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Comparison of Buprenorphine and Buprenorphine/naloxone in Detoxification of Opioid-dependent Men

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Original Article

Abstract

Background: Buprenorphine sublingual tablets are now available in Iran for opioid detoxification in clinics. Aim of the present study was to compare the efficiency of buprenorphine with buprenorphine/naloxone in short-term detoxification in a group of Iranian male opioid-dependent patients.

Methods: A double-blind trial was carried out on a group of male opioid dependent patients in a psychiatric hospital in Kerman, Iran, during year 2017. A group of 100 men who met the diagnostic criteria for opiate dependence were included in the study from individuals who had referred for detoxification. They were allocated to the two groups receiving either buprenorphine (n = 51) or buprenorphine/naloxone (n = 49). Severity of withdrawal symptoms and signs were evaluated by Clinical Opiate Withdrawal Scale (COWS) and Adjective Rating Scale for Withdrawal (ARSW).

Findings: The mean scores of COWS and ARSW in the two groups treated with buprenorphine and buprenorphine/naloxone significantly reduced from the first day to the fifth day of detoxification ($P < 0.050$). Moreover, there was no significant difference between the two groups in terms of objective and subjective symptom reduction ($P > 0.050$).

Conclusion: Buprenorphine/naloxone is as effective as buprenorphine in controlling opiate withdrawal symptoms.

Keywords: Addiction; Detoxification; Buprenorphine; Buprenorphine/naloxone

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Introduction

Substance abuse is a major social and public health problem in Iran. Opium and its derivatives are the most common used drugs. Studies have revealed that the rate of drug addiction nearly doubles every 12 years in Iran and annually, 8% is added to addicts' population.[1] Opioid dependents experience stressful withdrawal symptoms at the time of detoxification. Therefore, opioid detoxification should be done in a safe and effective manner to minimize the withdrawal symptoms.[2,3]

Medications that are currently used for symptomatic management of opioid detoxification are alpha-2 (α-2) adrenergic agonists (lofexidine, clonidine), complete and partial opioid agonists (methadone, buprenorphine), and opioid antagonists (naloxone, naltrexone).[4-6] Each of these medications has different levels of success rate and effectiveness.[7] The most effective way to control withdrawal symptoms is substituting methadone or buprenorphine. Although methadone is orally effective and long-acting and results in smoother withdrawal symptoms, in case of overdose it may lead to respiratory depression and death.[8,9] In 2002, the Food and Drug Administration (FDA) approved sublingual buprenorphine for opioid detoxification. Buprenorphine is a partial opioid agonist which has a high affinity to mu (μ)-opioid receptors (MORs). Buprenorphine is long-acting, effective, and safe in the management of withdrawal syndrome when using sublingually.[10,11] Nevertheless, the administration of buprenorphine is associated with opioid-like effects and its abuse by the parenteral route has been reported in different countries as well as Iran.

One way to minimize potential abuse of buprenorphine is the combination of buprenorphine with the short-acting opioid antagonist naloxone. Buprenorphine/naloxone is a combination of buprenorphine with the opiate antagonist naloxone.[11] The bioavailability of naloxone in buprenorphine/naloxone combination is relatively low in sublingual administration, whereas buprenorphine has sublingual absorption. As a result, if the combination is taken sublingually, the patient experiences buprenorphine effects.[12] However, in parenteral abuse of buprenorphine/naloxone, antagonistic effects of naloxone appear and the drug abuser experiences accelerated withdrawal symptoms.[12]

Relying on the safety and effectiveness of buprenorphine/naloxone as well as its low risk of parenteral abuse reported in various studies, buprenorphine/naloxone combination is currently among the first-line treatment strategy for opioid detoxification.[13] However, still generic formulation of buprenorphine is prescribed in Iran. Therefore, the present study aimed to compare effectiveness and safety of buprenorphine/naloxone combination with buprenorphine in the management of withdrawal syndrome in a group of Iranian opioid-dependent individuals.

Methods

This double-blind clinical trial was carried out on 100 male opioid-dependent patients admitted to a major psychiatric hospital in Kerman, Iran, in 2017. Inclusion criteria for this study were age of 18 to 69 years, opioid dependency diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-IV-TR), the willingness of the patient to be treated with buprenorphine, and no history of hypersensitivity to buprenorphine. Exclusion criteria consisted of presence of other major psychiatric disorders (except personality disorders), concomitant abuse of other substances, intelligence quotient (IQ) of less than 80, the presence of poisoning signs, and acute consumption of opioids.

Using the census method, all voluntary eligible patients were enrolled. The study was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman. Informed consent was obtained from all participants, and they were randomly allocated to either buprenorphine or buprenorphine/naloxone detoxification group. Then, psychiatric interview, demographic information, and information related to opioid treatment including type of substance used, concomitant use of other illegal substances, concomitant use of benzodiazepines, poisoning due to overuse of substances in the last month, presence of medical illness, and drug history were recorded by the researchers. Moreover, some essential laboratory tests including urine analysis for drugs of abuse (morphine, methamphetamine, cannabis), the level of liver enzymes, as well as urea and creatinine levels of patients were

ordered. For patients aged over 40 years, electrocardiogram (EKG) was also obtained.

Upon admission to the inpatient unit (study day 1), subjects were stabilized on sublingual buprenorphine or buprenorphine/naloxone 2 mg given two to four times daily, depending on individual response. The first dose was given when symptoms of withdrawal appeared. Subsequent to the initial dose, patients were checked for signs and symptoms of withdrawal every 2-4 hours, and then in the lack of evidence of acute poisoning, another tablet was taken. After complete management of withdrawal symptoms, medication was tapered off and eventually discontinued. This step was performed at different rates of discontinuation depending on the patient's tolerance.

The main outcomes examined in this study included the Clinical Opiate Withdrawal Scale (COWS) and Adjective Rating Scale for Withdrawal (ARSW). The COWS consists of 11 items (scored as 0-4 or 0-5). Obtained points of 5-12, 13-24, 25-36, and above 36 demonstrate weak, moderate, moderate to severe, and severe withdrawal signs, respectively. The COWS was filled out by a psychiatrist at 9 a.m. on days 1, 2, 3, and 5.

The ARSW consists of 16 items. Patients rate themselves on a scale ranging from 0 (none) to 9 (severe) (maximum cumulative score of 144). The ARSW was filled out by patients on days 1, 2, 3, and 5.

The independent t-test and chi-square test were used to compare nominal and numerical variables. Repeated measures analysis of variance (ANOVA) was used to compare severity of withdrawal symptoms in two groups by the COWS and ARSW. SPSS software (version 18, SPSS Inc., Chicago, IL, USA) was used to analyze the data. P-values less than 0.050 were considered significant.

Results

Out of 100 subjects, 51 patients received buprenorphine and 49 patients received buprenorphine/naloxone treatment. The mean age of patients was 34.1 ± 8.0 in the buprenorphine group and 34.4 ± 10.1 in the buprenorphine/naloxone group. In the buprenorphine group, 76.5% of patients were married, only 11.8% had university education, and 60.8% were employed; whereas in the buprenorphine/naloxone group, 65.3% of patients were married, 18.4% had university education, and 61.3% were employed.

Age, level of education, substance concomitant abuse, and type of opioid substance were not significantly different between the two groups (Table 1).

Table 1. Characteristics of the participants in this study

Characteristics		Buprenorphine	Buprenorphine/naloxone	P
Age (year) (mean ± SD)		34.1 ± 8.0	34.4 ± 10.1	0.880
Marital status [n (%)]	Single	11 (21.6)	13 (26.5)	
	Married	39 (76.5)	32 (65.5)	0.080
	Divorced	1 (2.0)	4 (8.2)	
Education [n (%)]	Middle school	25 (49.0)	20 (40.8)	
	High school	20 (39.2)	20 (40.8)	0.070
	University degree	6 (11.8)	9 (18.4)	
Occupation [n (%)]	Employed	31 (60.8)	31 (61.3)	0.790
	Unemployed	20 (39.2)	18 (36.7)	
Type of opioid substance [n (%)]	Opium	23 (45.1)	22 (44.9)	
	Heroin	11 (21.6)	17 (34.7)	0.070
	Methadone	12 (23.5)	3 (6.1)	
	Sap of opium	5 (9.8)	7 (14.3)	
Other substance abuse [n (%)]	Benzodiazepines	9 (52.9)	4 (28.6)	
	Methamphetamine	3 (17.6)	5 (35.7)	0.040
	Cannabis	2 (11.8)	1 (7.1)	
	Other	3 (17.6)	4 (28.6)	
Substance concomitant abuse [n (%)]	Yes	7 (15.2)	6 (14.3)	0.090
	No	39 (84.8)	36 (85.7)	

SD: Standard deviation

Table 2. Comparison of changes in Clinical Opiate Withdrawal Scale (COWS) and Adjective Rating Scale for Withdrawal (ARSW) scores in the two groups receiving buprenorphine and buprenorphine/naloxone

Variable	Drug group	Mean ± SD					P	P
		First day	Second day	Third day	Fourth day	Fifth day	Within group	Between group
COWS score	Buprenorphine	7.5 ± 12.0	3.3 ± 4.3	1.8 ± 2.6	1.0 ± 2.1	0.4 ± 1.2	0.470	0.640
	Buprenorphine /naloxone	6.9 ± 5.8	4.7 ± 5.3	2.3 ± 3.5	1.2 ± 2.2	0.4 ± 1.3		
ARSW score	Buprenorphine	40.3 ± 30.4	25.4 ± 25.2	15.6 ± 18.5	8.7 ± 15.1	3.7 ± 9.9	0.730	0.310
	Buprenorphine /naloxone	45.3 ± 31.3	31.0 ± 26.3	18.4 ± 18.1	11.5 ± 17.1	4.5 ± 13.9		

COWS: Clinical opiate withdrawal scale; ARSW: Adjective rating scale for withdrawal; SD: Standard deviation

The results showed that the mean scores of COWS and ARSW were not significantly different before the start of treatment comparing buprenorphine to buprenorphine/naloxone group (P > 0.050).

Table 2 shows changes in the mean scores of COWS and ARSW for each group. The COWS and ARSW scores have been compared between the two groups at the first, second, third, and fifth day of detoxification. For both the COWS and ARSW, the results showed a significant main effect of time (P < 0.001), suggesting that the severity of withdrawal symptoms gradually declined in the days after the onset of detoxification. However, the main effect of group was not significant (P > 0.050), indicating that buprenorphine and buprenorphine/naloxone were comparable in controlling withdrawal symptoms (Figures 1 and 2).

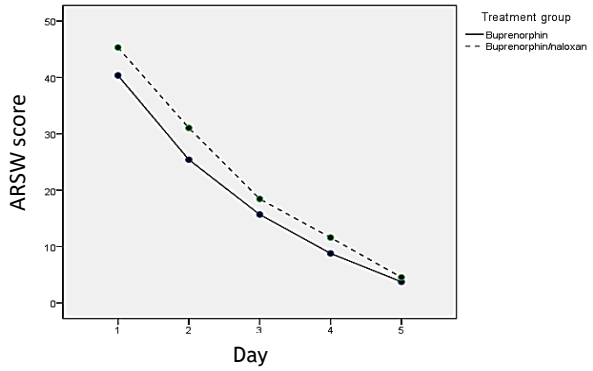

Figure 1. The trend of changes in severity of withdrawal symptoms based on Adjective Rating Scale for Withdrawal (ARSW) in different days in two groups

In an attempt to answer that whether buprenorphine/naloxone treatment due to having naloxone in combination may accelerate withdrawal symptoms at the start of treatment, the mean scores of the questionnaires were compared on the day after starting either buprenorphine or buprenorphine/naloxone. Results showed that the mean scores of the two questionnaires were not significantly different between the two groups, indicating that buprenorphine/naloxone did not cause acute withdrawal symptoms (Table 3).

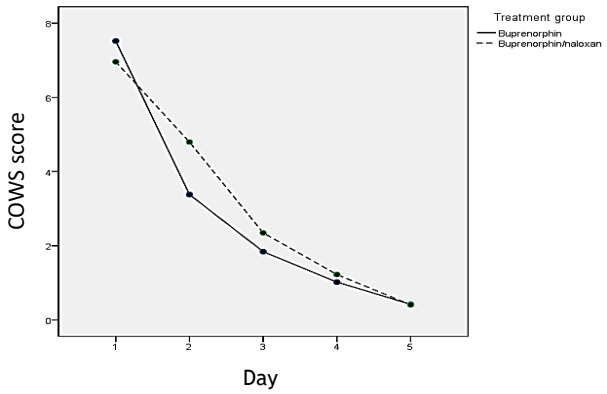

Figure 2. The trend of changes in severity of withdrawal symptoms based on Clinical Opiate Withdrawal Scale (COWS) in different days in two groups

Discussion

In Iran, the opioid-dependents are treated with sublingual buprenorphine tablets. Despite clinical efficacy of buprenorphine for opiate dependency, injecting buprenorphine has been reported.

Table 3. The mean score of Adjective Rating Scale for Withdrawal (ARSW) and Clinical Opiate Withdrawal Scale (COWS) in the first day after starting the treatment in the two groups of buprenorphine and buprenorphine/naloxone

Variable	Buprenorphine (mean ± SD)	Buprenorphine/naloxone (mean ± SD)	P
ARSW	40.3 ± 30.4	45.3 ± 31.3	0.420
COWS	7.5 ± 12.5	6.9 ± 5.8	0.780

ARSW: Adjective rating scale for withdrawal; COWS: Clinical opiate withdrawal scale; SD: Standard deviation

In order to prevent this problem, adding naloxone to buprenorphine is recommended.[14,15] Numerous studies have shown that individuals have not experienced euphoria when naloxone is combined with buprenorphine in parenteral use.[15,16] For the first time, this study aimed to compare the efficiency of buprenorphine with buprenorphine/naloxone in short-term detoxification in Iran. The results showed that in both groups, the severity of subjective and clinical withdrawal symptoms significantly decreased after the treatment. Moreover, the efficacy of both drugs in reducing opioid withdrawal symptoms was comparable.

The results of the present study are in agreement with previous studies.[13,17] Strain et al. examined the therapeutic effects of buprenorphine/naloxone and buprenorphine on the severity of withdrawal symptoms during detoxification treatment, using COWS questionnaire. Comparison of the COWS score in each group showed a reduction in withdrawal symptoms following detoxification treatment for both treatment strategies with no significant differences between groups.[17] In addition, in a double-blind clinical trial study on opioid addicts by Fudala et al., comparisons between the efficacy of three drugs including buprenorphine/naloxone, buprenorphine, and placebo were made. The results showed that combination of buprenorphine/naloxone and buprenorphine alone were more effective than placebo. Also, their study showed that the efficacy of buprenorphine/naloxone and buprenorphine was similar.[13]

The major concern about buprenorphine/naloxone was that there may be a potential possibility for the emergence of accelerated withdrawal symptoms caused by naloxone at the onset of treatment. In theory, the absorption of naloxone is negligible and its very short half-life, as compared to buprenorphine, prevents such a side effect which has been confirmed in several studies.[13,18,19] Consistent with previous reports, in our study, no one dropped out of the study due to report of any drug adverse effects.

Conclusion

According to the results of this study, both buprenorphine and buprenorphine/naloxone had a similar effect on the control of withdrawal symptoms in detoxification. This finding extends and complements those from previous studies showing that short-term opioid detoxification using the buprenorphine/naloxone is as safe and effective as buprenorphine.

Limitations: A limitation of this study could be the small sample size. Hence, further studies with larger sample size are recommended. Another limitation was the discrepancy between objective and subjective evaluation of symptoms. This means that some patients exaggerated the severity of symptoms or indicated the reduction of their symptoms as a result of drug use less than its objective values. The objective evaluation of symptoms with the COWS questionnaire greatly reduced this limitation.

Conflict of Interests

The authors have no conflict of interest.

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مقایسه بوپرنورفین و بوپرنورفین– نالوکسان در سم‌زدایی مردان وابسته به مواد مخدر اپیوئیدی

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مقاله پژوهشی

چکیده

مقدمه: در حال حاضر، قرص‌های زیرزبانی بوپرنورفین در ایران به عنوان یک سم‌زدای اپیوئیدی برای استفاده در کلینیک‌ها در دسترس می‌باشد. هدف از انجام پژوهش حاضر، مقایسه کارامدی بوپرنورفین و بوپرنورفین- نالوکسان در مدت کوتاه سم‌زدایی بر روی گروهی از مردان ایرانی وابسته به اپیوئیدها بود.

روش‌ها: این مطالعه به صورت یک کارآزمایی بالینی دو سوکور، بر روی بیماران وابسته به مواد مخدر اپیوئیدی در بیمارستان روان‌پزشکی شهید بهشتی کرمان طی سال‌های ۹۶-۱۳۹۵ انجام شد. یک گروه ۱۰۰ نفره از مردان مراجعه‌کننده به بخش سم‌زدایی که دارای علایم اعتیاد به اپیوئیدها بودند، در مطالعه شرکت نمودند و به دو گروه ۵۱ نفر دریافت‌کننده بوپرنورفین و ۴۹ نفر دریافت‌کننده بوپرنورفین- نالوکسان تقسیم شدند. شدت علایم و نشانه‌های ترک با استفاده از مقیاس علایم عینی ترک اپیوئیدها (Clinical Opiate Withdrawal Scale یا COWS) و مقیاس علایم ذهنی ترک اپیوئیدها (Adjective Rating Scale for Withdrawal یا ARSW) مورد ارزیابی قرار گرفت.

یافته‌ها: میانگین نمرات دو مقیاس COWS و ARSW در دو گروه درمان با بوپرنورفین و درمان با بوپرنورفین- نالوکسان از روز اول تا روز پنجم دوره سم‌زدایی کاهش معنی‌داری را نشان داد ($P < ۰/۰۵۰$). تفاوت معنی‌داری بین دو گروه از نظر علایم عینی و ذهنی مشاهده نشد ($P > ۰/۰۵۰$).

نتیجه‌گیری: بوپرنورفین- نالوکسان به اندازه بوپرنورفین در کنترل علایم ترک مؤثر است.

واژگان کلیدی: اعتیاد، سم‌زدایی، بوپرنورفین، بوپرنورفین- نالوکسان

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