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Effectiveness and Safety of Haloperidol Add-on Methadone in Acute Opium Withdrawal Symptoms of Opioid-dependent Patients: A Double-blind Randomized Placebo-controlled Clinical Trial

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Original Article

Abstract

Background: The aim of this double-blind clinical trial was to evaluate the efficacy and safety of haloperidol on acute opioid withdrawal symptoms.

Methods: In this randomized double-blind clinical trial, fifty-two eligible patients were assigned to two groups according to previous opioid consumption, low dose (LD) and high dose (HD). Then, patients in each group were randomly assigned to one of the two subgroups of haloperidol or placebo. Patients in the haloperidol subgroup in LD group received 2.5 mg and in HD group received 5 mg/day haloperidol with methadone. Methadone was discontinued ten days after the beginning of the study and haloperidol or placebo continued for up to two weeks after methadone discontinuation. The severity of opioid withdrawal symptoms was assessed with the Objective Opioid Withdrawal Scale (OOWS) every other day.

Findings: Although both treatment protocols either in LD or HD opioid consumption groups significantly increased the score of the OOWS over the trial period (all subgroups, $P < 0.001$), the combination of 2.5 mg/day of haloperidol and methadone in LD opioid consumption group showed a significant superiority over methadone alone in decreasing opium withdrawal symptoms during the study ($P = 0.001$). The frequency of adverse effects was comparable between two treatment protocols in both groups ($P > 0.05$).

Conclusion: The results of this study suggest that 2.5 mg/day of haloperidol may be an effective adjuvant agent in the management of opium withdrawal symptoms in patients with LD opioid consumption. Nevertheless, results of larger controlled trials are needed before recommendation for a broad clinical application can be made.

Keywords: Opium; Substance withdrawal syndrome; Methadone; Haloperidol

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Introduction

Opioid dependence is one of the major health and social concerns which is accompanied by high rate of morbidity and mortality in many countries.[1] Since the 1990s, the expanding rate of opioid-related deaths has found the features of an epidemic.[2]

Management of opioid withdrawal symptoms is the first step towards abstinence.[3] Opioid withdrawal is usually accompanied by severe symptoms,[4] including dysphoric mood, nausea, vomiting, yawning, fever, and insomnia.[5] Various pharmacological treatments have been suggested to help a safe transition to tide over the opioid detoxification processes,[6,7] but there is currently no consensus on optimal pharmacological treatment to achieve the lowest incidence of withdrawal symptoms, because the true mechanism of resistance, dependence, and withdrawal has not been fully elucidated.[8]

Haloperidol is a psychotropic drug commonly used in management of psychosis and some other psychiatric conditions.[9] Some studies indicated that adding haloperidol, a potent antagonist of sigma-1 receptor (σ_1R), to opioids can decrease tolerance to analgesic effects and potentiate analgesic and sedative effects of opioids without significant increase in the adverse effects of opioids.[10-12] These properties seem to be able to weaken a number of the opioid withdrawal symptoms. Moreover, haloperidol possesses potent anti-Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activities. There is some evidence that haloperidol reduces the physical dependence and antinociceptive tolerance in morphine-treated mice by suppressing CaMKII activity.[9,13]

Considering that most of the available data are limited to the results of animal studies,[9,14-16] a brief review indicates that despite the fact that non-addictive psychoactive drugs are sometimes used in the detoxification and maintenance of opiate addiction, these agents cannot be completely substituted for methadone in detoxification, and their effects on opioid withdrawal need further investigations.[14]

Regarding the lack of sufficient clinical information, we hypothesized that haloperidol might be an appropriate option for improving acute opioid withdrawal symptoms due to its inhibitory effects on CaMKII signaling system, low potential for overdose and abuse, being a non-scheduled drug, availability, and acceptable safety profile.[3,8,9] This study was designed to investigate the effectiveness and safety of haloperidol addition to methadone as augmentation therapy in acute opioid withdrawal symptoms in opioid-dependent patients without psychotic disorder in a randomized double-blind placebo-controlled clinical trial.

Methods

This randomized double-blind placebo-controlled parallel-group clinical trial (clinical trial registration ID: IRCT201702131457N12) was conducted in the Zare Hospital, a university-affiliated hospital located in Mazandaran Province in the north of Iran, between June 2018 and November 2018. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (ethical code: IR.MAZUMS.REC.95.2298). Written informed consent was obtained from eligible patients. Participants were informed that they were free to withdraw from the study at any time without any negative effect on their standard treatment process.

Male inpatients with the age ranging from 18 to 60 years old who fulfilled the opioid use disorder diagnosis, based on the Structured Clinical Interview (SCID-I) for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[17,18] by fourth-year residents of psychiatry and confirmed with a rapid urine test, were included in this study.

Exclusion criteria were existence of serious medical, neurological, or any other comorbid psychotic disorders in terms of DSM-5, intelligence quotient (IQ) < 70 (based on clinical judgment), electroconvulsive therapy (ECT) in the last 6 months, and history of polysubstance use (including alcohol, but except nicotine) as defined by DSM-5. In addition, patients were excluded if they were treated by antidepressants, other antipsychotics, beta-blockers, alpha-2 agonists, and known cytochrome P450 family 3 subfamily A (CYP3A) and cytochrome P450 family 2 subfamily D member 6 (CYP2D6) inhibitor drugs in the last month. Patients with a history of treatment with haloperidol and its derivatives during the past six months, and patients with hypersensitivity to haloperidol and its derivatives or placebo were also excluded from this study. No other psychotropic medications were allowed during the trial except medications given for pain (400 mg of ibuprofen, oral), insomnia (25 to 50 mg of trazodone, oral) in doses allowed by local

regulations as pro re nata (PRN), diarrhea (2 mg of loperamide, oral), agitation [4 mg/ml of lorazepam, intramuscular (IM)], and emergent extrapyramidal symptoms (2 mg of trihexyphenidyl, oral).

Because there was no evidence of human trial in previous studies and according to "rule of 12",[19] the minimum cases in each group was obtained 12. Considering a 10% attrition rate, a final sample size of 52 was achieved. According to previous opioid consumption, the eligible patients were divided into two main groups, low dose (LD) opioid consumption group and high dose (HD) opioid consumption group. Individuals who consumed ≤ 30 mg methadone or < 6 mg buprenorphine/daily were considered as LD group and participants who consumed ≥ 35 mg methadone or ≥ 6 mg buprenorphine/daily were considered as HD group. Then, patients in each one of main groups were randomized in a 1:1 ratio by using a computerized random number generator in order to receive either haloperidol or placebo, in addition to their standard detoxification treatment, methadone. Finally, 13 patients in each subgroup completed the study.

Those patients in HD group received either haloperidol tablet (Sobhan Co., Iran) 5 mg/daily (a quarter of tablet morning and noon, half a tablet at night) (HDH) or placebo (HDP). Those patients in LD group received either haloperidol tablet (Sobhan Co., Iran) 2.5 mg/daily (a quarter of tablet in morning and night) (LDH) or placebo (LDP). The schedule of dose for both placebo groups followed the schedule of the haloperidol tablet. All patients in HD group received trihexyphenidyl (Sobhan Co., Iran) 2 mg/daily (0.5 mg in morning and noon, 1 mg at night) and all patients in LD group received trihexyphenidyl (Sobhan Co., Iran) 1 mg/daily (0.5 mg in morning and night). Patients in the placebo group received the same identical tablets (with the same shape, color, and taste as haloperidol) along with their detoxification treatment regimen.

The placebo was prepared in the School of Pharmacy, Mazandaran University of Medical Sciences. At the beginning of the study and along with haloperidol-trihexyphenidyl/placebo-trihexyphenidyl administration, all patients went on the same detoxification regimen with methadone. Regarding the anticholinergic effects of trihexyphenidyl, which can affect the detoxification process, the placebo groups were also administered trihexyphenidyl tablet with the same dose as the haloperidol groups. The methadone dose was calculated according to the equivalent dosage of their previous opioid usage. Each 12 mg of buprenorphine was considered equal to 60 mg of methadone.[6] All patients were administered a fixed dose of methadone for 5 days according to the equivalent dosage of their previous opioid usage. Then, methadone was reduced gradually (20% every day) over a period of 5 days to reach abstinence. At the end of 10th day, methadone was discontinued. During the first week after methadone discontinuation, the doses of haloperidol and trihexyphenidyl were reduced to 1.25 mg/day and 0.5 mg/day (both in the morning) in LDH group and 2.5 mg/day and 1 mg/day (both divided in morning and night) daily in HDH group, respectively. Haloperidol and trihexyphenidyl were discontinued during the second week after methadone discontinuation.

Allocation concealment was accomplished by sequentially numbered, sealed, opaque, and stapled envelopes. The randomization and allocation of the treatment groups were conducted by the primary investigator of the study, which was not involved in the diagnosis and follow-ups. Separate individuals were responsible for randomizations, drug administration, rating, data entry, and statistical analysis. Furthermore, all individuals involved in this study, such as patients and researchers, were blinded to the assignments, except the primary investigator.

The main outcome was defined as the difference in Objective Opioid Withdrawal Scale (OOWS)[20] score changes between two groups from baseline to each point of the study. The OOWS was used to assess withdrawal symptoms. The Persian version of the OOWS has been validated, and was also applied in several clinical trials conducted on Iranian population.[20,21] OOWS was measured at baseline before the first dose of haloperidol/placebo, and on days 3, 5, 7, 9, 11, 13, 15, and 17 after starting of haloperidol-trihexyphenidyl/placebo-trihexyphenidyl administration.

Safety and tolerability were evaluated by monitoring the frequency of adverse events, clinical laboratory test results, and vital sign measurements. Extrapyramidal symptoms were assessed by interview and examination by rater at each visit and, if needed, dose of anticholinergic drug was added.

Laboratory evaluations were accomplished at baseline and at the end of study. A rapid urine test was performed at baseline and in the middle of trial. Furthermore, the patients were requested to instantly inform us about any unexpected unfavorable symptom during this study.

All data were assessed in terms of normality by the use of one-sample Kolmogorov-Smirnov test. Qualitative variables were documented according to frequency and percentage, and quantitative variables were presented as mean ± standard deviation (SD). For comparing the continuous variables in these two subgroups at baseline, the independent samples t-test or Mann-Whitney U test was applied, and to compare categorical variables, chi-square test or Fisher's exact test was used, where appropriate. General linear model (GLM) repeated measures analysis of variance (ANOVA) was used to investigate the time, treatment, and time-treatment interaction effects for OOWS. The two subgroups as a between-subjects factor (group) and the nine measurements during treatment as the within-subjects factor (time) were considered. The independent samples t-test was administrated to compare the score changes in OOWS items from baseline to each time point between both subgroups. Cohen's d effect sizes were determined by dividing the mean difference of the two subgroups at each time point by their pooled SD. Chi square test or Fisher's exact test was used to compare the number of adverse events between two subgroups. All statistical analyses were conducted using the SPSS software (version 21, IBM Corporation, Armonk, NY, USA), and P-values of less than 0.05 were considered as statistically significant.

Results

The flowchart and demographic data for the study population are presented in figure 1 and table 1, respectively.

OOWS scores in patients with low opioid consumption: The OOWS scores increased significantly compared to baseline in both LDH and LDP subgroups. Repeated measures ANOVA determined significant effects for time, group, and time by treatment interaction on OOWS scores, showing that behavior of the two treatment subgroups was different across time (Table 2, Figure 2). During the study, OOWS score changes from baseline were statistically significant on days 9th, 13th, and 17th in the haloperidol subgroup compared to the placebo subgroup (Figure 2).

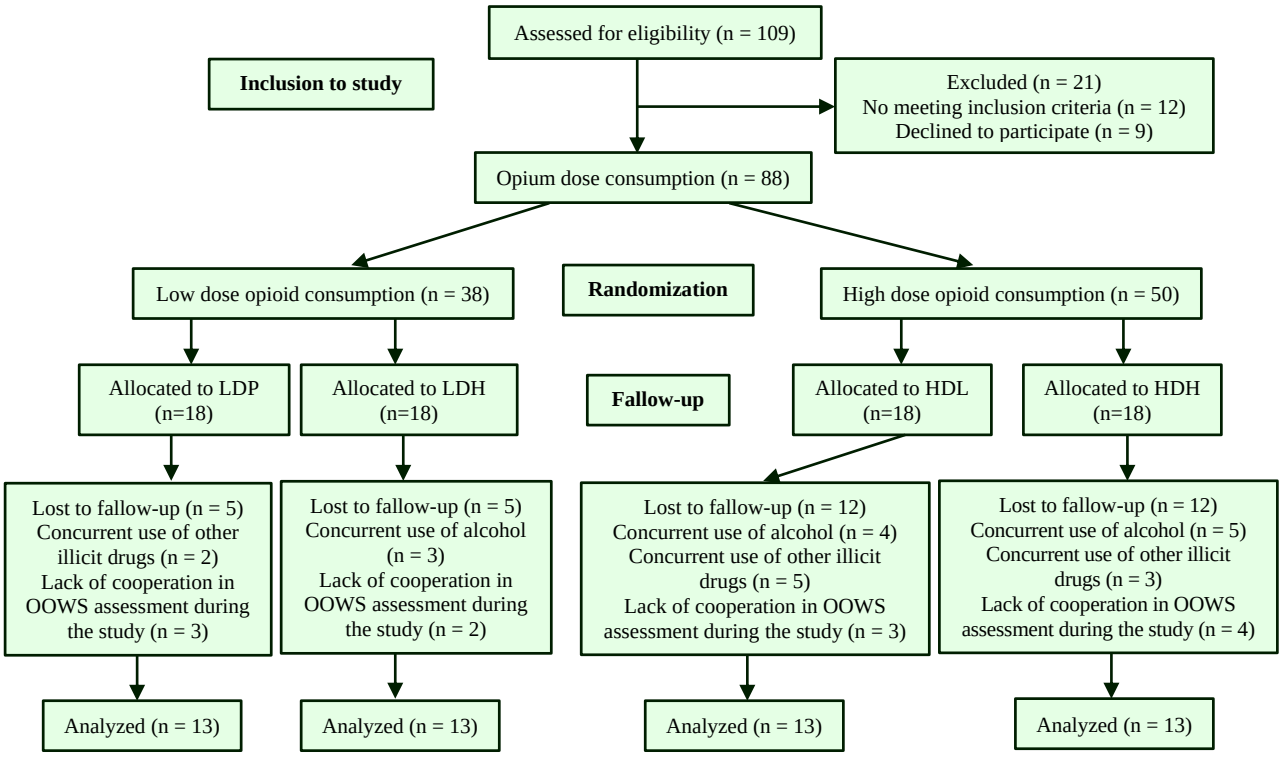

Figure 1. Flow chart of participants

Table 1. Baseline demographic characteristics and clinical parameters in all patients

Variable	Low dose			High dose		
	Haloperidol (n = 13)	Control (n = 13)	P	Haloperidol (n = 13)	Control (n = 13)	P
Age (year) (mean ± SD)	36.30 ± 5.90	37.90 ± 8.03	0.500	35.80 ± 7.90	32.50 ± 8.00	0.300
History of abstinence [n (%)]	6 (46.2)	2 (15.4)	0.200	9 (69.2)	9 (69.2)	> 0.999
Duration of substance dependence (year) (mean ± SD)	7.10 ± 3.90	6.50 ± 3.50	0.700	7.70 ± 4.50	7.50 ± 3.80	0.900
Detoxification methods [n (%)]						
Buprenorphine	4 (30.8)	6 (46.2)	0.700	3 (23.1)	4 (30.8)	> 0.999
Methadone	9 (69.2)	7 (53.8)		10 (76.9)	9 (69.2)	
Substance dose (mg/d)* (mean ± SD)	16.50 ± 7.50	20.40 ± 5.60	0.600	40.40 ± 5.20	47.70 ± 12.00	0.500

*Substance doses were converted into total daily methadone equivalents
SD: Standard deviation

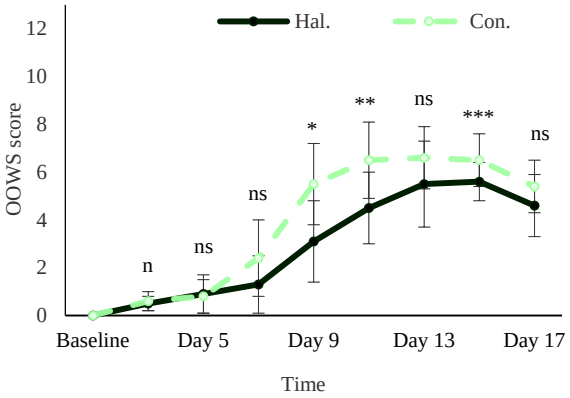

Figure 2. Mean ± standard deviation (SD) of the two treatments on Objective Opioid Withdrawal Scale (OOWS) score in low dose groups; P-values show the results of independent samples t-test for comparison of the score changes from the baseline between the two groups at each time point (*P = 0.002; **P = 0.003; ***P = 0.050; ns: Non-significant)

OOWS scores in patients with high opioid consumption: Repeated measures ANOVA determined that OOWS scores increased significantly compared to baseline in both HDH and HDP subgroups during the study, but the difference between the two treatment protocols was not significant as indicated by the effect of group. There was a significant effect for time by treatment interaction on OOWS scores, showing that behavior of the two treatment subgroups was not homogeneous across time (Table 2, Figure 3).

On day 9th, OOWS score change from baseline was statistically more significant in the haloperidol subgroup than the placebo subgroup, which returned to a non-significant difference by day 13th and was maintained throughout the entire 17th treatment period (Figure 3).

Clinical complications and side effects: No severe adverse events or death occurred. None of the patients left the study due to side effects.

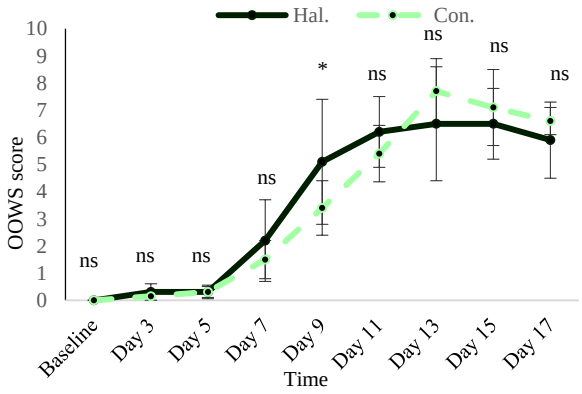

Figure 3. Mean ± standard deviation (SD) of the two treatments on Objective Opioid Withdrawal Scale (OOWS) score in high dose groups; P-values show the results of independent samples t-test for comparison of the score changes from the baseline between the two groups at each time point (*P = 0.010; ns: Non-significant)

The results of laboratory tests were found to be within normal range at the baseline and end of the study. Extrapyramidal symptoms were not reported by any of the patients. The difference between the haloperidol and placebo subgroups, either LD or HD, in the frequency of side effects was not significant (Table 3).

Discussion

Our findings showed that the addition of 2.5 mg per day haloperidol to methadone in patients with LD opioid consumption resulted in significant reduction in acute opium withdrawal intensity compared to the subgroup who received methadone alone.

Table 2. Mean of scores in the trial groups on Objective Opioid Withdrawal Scale (OOWS) scores

Subgroups*	Groups	Time					Within each group analysis	Between-groups analysis		
		Baseline	Day 5 (mean ± SD)	Day 9 (mean ± SD)	Day 13 (mean ± SD)	Day 17 (mean ± SD)		Time by treatment interaction	Time effect	Group treatment effect
Low opioid consumption	Haloperidol	0	0.90 ± 0.80	3.10 ± 1.70	5.50 ± 1.80	4.60 ± 1.30	F (3.4, 41.5) = 52.8, P < 0.001	F (4.1, 99.2) = 3.9, P < 0.001	F (4.1, 99.2) = 125.4, P < 0.001	F (1, 24) = 13.4, P = 0.001
	Control	0	0.80 ± 0.70	5.50 ± 1.70	6.60 ± 1.30	5.40 ± 1.10	F (3.4, 41.0) = 75.5, P < 0.001			
High opioid consumption	Haloperidol	0	0.31 ± 0.20	5.10 ± 2.30	6.50 ± 2.10	5.90 ± 1.40	F (3.7, 46.4) = 61.2, P < 0.001	F (4.5, 108.1) = 4.1, P = 0.003	F (4.5, 108.1) = 184.1, P < 0.001	F (1, 24) = 0.3, P = 0.500
	Control	0	0.31 ± 0.25	3.40 ± 1.00	7.70 ± 1.20	6.60 ± 0.50	F (3.2, 38.7) = 171.5, P < 0.001			

*The number of patients was 13 in each subgroup
SD: Standard deviation

Table 3. Frequency of adverse events in the trial groups

Adverse events	Low dose			High dose		
	Haloperidol (n = 13) [n (%)]	Control (n = 13) [n (%)]	P	Haloperidol (n = 13) [n (%)]	Control (n = 13) [n (%)]	P
Muscle pain	3 (23.1)	5 (38.5)	0.600	4 (30.8)	6 (46.2)	0.600
Restlessness	-	-		2 (15.4)	1 (7.7)	
Sleeplessness	1 (7.7)	-		3 (23.1)	4 (30.8)	
Headache	2 (15.4)	1 (7.7)		2 (15.4)	2 (15.4)	

Our results also indicated that the efficiency of 5 mg per day haloperidol in patients with HD opioid consumption on acute opioid withdrawal symptoms was similar to placebo. This may be due to the need for higher dosages of haloperidol to control the symptoms of withdrawal in HD opioid users. The haloperidol at dosages of either 2.5 mg/day in patients with LD opioid consumption or 5 mg/day in patients with HD opioid consumption in combination with methadone was associated with an incidence of adverse events similar to that associated with placebo, and most of them were of mild intensity. It appeared that haloperidol add-on to methadone in opioid-dependent patients without psychotic disorder was safe and well tolerated.

To the best of our knowledge, so far, the efficacy of haloperidol and trifluoperazine compared with methadone has been investigated in in vitro and in vivo settings previously,[14,22] and the present study is the first human placebo-controlled study that has evaluated the efficacy of adjunctive haloperidol to methadone on acute opioid withdrawal symptoms in non-psychotic population.

Our results were in line with the results of animal trials by Ansar et al.[23] and Sanaie Rad et al.[16] and a human study by Karkalas and Lal[22] in opioid addicts.

In the human study by Karkalas and Lal,[22] efficacy of haloperidol in the detoxification process was compared with methadone in 18 hospitalized heroin addicts (10 patients in haloperidol group and 8 patients in methadone group) with average use of 15 'bags' of heroin a day. Patients in haloperidol group received 1-2 mg three times a day of haloperidol orally and patients in methadone group took oral methadone, 10 mg four times a day for 48 hours. In that study, haloperidol was compared well with methadone and completely improved the heroin withdrawal symptoms in half of the patients by 4th day of treatment. Moreover, in those patients, the drug craving was completely eliminated by haloperidol use continuation. Four out of five patients in whom haloperidol failed to control withdrawal symptoms used 20 to 30 bags of heroin daily. They concluded that patients who used higher dose of heroin might need higher doses of haloperidol to control withdrawal symptoms, which seems to be the case in our study, and patients in HD opioid consumption group needed haloperidol at doses above 5 mg per day to alleviate the withdrawal syndrome.

In Karkalas and Lal study in 1973,[22] open-label method, short follow-up, and small sample size limit the ability to attribute outcomes to treatment with haloperidol in these populations.

The results of present study were different from unpublished results of studies by Ciccone el al.[14] and Karkalas and Lal.[22] Ciccone et al. reported that haloperidol had a limited place in the detoxification of heroin addicts. Their study consisted of two phases. In the first phase, they assessed the effectiveness of haloperidol in managing heroin withdrawal symptoms in 12 addicted patients. The results of the first phase reported that haloperidol provided less relief than that expected with methadone. In the second phase of their investigation, they designed a double-blind study to compare the effectiveness of haloperidol (4 to 16 mg daily) with trifluoperazine (12 to 48 mg daily) in the heroin detoxification of 25 outpatients (12 patients in haloperidol group and 13 patients in trifluoperazine group). The results of the second phase indicated that haloperidol and trifluoperazine reduced severity of withdrawal symptoms in a dose-dependent manner but provided less relief than that is usually seen with methadone. Besides, haloperidol and trifluoperazine failed to reduce the heroin craving.

Results of another study,[14] which evaluated the effectiveness of methadone (mean daily dose of 6-28 mg) and haloperidol (mean daily dose of 2-6 mg) in the detoxification process in 17 patients (9 patients in haloperidol group and 8 patients in methadone group) showed that methadone was superior to haloperidol in reducing the severity of withdrawal symptoms.

The inconsistencies observed in results of the aforementioned trials with present study can be in part explained by the differences in the study design.

Some evidence showed that the co-administration of methadone and haloperidol was more effective in reducing morphine tolerance and dependence than the effect of each drug alone.[9,16] To the best of our knowledge, there is no report regarding kinetic interactions between methadone and haloperidol, and this led to the assumption that the therapeutic effects shown by haloperidol on opioid withdrawal

symptoms are likely to result from a pharmacodynamic mechanism.[24] The sample size should be recognized as another reason for the inconsistencies reported between the results of the above trials and our study. The sample sizes in the three trials mentioned above were small to modest, which makes it difficult to detect significant differences in the results of changes in the withdrawal symptoms between the two treatment arms. In view of the small sample size and the relative lack of statistical power, it may be better to express the efficacy of treatment groups in terms of Cohen's effect size independent of the sample size. In the present study, in addition to power study, we calculated Cohen's effect size for OOWS score. Cohen's effect size for OOWS score from day 7 of study indicated that haloperidol in both LD and HD opioid consumption groups produced large effect size for OOWS scores.

Another probable explanation for the inconsistencies reported between the results of the above trials and present study is the differences in the mean daily dose of haloperidol. According to results of Yang et al.'s study,[9] haloperidol managed opioid-induced hyperalgesia and opioid withdrawal symptoms in a dose-dependent manner. They found that haloperidol, up to 1 mg/kg did not interrupt morphine-induced hyperalgesia, while haloperidol at dose of 3 mg/kg prevented this phenomenon in dependent male mice.

In the present study, haloperidol augmentation either in LD or HD was associated with an incidence of adverse events similar to that associated with placebo. Extrapyramidal symptoms were not reported by any of the patients, which may be due to prophylactic combination of haloperidol with trihexyphenidyl. Moreover, the overall tolerability of concomitant use of methadone and haloperidol was acceptable in our study.

This study has limitations that should be mentioned. The first limitation is the defined exclusion criteria which limit the generalizability of the findings to populations such as polysubstance abusers or chronic medical patients who receive opioid pain killers. Second, the assessments of the amount of opioid consumed and the duration of dependency were based on the statements of the study participants which may have been affected by recall or reporting bias. Third, the available samples were men, which might have limited interpretation of the current findings to male-predominant populations. Finally, the follow-up period was short and we did not evaluate the effectiveness of haloperidol in reducing drug craving during and after the study.

Further studies with larger sample sizes, different durations of intervention along with drug craving assessment during and after the study, and different haloperidol dosage regimens in patients of both genders are warranted.

Conclusion

Although both treatment protocols either in LD opioid consumption group or HD opioid consumption group significantly increased the score of the OOWS over the trial period, the combination of 2.5 mg/day of haloperidol and methadone in LD opioid consumption group showed a significant superiority over methadone alone in decreasing opium withdrawal symptoms during the study. It seems that the HD opioid users need higher than 5 mg/day of haloperidol to control the symptoms of opioid withdrawal. In addition, haloperidol add-on to methadone in opioid-dependent patients without psychotic disorder was safe and well tolerated.

Conflict of Interests

The Authors have no conflict of interest.

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The funding organization had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript and the decision to submit the paper for publication. The current study complies with contemporary laws and regulations in Iran.

Authors' Contribution

Designed the study, interpreted the clinical data and wrote the first draft of the manuscript: MZ, AA and NH; wrote the study proposal, engaged in data collection and wrote the first draft of the manuscript: FGH and PH; performed the statistical analysis and interpreted them: MM and NH.

All authors contributed to the critical revision of the manuscript and approved the final article.

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ارزیابی اثربخشی و ایمنی اضافه نمودن هالوپریدول به متادون بر علایم محرومیت حاد از مواد افیونی: یک کارآزمایی بالینی دو سوکور، تصادفی و کنترل شده با دارونما

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مقاله پژوهشی

چکیده

مقدمه: هدف از انجام کارآزمایی بالینی حاضر، ارزیابی اثربخشی و ایمنی هالوپریدول بر علایم سندرم محرومیت حاد از مواد افیونی در بیماران بدون علایم سایکوتیک بود.

روش‌ها: در این کارآزمایی بالینی تصادفی دو سوکور، ۵۲ بیمار مرد وابسته به مواد افیونی به طور تصادفی و بر اساس میزان مصرف قبلی مواد افیونی در روز، به دو گروه مصرف دز کم (Low dose یا LD) و مصرف دز بالای (High dose یا HD) مواد افیونی تقسیم شدند. سپس بیماران هر گروه به طور تصادفی به دو زیرگروه هالوپریدول (H) و دارونما (P) تقسیم شدند. بیماران در زیرگروه هالوپریدول در گروه LD، روزانه ۲/۵ میلی‌گرم و در گروه HD، روزانه ۵ میلی‌گرم دریافت کردند. در ابتدای مطالعه و همراه با هالوپریدول/ دارونما، تمام بیماران متادون را به مدت ۵ روز با دز ثابت دریافت نمودند. دز متادون معادل با اپیوم مصرفی بیمار تعیین گردید. سپس متادون جهت دستیابی به علایم محرومیت، به تدریج در مدت ۵ روز قطع شد. مصرف H یا P تا دو هفته پس از قطع متادون ادامه یافت. شدت علایم محرومیت از مواد افیونی با سنجه Objective Opioid Withdrawal Scale (OOWS) به صورت یک روز در میان مورد بررسی قرار گرفت.

یافته‌ها: نمرات سنجه OOWS در هر دو گروه LD و HD در مقایسه با گروه‌های شاهد به طور بارزی بهبود یافت (به ترتیب $P < ۰/۰۰۱$ و $P = ۰/۰۰۳$). تغییرات در نمره سنجه OOWS در روزهای نهم، سیزدهم و هفدهم از شروع مطالعه در گروه LD و در روز نهم از شروع مطالعه در گروه HD به طور معنی‌داری در مقایسه با گروه‌های شاهد مربوطه (به ترتیب LD و HD) از لحاظ آماری معنی‌دار گزارش گردید. فراوانی عوارض جانبی نیز بین دو گروه هالوپریدول و شاهد معنی‌دار نبود.

نتیجه‌گیری: اضافه نمودن هالوپریدول به رژیم درمانی متادون مؤثرتر از رژیم درمانی متادون به تنهایی در کنترل علایم سندرم محرومیت حاد از مواد افیونی در بیماران بدون علایم سایکوتیک می‌باشد.

واژگان کلیدی: مواد افیونی؛ سندرم ترک مواد؛ متادون؛ هالوپریدول

ارجاع: قادری بافتی فتانه، ضرغامی مهران، احمدی عبدالکریم، موسی‌زاده محمود، هادی نژاد پژمان، هندویی نرجس. **ارزیابی اثربخشی و ایمنی اضافه نمودن هالوپریدول به متادون بر علایم محرومیت حاد از مواد افیونی: یک کارآزمایی بالینی دو سوکور، تصادفی و کنترل شده با دارونما.** مجله اعتیاد و سلامت ۱۴۰۰؛ ۱۳ (۲): ۹۴-۸۵.

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