate in improving consciousness in patients with intoxication-related unconsciousness. Results demonstrated that methylphenidate significantly accelerated consciousness recovery, with 74.5% of treated patients

reaching full alertness by 48 hours, compared to 32% in the control group. Methylphenidate and similar neurostimulants offer a potential treatment option for healthcare providers caring for neurologically impaired patients. While there is growing evidence supporting the use of these medications in comatose or minimally conscious patients with traumatic brain injury, their efficacy in patients with decreased consciousness due to intoxication remains less well-established.

A difference of just 1 point leads to the patient waking up more quickly, thereby shortening their hospital stay. It also decreases the risk of hospitalization-related complications like venous thrombosis, pulmonary embolism, and bedsores.

In this study, men comprised more of the sample than women (56% vs. 45%). Gender distribution in poisoning cases varies across studies. Similar to our findings, Tabibzadeh et al.'s study on poisoning cases in Bandar Abbas also reported a higher prevalence of males than females (18). On the other hand, in Kazemifar et al.'s study on poisoned people in Qazvin, more women than men were reported (52.3% women and 47.7% men) (19). The selection of people in this study was completely random, so the number of male and female people in both groups is completely random. Since gender was not influential in this study, gender randomization will not affect the results of the study.

Our findings are consistent with previous studies, which identified benzodiazepines as the primary agents in poisoning cases across both study groups. Benzodiazepines bind to and activate GABA-A receptors in the central nervous system, leading to sedative and memory-impairing effects (20). Studies have shown that benzodiazepines are the main cause of drug overdose in Iran (19, 21-23). In this study, the mean age in the control group was 33.12 years, while in the methylphenidate group, it was 34.8 years, and the mean age of all subjects was 34 years. The average age of poisoned patients in the study by Ala et al. was 33.42 years, which is very similar to the average age in our study (24). Also, in the studies by Mehrpour, Akhlaghi, and Khodabandeh, the patients' age range was 25-40 years (23, 25, 26). According to Mohammed study, 64% of the participants were between 18 and 40 years old (2).

Latifi-Pour et al. investigated the effect of methylphenidate on individuals poisoned with benzodiazepines. They reported that the proportion of participants regaining consciousness in the methylphenidate group significantly differed from the control group. They concluded that methylphenidate is effective in improving the level of consciousness (REED score) in acute benzodiazepine-poisoned patients (16). In our study, the methylphenidate group had significantly lower average REED scores (0.33) compared to the control group (0.76) 48 hours after the treatment. In the methylphenidate group, 74.5% of the people achieved the most alert state (a REED score of zero) after 48 hours, compared to only 32% in the control group. These results showed that not only methylphenidate is effective in regaining consciousness of patients poisoned with benzodiazepines, but it can also be effective for other causes of reduced consciousness due to intoxication.

The study by Kamali et al. found that giving methylphenidate to people with traumatic brain injuries who were on mechanical ventilation in the intensive care unit led to a significantly and quickly normalized Glasgow Coma Score (GCS) score compared to the control group. They concluded that methylphenidate use in these patients was associated with reduced duration of intubation and earlier return to normal consciousness level (12). In our study, we also found that using methylphenidate significantly improves the level of consciousness.

In a study on comatose patients who had been arrested, Reynolds et al. looked at how methylphenidate and amantadine affected their outcomes. They found that neurostimulants like methylphenidate and amantadine can be used during intensive care, hospitalization, and rehabilitation to help people with neurological disorders who have brain damage from not getting enough oxygen (27). This finding was also consistent with the results of our study.

5. Limitations

Although gender does not interfere with the effect of methylphenidate, it is suggested that studies be conducted with a larger sample and an equal ratio of men and women among the groups. We considered all types of poisoning; a separate examination of each toxic agent can provide more useful information. The potential side effects of methylphenidate in intoxicated individuals were not investigated in this study, and it is recommended that future studies be designed to examine these side effects. Treatment began 48 hours after the onset, excluding patients who recovered within that timeframe. This approach may overlook the impact of methylphenidate in cases of mild intoxication. Further studies are also needed to investigate the effects of the drug in people with movement problems.

6. Conclusions

Our study stated that the use of methylphenidate in patients with intoxication can reduce the time it takes for their consciousness to return to a normal level. Since benzodiazepines are the leading cause of poisoning, this study suggests that methylphenidate could be beneficial in cases of benzodiazepine poisoning to aid in cognitive recovery. Additional research is required to apply these findings to other types of poisoning.

7. Declarations

7.1. Acknowledgments

The authors thank the Toxicological Research Center (TRC) of Loghman Hakim Hospital, affiliated with the Shahid Be-

heshti University of Medical Sciences, Tehran, Iran, for supporting this study period.

7.2. Authors' contributions

All authors equally contributed to preparing this article. All authors read and approved the final version of manuscript.

7.3. Conflict of interest

The authors declared no conflict of interest.

7.4. Data availability

The information analyzed in this study can be obtained through the designated corresponding author.

7.5. Founding and supports

Toxicological Research Center (TRC) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

7.6. Using artificial intelligences chatbots

The authors used artificial intelligence (Monica AI: deep chat & search, BUTTERFLY EFFECT PTE. LTD.) to check the grammar of the article.

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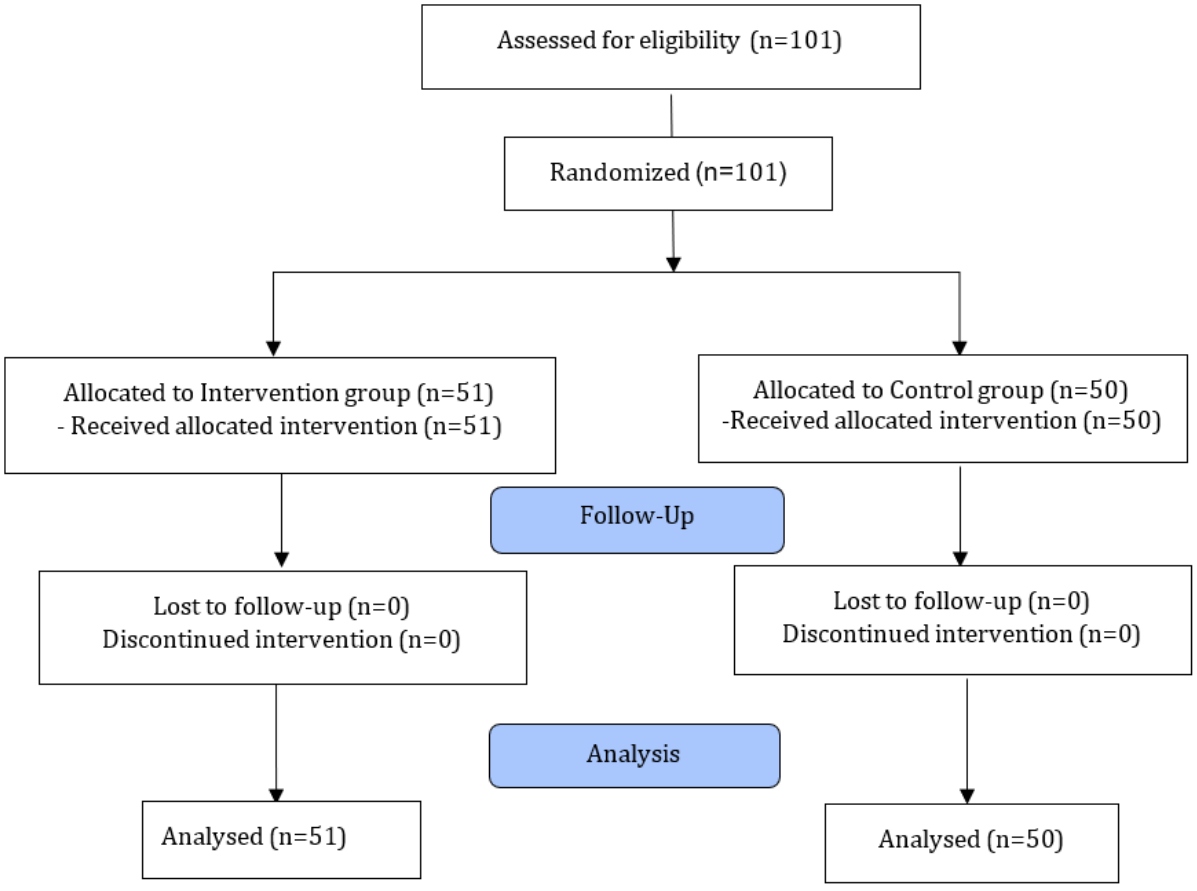

Figure 1: Flow diagram of enrollment of the participants, allocation, intervention, follow up, and analysis.

Table 1: Reed coma scale criteria

Stage	Consciousness level	Pain responses	Reflexes	Respiration	Circulation
0	Asleep	Normal	Normal	Normal	Normal
1	Coma	Decreased	Normal	Normal	Normal
2	Coma	None	Normal	Normal	Normal
3	Coma	None	None	Normal	Normal
4	Coma	None	None	Abnormal	Abnormal

Table 2: Comparing the baseline characteristics between intervention (Methylphenidate) and control groups

Variable	Groups		P-value
	Control (n= 50)	Intervention (n = 51)	
Gender			
Male	20 (40.0)	36 (70.6)	0.002
Female	30 (60.0)	15 (29.4)	
Age (year)			
Mean ± SD	33.1 ± 12.4	34.8 ± 17.0	0.546
GCS on arrival			
Mean ± SD	10.96 ± 1.9	9.94 ± 2.6	0.226
Reed scale on arrival			
Mean ± SD	2.04 ± 0.2	2.24 ± 0.7	0.054
Intubation			
Yes	10 (20.0)	18 (35.3)	0.086
No	40 (80.0)	33 (64.7)	

Data are presented as number (%) or mean ± standard deviation (SD). GCS: Glasgow coma scale.

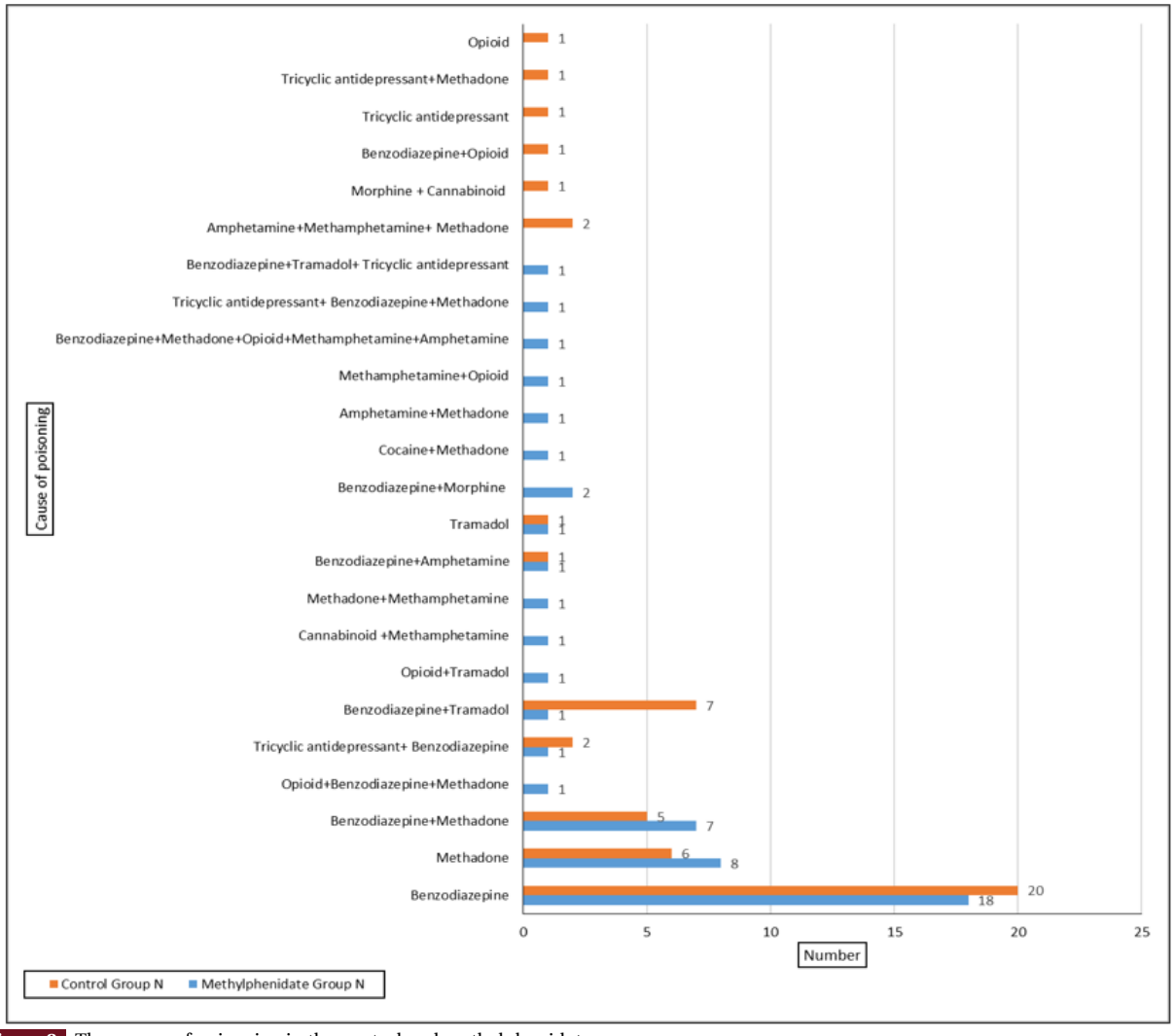

Figure 2: The causes of poisoning in the control and methylphenidate groups.

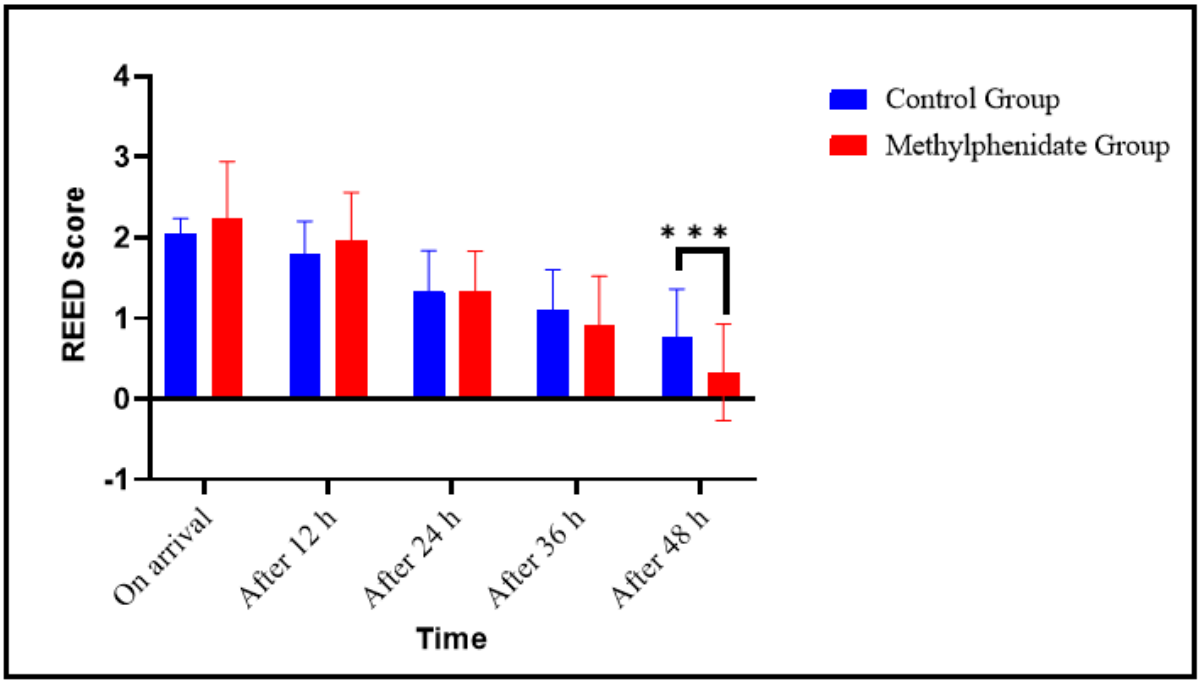

Figure 3: Change in patients' Reed coma scale in the two groups. ***: P = 0.001. The number of patients at all time points was 50 for the control group and 51 for the Methylphenidate group. Error bars are plotted based on standard deviation (SD).

Table 3: Comparison of the conciseness level (based on Reed coma scale) before and 12, 24, 36, and 48 hours after treatment between intervention and control groups

Reed scale	Groups		P-value
	Control (n= 50)	Intervention (n = 51)	
Before treatment			
0	0	0	<0.001
1	0	6 (11.8)	
2	48 (96.0)	28 (54.9)	
3	2 (4.0)	16 (31.4)	
4	0	1 (2.0)	
After 12 hours			
0	0	0	0.0062
1	10 (20.0)	11 (21.6)	
2	40 (80.0)	31 (60.8)	
3	0	9 (17.6)	
4	0	0	
After 24 hours			
0	0	2 (3.9)	0.3256
1	33 (66.0)	30 (58.)	
2	17 (34.0)	19 (37.3)	
3	0	0	
4	0	0	
After 36 hours			
0	3 (6.0)	11 (21.6)	0.0770
1	39 (78.0)	33 (64.7)	
2	8 (16.0)	7 (12.7)	
3	0	0	
4	0	0	
After 48 hours			
0	16 (32.0)	38 (74.5)	<0.001
1	30 (60.0)	9 (17.6)	
2	4 (8.0)	4 (7.8)	
3	0	0	
4	0	0	

Data are presented as number (%).

Table 4: Comparing the change in consciousness level of patients between the two groups

Consciousness	Control (n = 50)	Intervention (n = 51)	P-value
Reed coma scale			
On arrival	2.04 ± 0.2	2.24 ± 0.7	0.054
After 12 h	1.80 ± 0.4	1.96 ± 0.6	0.13
After 24 h	1.34 ± 0.5	1.33 ± 0.5	0.948
After 36 h	1.1 ± 0.5	0.92 ± 0.6	0.095
After 48 h	0.76 ± 0.6	0.33 ± 0.6	0.001
Glascow coma scale			
On arrival	10.96±1.8	9.94±2.6	0.026
After 12 h	11.42±1.8	10.76±2.2	0.105
After 24 h	12.1±1.7	11.86±2.1	0.533
After 36 h	12.72±1.8	12.76±1.8	0.908
After 48 h	13.2±1.8	14.06±1.8	0.018

Data are presented as mean ± standard deviation.

Table 5: Intra-group changes in mean consciousness level in each group using repeated measures ANOVA analysis

Reed scale	Control Group	P-value	Methylphenidate	P-value
On arrival- after 12 h	2.04±0.2 - 1.80±0.4	0.995	2.24±0.7 - 1.96±0.6	0.988
On arrival- after 24 h	2.04±0.2 - 1.34±0.5	0.182	2.24±0.7 - 1.33±0.5	0.018
On arrival- after 36 h	2.04±0.2 - 1.1±0.5	0.0122	2.24±0.7 - 0.92±0.6	<0.0001
On arrival- after 48 h	2.04±0.2 - 0.76±0.6	<0.0001	2.24±0.7 - 0.33±0.6	<0.0001
After 12 h- After 24 h	1.80±0.4 - 1.34±0.5	0.758	1.96±0.6 - 1.33±0.5	0.3098
After 12 h- After 36 h	1.80±0.4 - 1.1±0.5	0.182	1.96±0.6 - 0.92±0.6	0.0025
After 12 h- After 48 h	1.80±0.4 - 0.76±0.6	0.0029	1.96±0.6 - 0.33±0.6	<0.0001
After 24 h- After 36 h	1.34±0.5 - 1.1±0.5	0.995	1.33±0.5 - 0.92±0.6	0.851
After 24 h- After 48 h	1.34±0.5 - 0.76±0.6	0.441	1.33±0.5 - 0.33±0.6	0.0046
After 36 h- After 48 h	1.1±0.5- 0.76±0.6	0.953	0.92±0.6 - 0.33±0.6	0.4051

ANOVA: Analysis of variance.