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Comparison of the Intravenous Haloperidol and Diazepam on Recovery from Conversion Disorders in Emergency Ward Patients: Double Blind, Randomized Clinical Trial of Efficacy and Safety

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ABSTRACT

Objectives: Evaluation the efficacy of intravenous haloperidol compared to intravenous diazepam in patients with conversion disorders, referring to an emergency ward.
Design: A parallel double-blind randomized controlled, trial. Randomization was performed through a central Web-based randomization system. Blinding was performed while the nurse giving the medicines, the physician who complete questionnaire and medical personnel were blind to the medicines.
Methods:
Participants 182 patients over 18 year of age, who had conversion disorders, were divided into two equal groups using the randomization table.
Intervention One group received intravenous haloperidol and the other received intravenous diazepam. **Outcome** The patients were evaluated in relation to their response to treatment, physical symptoms and signs, and side effects up to discharge from the ward and at 24-hour and 1-week interval after discharge. T-test and chi-squared test were used to evaluate differences between the two groups. Kaplan-Meier curves were used to evaluate the outcomes during the patients' presence in the emergency ward. Statistical significance was set at $P<0.05$.
Results: One hundred eighty two patients were randomized. Complete recovery was observed in 85 patients of 91 patients (93.4%) receiving haloperidol; however, in the diazepam group only 34 patients of 91 patients (37.4%) exhibited full recovery ($P<0.001$). Two hours after injection of medications, 84 patients in the haloperidol group (92.3%) and 33 patents in the diazepam group (36.3%) were discharged ($P<0.001$). Restlessness, weakness, apnea and lethargy were the only side effects after injection of medications. Twenty-four hours after discharge, 20 patients in the haloperidol group (22.0%) had malaise and 1 patient in the diazepam group (1%) was lethargic ($P<0.001$). At 1-week interval, there was no relapse or any complication.
Conclusion: The results of the present study showed that intravenous injection of haloperidol and diazepam has an effective role in relieving symptoms and signs of conversion disorder patients referring to emergency units.
Trial registration number: IRCT201108317449N1
Funding: Shahid Beheshti University of Medical Sciences, Tehran, Iran, Deputy of Research.
KEYWORDS: Conversion disorders, emergency treatment, haloperidol, diazepam.

1. INTRODUCTION

Conversion disorder is defined as alteration or loss of sensory or motor functions of the body, without any justifiable somatic reason. It is believed that the associated signs and symptoms, including paralysis, speech and balance disorders, apnea, blindness, urinary retention, syncope etc, appear in response to stresses which influence the psychological health of the patient (1). The condition accounts for 5% of general hospital admissions and is more prevalent in young married females with low socioeconomic status (2). It should be pointed out that the prevalence of symptoms and signs similar to those of conversion disorder is 30–60% and it is not clear what fraction of these figures are related to this disorder (3–5). The treatment of choice for conversion disorder is psychotherapy, the aim of which is to eliminate the emotional aspects of symptoms and signs; in this context, rehabilitation might also be effective (6,7). A small number of studies have shown the efficacy of antidepressive agents in relieving the symptoms and signs of the condition; however, the specific effect of these medications on the somatic symptoms and signs and treatment of conversion disorders is not definite; rather, the therapeutic effect is only associated with a

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decrease in depression and anxiety (8). There is limited clinical evidence for the efficacy of drug therapy in conversion disorders and the majority of data is based on case reports, which have shown the therapeutic success of the administration of haloperidol (9), benzodiazepines (8,10), tricyclic antidepressants (11) and electroshock therapy (11,12). Haloperidol is a sedative of the butyrophenone family, which has satisfactorily been used for many years in the management of psychological problems (13,14). Diazepam, too, as a benzodiazepine, is highly effective in the treatment of anxiety disorders (15), and treatment of seizures (16) and depression (17). Therefore, the present clinical trial was undertaken to evaluate and compare the efficacy of haloperidol and diazepam in the treatment of patients with conversion disorders, referring to an emergency ward.

MATERIALS AND METHODS

In the present parallel randomized double-blind clinical trial, 247 patients who had referred to an educational hospital emergency room (Emam Hosein hospital, Tehran, Iran) and were diagnosed as having conversion disorder based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th Edition) and needed medicinal intervention were included. However, patients with abnormal vital signs; under 18 years; over 60 years; pregnant or lactated women; addicted patients, known renal or liver disease, parkinsonian patients, presence of severe cardiopulmonary disease, history of seizure or anticonvulsant therapy, history of long QT interval, allergy to norleptics or benzodiazepines and those who are not willing to participate in this study were excluded. But 182 patients remained in this study.

Before selection of patients, each patient signed an informed written consent form. The protocol of the study was prepared based on Helsinki Declaration and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with reference number: 90-1-134-8723-8303 and approved date: April 29, 2012. And pre-registered in IRCT with registration number: IRCT201108317449N1 and registered date: June 23, 2012.

Based on the protocol, on admission of each patient into the emergency ward a history was taken and a medical examination was carried out by a post-graduate student of emergency medicine under the supervision of the professor in charge. Patients divided into two equal groups after signing on informed written consent form using the randomization table. One of the groups randomly received intravenous haloperidol and the other received intravenous diazepam. Randomization was performed through a central Web-based randomization system. Blinding was performed while the nurse giving the medicines, the physician who complete questionnaire and medical personnel were blind to the medicines.

The nurse giving the medicines was blind to the medicines used and the aims of the study and had no contact with the physician in charge. For all the subjects a questionnaire was completed, which included demographic data, background diseases, history of psychotic disorders, history of taking medicines, the time of recovery and time of discharge from the emergency ward. The patients underwent cardiac monitoring and were placed under the direct supervision of the medical personnel from the time the medicines were administered until recovery. The signs and symptoms, recovery and possible complications were recorded by the physician. The doses of intravenous haloperidol and diazepam were 5 mg based on reliable guidelines. The patients were followed up to a week and the possible side effects were recorded. Subsequently, the patients were evaluated in relation to response to treatment, physical signs and symptoms, disappearance of the associated symptoms and signs and side effects up to discharge from the emergency ward and the results were recorded in the relevant data charts. In order to safeguard the double-blind design of the study, preparation of medicines, their administration and registration of the results were carried out by 3 operators who had no contact with each other during the clinical trial. It should be pointed out that data about the injected medications were submitted to the medical personnel only when untoward drug side effects or other clinical changes occurred, necessitating knowledge about the nature of the medications injected.

The patients were followed up to discharge from the emergency ward; 24-hour and 1-week follow-ups after receiving the medications were carried out by phone. Questioned were asked about the side effects and the possible mortality at these intervals. It should be pointed out that whenever Q-T prolongation and arrhythmias occurred the medications were immediately discontinued and the patient was placed under cardiac care. Such a case was registered as “no recovery” and “incidence of complications”. In the present study no complications arose. The sample size was determined to be at least 41 subjects in each group by considering the parameters of $\alpha=0.5$ and a power of 90% ($\beta=0.9$); however, 91 subjects were included in each group. Data were entered into the SPSS 11.5 statistical software program and analyzed after they were transferred into STATA 11.0.

T-test was used to evaluate quantitative factors and chi-squared test was used to evaluate qualitative variables. Kaplam-Meier curves were used to evaluate the outcomes of the medical condition during the patients’ stay in the emergency ward. Statistical significance was defined at $P<0.05$.

RESULTS

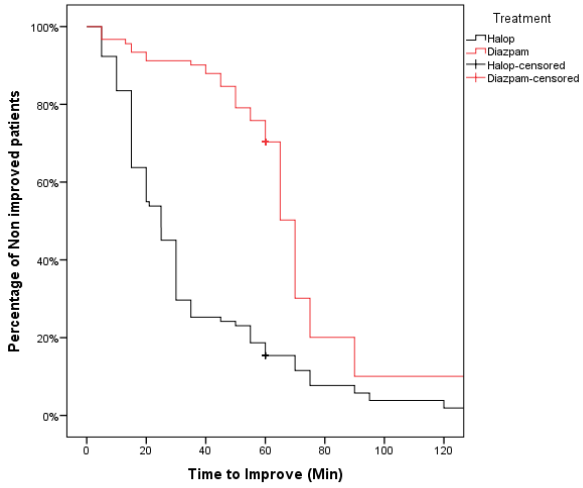
Ninety one patient remained in each group after The means and standard deviations of age in 91 patients in each of the haloperidol and diazepam groups were 33±10 and 31±11 years, respectively (P=0.2). In the haloperidol group, 59 subjects (64.8%) and in the diazepam group, 41 subjects (45.1%) were married (P=0.007). In the haloperidol group, the initial manifestation was unconsciousness in 35 subjects (38.5%), followed by seizures in 8 subjects (87.8%); 48 subjects (52.7%) had other symptoms and signs. In the diazepam group, the initial manifestation was unconsciousness in 28 patients (31.1%), followed by seizures in 9 patients (10%); 53 patients (58.9%) had other symptoms and signs (P=0.58). It should be pointed out that 9 patients (9.9%) in the haloperidol group and 6 patients (6.6%) in the diazepam group had a history psychiatric disease (P=0.42). In addition, there was a history of similar symptoms and signs in 26 patients (28.6%) and 33 patients (36.3%) in the haloperidol and diazepam group patients, respectively (P=0.27) (Table 2). In the haloperidol and diazepam groups, 85 (93.4%) and 34 (37.4%) patients exhibited full recovery, respectively (Table 3; Graph 1). Chi-squared that showed a statistically significant difference between the two groups (P<0.001), with more patients exhibiting full recovery in the haloperidol group compared to the diazepam group. At two-hour interval after administration of the medicines, 84 patients (92.3%) and 33 patients were discharged in the haloperidol and diazepam groups, respectively (P<0.001) (Table 3; Graph 2). Follow-up of the patients until discharge showed that restlessness, weakness, apnea and lethargy were the only complications after injections of the medications. Only 20 patients (10.9%) of all the patients developed complications. In the haloperidol group, 12 patients (13.1) were listless and developed extrapyramidal complications; in the diazepam group, 8 patients (8.7%) exhibited hypopnea or apnea (P=0.84). Follow-ups in the present study showed that 21 patients (11.5%) developed complications during the first 24 hours, which consisted of weakness in 20 patients (22.0%) in the haloperidol group and lethargy in 1 patient (1%) in the diazepam group (P<0.001). Comparison of recovery time between the two groups showed statistically significant differences between the two groups (P<0.001). The mean recovery time after injection of the medicines was significantly shorter in the haloperidol group compared to the diazepam group (31±23 minutes in the haloperidol group compared to 56±17 minutes in the diazepam group) (P<0.001), i.e. injection of haloperidol resulted in a much faster relief of symptoms compared to the injection of diazepam (Table 2). An important finding was the fact that one week after discharge there were no complications in the patients and none of the patients died.

Table 2. Frequency distribution and comparison of basic variables in the present study

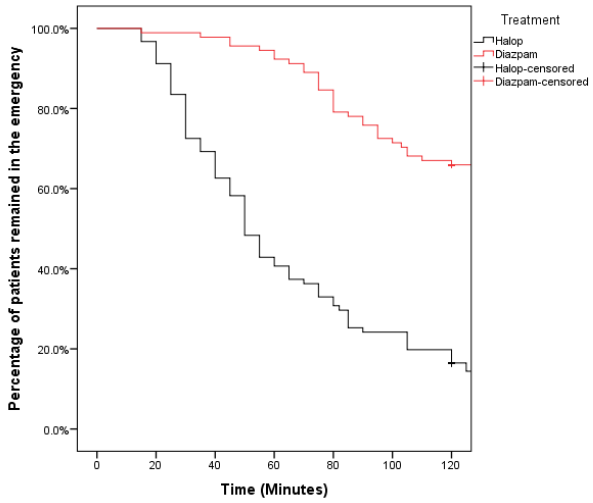
Characteristic		Total	Haloperidol	Diazepam	P
Age		32 ± 10	33 ± 10	31 ± 11	0.2
		30 (15 to 63)	31 (16 to 57)	28 (15 to 63)	
Marital status	Single	82 (45.1%)	32 (35.2%)	50 (54.9%)	0.007
	Married	100 (54.9%)	59 (64.8%)	41 (45.1%)	
Initial symptom	Loc	63 (34.8%)	35 (38.5%)	28 (31.1%)	0.58
	Seizure	17 (9.4%)	8 (8.8%)	9 (10.0%)	
	Other	101 (55.8%)	48 (52.7%)	53 (58.9%)	
History of psychotic disorders	No	167 (91.8%)	82 (90.1%)	85 (93.4%)	0.42
	Yes	15 (8.2%)	9 (9.9%)	6 (6.6%)	
History of same sign	No	123 (67.6%)	65 (71.4%)	58 (63.7%)	0.27
	Yes	59 (32.4%)	26 (28.6%)	33 (36.3%)	

Table 3. Patient outcomes after medicinal intervention

Outcome		Total	Haloperidol	Diazepam	P
Improvement	No	63 (34.6%)	6 (6.6%)	57 (62.6%)	<0.001
	Yes	119 (65.4%)	85 (93.4%)	34 (37.4%)	
Time to Improve (Min)		43 ± 24	31 ± 23	56 ± 17	<0.001
		55 (5 to 675)	25 (5 to 675)	60 (5 to 135)	
Discharge in 1 hr	No	65 (35.7%)	7 (7.7%)	58 (63.7%)	<0.001
	Yes	117 (64.3%)	84 (92.3%)	33 (36.3%)	
Improvement to discharge time (Min)		23 ± 17	24 ± 17	20 ± 19	0.38
		25 (0 to 55)	30 (0 to 55)	15 (0 to 50)	
Complicated in ED	No	162 (89.1%)	79 (86.9%)	83 (91.3%)	0.84
	Yes	20 (10.9%)	12 (13.1%)	8 (8.7%)	
Complicated during first 24 hrs	No	161 (88.5%)	71 (78.0%)	90 (99.0%)	<0.001
	Yes	21 (11.5%)	20 (22.0%)	1 (1.0%)	
Complicated during the first week	No	182 (100.0%)	91 (100.0%)	91 (100.0%)	0.99
	Yes	0 (0%)	0 (0%)	0 (0%)	



Graph 1. Comparison of the recovery of patients two hours after treatment.



Graph 2. Comparison of the number of patients discharged two hours after treatment.

DISCUSSION

Based on the results of the present study intravenous injection of haloperidol and diazepam gave rise to different results, i.e. haloperidol resulted in a faster effect and less dangerous complications and injection of diazepam resulted in overall less complications. On the other hand, one- and two-hour outcomes of patients receiving haloperidol were better than those of patients receiving diazepam. Budden et al carried out a study to compare the efficacy of haloperidol and diazepam on relieving anxiety and showed that haloperidol was significantly more effective and resulted in greater relief after 4 and 6 weeks. In that study, haloperidol and diazepam resulted in recovery in 93% and 83% of the patients, respectively (18).

Haloperidol has several side effects, including instability of the mood, dystonia, dyskinesia etc. The incidence of these side effects is variable depending on the nature of the disease and the dose administered; in this context, treatment of schizophrenia with haloperidol leads to acute dystonia in 7% of patients (19,20). Therefore, a lower incidence of side effects in the present study might be attributed to the type of the background disease. On the other hand, in the present study administration of a single dose of haloperidol was evaluated and as it was shown that administration of a single dose of haloperidol does not result in serious and dangerous complications. Some other studies (25–27), too, have confirmed the efficacy of low doses of haloperidol in the treatment of such disorders. Several clinical trials have shown that although haloperidol has efficacy comparable to that of other antipsychotic

medicines, such as olanzapine (22) and flunitrazepam (23), and in combination with promethazine in the treatment of anxiety disorders and psychosis, it has more side effects.

Diazepam, as a benzodiazepine, is highly efficacious in the treatment of anxiety disorders. Diazepam has been routinely used for the treatment of seizures (16), depression (17), anxiety and other psychological disorders (15) for many years because it is highly effective with minimum side effects. Although diazepam is an effective medicine in a large number of disorders, including epilepsy and anxiety disorders, habituation occurs for unknown reasons. Since patients with conversion disorders are highly inclined to take medicines, especially benzodiazepines, without prescription by a physician for pain relief or in order to attract the attention of family members and friends (29,30), they might develop drug resistance; therefore, their efficacy might decrease when the patients refer to an emergency ward.

There were some limitations in the present study, including the fact that 1-week follow-up of patients might not be adequate to definitely evaluate treatment results and it is advisable to follow such patients for a few months. On the other hand, different techniques have been recommended for the treatment of patients with conversion disorders, including drug therapy which is usually combined with other treatment modalities such as hypnotherapy, muscle relaxation exercises and psychotherapy to achieve better treatment results (24). In the present study, the effect of combination therapy was not evaluated; therefore, it is suggested that future studies evaluate such an effect. Another limitation of the present study was exclusion of the patients whose initial manifestation was blindness. It is recommended that the effect of injecting medicines on recovery from blindness be evaluated in these patients. Still another limitation of the present study was the absence of psychological tests. However, since the aim of the present study was to evaluate the effect of drug intervention in relieving the initial manifestations of conversion disorders in patients referring to an emergency ward, relief of initial symptoms was considered as the patient recovery from conversion disorder; therefore, no psychological tests were used in the present study.

CONCLUSION

Based on the results of the present study, haloperidol is a better candidate than diazepam for the emergency treatment of patients with conversion disorder, although it has more side effects compared to diazepam. Although these side effects decrease patient satisfaction, since they are not serious for the patient haloperidol is still preferable to diazepam

Registration:
This trial is accessible on IRCT (Iranian Registry of Clinical Trials): **http://www.irct.ir/**
Trial registration number: IRCT201108317449N1
And approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with reference number: 90-1-134-8723-8303.
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