Original Article

Comparison of the Efficacy of Buprenorphine and Clonidine in Detoxification of Opioid-Dependents

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Abstract

Background: Since the number of drug users is increasing, applying a method of detoxification with fewer side effects during withdrawal from opioids and greater reliability seems to be necessary. In addition, without maintenance treatment, there will be limited success of treatment. This study aimed to compare success rates of detoxification with sublingual buprenorphine and clonidine and to evaluate addiction relapse in patients using naltrexone in a six-month follow-up.

Methods: This double-blind trial was carried out on opioid dependent patients in a psychiatric hospital in Kerman (Iran) during 2007-09. The subjects were randomly selected from individuals who had referred for detoxification. They were allocated to two groups to receive either clonidine (n = 21) or buprenorphine (n = 14). The success rates of the two methods were assessed at the end of the course and patients were discharged while prescribed with 25 mg daily use of naltrexone. They were followed up for six months and the continuous use of naltrexone and relapse of substance abuse were evaluated.

Findings: A total number of 35 patients entered the study. Success of detoxification with naltrexone was confirmed in all cases. One person (8.4%) in the clonidine group and no patient in the buprenorphine group had a clinical opiate withdrawal scale (COWS) score of more than 12 ($P > 0.05$). The mean levels of objective signs and subjective symptoms of withdrawal and the desire for drug abuse had significant reductions during detoxification period in both groups ($P < 0.001$). However, the difference in these variables between the two groups was not statistically significant ($P > 0.05$). Naltrexone was used for an average of one month in 43% and 64% of subjects in the clonidine and buprenorphine groups, respectively. In addition, 62% of patients in the clonidine group and 92.8% of subjects in the buprenorphine group received maintenance treatment. Nevertheless, the mean number of days staying in treatment was not significantly difference between the two groups ($P > 0.05$).

Conclusion: Buprenorphine is as effective as clonidine in controlling withdrawal symptoms. A greater percentage of patients detoxified by buprenorphine received maintenance treatment, but there was not a significant difference in relapse rates between the two methods.

Keywords: Buprenorphine, Clonidine, Naltrexone, Opioid detoxification, Addiction relapse

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Introduction

Drug dependence, a psychiatric disorder with biological, psychological and social dimensions, is considered as a major problem in Iran. The prevalence of drug dependence among human societies has increased clearly.[1,2] Since medical issues, mental illness of companions, and other related factors such as family breakdown, unemployment, and legal issues are all of high prevalence among drug addicts, these individuals are a serious problem for the Iranian Department of Health and other social services in the country.[2] A previous study reported that 74.4% of patients who referred to an addiction treatment clinic used opium and 20.8% used heroin.[3]

Effective control of drug withdrawal symptoms and helping patients to tolerate the withdrawal stage are essential in attempts to quit drug abuse and to prevent its consequences such as relapse.[4,5] Withdrawal syndrome includes subjective symptoms and objective signs which begin within 6-8 hours after taking substances in drug dependent patients. Among the many available methods to control these symptoms is using alpha-adrenergic agonists like clonidine and guanfacine that prevent the occurrence of noradrenergic withdrawal syndrome.[6] Success rate of this method has been reported as 10-90%.[7,8] Opioid agonists such as methadone are also a standard method of withdrawal from opioids in many countries.[5,9,10] However, the use of methadone has some limitations due to its side effects risk of death when used excessively and uncontrolled.[2,11]

The efficacy of buprenorphine in controlling the symptoms of withdrawal syndrome has been recently evaluated.[4,11] Buprenorphine is a partial agonist with high affinity and low intrinsic activity at mu receptors and antagonist activity at kappa receptors. It is safer than methadone since it does not slow down breathing and has less autonomous withdrawal symptoms, and reduced psychomimetic effects or dysphoria.[12]

Similar to methadone, overuse of buprenorphine is dangerous. Therefore, a combination of buprenorphine and naloxone (called Suboxone) has been introduced and confirmed by the US Food and Drug Administration (FDA)[13,14] to reduce the risk of excessive intravenous injection by the naloxone component.[2,11]

Different drug regimens, impurities of substances used in each country, different drug metabolism of people, and different races are all effective in detoxification. Since there are inconsistencies in the findings of previous studies, the present study compared the success of sublingual buprenorphine prescription in controlling opium withdrawal syndrome with clonidine and evaluated relapse rate during a six-month period of naltrexone maintenance treatment.

Methods

This double-blind clinical trial was conducted on male opioid-dependent patients seeking for detoxification in Shahid Beheshti Hospital (Kerman, South East Iran) during 2007-09. Subjects were diagnosed as opioid-dependent according to the Fourth Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[15] They aged 18-40 years old and were visiting for detoxification for the first time. In addition, they were able to read and write.

Exclusion criteria were serious medical conditions such as acute hepatitis, liver disease (serum glutamic oxaloacetic transaminase > 50), diabetes, acute psychotic disease and personality disorder, concomitant abuse of methadone, beta-blockers, or calcium channel blockers, any medical condition interfering with clonidine such as heart disease, cardiovascular disease, and renal disease, and finally, a history of allergy to clonidine, buprenorphine, or naltrexone. In addition, patients with blood pressure below 90/60 mmHg and a pulse below 60 beats per minute during treatment were excluded from the study.

The study procedure was confirmed by the Ethics Committee of the Neuroscience Research Center (Kerman, Iran). Afterward, 50 patients seeking addiction therapy were evaluated. Since 15 subjects were excluded due to ineligibility or unwillingness to participate, 35 subjects were finally included. After being thoroughly explained about the study and signing a written consent form, the participants were randomly allocated to either clonidine or buprenorphine detoxification group. In the next stage, psychiatric interviews, clinical examination, and medical history taking were performed by a psychiatry resident. Complete blood count (CBC) test, kidney and liver function tests,

hepatitis and human immunodeficiency virus (HIV) tests were also conducted.

To ensure blinding, the placebo of each drug was also prepared by the Department of Pharmacology of Kerman University of Medical Sciences (Kerman, Iran). Therefore, group 1 (n = 14) received buprenorphine and clonidine placebo and group 2 (n = 21) received clonidine and buprenorphine placebo. All drugs and placebos were assigned a code and kept by a person who was not involved in the study. In group 1, 2 mg sublingual tablets of buprenorphine hydrochloride were used. On days 1-5, one oral clonidine placebo tablet and 2, 4, 6, 4, and 2 mg/day buprenorphine were administered, respectively. In some cases, depending on the severity of symptoms, 2-4 mg buprenorphine were added in the withdrawal phase.[14,16,17] In group 2, 0.2 mg oral clonidine tablets and sublingual buprenorphine placebo tablets were administered. They received one tablet twice on the first day, one tablet three times daily on the second and third days, and one tablet daily on the fourth and fifth days. Moreover, 0.2-0.4 mg/day additional drug was administered if indicated.[5,18,19] Vital signs of patients were controlled four times a day and before administration of each drug dose. Patients were also evaluated for appearance of side effects by a physician and a nurse according to various references. Urine test for opioid substance was performed using thin layer chromatography.

The main outcomes investigated in this study included the clinical opiate withdrawal scale (COWS) score above 12 on day 5, the success rate of detoxification with naltrexone two days after the end of detoxification phase, the rate of remaining in treatment with naltrexone in a six-month monitoring period, and also the rate of positive urinary samples for opioids at the end of six months. The intensity of signs and symptoms of withdrawal in the detoxification phase and the desire for substance abuse were also evaluated in these patients. In order to assess the intensity of signs, the COWS was applied. It consists of 11 items (scored as 0-4 or 0-5). A total of 5-12 points indicates weak withdrawal signs, 13-24 stand for moderate withdrawal signs, 25-36 show moderate to severe withdrawal signs, and points above 36 demonstrate severe withdrawal signs.[20,21] The COWS was filled out by a psychiatric technician at 9 a.m. on days 1, 2, 3, and 5. The intensity of psychiatric withdrawal signs was evaluated using the Adjective Rating Withdrawal Scale (ARWS) which consists of 16 items rated as 0-9 by the patient.[22] The desire for substance abuse was assessed using a visual analogue scale (VAS) in which a 10 cm line was marked by the patient to indicate his desire for substance abuse.[23]

To ensure the success of detoxification, patients received naltrexone two days following detoxification. They were then discharged while prescribed with 25 mg/day naltrexone for six months. They were monitored every two months by questioning the patient and his family on the phone about continuing the use of naltrexone and maintaining the treatment. In cases of contradiction between the statements of patients and their families, the family was considered to be the main reference. Since the validity and accuracy of self-proclaimed statements depend on the confidentiality of information, data should be collected in a safe place within acceptable limits.[24] Previous studies have indicated the accuracy of self-proclaimed data in Iran.[25] Monitoring was completed at the sixth month through obtaining urine tests. Withdrawal symptoms were controlled with trazodone, lorazepam, hydroxyzine, acetaminophen, and hyoscine as required.

Chi-square test, Fisher's exact test, and t-test were used to compare nominal and numerical variables. The mean days of stay in treatment were determined by Kaplan-Meier test and compared between the two groups by log-rank test. All data analyses were performed with SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA). P values less than 0.05 were considered significant.

Results

The mean age of subjects in the clonidine and buprenorphine groups were 25.1 ± 1.6 and 25.7 ± 1.2 years, respectively ($P > 0.05$). The mean amount of substance-taking was 3.4 ± 0.2 mg in clonidine group and 3.4 ± 0.3 mg in the buprenorphine group ($P > 0.05$). In the clonidine group, 71.4% of the subjects were employed, 33.3% were married, and only 8.4% had university education. In the buprenorphine group, 42.9% of patients were employed, 35.7% were married, and 14.3% had university education ($P > 0.05$).

Changes in the mean scores of COWS and ARWS and desire for substance abuse (craving) are presented in table 1. One subject (4.8%) in the clonidine group and none in the buprenorphine group had a COWS score above 12 on day 5 (P > 0.05).

The mean number of days remaining in treatment and the mean number of days receiving naltrexone in the two groups are presented in table 2. Frequency of naltrexone use and the number of people who remained in treatment in the two groups are shown in tables 3 and 4.

According to personal and family statements and with confirmation of urine test, two patients maintained withdrawal in the six-month monitoring after detoxification and discharge. In the buprenorphine group, three subjects completed the treatment. Since none of the subjects referred for urine test, the statements of families could not be confirmed. All patients took naltrexone at the end of the detoxification period. In one case, clonidine was discontinued on the second day due to blood pressure below 90/60 mmHg. Moreover, one patient in the clonidine group complained of dysphoria.

Discussion

Although many cases faced an increased severity of withdrawal symptoms after the last period of use, the symptoms were mild and moderate and were eliminated after 48-72 hours after taking the medicine.

This investigation showed that administration of buprenorphine for a few days can be as effective as clonidine in controlling the signs and symptoms of opioids withdrawal. In fact, comparing the effectiveness of these two drug groups in terms of detoxification did not show statistically significant differences. In contrast, Gowing et al. reviewed 22 studies on a total number of 1763 people and found that buprenorphine was more effective than clonidine or lofexidine in eliminating the signs of withdrawal. They also reported that patients receiving buprenorphine completed the

Table 1. Comparison of changes in clinical opiate withdrawal scale (COWS) and adjective rating withdrawal scale (ARWS) scores and craving in the two groups receiving clonidine and buprenorphine

Variables	Drug group	First day	Second day	Third day	Fifth day	P	
						Within groups	Between groups
COWS score	Clonidine	12.0 ± 1.7	17.0 ± 1.6	12.5 ± 1.6	3.5 ± 0.9	< 0.001	0.615
	Buprenorphine	11.1 ± 1.5	15.0 ± 2.2	11.1 ± 2.6	3.1 ± 1.0		
ARWS score	Clonidine	53.1 ± 4.0	54.8 ± 4.2	46.5 ± 4.7	24.1 ± 3.0	< 0.001	0.182
	Buprenorphine	47.4 ± 3.4	49.1 ± 4.0	34.7 ± 6.0	17.5 ± 3.5		
Craving	Clonidine	89.1 ± 2.3	81.4 ± 3.5	73.3 ± 3.5	62.0 ± 3.8	< 0.001	0.870
	Buprenorphine	72.1 ± 2.8	72.1 ± 2.8	82.1 ± 3.2	92.1 ± 2.6		

Values are expressed as mean ± SD; COWS: Clinical opiate withdrawal scale; ARWS: Adjective rating withdrawal scale

Table 2. Number of days remaining in treatment and receiving naltrexone in the two groups during a six-month follow-up

Drug Group	Naltrexone consumption	P	Stay in treatment	P
Clonidine	30.7 ± 9.1	0.743	87.7 ± 14.9	0.301
Buprenorphine	38.4 ± 13.2		59.7 ± 19.6	

Table 3. Frequency distribution of naltrexone consumption in the two groups receiving buprenorphine and clonidine during a six-month follow-up

Group	Continued naltrexone	Discontinued naltrexone	Not reachable
Clonidine	9 (43)	10 (48)	2 (9)
Buprenorphine	9 (64)	5 (36)	-

Values are presented as number (%)

Table 4. Frequency distribution of number of subjects who received maintenance treatment in the two groups

Group	Received maintenance treatment		Not reachable
	Yes	No	
Clonidine	13 (62.0)	6 (28.5)	2 (9.5)
Buprenorphine	13 (92.8)	1 (7.2)	-

Values are presented as number (%)

detoxification period more effectively. Moreover, although there was no significant difference in the occurrence of side effects, it seemed that more patients abandoned treatment due to the side effects of clonidine.[4] The difference between our findings and those of Gowing et al. may be due to different number of samples, consumption of opioids with stronger effects, differences in detoxification periods during regimens, and different drug metabolism in subjects.[1] Similar to Gowing et al., Nigam et al. reported the superiority of buprenorphine to clonidine in controlling the signs and symptoms of withdrawal from opioids.[14] These inconsistencies suggest that in addition to the dose of medication, the length of detoxification period can also play an important role in treatment results. Cheskin et al. compared a three-day high-dose buprenorphine regimen with a standard five-day clonidine regimen in an inpatient and double-blind study on 25 men and women dependent on heroin. They found no difference in physiological and subjective factors of the two groups. However, clonidine had more effects on hypotension and buprenorphine eliminated the signs of withdrawal earlier.[16] This difference with our study can also be due to differences in the effectiveness of the used drugs and the use of high-dose medicine regimens.

Our study was conducted on patients admitted to a detoxification center. A previous study on four groups (outpatients and inpatients receiving either buprenorphine or clonidine for 13 days) showed that patients in the clonidine group had milder withdrawal signs, stayed in treatment longer, and obtained better results.[24]

A comparison between three detoxification methods including clonidine, clonidine with naltrexone, and clonidine with buprenorphine showed treatment success rates of 65%, 81%, and 81%, respectively. Moreover, patients receiving the two combinations completed treatment more efficiently than those under clonidine alone.[11] Benefits of the combination of buprenorphine and clonidine for opium detoxification have been supported by other research.[26]

Preventing the recurrence of drug abuse is a crucial step following detoxification. It can be achieved by drug or non-drug methods, independent or combined. Due to the wide range of social workers involved in substance abuse and its legal consequences, studies on the efficacy of these methods are different in various communities and lack certain criteria.[27] The excessive desire for drug abuse is related to the euphoria caused by opioids which is mediated by the mu receptors. Naltrexone, an antagonist of the mu receptor, has been approved by the US FDA for treatment of alcohol dependence and blockade of the effects of opioids.[5,27] Studies have reported the combination of buprenorphine and naltrexone to be associated with lower recurrence rate, lower tendency to use drugs, and higher percentage of negative urine samples.[4]

In the present study, 43% of the subjects detoxified with clonidine and 64% of those detoxified with buprenorphine continued taking naltrexone for one month. This difference, which was considerable but not statistically significant, might have been caused by better family support and better personal skills in dealing with stress after detoxification with buprenorphine.[28] It is noteworthy that subjects in both groups had stopped using naltrexone in the 6-month follow-up which shows the importance of supervised use of naltrexone during the follow-up period. In another study, 20-30% of patients remained under treatment with naltrexone after six months.[29]

In the present study, 62% of patients in the clonidine group and 92.8% of subjects in the buprenorphine group received maintenance treatment. A survey on maintenance treatment after five methods of detoxification indicated that the highest number of individuals who received maintenance treatment had been detoxified with buprenorphine.[30] However, we did not find statistically significant differences in mean days of stay in treatment between the two groups.

Developing a method of opioid withdrawal with shorter time period and lower costs to help patients transfer from the state of dependence to the maintenance period with minimum loss would be absolutely beneficial. Many researchers including Bearn et al.,[31] Charney et al.,[32] and Koyuncuoglu[33] have confirmed the usefulness of maintenance treatment with naltrexone. Naltrexone has in fact been suggested as an alternative to maintenance treatment with opioid agonist (methadone).[34]

In this study, patients and their families claimed reduced amount and frequency of drug abuse in those who failed to maintain abstinence compared to conditions before detoxification. Vining et al.[35] and Bearn et al.[36] reported similar findings. However, our success rates were lower than studies which included non-pharmacological programs such as group therapy, family therapy, or community-based treatment. This shows the advantage of these methods in controlling signs of opioid withdrawal. Therefore, the main disadvantage of naltrexone consumption may be the lack of a mechanism to induce patients to continue taking the drug.[5]

Conclusion

Although buprenorphine did not have a significant statistical difference with clonidine in controlling the symptoms of opioid withdrawal, patients detoxified with buprenorphine entered maintenance treatment to a greater extent. However, the recurrence rate was not significantly different between the two groups. Hence, it is suggested to choose one of the two methods based on each patient's willingness and physical conditions, health care costs, and physician's clinical judgment. The side effects should also be considered when selecting a drug. Future studies to maintain abstinence and reduce recurrence rates after detoxification are recommended to supervise and control the prescription of naltrexone more precisely, carry out a greater follow-up for urine test of morphine, and include non-medicinal programs such as individual psychotherapy, behavioral therapy, cognitive therapy, family therapy, support groups and social skills training to enhance individual, interpersonal, psychological, and social capabilities of patients.

The limitations of this study were low number of subjects, two groups of non-equal number, and lack of more accurate monitoring of the use of naltrexone and morphine urine test. More comprehensive supervision in further studies would reveal more precise results.

Conflict of Interest: The Authors have no conflict of interest.

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مقاله پژوهشی

مقایسه کارایی بوپرنورفین و کلونیدین در سم‌زدایی افراد وابسته به تریاک و میزان پرهیز از مصرف مواد با مصرف نالترکسون در یک پیگیری شش ماهه

دکتر حسن ضیاء الدینی[1]، دکتر منصوره نصیریان[2]، دکتر نوذر نخعی[3]

چکیده

مقدمه: به کارگیری روش سم‌زدایی با عوارض کمتر در دوره بازگیری از اپیوییدها و پایایی بیشتر آن با توجه به افزایش تعداد مصرف کنندگان مواد مخدر ضروری به نظر می‌رسد و چنان چه بعد از سم‌زدایی، بیمار وارد درمان نگهدارنده نشود، موفقیت چندانی نخواهد داشت. این مطالعه به مقایسه میزان موفقیت‌آمیز بودن سم‌زدایی با دو روش استفاده از بوپرنورفین زیر زبانی و کلونیدین پرداخت و سپس میزان عود مصرف مواد در یک پیگیری شش ماهه در بیماران با مصرف نالترکسون را مورد ارزیابی قرار داد.

روش‌ها: مطالعه حاضر از نوع کارآزمایی دو سو کور بود که در بیمارستان روان‌پزشکی کرمان و در سال‌های ۸۸-۱۳۸۶ بر روی افراد وابسته به تریاک جستجوی درمان سم‌زدایی، انجام شد. این افراد با روش نمونه‌گیری تصادفی در دو گروه دریافت کننده کلونیدین و بوپرنورفین سم‌زدایی شدند و موفقیت سم‌زدایی با مصرف نالترکسون در پایان دوره، ارزیابی و سپس بیماران با مصرف روزانه ۲۵ میلی‌گرم نالترکسون ترخیص شده و برای ۶ ماه از نظر ادامه مصرف نالترکسون و عدم عود مصرف مواد پیگیری شدند.

یافته‌ها: در مجموع، ۳۵ نفر وارد مطالعه شدند که موفقیت‌آمیز بودن سم‌زدایی با مصرف نالترکسون در همه افراد تأیید گردید. در گروه دریافت کننده کلونیدین (تعداد = ۲۱ نفر)، یک نفر (۴/۸ درصد) میانگین COWS (Clinical opiate withdrawal scale) بیشتر از ۱۲ را در روز پنجم نشان داد و در گروه دریافت کننده بوپرنورفین، هیچ کدام میانگین COWS بیش از ۱۲ را در روز پنجم نداشتند ($P > ۰/۰۵$). میانگین علایم عینی و نشانه‌های ذهنی ترک و میل به مصرف مواد در هر دو گروه طی دوره سم‌زدایی کاهش چشمگیری داشت ($P < ۰/۰۱$)، اما مقایسه این متغیرها بین دو گروه از نظر آماری معنی‌دار نبود ($P > ۰/۰۵$). ۴۳ درصد از افراد سم‌زدایی شده با کلونیدین و ۶۴ درصد از افراد سم‌زدایی شده با بوپرنورفین، مصرف نالترکسون را به طور متوسط برای یک ماه ادامه دادند و ۶۲ درصد افراد سم‌زدایی شده با کلونیدین و ۹۲/۸ درصد افراد سم‌زدایی شده با بوپرنورفین وارد درمان نگهدارنده شدند، اما میانگین روزهای باقی ماندن در درمان در دو گروه از نظر آماری تفاوت معنی‌داری را نشان نداد ($P > ۰/۰۵$).

نتیجه‌گیری: بوپرنورفین نیز مانند کلونیدین در کنترل مؤثر نشانگان محرومیت از مواد تأثیرگذار بود و درصد بیشتری از افراد سم‌زدایی شده با بوپرنورفین وارد درمان نگهدارنده شدند، ولی میزان عود مصرف مواد در دو روش تفاوت چندانی نداشت.

واژگان کلیدی: بوپرنورفین، کلونیدین، نالترکسون، سم‌زدایی تریاک، عود مصرف

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