



Comparative Efficacy of Diazepam Monotherapy Versus Diazepam-haloperidol Combination in the Treatment of Stimulant-induced Agitation: A Double-blind Clinical Trial

Uyarıcı Kaynaklı Ajitasyonun Tedavisinde Diazepam Monoterapisi ile Diazepam-haloperidol Kombinasyonunun Karşılaştırmalı Etkinliği: Çift Kör Klinik Çalışma

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ABSTRACT

Objective: This study aimed to compare the efficacy of diazepam monotherapy versus diazepam combined with haloperidol in managing stimulant-induced agitation.

Methods: A double-blind clinical trial was conducted on 58 patients presenting with agitation due to stimulant intoxication. Agitation severity was assessed using the Richmond Agitation-Sedation Scale at baseline and at 15, 30, 45, and 60 minutes after treatment.

Results: Both treatment regimens significantly reduced agitation within 15 minutes. No statistically significant differences were observed between groups at any time point. Baseline-adjusted analyses confirmed comparable treatment effects.

Conclusion: Diazepam alone and in combination with haloperidol showed similar efficacy in controlling stimulant-

ÖZ

Amaç: Bu çalışmada, uyarıcı madde kullanımına bağlı ajitasyonun yönetiminde diazepam monoterapisi ile diazepam ve haloperidol kombinasyonunun etkinliğinin karşılaştırılması amaçlandı.

Yöntemler: Uyarıcı madde intoksikasyonuna bağlı ajitasyon ile başvuran 58 hastanın dahil edildiği çift kör bir klinik çalışma yürütüldü. Ajitasyon şiddeti, başlangıçta ve tedavi sonrası 15, 30, 45 ve 60. dakikalarda Richmond Ajitasyon-Sedasyon Ölçeği kullanılarak değerlendirildi.

Bulgular: Her iki tedavi rejiminin de 15 dakika içerisinde ajitasyon şiddetini anlamlı düzeyde azalttığı görüldü. Hiçbir zaman noktasında gruplar arasında istatistiksel olarak anlamlı bir fark saptanmadı. Başlangıç değerlerine göre düzeltilmiş analizler de tedavi etkilerinin gruplar arasında benzer olduğunu doğruladı.

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ABSTRACT

induced agitation. Adverse effects were not systematically assessed; therefore, no conclusion regarding the relative safety of the two regimens can be drawn.

Keywords: Psychomotor agitation, central nervous system stimulants, poisoning, emergency medical services, diazepam, haloperidol

ÖZ

Sonuç: Diazepam monoterapisi ile diazepam ve haloperidol kombinasyonunun uyarıcı madde kullanımına bağlı ajitasyonun kontrolünde benzer etkinlik gösterdiği saptandı. Advers etkiler sistematik olarak değerlendirilmediğinden, iki rejimin göreceli güvenliliği konusunda bir sonuç çıkarılamaz.

Anahtar Kelimeler: Psikomotor ajitasyon, merkezi sinir sistemi uyarıcıları, zehirlenme, acil sağlık hizmetleri, diazepam, haloperidol

Introduction

Agitation is linked to various psychiatric conditions, such as schizophrenia, bipolar disorder, personality disorders (primarily antisocial and borderline), generalized anxiety disorder, panic disorder, major depression, as well as substance use or intoxication (1). Stimulants, substances known for their high potential for addiction, are becoming more common globally (2,3). These substances work by increasing the levels of central monoamines, which are neurotransmitters found in the midbrain and brainstem (2,3). These neurotransmitters are crucial for learning, thinking, problem-solving, and the brain's reward system (2,3). People who have recently used stimulants might show symptoms like restlessness, irritability, euphoria, increased sexual activity, paranoia, delusions, disorganized thinking, or even violent behavior (4).

Emergency room doctors face significant challenges when treating people who use methamphetamine and synthetic cathinones, mainly because of the increased agitation and paranoia these substances cause (5), coupled with the prolonged half-lives of these substances. Methamphetamine can lead to psychotic symptoms (6). These psychotic effects can cause significant agitation and may necessitate immediate medical intervention (5,6).

The standard treatment for this condition typically includes an intramuscular antipsychotic, such as haloperidol (5 mg) or olanzapine (10 mg), a benzodiazepine like lorazepam (2 mg) or midazolam (5 mg), or a combination of both (7). Research indicates that agitation resulting from stimulant use is best managed with high-dose benzodiazepines rather than neuroleptics (4,8). While neuroleptics like haloperidol or olanzapine are typically first-line treatments for agitation and psychosis, their use should be approached cautiously in these patients (4,8-10).

Current trials lack sufficient evidence to confirm or deny the effectiveness of benzodiazepines alone or in combination with other medications for urgent tranquilization or sedation (11). Due to the contradictions in the literature, this study explored and compared two approaches for treating agitated patients poisoned by stimulants: administering diazepam alone versus administering diazepam in combination with haloperidol.

Methods**Study Design and Setting**

A double-blind clinical trial was carried out at the Emergency Department of Loghman Hakim Hospital in Tehran, Iran, from April to July 2025. The study protocol received approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences (approval no: IR.SBMU.RETECH.REC.1402.451, date: 12.11.2023) and was registered with the Iranian Registry of Clinical Trials (IRCT20210720051946N6). Written informed consent was obtained from the patients' legal guardians.

Participants

Eligible participants were adults aged over 18 years who presented with agitation caused by stimulant intoxication, as diagnosed based on DSM-5 criteria (12). Stimulant intoxication was primarily related to methamphetamine use, as confirmed by patient history and clinical presentation. Individuals were excluded if they declined participation or had a history of neurological conditions such as seizures, dementia, or Parkinson's disease; moderate-to-severe head trauma; glaucoma; psychosis unrelated to stimulant use; substance dependence other than stimulants; reduced consciousness; or cardiac issues, including long QT syndrome. Alcohol consumption and previous sedative-hypnotic medication were noted because they may have an impact on the degree of agitation and the pharmacological reaction to benzodiazepines. To ensure the groups had similar starting points, these variables were examined.

Randomization and Intervention

Using a dice-based allocation method, sixty patients were recruited and randomly assigned to two groups (the first group was represented by black dice, and the second group by white dice). Group 1 received diazepam 10 mg (maximum 1 mg/kg). Group 2 received diazepam 10 mg plus haloperidol 5 mg (maximum 30 mg/day). The allocation process was blinded, and outcome assessors were not involved in randomization. Double-blinding in this study meant that both patients and outcome assessors were blinded. An independent clinician who was not involved in agitation assessment or data analysis prepared

and administered the medications. Throughout the study, outcome assessors were not informed of group allocation.

Measures of Outcomes

The Richmond Agitation-Sedation Scale (RASS) was used to assess agitation at baseline and 15, 30, 45, and 60 minutes after treatment began. A validated instrument that is frequently utilized in critical care and emergency situations is the RASS. It has demonstrated excellent inter-rater reliability (intraclass correlation coefficient >0.9) and strong validity for assessing agitation and sedation levels (13). It is also explained in Table 1. Agitation was defined as a RASS score of +2 or higher, and the proportion of patients who remained agitated (RASS ≥+2) at 15 minutes was used as the binary outcome for the risk-based measures described below.

Statistical Analysis

With an 80% power, a 95% confidence level, and an effect size of 0.8, the sample size was calculated using G*Power (version 3.1.9.2), yielding 26 participants per group. Sixty patients were recruited to account for possible dropouts.

The SPSS version 26 was used for data analysis. To determine normality, the Kolmogorov-Smirnov test was used. The chi-square test was used to analyze categorical variables (Fisher’s exact test when expected cell counts were <5), while independent t-tests were used for continuous data, with the Mann-Whitney U test as a sensitivity analysis because RASS is an ordinal scale. Eta squared (η^2) was used to express effect sizes. Additional measures, calculated for the proportion of patients who remained agitated at 15 minutes with the diazepam + haloperidol group as the reference, included the absolute risk reduction (ARR), relative risk (RR), RR reduction (RRR), and number needed to treat (NNT), each with 95% confidence intervals (CIs). A p-value of ≤0.05 was considered statistically significant.

Because the groups started with significantly different levels of agitation, we used an analysis of covariance (ANCOVA) to compare the RASS scores after treatment. This analysis was adjusted for the initial RASS scores. We checked the assumption that the regression slopes were the same, and we found no issues. Adjusted mean values and effect sizes were reported where appropriate.

Results

Based on inclusion and exclusion criteria, 60 patients were divided into two groups. However, two patients were excluded from the study after it was found that they were allergic to diazepam prior to starting treatment. Finally, the study was conducted with 58 patients, with 31 assigned to the diazepam group and 27 to the diazepam plus haloperidol group. One patient in each group had no RASS assessment at 45 and 60 minutes; therefore, analyses at these time points included 30 patients in the diazepam group and 26 in the diazepam plus haloperidol group.

The average ages were 30.5±12.9 years and 27.9±8.9 years, respectively, with no significant differences in demographic characteristics between the groups (p>0.05) (Table 2). A history of alcohol consumption was reported in 3 patients (9.68%) from the diazepam group and 6 patients (22.22%) from the diazepam + haloperidol group (p=0.279, Fisher’s exact test) (Table 2). The history of using sedative-hypnotic drugs was 13 (41.94%) in the diazepam group and 11 (40.74%) in the diazepam combined with haloperidol group (Table 2).

According to Table 1, a patient scoring +2 or higher is classified as agitated, scores from 0 to below +2 are considered normal, and negative scores indicate sedation. The comparison of mean scores between the two groups at various time points is presented in Table 3. According to the RASS, both treatment regimens successfully decreased agitation within 15 minutes. No significant differences were noted between the two groups at 15, 30, 45, or 60-minutes following treatment. The Mann-Whitney U test gave consistent results (p=0.294, 0.264, 0.624, and 0.571 at 15, 30, 45, and 60 minutes, respectively). Mean RASS scores were numerically lower in the diazepam group at all time points, but these differences were not statistically significant. In an exploratory analysis, deep sedation (RASS ≤-3) at 60 minutes was observed in 4 of 30 patients (13.3%) in the diazepam group and 1 of 26 patients (3.8%) in the combination group (Fisher’s exact p=0.358). An ANCOVA was used to compare post-treatment RASS scores while controlling for baseline values because baseline agitation scores varied significantly between groups. There were no statistically significant differences between the diazepam and diazepam plus haloperidol groups at any follow-up time point after adjusting for baseline agitation severity (Table 4).

Table 1. Richmond Agitation-Sedation Scale (RASS) score	
RASS score	Description
+4	Combative, violent, danger to staff
+3	Pulls or removes tube(s) or catheters; aggressive
+2	Frequent non-purposeful movement, fights ventilator
+1	Anxious, apprehensive, but not aggressive
0	Alert and calm
-1	Awakens to voice (eye opening/contact) >10 seconds
-2	Light sedation; briefly awakens to voice (eye opening/contact) <10 seconds
-3	Moderate sedation; movement or eye opening. No eye contact
-4	Deep sedation; no response to voice, but movement or eye opening to physical stimulation
-5	Unarousable; no response to voice or physical stimulation

At 15 minutes, 10 of 31 patients (32.3%) in the diazepam group and 11 of 27 patients (40.7%) in the diazepam + haloperidol group were still agitated (RASS $\geq +2$) (Table 5; Fisher's exact $p=0.588$). With the combination group as the reference, the ARR was 8.5% (95% CI: -16.3% to +33.3%), the RR was 0.79 (95% CI: 0.40-1.57), and the RRR was 20.8% (95% CI: -56.8% to +60.0%). The NNT was approximately 12; however, because the CIs included the null value (the 95% CI of the NNT ranged from an NNT for benefit of 3 through infinity to an NNT for harm of 6), no clear advantage could be demonstrated for either treatment approach. The effect size of the group difference in 15-minute RASS scores was small ($\eta^2=0.023$).

Discussion

In the present study, we evaluated the effectiveness of diazepam alone versus the combination of diazepam and haloperidol in treating poisoned patients. The findings indicated that both medication groups effectively

managed agitated patients. Although entirely by chance, the group receiving diazepam combined with haloperidol had a higher average score on the Richmond scale before treatment began. However, when comparing the averages at 15, 30, 45, and 60-minutes post-treatment, no significant differences were observed between the two groups. In both groups, the average score decreased significantly after 15 minutes. Furthermore, mean RASS scores were negative (indicating sedation) in both groups from 30 minutes onward and were numerically lower with diazepam alone, although the difference was not statistically significant. ANCOVA was used with baseline RASS as a covariate to address the baseline imbalance in agitation severity. This adjusted analysis showed no statistically significant difference between the treatments after accounting for baseline severity. Because the study was not designed to demonstrate equivalence or non-inferiority, these findings indicate that no difference was detected rather than proving that the two regimens are equivalent.

Table 2. Demographic data of patients in two groups

		Diazepam group	Diazepam + haloperidol group	p-value
Gender (number (%))	Male	16 (51.61%)	11 (40.74%)	0.408
	Female	15 (48.39%)	16 (59.26%)	
Age (year) (mean ± SD)		30.52±12.9	27.93±8.9	0.383
History of alcohol use [number (%)]	Yes	3 (9.68%)	6 (22.22%)	0.279
	No	28 (90.32%)	21 (77.78%)	
History of taking sedative-hypnotic medication [number (%)]	Yes	13 (41.94%)	11 (40.74%)	0.927
	No	18 (58.06%)	16 (59.26%)	
The p-value for history of alcohol use was calculated with Fisher's exact test SD: Standard deviation				

Table 3. The analysis of average RASS scores across the two groups at different time intervals

	Diazepam group	Diazepam + haloperidol group	p-value
Richmond scale before treatment	2.65 $\pm$ 0.71	3.07 $\pm$ 0.68	0.022*
Richmond scale 15 minute after treatment	0.65 $\pm$ 1.36	1.07 $\pm$ 1.47	0.252
Richmond scale 30 minute after treatment	-0.94 $\pm$ 1.48	-0.48 $\pm$ 1.50	0.253
Richmond scale 45 minute after treatment	-1.13 $\pm$ 1.78	-1.00 $\pm$ 1.36	0.756
Richmond scale 60 minute after treatment	-1.17 $\pm$ 1.86	-1.04 $\pm$ 1.43	0.776
Values are mean $\pm$ SD. At 45 and 60 minutes, n=30 (diazepam) and n=26 (diazepam + haloperidol) *: $P<0.05$, SD: Standard deviation			

Table 4. Baseline-adjusted comparison of RASS scores between treatment groups

Time point	Adjusted mean RASS (diazepam)	Adjusted mean RASS (diazepam + haloperidol)	Mean difference (95% CI)	p-value
15 min	0.86	0.83	0.03 (-0.63 to 0.70)	0.92
30 min	-0.86	-0.57	-0.28 (-1.10 to 0.53)	0.49
45 min	-1.18	-0.94	-0.24 (-1.14 to 0.66)	0.60
60 min	-1.20	-1.01	-0.19 (-1.14 to 0.76)	0.69
Covariate: Baseline RASS score/model: One-way ANCOVA/significance: $p\leq 0.05$. Mean difference = diazepam minus diazepam + haloperidol; n=56 at 45 and 60 minutes RASS: Richmond Agitation-Sedation Scale, ANCOVA: Analysis of covariance, CI: Confidence interval				

Our results are in line with earlier research showing that benzodiazepines by themselves are useful in treating agitation brought on by stimulant intoxication. Because of their anxiolytic, sedative, and muscle-relaxant properties, benzodiazepines are regarded as first-line treatments for agitation brought on by methamphetamine and related stimulant use, which is primarily mediated by excessive central monoaminergic activity (4,7,10). Klein et al. (14) demonstrated that, without raising the risk of side effects, intramuscular midazolam produced more rapid and effective sedation in agitated emergency department patients than haloperidol and other antipsychotics. Furthermore, benzodiazepine monotherapy is at least as effective as antipsychotic treatment for acute agitation and has fewer extrapyramidal and cardiovascular side effects, according to a Cochrane systematic review by Zaman et al. (11).

Despite the fact that antipsychotic combination therapy is frequently used in emergency situations, there is currently insufficient evidence to support its superiority over benzodiazepine monotherapy. Wilson et al. (15) found that concurrent use of benzodiazepines and antipsychotics might raise the risk of oxygen desaturation and respiratory depression, especially in patients who were intoxicated or who also consumed alcohol. Accordingly, after controlling for baseline agitation severity, the current study did not show any further advantages of combining haloperidol with diazepam. Because adverse effects were not assessed in our study, we cannot draw conclusions regarding the relative safety of the two regimens; the safety concerns noted above derive from previous studies and should be evaluated in future trials.

Managing acute agitation in the emergency room, especially among patients who are intoxicated, is a common challenge for emergency physicians from a clinical standpoint. Non-pharmacological methods are frequently

given priority, and many professionals advise verbal de-escalation or seclusion as first tactics for both sober and drunk people (15). The ideal drug should have a quick onset of action, show little variation in pharmacodynamics and pharmacokinetics between patients, and have a low risk of side effects when pharmacological intervention is required. In order to preserve physical examinations, diagnoses, and subsequent treatment choices, it should also provide tranquilization without causing undue sedation (16).

Haloperidol has been used in studies alone and in combination with other medications to control agitation (17). The combination of haloperidol, lorazepam, and diphenhydramine, as well as the combination of haloperidol and lorazepam, rarely required additional agitation medication (17). However, the combination including diphenhydramine was associated with higher rates of oxygen desaturation, hypotension, increased use of physical restraints, and longer hospital stays (17). Research conducted by Klein et al. (14) revealed that intramuscular midazolam resulted in more effective sedation in agitated emergency department patients within 15 minutes compared to haloperidol, ziprasidone, and possibly olanzapine. Additionally, olanzapine was proved to be more effective than haloperidol. No significant differences in adverse events were observed (14).

In comparison to the haloperidol-promethazine group, Mwankemwa (18) observed that the haloperidol-diazepam group exhibited stronger sedative effects, acted more quickly within 15 minutes, and had lower Positive and Negative Syndrome Scale-Excited Component scores at 15 and 30 minutes. Furthermore, the haloperidol-diazepam group contained more drowsy or stuporous patients at 15, 30, and 60 minutes, whereas the haloperidol-promethazine group contained more alert or drowsy patients with fewer cases of stupor. Asadollahi et al. (16) found that postintervention Agitation-Calmness Evaluation Scale

Table 5. Patient count per RASS scale level across various time points

RASS scale	Diazepam + haloperidol group					Diazepam group				
	Before treatment	After 15 min	After 30 min	After 45 min	After 60 min	Before treatment	After 15 min	After 30 min	After 45 min	After 60 min
+4	7	1	0	0	0	4	0	0	0	0
+3	15	3	1	1	1	12	2	1	1	1
+2	5	7	2	1	1	15	8	2	3	3
+1	0	9	5	1	1	0	8	1	1	1
0	0	0	3	4	3	0	3	6	4	5
-1	0	7	7	6	9	0	10	7	4	3
-2	0	0	9	13	10	0	0	13	14	13
-3	0	0	0	0	0	0	0	0	0	0
-4	0	0	0	0	1	0	0	1	3	4

Counts at 45- and 60-minutes sum to 30 (diazepam group) and 26 (diazepam + haloperidol group) because one patient in each group had no assessment at these time points
RASS: Richmond Agitation-Sedation Scale

scores were 4.73 for valproate and 5.45 for haloperidol ($p=0.028$). Haloperidol caused more intense sedation (36.2% vs. 2.5%) and extrapyramidal symptoms (8.7% vs. 0%) than valproate. Intravenous valproate was effective in reducing agitation with a better safety profile in emergency psychiatry (16).

Wilson's research on drug safety for managing agitation revealed that olanzapine, whether used alone or combined with a benzodiazepine, did not lead to higher rates of hypotension compared to haloperidol. However, the combination of olanzapine and benzodiazepines was linked to reduced oxygen saturation levels compared to haloperidol paired with benzodiazepines in patients who consumed alcohol, but not in those without alcohol use (15).

Diazepam alone was used in very few studies. A study contrasting diazepam and haloperidol was highlighted in an intervention review. The findings showed that, following two days of drug-free observation, 20 newly admitted psychotic patients were administered 20-35 mg of haloperidol intravenously, while another 20 patients received 30-40 mg of diazepam intravenously. Post-treatment assessments conducted at 4 and 24 hours using the Brief Psychiatric Rating Scale and The Clinical Global Impressions demonstrated significant improvement in both groups, with no notable differences observed between the two treatments (11). Additionally, this review showed that although benzodiazepines alone might have fewer adverse effects than older antipsychotics, taking them with other drugs may result in preventable side effects (11). According to prior research and the findings of our study, both methods appear to be effective. Although previous studies suggest that combination treatment may carry additional risks, adverse effects were not assessed in the present study, and the difference in the proportion of patients who remained agitated at 15 minutes (32.3% vs. 40.7%) was not statistically significant.

Study Limitations

This study exclusively utilized the RASS. Employing multiple scoring scales could potentially have yielded more robust results. Additionally, complications, particularly extrapyramidal complications, were regrettably not examined in the patients. The study primarily concentrated on efficacy; therefore, no conclusion can be drawn regarding the relative safety of the two regimens. The findings of this study primarily reflect agitation related to methamphetamine intoxication, which may limit generalizability to other stimulant substances. The study was not designed to demonstrate equivalence or non-inferiority, and RASS data at 45 and 60 minutes were missing for one patient in each group.

Conclusion

Diazepam alone and diazepam combined with haloperidol showed similar efficacy in reducing stimulant-induced agitation in emergency situations, with no statistically significant difference between the groups. Because adverse effects were not systematically assessed, no conclusion regarding the relative safety of the two regimens can be drawn. Larger randomized controlled trials are needed to validate these findings and further investigate safety outcomes.

Ethics

Ethics Committee Approval: The study protocol received approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences (approval no: IR.SBMU.RETECH.REC.1402.451, date: 12.11.2023) and was registered with the Iranian Registry of Clinical Trials (IRCT20210720051946N6).

Informed Consent: Written informed consent was obtained from the patients' legal guardians.

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Declaration on the Use of Artificial Intelligence (AI)

In this study, the Claude artificial intelligence language model (developed by Anthropic) was used to translate the original text into English and to revise and improve the quality of the initial translation. All outputs generated by this tool were reviewed and verified by the authors before being incorporated into the final version of the manuscript. The authors assume full responsibility for the final content.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.E., Concept: F.Z., P.E., Design: P.E., Data Collection or Processing: F.Z., P.E., Analysis or Interpretation: F.Z., P.E., Literature Search: S.S., B.M., M.R., E.K., J.D.D.D., Writing: F.Z., M.R., P.E.

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