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CLINICAL TRIAL STUDY

The Effect of Methylphenidate on Reed Scaling in Benzodiazepine Poisoning: A Prospective Trial

Masoud Latifi-Pour[1], Hossein Hassanian-Moghaddam[1], Helya-Sadat Mortazavi[1], Shahin Shadnia[1], Nasim Zamani[1] and Mitra Rahimi[1,*]

[1]*Toxicological Research Center and Excellence Center of Clinical Toxicology, Department of Clinical Toxicology, Loghman Hakim Hospital Poison Center, Shahid Beheshti University of Medical Sciences, Kamali Avenue, South Karegar Street, Tehran, Iran*

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Abstract: ***Background***: Benzodiazepine is one of the most important causes of substance abuse and intoxication throughout the world and Iran.

Objective: The aim of our study is to determine the role of stimulants in reversing CNS level in acute Benzodiazepine poisoning patients who were hospitalized at referral poison center.

Method: This was a randomized double-blind placebo-controlled trial study on 32 cases with pure acute Benzodiazepine poisoning from March 2016 to February 2017. Diagnosis of pure acute poisoning was based on history, and laboratory confirmation. We gathered the demographics, clinical data, laboratory data, hospitalization and outcome. Participants were randomized into two groups: Methylphenidate Group (MPH) and *Placebo* Group (PBO).

Results: The randomized sample consisted of 32 participants who were predominately female (83%). The majority of the PBO group and the MPH group reported improvement in their consciousness with a significant difference between the two groups (p = .005). Paired sample t-test analyses on Reed Scale data revealed an increase in the probability of improvement during the trial for the MPH group compared to the PBO group. Furthermore, the HCo3 (bicarbonate) level has a significant p-value with respect to age groups (p = .02). None of our cases required either the ICU facility or intubation.

Conclusion: Our study provided the MPH superiority over PBO in reversing CNS symptoms in loss of consciousness in acute BZD poisoned patients. Thus, this trial provides concrete evidence that improvement in consciousness levels (Reed Scale rated) among those patients receiving MPH was associated with a methylphenidate use.

Keywords: Benzodiazepines, poisoning, central nervous system stimulants, methylphenidate, *placebo* effect, clinical trial.

1. INTRODUCTION

Benzodiazepines are γ-aminobutyric acid type A receptor agonists that adhere to positions in the Central Nervous System (CNS) and apply sedative and amnestic effects [1]. Over the past six decades, the number of benzodiazepines on each prescription has increased, with each new drug representing distinctive and intricate pharmacology [2]. Alprazolam became the second most popular drug, enhancing more than eightfold [3]. They are commonly used for the short-term treatment of anxiety, insomnia, seizures, and alcohol and sedative-hypnotic withdrawal [4-7].

Benzodiazepines are responsible for one of the most common drug overdoses in our country Iran [8]. Sole benzodiazepine overdose has low mortality, and death is rare [9]. However, increased rates of morbidity do result from a mixed overdose, especially in combination with opioids. Isolated overdose with high-effective short-lasting agents, such as alprazolam, temazepam, and triazolam, is related to higher incidences of intensive care unit admissions, coma, and mechanical ventilation with toxicity compared to other benzodiazepines, such as diazepam [10]. There is significant concern regarding the over prescribing of benzodiazepines and the resultant harms. People who are benzodiazepine dependent or are at risk of abuse need to be identified and appropriately assessed in order to determine their condition. Depending on patient characteristics, benzodiazepines can be withdrawn or the patient stabilized on a maintenance program.

*Address correspondence to this author at the Department of Clinical Toxicology, Loghman-Hakim Hospital Poison Center, Kamali Avenue, South Karegar Street, Tehran, Iran; Tel/Fax: +98-21-55424041, Cell Phone: +98-912-1351330; E-mail: Mrahimi744@gmail.com

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Besides, methylphenidate (Ritalin) was first introduced to literature in its "New and Nonofficial Drugs" section in 1957. It is a CNS stimulant that is the most frequently prescribed remedy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [11, 12]. The report proclaimed the new drug to be a "central nervous system stimulant, less potent than amphetamine but more than caffeine." The therapeutic effect of MPH has been linked to its blockade of the dopamine transporter, resulting in enhanced levels of synaptic dopamine [13]. Hence, MPH is the CNS stimulant which acts on the CNS arousal system and cortex and it seems to block the reuptake of norepinephrine and dopamine into the area of presynaptic neuron, it leads to an enhancement in the level of monoamines in the extraneural space. MPH action mechanism will assist to increase the level of consciousness in benzodiazepine intoxicated cases. Intravenoususage of this product (10-30 mg, three times daily) has been shown to improve the majority of 164 patients manifesting a variety of symptoms including sleepiness, tremors, drooling, and nasal congestion [14].

As there is almost no study regarding other probable uses of Ritalin as an enhancer of consciousness in poisoned patients, we aimed to illustrate this positive aspect of Ritalin. Therefore, we planned a pilot double-blind clinical trial study to investigate whether Methylphenidate (Ritalin) can help poisoned patients with benzodiazepines to be conscious sooner or not (null hypothesis). This can have a tremendous effect on the length of hospital stay and the rate of complications in our patients. Thus, the purpose of this study was to compare the efficacy of Methylphenidate (MPH) and placebo in benzodiazepine overdose subjects.

2. MATERIALS AND METHODS

2.1. Participants

Participants were recruited at Loghman Hakim Hospital, *i.e*. a unique referral center for poisoned patients of Iran, using interview, observation, and examination processes from March 2016 to February 2017. At this point, subjects that aged between 15 to 60 years and had various grades in reduced consciousness due to consumption of pure benzodiazepines were asked to attend on a screening visit. Agitated cases were excluded at this point.

Data was collected using a biography of the patient (according to the relative's statement) along with the initial examination that was done by a toxicology fellowship. The presence of benzodiazepine residue in the urine of subjects did confirm a benzodiazepine pure toxicity. In addition, an Electrocardiogram (ECG), specific laboratory tests and interview were taken from all subjects to check the contraindications of methylphenidate consumption. As a result, individuals with cardiovascular disease, Glaucoma, Parkinson, hyperthyroidism condition, hepatic and renal disease, anxiety disorder known subjects, and pregnant women were excluded from our study.

All participants gave written informed consent before both the screening and the study procedures. This study approved and granted by the Toxicological Research Center of Shahid Beheshti University of Medical Sciences' research council (IR.SBMU.RETECH.REC.1396.318).

2.2. Settings and Study Procedures

This study was a randomized double-blind, placebo-controlled trial. The pilot study elapsed for 16 weeks and included a placebo lead-in phase followed by a stable dose period. Starch was added to all placebo and MPH capsules in an attempt to improve the blind. On the other hand, MPH capsules contained 20 mg of Methylphenidate obtained from SWARS Company. Both types of capsules were transferred following a gavage administration. All patients received one capsule every 12 hours, even when maintained on placebo.

A physician determined medication adjustments. During the study, the vital signs obtained every three hours and Reed Coma Scale was employed for the clinical assessment of consciousness (Table **1**) [15, 16]. According to the inclusion criteria, 32 patients incorporated in this study. Performing a decussate randomization process, participants were randomized to either the MPH or the PBO group.

2.3. Assessments

Our preliminary laboratory tests for participants were as follows:

Complete blood count (CBC), Blood sugar level, Serum creatinine, Blood urea nitrogen (BUN), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Sodium blood test (Na+), Potassiumbloodtest (K+), Blood gases, pH, Urine analysis, and Human chorionic gonadotropin (hCG).

Substance use assessments included patients' self-report and urine toxicology evaluation which was completed in each visit. Urine samples tested for cocaine, opiates, methadone, benzodiazepines, amphetamine, and marijuana metabolites, and scored as positive or negative based on standard National Institute on Drug Abuse (NIDA) guidelines for cut-off points.

After taking medications and within every three-hour interval, we assessed Blood pressure (S/D), pulse rate, respiratory rate, and the level of decreased consciousness based on Reed Scale table. Furthermore, a questionnaire administered at the screening to assess patterns.

Diagnoses were determined by an assistance fellowship of Clinical Toxicology who carried out the diagnostic assessment for the patients enrolled in the study. Clinical assessment of consciousness scores in three hours' intervals was used as the primary MPH outcome measure in order to determine an early consciousness. The secondary outcome measures based on MPH usage were agitation and tachycardia that did not present.

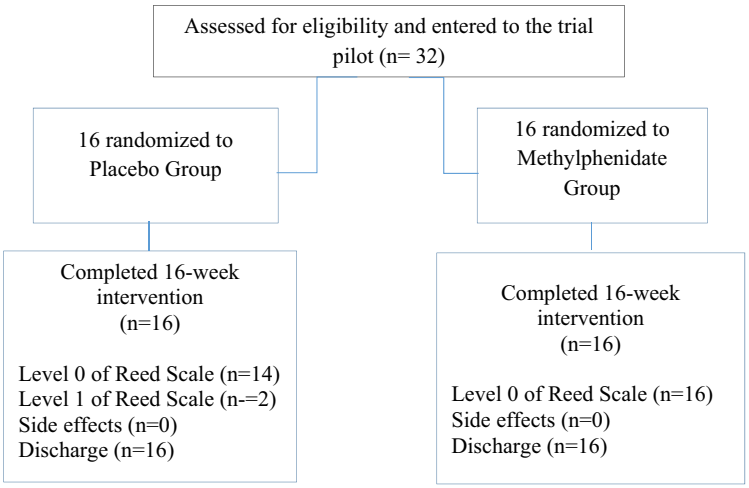
2.4. Data Analysis

Data were analyzed using the Statistical Package For Social Sciences (SPSS) version 22 and the p-value below 0.05 were considered statistically significant. Continuous data were analyzed by student's t-test if the data were normally distributed (using Kolmogorov-Smirnov); otherwise, the Mann-Whitney U-test was applied. Categorical data were compared using Pearson's chi-square test. Baseline demographic variables and screening measure variables were compared across groups using chi-square for categorical

Table 1. The Reed Scale criteria for the clinical assessment of consciousness.

Grade	Description
0	Asleep, arousable, answers questions
1	Comatose, withdraws from painful stimuli, intact reflexes
2	Comatose, does not withdraw from painful stimuli, no respiratory or circulatory depression, intact reflexes
3	Comatose, absent reflexes, no respiratory or circulatory depression
4	Comatose, absent reflexes, respiratory or circulatory problems

A:



B:

Fig. (1). A. Participants' progress through the screening, entry, randomization and medication phases of the treatment trial. **B.** Placebo and methylphenidate capsules. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

variables and one-factor (treatment) ANOVA for continuous variables.

3. RESULTS

3.1. Participant Flow

Totally, from March 2016 until February 2017, 22491intoxicated patients were documented in the Loghman Hakim Hospital Poison Center. 11949 patients hospitalized in the Toxicological ward and 931 subjects hospitalized in the medical toxicology Intensive Care Units. Fig. (**1**) outlines the patient flow during the screening process and throughout the randomized trial, and it illustrates the placebo and methylphenidate capsules.

Table 2. Baseline demographic and clinical features of randomized patients.

	Control Group (n=16)	Treatment Group (n=16)	χ2 or t, *p*	d.f.	n
Demographics					
Age (yr)	33±9.93	32.73±6.87	.931	26.752	32
Male	8 (25 %)	6 (18.75 %)	*.476*	1	14
Female	8 (25 %)	10 (31.25 %)			18
History of sedative substance use	3 (9.37 %)	4 (12.5 %)	*.5*	-	7
Duration of hospitalization (hr)	14.19±16.36	10.75±4.96	*.432*	17.733	32
Values in the table are n (%) for categorical variables or mean (S.D.) for continuous variables.					

Table 3. Baseline mean of laboratory assessment in randomized patients.

Age Group	HCo3	PCo2	pH	ALT	AST	Cr	BUN
15-20 *N=2*	23.35±4.17	48.75±3.18	7.28±0.04	14±5.66	15.5±6.36	0.9	17.5±0.7
21-25 *N= 6*	26.86±3.45	46.75±5.63	7.36±0.03	19±10.8	21.5±9.56	0.98±0.23	24.17±7.02
26-30 *N= 4*	24.45±2.63	42.45±6.4	7.36±0.03	9.22±5.72	13.32±8.73	0.95±0.12	25±2.82
31-35 *N= 7*	24.88±2.73	44.97±8.37	7.38±0.04	21.71±10.54	23.85±7.33	1.01±0.03	28±9.38
36-40 *N= 6*	28.15±3.79	53.43±9.35	7.35±0.04	23.66±20.4	28.33±26.88	0.96±0.16	27±6.78
41-45 *N= 3*	37.43±14.79	48.40±4.78	7.37±0.01	13.66±12.66	13.26±11.69	0.8±0.1	26±9.53
46-50 *N= 3*	29.7±1.73	48.73±7.21	7.4±0.05	14.66±4.72	17.66±3.51	0.9±0.2	21.33±11.15
Total *N=32*	27.42±6.03	47.56±7.46	7.36±0.04	17.99±12.31	20.47±13.96	0.95±0.15	25.16±7.54
pValue	*.02**	*.31*	*.07*	*.8*	*.8*	*.3*	*.5*

3.2. Sample Description and Retention in Treatment

Table **2** summarizes the demographic and baseline clinical characteristics. Fourteen (43.8 %) out of 32 participants randomized for this study were male. The sample had a mean age of 37 years (range 23-52 years). There were no statistically significant group differences with respect to demographics.

The results of initial laboratory assessment of randomized patients included in Table **3**. The level of HCo3 has a significant p-value with respect to age groups (p = .02). Of the 32 randomized participants, all completed the entire trial. For the primary outcome criterion, 30 participants (93.75%) met the standard response criterion and obtain consciousness and there was a significant difference between groups showing in Table **4**. For the secondary outcome measures, no cases of agitation and tachycardia were reported.

The vital signs of patients were assessed every 3 hours after intervention. The relationship between systolic/diastolic blood pressure, heart rate and respiratory rate with the hours elapsed until the patient gain the consciousness is illustrated in Table **5**. We found no significant p-value between vital signs and treatment hours. It was further examined whether an improvement in loss of consciousness was associated with consumption of Ritalin. The proportion of participants that achieve consciousness in the MPH group differed significantly from PBO receivers [$\chi^2 = 2.634$, d.f. = 11, p = .005]. Efficiency ratio of MPH was estimated as 0.142 in participants who treated with MPH. No side effects were reported

Table 4. Primary Outcome Criterion for 32 Participants.

Reed Scale Level	PBO n (%)					MPH n (%)				
	Before Treatment	After 3 hrs	After 6 hrs	After 9 hrs	After 12 hrs	Before Treatment	After 3 hrs	After 6 hrs	After 9 hrs	After 12 hrs
0	-	7 (43.75)	5 (31.25)	2 (12.5)	-	-	11 (68.75)	3 (18.75)	2 (12.5)	-
1	13 (81.25)	7 (43.75)	2 (12.5)	1 (6.25)	2 (12.5)	14 (87.5)	5 (31.25)	2 (12.5)	-	-
2	3 (18.75)	2 (12.5)	1 (6.25)	1 (6.25)	-	2 (12.5)	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	-

Related Samples Wilcoxon Signed Rank Test

	Standardized Test Statistic	*P value*
Before treatment And After 3 hrs	-4.185	***.000****
After 3 hrs And After 6 hrs	-3.000	***.003****
After 6 hrs And After 9 hrs	-2.000	***.046****
After 9 hrs And After 12 hrs	-1.000	***.317***
Before treatment And After 6 hrs	-5.135	***.000****
Before treatment And After 9 hrs	-5.353	***.000****

Odds Ratio

	OR	Cl
After 3 hours of treatment	1.57	0.823-2.999
After 6 hours of treatment	1.080	0.429-2.721
After 9 hours of treatment	2	0.751-5.329

across both groups. It is noticeable that none of our cases required either the ICU facility or intubation.

4. DISCUSSION

Benzodiazepine poisoning is principally exhibited as the significantly greater level of CNS depression, with the more common incidence of coma. Accordingly, the occurrence of related complications is greater and the hospital stay is elongated. The results of this randomized, placebo-controlled trial suggest that Methylphenidate produced a greater improvement in consciousness symptoms based on data collected using standard outcome measures. All of 16 Methylphenidate cases gained consciousness after 12 hours of intervention, whereas only 14 placebo group patients had achieved this outcome.

In this clinical trial study, the population of poisoned females was greater than the other gender. Hausken and colleagues assessed benzodiazepines as the exclusive contributory agent causing mortality in middle-aged people over 3-year intervals. The drug abuse frequency was about 2.5 times higher in women [17]. Usually, females report benzodiazepine abuse with twofold the frequency of males [18-22]. Substance use disorders arise from a combination of genetic impression and environmental factors. Latest studies suggest the contribution of a large number of genes with comparatively slight effect sizes for substance use disorder [23, 24]. Nevertheless, in one study, two human *BAIAP3* risk genotypes were identified to be associated with anxiety in women and benzodiazepine use disorder in men. They found that *Baiap3* absence in mice caused faster progress of tolerance to benzodiazepines in male mice [25].

In this study, the mean age of benzodiazepine addicts was 37 years. Most studies consistently find that higher rates of usage pattern occur in older participants, especially those aged 55 or over [18-21]. The national AAPCC data from 2006 to 2011indicates that adults include the mainstream of cases from 20 to 51 years contributing 72% of benzodiazepines reports [22]. We can infer that adults would more probably contact toxicological centers for unfavorable effects of benzodiazepines compared to children, juveniles, and the elderly. In general, the elderly may influence the increase in the eradication half-life of both parent compound and metabolites, and older age can contribute to the more noticeable

Table 5. Vital signs and treatment hours after intervention for loss of consciousness.

Treatment Hours		Systolic BP	Diastolic BP	Heart Rate	Respiratory Rate
3 *(n=18)*	0	111.94±11.77	72.72±8.96	75.72±19.23	15.22±2.84
	3	116.67±10.71	75.56±8.56	87.94±13.03	16.28±2.16
	6	-	-	-	-
	9	-	-	-	-
	12	-	-	-	-
6 *(n=8)*	0	107.5±11.65	67.5±4.62	85.5±10.66	16±2.56
	3	106.88±8.83	68.75±6.4	82.75±14.89	16±2.61
	6	116.25±10.6	76.25±7.44	89.38±11.78	15.75±1.98
	9	-	-	-	-
	12	-	-	-	-
9 *(n=4)*	0	105±5.77	65±5.77	74.75±15.39	16
	3	110±8.16	72.5±9.57	87±8.71	16
	6	110±8.16	70±8.16	87.5±9.57	16±1.63
	9	110±8.16	72.5±5	86.25±9.46	15.5±1
	12	-	-	-	-
>12 *(n=2)*	0	125±21.21	80±14.14	99±1.41	22±2.82
	3	122.5±24.74	75±7.07	90±14.14	18±2.82
	6	120±28.28	75±7.07	92.5±10.6	18±2.82
	9	125±21.21	75±7.07	87.5±10.6	17±1.41
	12	115±21.21	75±7.07	87.5±10.6	17±1.41

sedation [26]. It should be mentioned that we found no significant correlation between sedative substance use history across placebo (9.37%) and methylphenidate (12.5%) groups in our study.

In the current study, initial laboratory evaluations and ECG indices in both groups were not significantly different on admission except for significant elevation in HCo3 (bicarbonate) that presented in cases with 36-50 years of age (p=0.02). Moreover, PCo2 levels were increased in cases with 15-25 and 36-50 years of age. Therefore, our subjects who were younger than 20 years of age demonstrated a respiratory acidosis condition on admission. In one study, Arterial Blood Gas (ABG) parameters in patients with Benzodiazepine (BZD) poisoning were measured and the mean pH level was significantly lower than that in patients with TCA poisoning [27]. It is known that rapid Na+ channel blockade in the heart is sensitive to arterial blood pH, thus acidosis can aggravate cardiovascular toxicity [28].

Patients who were intoxicated with benzodiazepines when hospitalized had a longer length of stay. We demonstrated that using methylphenidate capsules could decrease the duration of hospital stay (14.19±16.36 hours in the placebo group and 10.75±4.96 in the MPH group). Observational studies revealed that alprazolam, temazepam and oxazepam overdoses resulted in significantly longer hospital stays and the use of reversal agents, such as flumazenil [29, 30]. The use of flumazenil has been associated with the occurrence of seizures, particularly in benzodiazepines dependent cases. Furthermore, flumazenil can induce >10% gastrointestinal and 1% to 10% cardiovascular adverse reactions [31]. Our results identify that greater burden of health impacts in certain populations can be controlled without any harmful adverse effects, simply by using methylphenidate. In one randomized trial on Traumatic Brain Injury (TBI) patients, the use of methylphenidate was linked to a 23% reduction in hospital length of stay (p=0.029) [32].

The finding of significantly better consciousness, as noted on the performed pilot at less than 12 hours (p=0.005), is consistent with the results of studies on ADHD [33, 34], physostigmine treatment following TBI [35, 36], and improvement of long-term outcome after stroke [37]. Our odds ratio suggests the positive connection between treatment and regains consciousness after 3,6 and 9 hours of intervention. The findings of improved functioning following methylphenidate treatment between this study and other studies assert that methylphenidate needs to be further identified as a viable clinical treatment.

CONCLUSION

Our study designates that benzodiazepines overdose may be attendant with substantial morbidity. Methylphenidate is indicated to prevent complications of prolonged unconsciousness. Nevertheless, supportive treatment and appropriate airway management of comatose patients are the pillars of treatment in these patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study approved by the Toxicological Research Center of Shahid Beheshti University of Medical Sciences' research council Iran, (IR.SBMU.RETECH.REC.1396.318).

HUMAN AND ANIMAL RIGHTS

No animals were involved in the study. All human research procedures followed were in accordance with the

ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT TO PARTICIPATE

All participants gave written informed consent before both the screening and the study procedures.

STANDARD OF REPORTING

Consort Guidelines were followed.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

AVALAIBILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, Dr. Mitra Rahimi, upon reasonable request.

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