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A Comparison of the Efficacy of Buprenorphine and Clonidine in Detoxification of Heroin-Dependents and the Following Maintenance Treatment

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Background:	Abstract
Methods:	This study compared the success rates of buprenorphine and clonidine in detoxification of heroin-dependents and evaluated the recurrence of drug abuse in patients taking naltrexone in a 6 month follow up.
Findings:	A double-blind study was carried out in Kerman's psychiatric hospital on heroin-dependents seeking detoxification during the years 2007-2009. These patients were randomized into 2 groups receiving clonidine and buprenorphine. The success rate of detoxification was evaluated at the end of the trial and each patient was discharged with a daily consumption of 25 mg naltrexone. They were monitored for 6 months with respect to naltrexone consumption and withdrawal from drug abuse.
Conclusion:	Overall 49 patients participated in the study. The success rate of detoxification with naltrexone was confirmed in all subjects. In the group receiving clonidine, 2 subjects (9.5%) had a clinical opiate withdrawal scale (COWS) above 12 in day 5 ($P = 0.186$) and none of the subjects in the group taking buprenorphine had a COWS above 12 in day 5. The signs and symptoms of withdrawal and the desire for substance abuse was declined significantly in both groups over time; 19% of subjects detoxified with clonidine and 39% detoxified with buprenorphine continued taking naltrexone for one month and 52% detoxified with clonidine and 53.5% detoxified with buprenorphine entered the maintenance treatment. The average days remaining in treatment and being free of recurrence of drug abuse was not significantly different between the two groups in a 6 month follow-up.
Key words:	Administration of buprenorphine within a few days was more efficient in reducing the signs and symptoms of withdrawal when compared to clonidine. However, recurrence of drug abuse was not significantly different between the two groups.
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Introduction

The prevalence of addiction to heroin and other drugs has increased significantly in the recent years. According to official statistics, the number of opioid addicts ranged from 1,200,000 to 2,000,000 in Iran, although non-official statistics estimated a total of 4,000,000.¹ At this time our country has the most opiate substance users in the world.² Detoxification is the first step in treating these patients. Various methods are used in opioid detoxification in the recent years. Alpha adrenergic agonists such as clonidine act on locus coeruleus nucleus and suppress the overwork of adrenergic system in the detoxification phase, however they produce side effects including hypotension, dizziness, drowsiness, nausea, vomiting, xerostomia (dry mouth) and do not completely eradicate the symptoms of withdrawal.^{3,4} It is speculated that clonidine is responsible for the death of two heroin-dependent patients which necessitated close observation and limitation in the use of this drug.⁵ The use of opioid agonists such as methadone also has limitations due to the death risks associated to its overuse and uncontrolled consumption.^{6,7} Buprenorphine is a semi-synthetic thebaine derivative with partial agonist actions at the Mu opioid receptor and weak antagonist actions at the kappa opioid receptors. It has certain advantages over methadone such as lower death risk due to overdose and lower respiratory depression.⁶⁻⁸ Roughly, all the bioavailability of oral buprenorphine is eliminated due to very high first pass metabolism and therefore, buprenorphine as detoxificant is administered as liquid solution or sublingual tablet containing buprenorphine alone or in conjunction with naloxone 1:4. The latter form has a lower risk of substance abuse with IV injection and lower associated side effects such as AIDS and hepatitis transmission in heroin-dependents.^{8,9} The initial elimination of buprenorphine takes place in 3-5 hours and the final elimination has a half-life of over 24 hours and is slowly released from the receptor making it possible for an every other day administration.¹⁰ In October 2002, the food and drug administration (FDA) approved subutex and suboxone sublingual tablets for this purpose.¹⁰⁻¹²

Effective monitoring of signs and symptoms of withdrawal is a crucial step in preventing the recurrence of drug abuse and should begin in 6 to

8 hours after the last usage of drug. Buprenorphine, as a control for withdrawal symptoms, is used in dose-tapering regimens over a few weeks or shorter periods such as 7 to 10 days, all of which had desirable clinical outcomes and therefore, make it difficult to select a regimen with minimum effective buprenorphine.¹³ With respect to the growing number of opioid abusers and its adverse consequences for health care units and other social services, the use of a detoxification method along with the best control of withdrawal symptoms, lower side effects. Lower period, lower amount of drugs and higher reliability seem to be necessary. Therefore, the present study as a randomized, double-blind clinical trial, evaluated the impact of sublingual buprenorphine and clonidine in controlling the signs of heroin withdrawal in a short-term period, to compare the efficacy of sublingual buprenorphine and clonidine in controlling the symptoms of heroin withdrawal and to assess recurrence in a 6-month maintenance treatment using naltrexone following detoxification.

Methods

This study, as a double-blind clinical trial, was carried out on a group of opioid-dependent patients seeking detoxification admitted to Kerman's Shaid Beheshti hospital (in the south-east of Iran) from the year 2007 till 2009. This study was conducted with the support of the neuroscience research center. Participants were men aged 18 to 40 years and were diagnosed with opioid-dependent according to the DSM IV criteria¹⁴ having their first visit for detoxification. Exclusion criteria included acute hepatitis, liver disease (SGOT > 50), diabetes, acute psychotic disease, personality disorder, concomitant abuse of methadone, beta-blockers, and calcium channel blockers, any medical condition interfering with clonidine such as cardiovascular disease, renal disease and finally, a history of allergy to clonidine, buprenorphine and naltrexone. In addition, patients with a blood pressure below 90/60 and a pulse below 60 per min during treatment were excluded from the study. Patients were able to read and write the questionnaire and were thoroughly informed before being placed into two groups. After signing a written consent form, they were put in either of the two detoxification groups, clonidine and

buprenorphine, using randomization method. To ensure ethical principles, the ethical committee of Kerman's neuroscience research center devoted the code K/87/2 to this study. Initially, 50 patients seeking addiction therapy were evaluated, from which, 15 subjects were excluded due to lack of participation criteria or unwillingness to participate and an overall 35 subjects entered the study. Psychiatric interview, clinical examination and medical history taking were done by the psychiatric resident. CBC tests, kidney and liver function tests, hepatitis and HIV tests were also obtained. In order for the researcher and patient to be unaware of the type of therapy, the placebo of each drug was given in the other drug group and each drug was assigned with a code, kept by a third party not involved in the study. The first group received sublingual buprenorphine hydrochloride, 2 mg tablets, and the placebo of clonidine and the second group received clonidine and the placebo for buprenorphine. In group one oral clonidine placebo tablets and buprenorphine were administered 2, 4, 6, 4 and 2 mg/day during days 1 to 5, respectively. In some cases, depending on the severity of symptoms, a 2-4 mg buprenorphine was added in the withdrawal phase.¹⁵⁻¹⁷ In group two, oral clonidine, 0.2 mg tablets, and sublingual buprenorphine placebo were administered in days 1 to 5 with one tablet twice in the first day, one tablet three times in the second and third days, one tablet in the fourth day and one tablet in the fifth day and if indicated, 0.2-0.4 mg/day additional drug was administered.^{10,18} The placebo for both drugs was provided by the pharmacology department of Kerman University of Medical Sciences.

Vital signs were controlled four times a day. Also, before administration of each dosage, the patient was monitored by the nurse and physician for appearance of side effects.

The main outcomes investigated in this study included the clinical opiate withdrawal scale (COWS) above 12 in 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 6-month monitoring period and also, the rate of positive urinary samples for opioids at the end of 6 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 which consists of 11 items (each item having 0 to 4 or 5 points). A total of 5-12 points indicate a weak withdrawal sign, 13-24 stand for moderate withdrawal sign, 25-36 show moderate to severe withdrawal sign and points above 36 demonstrate a severe withdrawal sign.¹⁹⁻²⁰ The intensity of psychiatric withdrawal signs was evaluated using the adjective rating withdrawal scale (ARWS) consisting of 16 items rated 0 to 9 by the patient.²¹ The desire for substance abuse was assessed using a visual analogue scale (VAS) in which a 10 cm line was marked by the patient indicating the desire for substance abuse. One end indicated lack of interest for substance abuse and the other end indicated the highest desire for substance abuse.²² COWS questionnaire was filled out by the psychiatric technician at 9 AM in days 1, 2, 3 and 5 and the ARWS questionnaire was filled out by the patient.

Vital signs were controlled four times a day and before administration of each drug dose, and the patient was evaluated by physician and nurse for appearance of side effects according to various references. Urine test for opioid substance was performed using thin layer chromatography. To ensure the success of detoxification, patients were administered naltrexone two days following detoxification and then, discharged with administration of naltrexone 25 mg/day for 6 months. They were monitored every 2 months by questioning the patient and his/her family on the phone in terms of continuing the use of naltrexone and maintaining the treatment. In cases of contradiction between the statements of patient and his/her family, the family was considered to be the main reference.

It should be noted that the validity and accuracy of self-proclaimed statements expressed in different studies are dependent on the confidentiality of the data and that the data should be collected in a safe place within acceptable limits.²³ Previous studies indicated the accuracy of self-proclaimed data in Iran.²⁴ Monitoring was completed at the 6th month in person through obtaining urine tests. In cases of controlling withdrawal symptoms, trazodone, lorazepam, hydroxyzine, acetaminophen and hyoscine were used.

In order to compare nominal and numerical variables, chi-square test, fisher's exact test and

t-test were utilized. For comparing the average deprivation score between the two groups in consecutive days repeated measure ANOVA was applied.

Results

There was no significant difference between the two groups in terms of basic variables (except marital status) (Table 1). Overall, the frequency of signs and symptoms of withdrawal either psychiatric or objective were significantly declined from the 3rd day in both groups. Changes in the average COWS, ARWS and desire for substance abuse are presented in table 2 and the average days remaining in treatment and also the average days of naltrexone consumption in the group receiving clonidine and buprenorphine are presented in table 3. In the group receiving clonidine, 2 (9.5%) subjects

had a COWS above 12 in day 5 and none of the subjects in the group receiving buprenorphine had an average COWS above 12 in the 5th day ($P = 0.186$). All patients took naltrexone at the end of the detoxification period. Clonidine was discontinued in the 3rd day in 2 patients of the group receiving clonidine due to blood pressure below 90/60; and one patient complained of dizziness. In the group receiving buprenorphine, no significant side effect was observed except in one patient experiencing euphoria. According to the personal and family statements and with confirmation of urine test, one patient maintained withdrawal in the 6 months monitoring after detoxification and discharge. In the group receiving buprenorphine, 3 subjects completed the treatment for 6 months and only one visited for urine test which was confirmed with a negative test result.

Table 1. Comparison of some of the variables in two therapeutic groups receiving clonidine and buprenorphine

Variables	Clonidine group	Buprenorphine group	P value
Mean age (\pm SD)	28.4 (45)	26.3 (5.7)	0.178
Average consumption (g) (\pm SD)	3.1 (1.0)	3.5 (2.0)	0.06
Average years of consumption	9.1 (4.3)	6.9 (4.1)	0.08
Illiterate or elementary education (%)	19 (90.5)	2 (9.5)	0.629
Higher (%)	27 (96.4)	1 (3.6)	
Marriage Status			0.0008
Single	7 (33.3)	20 (71.4)	
Married (%)	14 (66.7)	8 (28.6)	
Occupational Status			0.523
Employed (%)	16 (67.9)	19 (71.4)	
Jobless (%)	5 (32.1)	9 (28.6)	

Table 2. Comparison of the trend of changes in COWS, ARWS and craving in two groups receiving clonidine and buprenorphine

Variables	Types	First day	Second day	Third day	Fifth day	P value	
						Within groups	Between groups
COWS*	Clonidine	12.6 (1.3)	19.3 (1.5)	16.8 (2)	5.7 (1.0)	< 0.001	< 0.001
	Buprenorphine	7.1 (1.0)	13.3 (1.3)	10.5 (1.2)	1.7 (0.4)		
ARWS**	Clonidine	52.7 (3.0)	62.3 (4.1)	62.4 (6.3)	34.1 (1.8)	< 0.001	< 0.012
	Buprenorphine	43.4 (2.8)	53.5 (3.0)	48.2 (3.2)	24.1 (1.8)		
Craving***	Clonidine	96.2 (1.1)	88.1 (2.1)	81.0 (3.1)	67.5 (3.5)	< 0.001	< 0.004
	Buprenorphine	89.2 (1.8)	76.2 (2.8)	68.5 (3.1)	55.1 (3.0)		

*Consisting of 11 items each having 0 to 5 points.

**Consisting of 16 items each having 0 to 9 points.

***Using the VAS scale in which the total score can be between 0 to 100 points.

Table 3. The average days remaining in treatment and the average days of naltrexone consumption in the two groups receiving clonidine and buprenorphine in a 6-month follow-up

Drug group	Naltrexone consumption	P value	Remaining in treatment	P value
Clonidine	32.5 (10.3)	0.741	70.2 (17.4)	0.958
Buprenorphine	31.6 (10.9)		66.7 (17.9)	

Table 4. The frequency distribution of Naltrexone consumption in the two groups receiving buprenorphine and clonidine

Drug group Naltrexone consumption	Clonidine		Buprenorphine	
	frequency	percent	frequency	percent
Still remaining	4	19	11	39
Not remained	13	62	12	43
Not access to patient	4	19	5	18

Table 5. The frequency distribution of the number of subjects who remained in treatment in the two groups

Drug group Remaining in treatment	Clonidine		Buprenorphine	
	frequency	percent	frequency	percent
Patients continued treatment	11	52	15	53.5
Patients did not continue treatment	5	24	7	25
Not access to patient	5	24	6	21.5

Discussion

This investigation showed that administration of buprenorphine for a few days can not only be as effective as clonidine in controlling the signs and symptoms of withdrawal from heroine, it is significantly superior to clonidine in that respect.

On the other hand, a comparison between the findings of the current study with those of other investigations concerning heroine withdrawal indicates the high success rate of buprenorphine in detoxification. Niagam et al and Cheskin et al also¹⁵, reported the superiority of buprenorphine to clonidine in controlling the signs and symptoms of withdrawal from opioids. Gowing et al found that buprenorphine was more effective in eliminating the signs of withdrawal compared to clonidine or lofexidine and patients completed the detoxification period more effectively. Although there was no significant difference in the appearance of side effects with these drugs, it seems that more patients abandoned the study due to side effects in the group receiving clonidine.²⁵ In contrast, Talias et al¹⁵ reported a success rate of 73% in 82 subjects in detoxification and withdrawal at the end of a 10-day detoxification period detoxified with buprenorphine and 81% in 32 subjects detoxified with clonidine, although buprenorphine was more accepted by patients. The difference with the results of the present study may be due to different number of samples, consumption of opioids with stronger effects, and differences in detoxification periods during regimens and also, different drug metabolism in subjects. A study performed on 4 detoxification groups (outpatient and inpatient buprenorphine and outpatient and

inpatient clonidine) showed that inpatients received buprenorphine had a better chance of following the therapy compared to those received clonidine and compared to the outpatients. Also, they had milder signs of withdrawal and better maintenance in treatment.²³ Therefore, the current study was performed on patients admitted to the hospital. The prevention of recurrence of drug abuse is a crucial step following detoxification which is achieved by drug or non-drug methods, independent or combined. Due to the wide range of social workers and substance abuse and its legal consequences, studies on the efficacy of these methods are different in various communities and do not have a certain criteria.⁹ 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, is approved by the united states FDA for treatment of alcohol dependence and blockade of the effects of opioids.^{9,26} In the present study, 19% of the subjects detoxified with clonidine and 34% subjects detoxified with buprenorphine continued taking naltrexone for one month. Although this difference was considerable, it was not statistically significant and it may be related to better family support and better personal skills in dealing with stress after detoxification with buprenorphine.²⁷ In the current study, 52% of subjects detoxified with clonidine and 53.5% of subjects detoxified with buprenorphine entered the maintenance treatment. The days remaining in therapy and the withdrawal from drug abuse was not significantly different in a 6-month follow-up. A study conducted by O'connor et al

reported that withdrawal from drug abuse in three drug groups receiving clonidine, clonidine with naltrexone and buprenorphine was not significantly related to the types of drug used for detoxification which is in agreement with the results of our study.⁷ Ling et al also suggested that regardless of the type of drug used for detoxification of heroine, the rate of recurrence of drug abuse is almost identical.²⁸ The two main limitations to this study was the relatively small volume of samples which is justified considering the difficulty in obtaining the samples with the required characteristics and the lack of cooperation from patients at the follow-up period after detoxification which made it sometimes impossible to contact some patients. With respect to maintaining the treatment with the use of naltrexone, our results were in agreement with other investigations avoiding non-drug methods including Vining et al²⁹ and also Bearn et al³⁰ but success rate was lower compared to studies involving non-drug programs such as group therapy, family therapy or socio-therapy. This shows the advantage of these methods in controlling the signs of opioid withdrawal. Thus, the main disadvantage of naltrexone consumption may be the lack of a mechanism to induce patients to continue taking the drug.⁹ Although the rate of recurrence was considerably high in this study, it could be due to the nature of

the disease which is associated with high recurrence⁹ or the limitations of the study. It may be better to use non-drug programs in addition to the use of naltrexone.

Although buprenorphine has been more effective than clonidine in controlling the withdrawal syndrome in this study, the method of detoxification applied did not significantly affect the results of withdrawal maintenance. Perhaps it is better to choose the method of detoxification on the basis of patient's physical condition, patient's desire, available facilities, treatment expenses and clinical judgment of the physician. In order to appropriately maintain the treatment and decrease the rate of recurrence following detoxification, naltrexone should be administered in addition to sufficient control and observation along with consideration of the personal, psychological and community factors. It is suggested that in subsequent studies in addition to naltrexone consumption, non-drug programs such as individual psychotherapy, behavior therapy, cognitive therapy, family therapy, supportive groups and social skill training also be taken into account. The maintenance treatment of addiction coupled with strict community supervision probably obtains more appropriate therapeutic results.

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

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مقایسه کار آیی بوپرنورفین و کلونیدین در سم زدایی افراد وابسته به هروئین و درمان نگهدارنده پس از آن

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چکیده

این مطالعه به مقایسه میزان موفقیت آمیز بودن سم زدایی با دو روش استفاده از بوپرنورفین زیرزبانی و کلونیدین در سم زدایی افراد وابسته به هروئین و درمان نگهدارنده پس از آن و سپس ارزیابی میزان عود مصرف مواد در یک پی‌گیری شش ماهه در بیماران با مصرف نالتراکسون پرداخت.

این کارآزمایی دو سوکور در بیمارستان روان‌پزشکی کرمان در خلال سال‌های ۸۸-۱۳۸۶ بر روی افراد وابسته به هروئین در جستجوی درمان سم زدایی انجام شد؛ این افراد با روش نمونه‌گیری تصادفی در دو گروه دریافت‌کننده کلونیدین و بوپرنورفین قرار گرفتند و موفقیت سم زدایی با هر روش با استفاده از مصرف نالتراکسون در پایان دوره ارزیابی شد. سپس بیماران با مصرف روزانه ۲۵ میلی‌گرم نالتراکسون ترخیص شده، برای ۶ ماه از نظر ادامه مصرف نالتراکسون و عدم مصرف مواد پی‌گیری شدند.

به طور کلی ۴۹ نفر وارد مطالعه شدند. موفقیت آمیز بودن سم زدایی با مصرف نالتراکسون در تمامی افراد تأیید گردید. در گروه دریافت‌کننده کلونیدین، دو نفر (۹/۵ درصد) میانگین ارزیابی بالینی بازگیری از اپیوئید (COWS یا Clinical Opiate Withdrawal scale) روز پنجم بیش از ۱۲ داشتند و در گروه دریافت‌کننده بوپرنورفین، هیچکدام میانگین COWS روز پنجم بیش از ۱۲ نداشتند ($P = ۰/۱۸۶$). میانگین علائم عینی و نشانه‌های ذهنی ترک و میل به مصرف مواد در هر دو گروه با گذر زمان کاهش مشخص داشت. ۱۹ درصد افراد سم زدایی شده با کلونیدین و ۳۹ درصد افراد سم‌زدایی شده با بوپرنورفین مصرف نالتراکسون را به طور متوسط برای یک ماه ادامه دادند و ۵۲ درصد افراد سم‌زدایی شده با کلونیدین و ۵۳/۵ درصد افراد سم زدایی شده با بوپرنورفین وارد درمان نگهدارنده گردیدند. میانگین روزهای باقی ماندن در درمان و عدم عود مصرف مواد در پی‌گیری شش ماهه در دو گروه از نظر آماری تفاوت معنی‌داری نداشت.

تجویز بوپرنورفین طی چند روز به طور مؤثرتری نسبت به کلونیدین علائم و عوارض نشانگان محرومیت از مواد را کنترل می‌کند ولی میزان عود مصرف مواد در دو گروه تفاوت بارزی ندارد.

کلونیدین، بوپرنورفین، نالتراکسون، سم زدایی هروئین، عود.

مقدمه:

روش‌ها:

یافته‌ها:

نتیجه‌گیری:

واژگان کلیدی:

تعداد صفحات: ۸

تعداد جدول‌ها: ۵

تعداد نمودارها: -

تعداد منابع: ۳۰

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