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Hab-o Shefa (an Iranian traditional medicine compound) in withdrawal syndrome and its effects in acute detoxification of opiates addict: A randomized, double blind, clinical trials

Seyed Mohammad Nazari[1], Mohsen Naseri[1]*, Azarakhsh Mokri[2], Ali Davati[3] and Mohammad Kamalinejad[4]

[1]Traditional Medicine Clinical Trial Research Center, Shahed University, P. O. Box: 14179-53836, Tehran, Iran.
[2]Psychiatry Department and National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran.
[3]Community Medicine Department, Shahed University, P. O. Box 14179-53836, Tehran, Iran.
[4]Pharmacognosy Department, Shahid Beheshti University of Medical Sciences, P. O. Box 14179-53836, Tehran, Iran.

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Hab-o Shefa is a natural traditional Iranian medicine (TIM) product that many centuries used as a replacement for opium addiction treatment. In this randomized, double blind, controlled, clinical trial the effect of Hab-o Shefa was studied in the treatment of opiates addiction. In a double-blind placebo-controlled clinical trial, 90 in-patients with opiates dependency that received an assisted self-help intervention, were randomly divided into the three groups. Hab-o Shefa was administered to the first group: 3 g/day four times daily on days 1 to 7, tapered down over 14 days. Clonidine was prescribed to the second group: 0.2 to 0.4 mg/day on days 1 to 2, 0.6 mg/day on days 3 to 18 and 0.4 to 0.2 mg/day on days 20 to 21. Placebo was administered to the third group. Studied variables included treatment retention, detoxification success rate, daily check of subjective, objective and clinical opiate withdrawal scale, depression scales, craving intensity, side effects, vital signs and electrocardiography (ECG) and biochemical tests at the beginning and end points of the study. Control of withdrawal symptoms and depression in Hab-o Shefa group was better than the other groups (P<0.05).

Key words: Hab-o Shefa, acute detoxification, opiates addiction, traditional Iranian medicine, withdrawal symptoms.

INTRODUCTION

Today, substance abuse and opiate dependency are among the most important health problems in the world (Ekhtiari, 2009; Nadery et al., 2008). Different medical treatments have been presented for the treatment of opiate addiction. Although, these drugs have been successful in managing some withdrawal symptoms, but they have not been able to fully control them; also, some types of these drugs are not globally available, or have

*Corresponding author. E-mail: Naseri@Shahed.ac.ir

been abused by the patients (Assadi et al., 2004; Mokri, 2002; Nazari et al., 2012). Clonidine, a specific a_2-adrenergic receptor agonist, is probably the most common prescribed agent for this purpose in Iran and has been widely used in many other countries as well. Clonidine has been shown to be effective in the suppression of autonomic symptoms of opiates withdrawal (Janiski et al., 1985). However, this drug may cause severe adverse effects including hypotension and excessive sedation. Moreover, there is evidence that clonidine does not completely block withdrawal syndrome (Gowing et al., 2002).

Therefore, herbal medicines due to their high social acceptance, low side effects, high effectiveness, availability and low cost can be an excellent option for solving this problem (Ekhtiari, 2009). According to the World Health Organization recommendations on the use of traditional medicine in the health systems, the addiction treatment from the perspective of traditional Iranian medicine (TIM) scientists were accessed in order to have a role in overcoming this worldwide issue (Naseri, 1994, 2009). Different methods have been suggested for the treatment of opiate addiction in TIM (Nazari et al., 2012). One of these methods is the replacement of natural narcotic drugs instead of opium (Shirazi, 2009; Nazari et al., 2012). Several natural narcotic drugs have been introduced in the TIM text books (Aghili, 2005, 2001; Ansari, 1992, Arzani, 2009; Nazem, 2003; Shirazi, 2009; Tonekaboni, 2007).

Hab-o Shefa is a natural combination of drugs that most of the TIM scientists have a consensus about its positive effects in addiction treatment. It has been used as a viable alternative to opium in the treatment of addiction in recent centuries (Nazari et al., 2012). This compound also is used in treatment of chronic headaches, chronic cough, and pain relief (Aghili, 2005).

In previous study, efficacy of Hab-o Shefa was investigated, in controlling symptoms of morphine withdrawal in rats, this combination significantly controlled all the withdrawal symptoms as compared to placebo ($P<0.05$), and in the toxicology study, did not make toxicity signs in animals.

In this randomized, double blind, clinical trial, the effect of Hab-o Shefa in the control of withdrawal symptoms in addiction treatment was evaluated.

MATERIALS AND METHODS

This compound contains *Datura stramonium* seeds (19.5%), *Rheum palmatum* root (34.8%), *Zingiber officinale* rhizome (27.8%) and *Acacia arabica* gum (17.4%) (Aghili, 2005; Arzani, 2009; Ghafari, 2010; Nazem, 2003; Shirazi, 2009) purchased from the local market of Iran, and was approved by the Department of Pharmacognosy of Shahid Beheshti University of Medical Sciences, and prepared in the pharmaceutical laboratories of traditional medicine in Shahed University of Tehran, Iran. This compound is cheaper, in comparison with clonidine and other common drugs used in the treatment of addiction. Clonidine was purchased from Pharmaceutical Company of Toulid Daru, Iran.

Hab-o Shefa, clonidine and placebo (sugar) in unit size capsules packed in the boxes that were encoded by computerized random numbers for each patient individually and were distributed by a third person who had no contact with neither the investigator nor the patients.

Subjects

Inclusion criteria for the study based on the DSMIV (American Psychiatric Association, 1994) criteria were as follows: 25 to 40 year-old male, opiate dependency, a positive urinary morphine test and a negative urinary amphetamine test. The exclusion criteria included concurrent dependency to alcohol and amphetamines, suffering from an acute or untreatable medical disorder, history of psychosis, mania or severe major depression, antisocial or borderline personality, inability in filling the questionnaire, not giving an informed consent for the study and severe withdrawal symptoms or drug allergies and side effects.

Setting and ethics

In a double-blind placebo-controlled clinical trial conducted from October 2011 through December 2011, 90 inpatients were randomly selected and divided into three groups of 30 individuals each. This study was performed in the self-help opiate addiction treatment group centers of TAVALOD-E DOBARE (non-governmental centers affiliated to the Welfare Organization of Iran). Their method was based on behavioral therapy and twelve-step principles (Frydrych et al., 2009; Kumar et al., 2012) without using drugs and the patients were treated as residential inpatients; they are opiates-addicted patients who voluntarily visited such centers for addiction treatment and who fulfilled the inclusion criteria. The initial step was gaining an informed consent and then their identity (ID), demographic characteristics, medical history, physical examination and electrocardiography (ECG) data were recorded by a physician in each center. Subsequently, a urine morphine test and an amphetamine test were requested. Cases with a positive morphine test and a negative amphetamine test entered the study. Afterwards clinical toxicology tests including complete blood count, fasting blood sugar, triglyceride, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, creatinine, sodium and potassium were tested at the initiation and termination points of the study. Vital signs assessments including blood pressure, body weight, temperature, pulse rate and respiratory rate were recorded on a daily basis. All subjects received an encoded box of drugs immediately after the appearance of withdrawal symptoms. A physician under supervision of the psychiatrist, who was trained in the use of the scales and was blind to capsules content, performed all the clinical assessments.

Subjects were allowed to withdraw from the study at any point and shift to a conventional detoxification treatment focusing on relapse prevention. The study was conducted in accordance to the declaration of Helsinki and was approved by the Ethical Committee of Shahed University and registered in the Iranian Registery of Clinical Trial.

Study design

In this study, each patient was given a box of capsules. A joint treatment plan for the three groups was performed as follows: Hab-o Shefa group; 3 g/day on days 1 to 7 (4 divided doses at 8 am, 12 noon, 4 and 8 pm), 2 g/day on days 8 to 14 (3 divided doses at 8 am, 12 noon and 8 pm), 1 g/day on days 15 to 18 (2 divided doses at 8 am and 8 pm), 0.5 g/day on days 19 to 20 (once a day at 8

am). Clonidine group was administered as 0.2 and 0.4 mg/day on day 1 to 2 (2 divided doses at 8 am and 8 pm), 0.6 mg/day on days 3 to 18 (3 divided doses at 8 am, 12 noon and 8 pm), 0.4 mg/day on day 19 (2 divided doses at 8 am and 8 pm), 0.2 mg/day on day 20 (once a day at 8 pm). Placebo group was administered capsules based on the same treatment plan. In addition, all subjects received an assisted self-help intervention (behavioral therapy and the twelve-step principles). No other medication was prescribed. Patients were closely monitored for adverse effects around the clock. All the studied subjects remained in the medical center for 21 days. On the last day (day 21), a naloxone challenge test (intramuscular injection of 0.8 mg of naloxone) was performed in order to ascertain the success rate of the detoxification treatment.

Assessments

Demographic characteristics and other variables which could influence the outcomes of detoxification were recorded. The primary outcomes of interest for this study were days of retention in treatment and the success rate of detoxification. Treatment retention was defined as the number of days that each patient remained in this 21-day study. Participants were discharged from the study prematurely due to consent withdrawal or unmanageable medical complications. Detoxification was considered successful if a participant had a negative result on the naloxone challenge test. The secondary outcomes of interest for this study were opiates withdrawal that was assessed with the Subjective Opiate Withdrawal Scale (SOWS), the Objective Opiate Withdrawal Scale (OOWS) (Assadi et al., 2004) and the Clinical Opiate Withdrawal Scale (COWS) (Handelsman et al., 1987) which have been shown to be reliable and valid measures for evaluating withdrawal symptoms in the opiate withdrawal syndrome. The SOWS consisted of 13 items; each was rated as absent (0) or present (1). Consequently, the minimum possible SOWS score was 0 and the maximum 13. Subjects completed this scale each morning. The OOWS consisted of 16 items; patients rated each item on a scale of 0 to 4. The minimum possible OOWS score was 0 and the maximum 64. The latter mentioned physician performed the OOWS during a 5-min observation period. The COWS consisted of 11 items; patients rated each item on a scale of 0 to 4 or 5. The minimum possible COWS score was 0 and the maximum 48. The tertiary outcomes of interest for this study were Beck (Akyol et al., 2010) and Hamilton (Kou, 2012) depression criteria which were both assessed by physician at 9:00 am during a 3-min observational period. The Hamilton depression inventory consisted of 21 items; patients rated each item on a scale of 0 to 3. Consequently, the minimum possible Hamilton depression score was 0 and the maximum 63. The Beck depression criteria consisted of 20 items; patients rated each item on a scale of 0 to 3 or 4 and therefore the minimum possible Beck depression score was 0 and the maximum was 62. The fourthly outcomes of interest for this study were opiate craving (Halikas and Crosby, 1991) that was assessed daily with a visual analogue scale (VAS). Patients reported their level of craving by making a mark on a 100-mm line, ranging from no craving at one end to the most intensive craving ever experienced at the other.

Patients were systematically examined each day and rated by a score sheet for symptoms typically related to pharmacological side effects of clonidine and Hab-o Shefa, including headache, sedation, constipation, dizziness, urinary disorders, irregular heartbeat, blurred vision, and increased body temperature. Each item was rated as absent (0) or present (1). The total score was calculated by adding the scores on each variable. Vital signs including measurements of blood pressure, temperature, respiratory rate, heart rate, and body weight were recorded daily by a single investigator.

Statistical analysis

Data analyses were conducted on the enrolled subjects who met the eligibility criteria for participation in the trial (intention-to-treat analysis). Missing data were replaced using a last-observation-carried-forward approach.

The SOWS, OOWS, COWS, Beck depression criteria, Hamilton depression criteria, VAS scores and drug side effect were analyzed using Statistical Package for Social Sciences (SPSS) software, version 11.5 and least significant difference (LSD) testing. Analysis of variance (ANOVA) was applied for bi-group comparisons (Sarafraz and Ghafarzadegan, 2004).

RESULTS

Sample characteristics

Ninety eligible opiate-dependent patients were enrolled in the study; and 30 subjects were assigned to each treatment group (Badiei, 2004). The three groups were apparently well matched and there were no statistically significant differences between the three groups in socio-demographic characteristics or drug usage and the three groups in Beck and Hamilton depression scale ($P<0.05$) (Table 1).

Treatment retention and successful detoxification

All subjects remained on treatment and completed the study, and they had a negative result on the naloxone challenge test considered as successfully detoxified. There was no difference in the success rate of detoxification between the three groups.

Severity of subject-rated opiates withdrawal

The daily mean SOWS and OOWS and COWS scores for participants in each group are shown in Figure 1. The daily mean severity scores of COWS, OOWS and SOWS, respectively were 5.5±4.16, 4.35±1.4 and 10.98±8.57 for patients receiving the placebo protocol. The same values. respectively were 4.34±4.27, 4.16±3.4 and 10.24±9.18 for those treated with the Hab-o Shefa protocol and 5.25±3.98, 3.5±3.4 and 9.12±7.26 for those treated with the clonidine protocol. In the Hab-o Shefa group before and after the study period, a significant difference was seen as compared to the placebo and clonidine groups ($P<0.05$).

Severity of subject-rated craving

The mean score for patients receiving the placebo protocol was 7.8±2.3, and for those treated with the Hab-o Shefa protocol was 6.7±2.8 and for cases receiving the clonidine protocol was 7.3±2.8. During the study period

Table 1. Baseline characteristics and addiction history of patients.

Variable	Subgroup	Placebo (N = 30)	Hab-o Shefa (N = 30)	Clonidine (N = 30)
Age (%)	25 – 40 year	100	100	100
Sex (%)	Male	100	100	100
Marital status (%)	married	46.6	66.6	66.6
	single	53.3	33.3	33.3
Education (%)	Yes	80	90	96.6
	No	20	10	3.3
Employment (%)	Yes	100	96.6	100
	No	0	3.3	0
Type of opiate (%)	Opium	93.30	90	96.60
	Opium extract	66.60	40	20
	Morphine	0	0	0
	Heroine	26.60	36.60	23.30
	Crack	66.60	73.30	83.30
Route of opiates usage (%)	Injection	20	16.60	23.30
	Smoking	90.00	96.60	43.30
	Oral	6.60	43.30	40
Duration of opiate usage	Years (mean±Std)	8.5±5.4	11.2±6.6	9.7±5.8
Number of previous abstinences	(mean±Std)	1.9±2.7	2.8±3.9	4.3±4.9
Beck* depression on 1thday	(mean±Std)	(36.2±7.01)	(23.6±7.66)	(28.3±6.7)
Hamilton* depression on 1thday	(mean±Std)	(19.9±4.8)	(13,73±5.2)	(16.6±3.82)

*Significant at the P<0.05.

there was no statistically significant difference between the three groups.

Severity of subject-rated depression

The daily mean scores of Beck and Hamilton depression criteria for participants in each group are as shown in Figure 2. The mean Beck and Hamilton scores, respectively for the placebo group were 23.3±7.69 and 12±4.1; and for the Hab-o Shefa group were 10.9±7.1 and 6.25±4.26 and for the clonidine group were 17.27±6.1 and 9.38±3.75. Hab-o Shefa group showed a significant decrease as compared to the placebo and clonidine groups (P<0.05).

Bi-groups comparisons

The results of bi-groups comparisons are summarized in Table 2. Control of withdrawal symptoms and depression showed a significant difference between the Hab-o Shefa and placebo groups (P<0.001), and was also significant between the clonidine and placebo groups (P<0.05) and control of withdrawal symptoms was significant between the clonidine and Hab-o Shefa groups (P<0.05) and control of depression was significant between the clonidine and Hab-o Shefa groups (P<0.001).

Other outcomes

The daily means score of side effect for the placebo, Hab-o-Shefa and clonidine groups, respectively were 3.97±3.62, 3.77±4.38 and 3.97±3.62. There were no statistically significant differences between the three groups during the study period. All patients had a positive urine morphine test at study entrance, it was repeated once every three days and the results were all negative during the study period. All patients were negative for their urine amphetamine test at study entrance, it was repeated once a week and the results were all negative during the study period. Biochemical lab tests and ECGs were performed twice at the beginning and at the end of

Table 2. Bi-groups comparisons.

Variable	Placebo (Mean±Std)	Hab-o Shefa (Mean±Std)	Clonidine (Mean±Std)	Bigroups comparison
COWS	43.1±0.2	25.1±0.1	35.8±0.2	(H – P)** (C – P)* (H – C)*
OOWS	31±0.2	30±0.5	30.4±0.4	(H – P)* (C – P) (H – C)
SOWS	35.9±0.2	22±0.5	25.1±0.5	(H – P)** (C – P)* (H – C)**
Craving	34.5±3.6	30.5±0.5	26.5±0.5	(H – P) (C – P) (H – C)
Beck depression	33.6±3.6	19.7±0.8	27.3±5.4	(H – P)** (C – P)* (H – C)**
Hamilton depression	35.2±1.8	21.4±1.7	25.8±3.1	(H – P)** (C – P)* (H – C)**
Side effect	27±0.1	27±0.1	34±0.5	(H – P) (C – P) (H – C)

The mean scores of bi-groups comparisons on last day of the study in control of withdrawal symptoms, depression, craving and side effects (*P<0.05; **P<0.001). COWS = Clinical Opiate Withdrawal Scale; OOWS = Objective Opiate Withdrawal Scale; SOWS= Subjective Opiate Withdrawal Scale; H = Hab-o Shefa; P = Placebo; C = Clonidine.

the study and their results did not show any pathological changes and no addiction to this formulation was observed. The vital signs were performed daily and did not demonstrate any pathological changes during the study period. None of the studied cases received any type of adjuvant medication during the study period.

DISCUSSION

This randomized, double blind, controlled, clinical trial, was the first study of Hab-o Shefa in human. In the previous study, efficacy of Hab-o Shefa, in controlling symptoms of morphine withdrawal in rats was investigated; this combination significantly controlled the withdrawal symptoms when compared with placebo and was better than methadone in control of some symptoms such as diarrhea and salivation and ptosis. In a similar study, the effect of *D. stramonium* seed extract was investigated in control of morphine withdrawal symptoms in rats. *D. stramonium* seeds extract significantly controlled the withdrawal symptoms in comparison with placebo (Khalili et al., 2007).

In this study, control of objective and subjective and clinical withdrawal symptoms in the Hab-o Shefa group showed a significant difference as compared to the placebo and clonidine groups (Figure 1). The point was that immediately after receiving the medication, the slope of all three diagrams turned downwards while physiological withdrawal symptoms were expected to increase during the second and third days of the study. This change could probably be due to the effect of cohort which causes better response to treatment. Also, this change could probably be due to the most consumed type of drug (crack) and it consumption route (smoking) which has affected the severity of symptoms (Table 1).

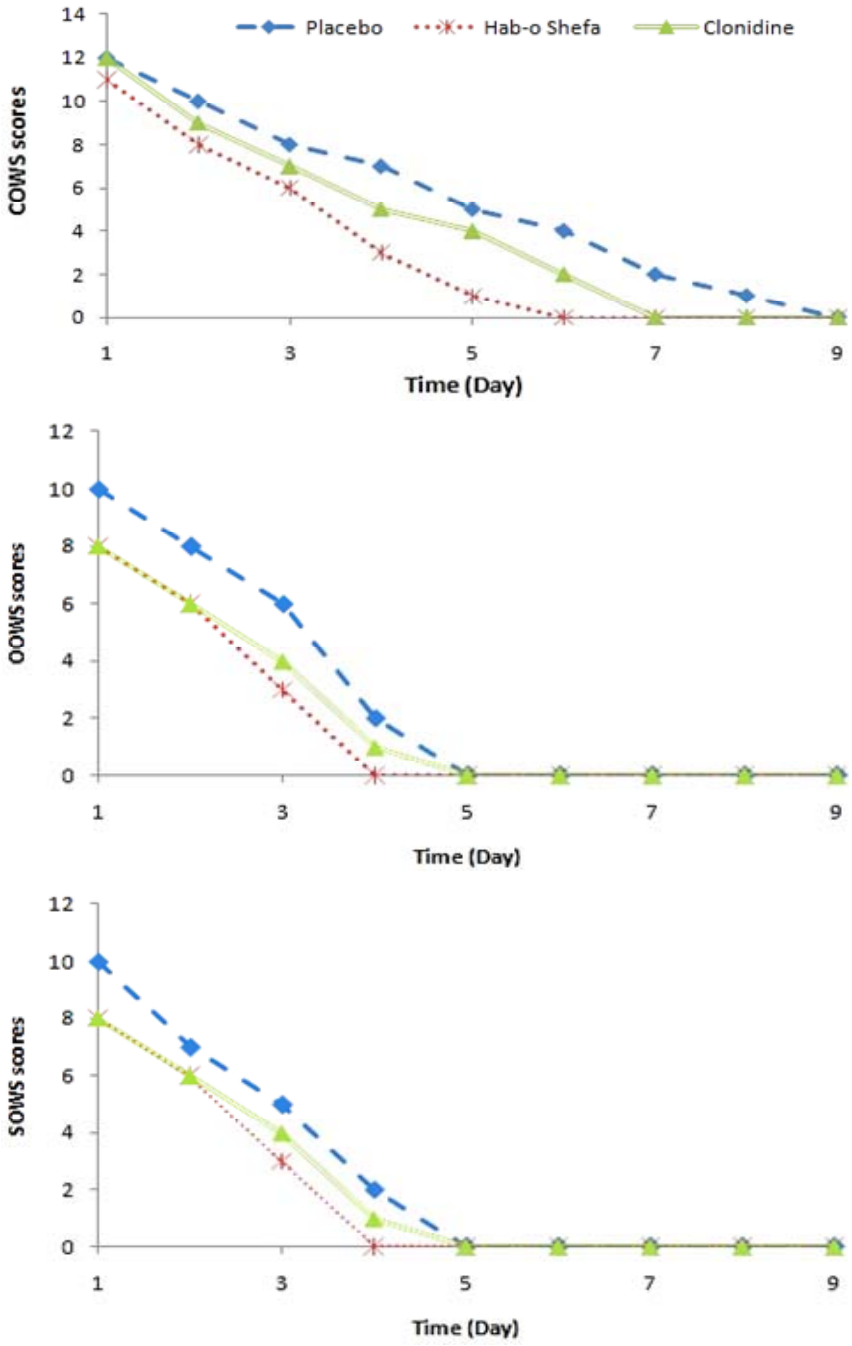

Figure 1. The daily mean scores of the SOWS, OOWS and COWS. All values are mean±Std for 30 subjects in each group. SOWS = Subjective Opiates Withdrawal Scale; OOWS = Objective Opiates Withdrawal Scale; COWS = Clinical Opiates Withdrawal Scale.

On the other hand, the review of sub data showed the highest rate of scattering on the third day of the study, distance from ceiling to floor of patients response to treatment was more than the former two days and all the following days and the number of patients who had responded to treatment and their symptoms resolved were higher than the non-responded group or those who showed a slight response (especially in the Hab-o Shefa group) so that the mean scores graph indicated a downward pattern (a decline). Regarding craving symptoms, no significant difference was observed between the three groups; yet up to the eighth treatment day the curve had a downward trend, with a similar slope which then showed a steady course. At this point, the patients

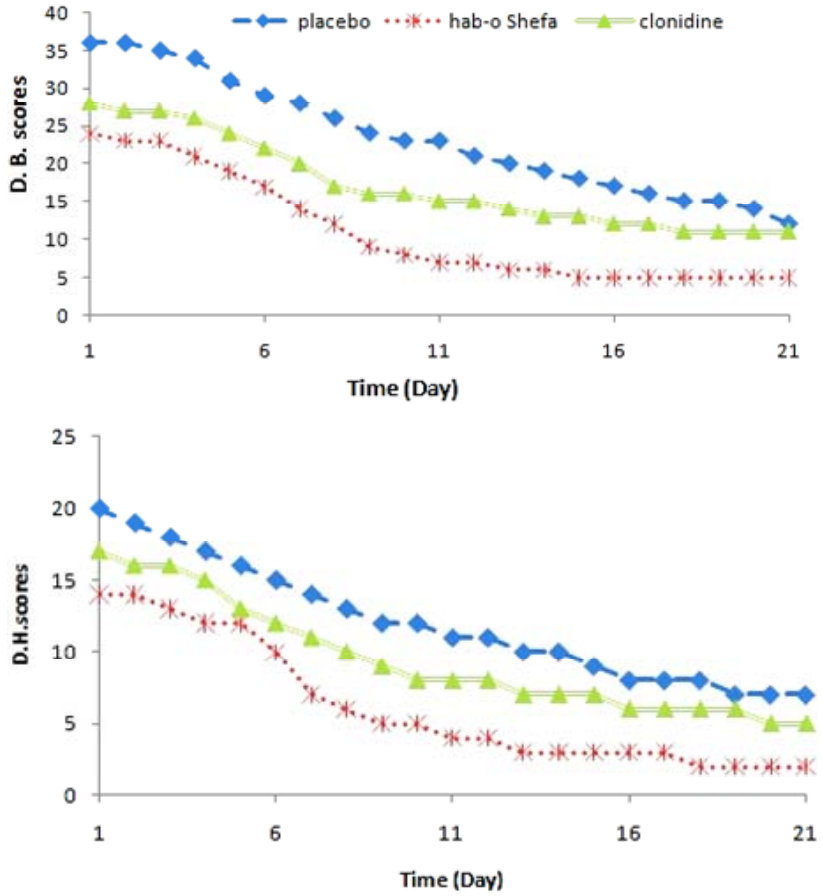

Figure 2. The daily mean scores of the Beck depression scale and the Hamilton depression scale. All values are mean±Std for 30 subjects in each group. D. B. = Beck Depression; D.H. = Hamilton Depression.

physiologic craving rate had probably reduced because at the same time a reduction in their withdrawal symptoms was also diagnosed.

Reduction in depression symptoms during the study period in the Hab-o Shefa group had a significant difference in comparison to the other two groups (Figure 2). A decline in the diagrams immediately after drug administration is seen whereas major depression cannot be controlled rapidly with this type of treatment and therefore this is probably due to the lethargy that follows addiction treatment.

This randomized, double-blind, clinical trial showed the effect of Hab-o Shefa in controlling the withdrawal symptoms, depression, craving and side effects of opiate addicts was demonstrated in acute detoxification of inpatients in comparison to clonidine and placebo. Considering that this was the first study that was done in human about the effectiveness of Hab-o Shefa on controlling withdrawal symptoms, but complementary studies is needed to prove that this combination is addictive or non addictive. In future studies, assessment of this drug on a greater sample size, in office-based detoxification conditions, and also treatment retention assessment in a three to six-month interval would be taken into consideration. Regarding its mechanism of action, traditional Iranian scientists have believed that natural medicinal compounds have certain properties of their own; this means that the effects of a pharmaceutical composition cannot be attributed to a specific component in the combination; for example, it cannot be said that the effects of Hab-o Shefa in opiate addiction are related to the distinct effects of anticholinergic alkaloids in *D. stramonium* or anti serotoninergics contained in the *Z. officinalea* or polysaccharides contained in the *A. arabica* gum or flavonoids and the other active ingredients contained in the *R. palmatum*, but it is the overall effect of all these ingredients which leads to its major effects on various diseases. Nevertheless, in order to clarify its mechanism of action and verify that which withdrawal symptom benefits more from it, further studies are highly recommended.

Conclusion

Hab-o Shefa showed promising results in controlling the

objective, subjective and clinical withdrawal symptoms and also in reducing depressive symptoms in comparison to clonidine and placebo. It did not cause any more side effects than the other two groups. However, no significant difference was observed in craving control between the three groups.

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