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ORIGINAL RESEARCH

Intravenous Haloperidol versus Midazolam in Management of Conversion Disorder; a Randomized Clinical Trial

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Abstract: **Introduction:** Conversion disorder is a condition in which the patient shows psychological stress in physical ways. This study aimed to compare the effects of haloperidol versus midazolam in patients with conversion disorder. **Methods:** This double-blind randomized clinical trial was conducted on patients with conversion disorder who had presented to the emergency department, throughout 2015. Patients were randomly divided into two groups and were either treated with 2.5 mg of intravenous (IV) haloperidol or 2.5 mg of IV midazolam. Recovery rate, time to recovery, and side effects of both drugs 1 hour, 24 hours, and 1 week after treatment were compared using SPSS19. **Results:** 140 patients were divided into two groups of 70. There were no significant differences between the groups regarding the baseline characteristics. 12 (17.1%) patients who were treated with IV haloperidol experienced drug side effects within 1 hour and 12 (17.1%) within 24 hours, while only 3 (4.3%) patients in IV midazolam experienced side-effects within 1 hour after drug administration (p = 0.026). The symptoms of the disease subsided in 45 (success rate: 64.3%) patients in midazolam and in 64 (success rate: 91.5%) participants in haloperidol group (P<0.001). Mean recovery time was 31.24 ± 7.03 minutes in IV midazolam and 30.53 ± 7.11 minutes in IV haloperidol group (p = 0.592). Absolute risk reduction (ARR) of treating patients with haloperidol compared to midazolam is about 27%. **Conclusion:** The response of patients to treatment with haloperidol is clearly better than midazolam. Although more transient and minor side-effects were observed in the group treated with haloperidol compared to midazolam group, serious side-effects were rare for both treatments.

Keywords: Conversion disorder; hysteria; Haloperidol; Midazolam; side effects; intravenous

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1. Introduction

A large number of patients with physical manifestations of underlying psychological disorders present to the emergency department annually (1). Conversion disorder (CD) or hysteria is a diagnostic category defined in some psychiatric classification systems under the main branch of somatoform disorders. This disorder is more prominent in women, early adulthood, and uneducated patients. The symptoms may be established unconsciously and involuntarily (2). This illness is more frequent in histrionic personalities. Clinical signs of the disease include a wide range of different organs being involved: Movement disorders including paralysis, ataxia, and aphonia, sensory disorders including blindness, anosmia and Stocking-Glove paresthesia, and consciousness disorders including coma and pseudo-seizure (3-6). Based on studies in non-emergent cases, the best management for long-term treatment is behavioral therapy accompanied by treating other underling psychological impairments (4-6). However, the management of patient's signs and symptoms in the emergency department is quite necessary because it helps the patients and

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their families to overcome one of the most stressful situations they have ever been faced with. So, administration of the required drugs is essential to alleviate the symptoms as soon as possible. Since years ago, administration of haloperidol and some types of benzodiazepines like Lorazepam and Diazepam as well as Lithium and Sodium valproate was a common practice in management of psychiatric emergencies, particularly in conversion disorders, and their efficacies have been approved so far (7, 8).

Considering the high frequency of patients with psychological or neurological problems, especially conversion disorders, admitted to emergency departments and the urgent need to reduce the severity of symptoms in order to tranquilize tremulous patients and their relatives, and since haloperidol has more side-effects than midazolam, which has a rapid effect and is available in most cases (2, 6, 7), we decided to evaluate and compare the effects of intravenous (IV) haloperidol and midazolam in patients with conversion disorders presenting to emergency departments.

2. Methods:

2.1. Study Design and setting

This double-blind parallel randomized clinical trial was conducted on 140 patients with conversion disorder (based on DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) who had presented to emergency department of Shahid Sadoughi Hospital, Yazd, central Iran, in 2015. The protocol of this research project was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences and registered on Iranian Registry of Clinical Trial (Trial registration number: IRCT 2015100712050N2). We did not perform any additional invasive procedures and patient's written consent was taken. The purpose of the study was explained to the patients. A written consent form was obtained from all patients and patients' information remained confidential. Patients were informed of the probable drug side-effects and recommended to come back in case of the mentioned complications happening. Ethical issues related to human studies (according to the Helsinki Statement) were considered.

2.2. Participants

All patients aged 18 to 60 years who met the following inclusion criteria were enrolled in the study: any alteration or impairment in daily performances, an experience of recent emotional stress, a symptom or deficit that could not be explained by another medical or mental disorder, and a symptom or deficit that was not restricted to pain or sexual disorders.

The exclusion criteria were as follows: patients with abnormal vital signs, pregnant or lactating women, addicted patients, patients with known hepatic or renal failure, severe cardio-pulmonary impairment, cases of parkinsonism, a history of recent seizure or patients who were taking antiepileptic agents, long Q-T syndrome, having allergies to neuroleptics or benzodiazepines, a history of psychiatric disorders, and patients who did not sign the informed written consent.

2.3. Procedures

After patients' admission to the emergency department, conversion disorder diagnosis was made by an emergency medicine specialist, based on DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. After evaluating eligibility criteria, history taking and physical examination were done by an emergency medicine resident and the data were recorded.

The participating patients were randomly assigned to the two groups based on the table of random numbers by an independent physician blind to the study (random sequence number generation was done by a computer).

2.5 mg of IV haloperidol (HALODIC, 5 mg/1mL, Exir Pharmaceutical Co.) was administered to the patients in group A and 2.5 mg of IV midazolam (Midazolam Aburaihan, 5 mg/1ml, Aburaihan Pharmaceutical Co.) was prescribed for patients in group B (based on reliable guidelines). The drugs were administered to the patients by a trained nurse, and the assessor was blind. After drug administration, all patients remained under direct supervision of an emergency medicine resident with concurrent cardiac monitoring (heart rate, O_2 saturation, diastolic blood pressure, systolic blood pressure). The patients were followed up through the next 24 h and 1 week after treatment. The outcomes were recorded. All patients and emergency staff including physicians, nurses, and researchers were blind to the therapeutic groups.

2.4. Data Gathering

A questionnaire was completed for all the patients including demographic data, marital status, level of education, recent emotional stress, taking medications, underlying physical illness, movement disorders, sensory disorders, consciousness disorders, recovery rate, time of recovery, and side-effects in both groups. A trained emergency medicine resident was responsible for data gathering.

2.5. Outcome

Recovery rate (acute symptoms subsiding), time to recovery, and side-effects of haloperidol (extrapyramidal and anticholinergic side-effects, and hypotension) and midazolam (decreased respiratory rate, apnea, drowsiness, nausea, vomiting) at 1 hour, 24 hours, and 1 week after treatment were considered as main study outcomes and compared between the groups.

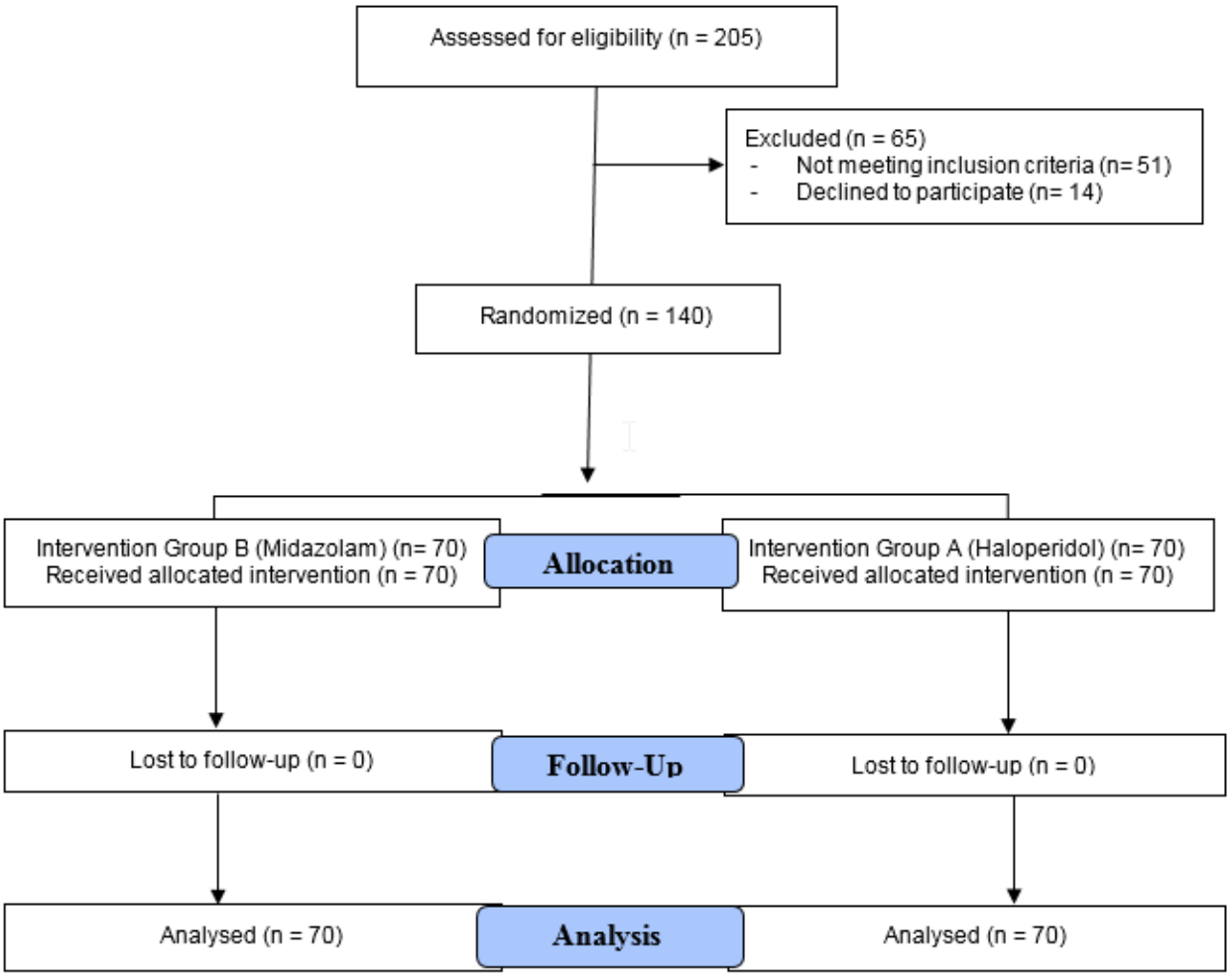

Figure 1: Follow-up of candidates for receiving intravenous haloperidol or midazolam (according to consort statement).

2.6. Statistical analysis

The participants were selected via convenience sampling method. The sample size was determined to be at least 52 patients in each group and it was achieved by 95% confidence coefficient (α=0.05) and power of 80% (β=0.2); however, 70 subjects were included in each group. The data were analyzed by an experienced statistics consultant. All the collected data were imported to SPSS19 (IBM, SPSS statics for windows, Armonk, IBM Corp.) and analyzed using statistical tests. Mean and standard deviation (SD) for quantitative variables and frequencies (percentages) for qualitative variables were calculated. To compare the quantitative variables between two groups, independent Student's t-test (or Mann-Whitney test) was used and categorical variables were compared between the two groups using the Chi-square test. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Baseline characteristics

140 patients with conversion disorder manifestations were enrolled (Figure 1). Patients were randomly divided into two groups of 70: group A who were treated with haloperidol, and group B who received midazolam. The mean age of patients in midazolam and haloperidol groups was 29.67± 7.50 and 29.54 ± 7.22 years, respectively (p = 0.918). Table 1 compares the baseline characteristics of studied patients between the groups. There were no significant differences between the groups regarding the means of educational level (p = 0.988), marital status (p = 1.00) and sex (p = 0.365).

3.2. Outcomes

12 (17.1%) patients who were treated with IV haloperidol experienced drug side-effects within 1 hour and 12 (17.1%) within 24 hours, while only 3 (4.3%) patients in IV midazolam

Table 1: Comparing baseline characteristics of patients with conversion disorder treated with IV midazolam (n = 70) and IV haloperidol (n = 70)

Variable	Midazolam	Haloperidol	P
Age (year)			
Mean ± SD	29.67 ± 7.50	29.54 ±7.22	0.918
Sex			
Male	29 (41.4)	26 (37.1)	0.365
Female	41 (58.6)	44 (62.9)	
Marital status			
Single	23 (32.9)	24 (43.3)	1.000
Married	47 (67.1)	46 (65.7)	
Level of education			
Uneducated	4 (5.7)	4 (5.7)	
Junior school	30 (42.9)	28 (40.0)	0.998
High school	23 (32.9)	24 (43.3)	
Bachelor and higher	13 (18.6)	14 (20.0)	
Recent emotional stress			
Yes	-	-	-
No	70 (100.0)	70 (100.0)	
Taking medications			
Yes	-	-	-
No	70 (100.0)	70 (100.0)	
Underlying physical illness			
Yes	-	-	-
No	70 (100.0)	70 (100.0)	
Movement disorders			
No	44 (62.9)	43 (61.4)	
Paralysis	16 (22.9)	15 (21.4)	0.893
Aphonic	10 (14.3)	12 (17.1)	
Sensory disorders			
No	54 (77.1)	53 (75.7)	1.000
Stocking-glove	16 (22.9)	17 (24.3)	
Consciousness disorders			
No	42 (60)	44 (62.9)	
Coma	13 (18.6)	14 (20)	0.812
Seizure	15 (21.4)	12 (17.1)	
Vital signs			
Heart Rate	79.59 ± 4.14	79.60 ± 3.99	0.983
O_2 Saturation	95.39 ±1.19	95.41 ± 1.25	0.891
DBP	76.43 ± 7.80	76.57 ± 7.64	0.913
SBP	117.86 ± 8.14	118.43 ± 8.45	0.684

Data were presented as mean ± standard deviation or frequency (%). DBP: Diastolic blood pressure, SBP: Systolic blood pressure.

experienced side-effects within 1 hour after drug administration (p = 0.026). The symptoms of the disease subsided in 45 (success rate: 64.3%) patients in midazolam and 64 (success rate: 91.5%) patients in haloperidol group (P<0.001). Mean recovery time was 31.24 ± 7.03 minutes in IV midazolam and 30.53 ± 7.11 minutes in IV haloperidol group (p = 0.592). Absolute risk reduction (ARR) of treating patients with haloperidol compared to midazolam is about 27%.

4. Discussion

The results of this clinical trial showed that the success rate of IV haloperidol in managing conversion disorder is significantly higher than midazolam (91.5% versus 64.3%). However, patients who were treated with IV haloperidol experienced more transient and minor side-effects 1 hour, 24 hours, and 1 week after treatment. Serious side-effects for both treatments were rare.

In a study conducted by Esmailian et al. (2015) the efficacy and safety of haloperidol and midazolam have been evaluated in management of 48 patients with manifestations of conversion disorder, who were admitted to the emergency department. The efficacy of both drugs in alleviating the symptoms of the disease was reported to be the same (9).

In another study conducted by Nobay et al. (2003), the effects of 3 medications including midazolam, haloperidol, and Lorazepam were evaluated in patients with behavioral disor-

ders. The results showed that the efficacy of all 3 drugs was the same (10). The effects of haloperidol plus promethazine vs midazolam were investigated in sedation of agitated patients presenting to the psychiatric emergency room in another study. Their study showed that both treatments were effective (11). The difference between the results of this study and previous studies almost all of which indicate that midazolam is more effective on psychological stresses, may be attributed to the design and the drugs used. In addition, our study was held in the emergency department of a large teaching hospital in South and South East of Iran with a high frequency of new patient admission. This means that the researchers of the study were often under excessive pressure and that they may have been at the risk of over-assessment (12). Despite the complications of haloperidol, it is currently still the drug of choice in emergency situations (13). In the mid-1980s, several studies looked at the effect of haloperidol in treatment of devastating diseases (10, 14).

In this study, we observed that haloperidol is effective in 91.5% of cases. However, midazolam was only effective in 64.3% of patients. In another study, similar results have been reported in 81 patients. In addition, further research is required to discover drugs with faster and better effect to use in combination with other drugs (15).

The present study investigated the clinical effects of midazolam and haloperidol in patients with conversion disorder at 1 h, 24 h and one week after administration. In the two intervals of 1 and 24 h after initiation of treatment, the side-effects of haloperidol were significantly higher than midazolam. Contrary to the results of the present study, Huf et al. (2003) reported that side-effects of haloperidol plus promethazine are not significantly more than midazolam in patients with conversion disorder (11). In another study, Powney et al. (2012) reported the results of 32 previous studies that measured the effects of haloperidol compared to other therapies. According to the study, two clinical trials have reported that patients in the haloperidol group had experienced one or more adverse events compared to the placebo group (n=395, RR=1.64, CI 1.2323-2.20) (16).

According to the results of the present trial as well as previous studies, it is clear that the probable side-effects of both drugs are mostly seen within the first few minutes after administration. In the study by Huf et al. (2003), it is reported that both cases of severe side-effects occurred in the first 20 min after injection of haloperidol and midazolam and they have been associated with other factors. So, preparing for probable side-effects in the first few minutes after injection as well as considering the patient's clinical records such as a history of epilepsy or drug consumption are necessary (11). It suggested that future studies investigate the sedation speed, type and severity of side-effects, and optimal dose of haloperidol and midazolam, and the effect of combination therapy with haloperidol and midazolam in patients with conversion disorder. In addition, to assess the possible influence of stressful situations in emergency department, doing further studies in other wards of the hospital with calmer conditions is recommended.

5. Limitation

Sedation speed and severity of side-effects were not investigated in this single-center study. The main limitation of the present study was that we did not consider a group treated by combination therapy with haloperidol and midazolam.

6. Conclusion

Based on the results, the response of patients to treatment with haloperidol is clearly better than midazolam. Although transient and minor side-effects in the group treated with haloperidol were more than midazolam, serious side-effects were rare for both treatments.

7. Appendix

7.1. Acknowledgements

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7.2. Author's contribution

All the authors meet the standard criteria of authorship based on the recommendations of the international committee of medical journal editors.

7.3. Funding/Support

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7.4. Conflict of interest

All authors declare that they have no conflicts of interest.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association. 2013.
2. Spiegel D, Lewis-Fernandez R, Lanius R, Vermetten E, Simeon D, Friedman M. Dissociative disorders in DSM-5. Annu Rev Clin Psychol. 2013;9:299-326.

3. HI K, BJ S. Synopsis of Psychiatry. New York: Williams & Wilkins. 1998;8th ed:634-39.
4. Stone J, LaFrance WC, Jr., Brown R, Spiegel D, Levenson JL, Sharpe M. Conversion disorder: current problems and potential solutions for DSM-5. J Psychosom Res. 2011;71(6):369-76.
5. Bidaki R, Zarepur E, Akrami M, Mohammad M. Functional Neurological Symptom Disorder: Mismanagement, Misdiagnosis, Chronic Cough Following Sexual Abuse: A Rare Case Report. Iran J Child Neurol. 2016;10(2):90-2.
6. Brown RJ, Cardena E, Nijenhuis E, Sar V, van der Hart O. Should conversion disorder be reclassified as a dissociative disorder in DSM V? Psychosomatics. 2007;48(5):369-78.
7. Stone J, Zeman A, Simonotto E, Meyer M, Azuma R, Flett S, et al. FMRI in patients with motor conversion symptoms and controls with simulated weakness. Psychosom Med. 2007;69(9):961-9.
8. Bidaki R, Zarepur E. Intermittent Hemiplegia in a Boy with Primary Moyamoya Disease: A Case Report from Iran. Iran J Child Neurol. 2017;11(2):65-8.
9. Esmailian M, Ahmadi O, Taheri M, Zamani M. Comparison of haloperidol and midazolam in restless management of patients referred to the Emergency Department: A double-blinded, randomized clinical trial. J Res Med Sci. 2015;20(9):844-9.
10. Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Acad Emerg Med. 2004;11(7):744-9.
11. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. BMJ. 2003;327(7417):708-13.
12. Baldacara L, Sanches M, Cordeiro DC, Jackoswski AP. Rapid tranquilization for agitated patients in emergency psychiatric rooms: a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. Rev Bras Psiquiatr. 2011;33(1):30-9.
13. Cascella M. Anesthesia awareness. Can midazolam attenuate or prevent memory consolidation on intraoperative awakening during general anesthesia without increasing the risk of postoperative delirium? Korean J Anesthesiol. 2015;68(2):200-2.
14. Clinton JE, Sterner S, Stelmachers Z, Ruiz E. Haloperidol for sedation of disruptive emergency patients. Ann Emerg Med. 1987;16(3):319-22.
15. Griffin CE, 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214-23.
16. Powney MJ, Adams CE, Jones H. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database Syst Rev. 2012;11:CD009377.