

Evaluation of the effect of oral administration of Hab-o Shefa on morphine withdrawal syndrome in rats: a behavioral study

Seyed Mohammad Nazari¹, Mohsen Naseri^{2*}, Azarakhsh Mokri³, Mohsen Khalili⁴, Seyed Abbas Hasheminejad⁵, Tayebe Tavakoli Rad²

1. Ph.D. Student of Traditional Iranian Medicine, Shahed University, Tehran, Iran.

2. Clinical Research Center of Traditional Iranian Medicine, Shahed University, Tehran, Iran.

3. Psychiatry Department and National Center for Addiction Studies, Tehran, Iran.

4. Neurophysiology Research Center, Shahed University, Tehran, Iran.

5. Department of Traditional Iranian Medicine, Shahed University, Tehran, Iran.

Article info:

Received: 24 Dec 2012

First Revision: 02 March 2013

Accepted: 05 May 2013

A B S T R A C T

Background and Objective: Traditional Iranian Medicine (TIM) has a long history in the field of diagnosis and treatment of various diseases, particularly addiction. Different therapeutic methods have been recommended in this respect. One of these methods is the replacement of natural narcotics instead of opium. Hab-o Shefa is a natural product of TIM which has been used as an alternative for opium in the treatment of addiction since centuries ago. In this study, the effect of Hab-o Shefa was investigated on behavioral quantities of morphine withdrawal syndrome.

Materials and Methods: A total of 30 rats were divided into three groups of ten cases each. The control group received solely morphine at a dosage of 10 mg/kg daily for 8 days by the intraperitoneal route. In the second group, in addition to morphine with the same dosage, methadone at the dosage of 25 mg/kg was daily administered by gavage. Hab-o Shefa at a dosage of 2000 mg/kg through gavage was administered in addition to 10 mg/kg of morphine daily for the third group. Finally and 4 to 24 hours after the last injection of morphine, naloxone was injected i.p. at a dosage of 2.5 mg/kg and the desired withdrawal parameters were evaluated.

Results: Considering uncountable parameters, a significant difference was seen when comparing methadone and Hab-o Shefa with placebo in regarding diarrhea symptoms ($p < 0.05$). Regarding jumping between Hab-o Shefa and placebo and also between methadone and placebo, the difference was also statistically significant ($p < 0.05$).

Conclusion: In summary, Hab-o Shefa better controlled the withdrawal symptoms in comparison with placebo and it also better improved the symptoms of diarrhea and salivation as compared to methadone.

Key Words:

Hab-o Shefa

Morphine

Traditional Iranian Medicine

Withdrawal symptoms

1. Introduction

Opiate abuse and dependence is one of the world's major health problems. (7,11). Different therapeutic methods have been presented for the treatment of opiate addiction. Although these drugs have been successful in

controlling some of withdrawal symptoms, they have not been able yet to control the symptoms completely, some of them are not available everywhere or are abused in other ways. (5,10). Therefore, herbal medicines can be an excellent option for solving this problem given the high

*Corresponding Author:

Mohsen Naseri

Traditional Medicine Clinical Trial Research Center of Shahed University, No. 117, Between Avenue of Forsat and Nosrat, North Kargar Avenue, Enghelab Square, Tehran, Iran.

Tel: 00982166418331, Fax: 00982166464322, E-mail: Naseri@Shahed.ac.ir

social acceptance due to the low complications, high effectiveness, their availability and low cost (13). According to the World Health Organization recommendations regarding the use of traditional medicine in health systems (12,14), addiction treatment has been reviewed from the perspective of TIM scientists so that they can play their role in solving this problem. Various therapies for addiction treatment have been introduced in TIM (8). One of these methods is the replacement of opium with natural narcotic drugs (16,2). Several natural narcotic drugs as isolated or in a combination have been introduced in TIM text books (8,16,2,4,15,17,2,3). Hab-o Shefa is a natural combination of drugs which most of TIM scientists have a consensus on the positive effects of this combination in addiction treatment and it has been used for several centuries as a viable alternative for opium in the treatment of opium addiction. This compound contains *Datura stramonium*, *Rheum palmatum*, *Zingiber officinale* and *Acacia Arabica* (8,16,1,4,15,16). In this study, the efficacy of this drug in controlling morphine withdrawal symptoms was evaluated in rats.

2. Materials and Methods

Habo- Shefa is a natural combination of *Datura stramonium*, *Heum palmatum*, *Zingiber officinale* and *Acacia arabica* which was prepared in the pharmaceutical Laboratory of Traditional Medicine of the Shahed University of Tehran (Iran).

Methadone and morphine were purchased in the form of powder from the Daroupakhsh Company.

2.1. Animals

In this study, 30 male rats of the NMRI strain (Razi Institute of Iran), weighing 250-330 g, were used. These rats were placed in cages quaternary and the temperature was set between 22-25 °C. Ambient light as a 12- hour light 12-hour dark cycle was controlled by a timer. The required amount of water and food was available to each rat. In all the performed experiments the research ethics on animals were fully observed.

2.2. Dependency induction

For creating dependency in animals, morphine at a daily dosage of 10 mg/kg for 8 days was

injected i.p. (18).

2.3. Behavioral evaluation

For the study of behavioral dependency after the 8-day morphine injection and 4 to 24 hours after the final injection of morphine to one of the rats in each group, 2.5 mg/kg of naloxone was injected i.p. and the behavioral symptoms were assessed during the following forty minutes. Subsequently, the other rats in each group were also studied one by one. Behavioral indices of withdrawal syndrome including diarrhea, ptosis and teeth chattering are indicative of morphine dependency of such animals. In general, behaviors that occur during the withdrawal syndrome in terms of being countable or non-countable are divided into two categories by the standard agreement; graded signs and chocked signs. Graded signs included jumping, abdominal contraction, wet dog shakes and chocked signs included diarrhea, teeth chattering, salivation, ptosis and genital grooming/ejaculation.

2.4. Experimental groups

In this study, 30 rats were divided into three groups of 10 cases each; the first group named as the control group only received morphine 10 mg/kg daily for 8 days injected i.p.; the methadone group received the same dose of morphine injection plus 25 mg/kg of methadone daily for 8 days by gavage. In the Hab-o Shefa group besides administering the same dose of morphine injection, Hab-o Shefa was prescribed at a dosage of 2000 mg/kg daily for 8 days through gavage.

2.5. Statistical analysis

For data analysis, the graded signs data were recorded as the number of behaviors occurring in a certain time duration in each rat. After confirming that behaviors of the withdrawal syndrome have a quantitative entity, the number of such behaviors was compared in different groups with ANOVA and Tukey post-hoc test.

3. Results

Figure 1 shows the number of diarrhea, ptosis and salivation in the three groups. Comparing these numbers between the methadone and Hab-o Shefa groups did not reveal a statistically significant difference ($p>0.05$), but the difference

was significant when comparing these two groups with the placebo group ($p < 0.05$). Regarding genital grooming/ejaculation and teeth chattering, no statistically significant difference was observed between the three groups ($p > 0.05$).

Figure 2 shows the number of jumps in the three groups. Comparing the number of jumps between Hab-o Shefa and methadone with placebo showed a statistically significant difference ($p < 0.05$). No statistically significant difference was observed when comparing the number of abdominal contractions and wet dog shakes between the three groups ($p > 0.05$).

4. Discussion

In the previous study by Mohsen Khalili and Mohsen Naseri et al (9), the effectiveness of datura seeds extracts in controlling morphine withdrawal symptoms in rats was studied. In the latter study, the efficacy of datura seeds extract was significantly superior to placebo, whereas no significant difference was seen in comparison with methadone. Hab-o Shefa acted better than datura extract in controlling symptoms such as diarrhea, salivation and ptosis as compared to methadone. Considering that Hab-o Shefa is a natural compound and datura is its main

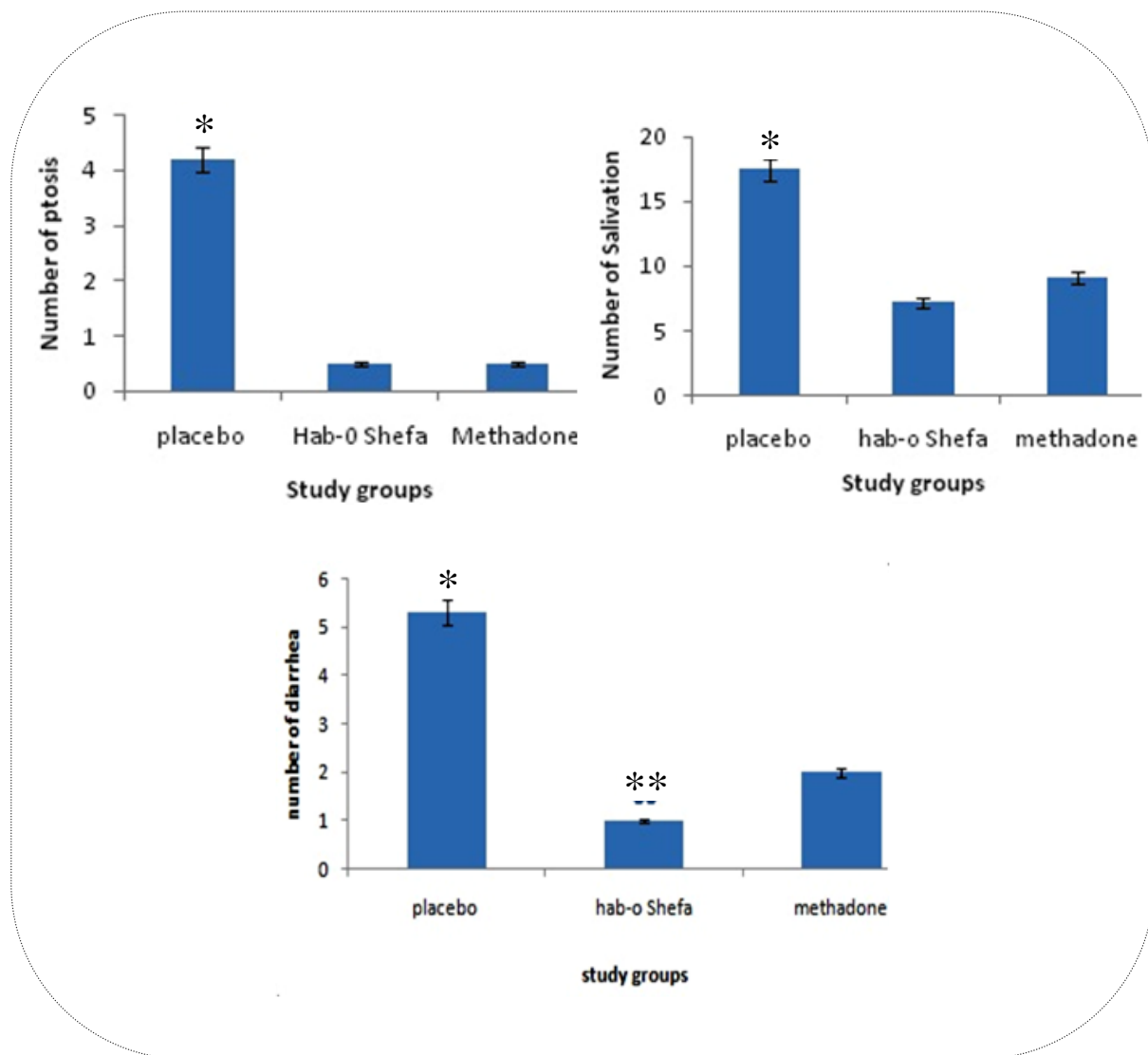


Figure 1. Comparison of innumerable withdrawal symptoms in rats. As can be seen, the parameters of diarrhea, ptosis and salivation for Hab-o Shefa and methadone groups as compared together was not significant ($p > 0.05$) and between these two and placebo was significant ($p < 0.05$) * $p < 0.05$ ** .

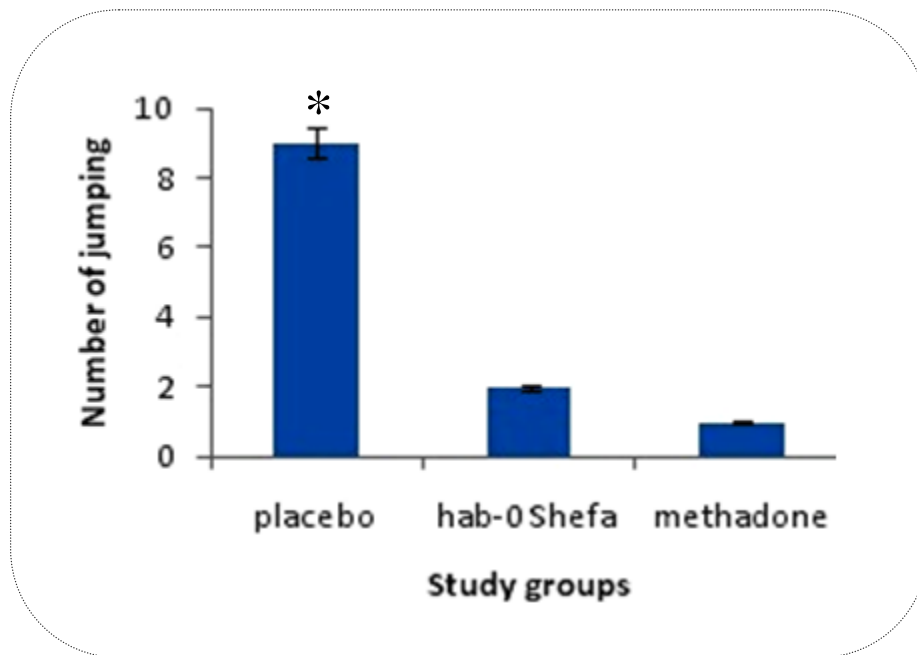


Figure 2. Comparison of countable jumps in the three groups. As can be seen, jumping between the Hab-o Shefa and methadone was not statistically significant ($p>0.05$) and was statistically significant between these two groups and the placebo * $p<0.05$

component and the other herbs in this combination act as modifiers of stramonium effects, it can be concluded that natural drug combinations have a better efficacy than natural isolated drugs and also reduce the risk of adverse drug reactions. In addition, in relation to mechanism of action of natural combination drugs, TIM scientists believe that these compounds have their unique properties in general and certain effects cannot be attributed to a specific substance contained in the combination; for example, regarding Hab-o Shefa, the effectiveness of its pharmaceutical composition cannot be attributed to the alkaloids contained in datura plant or to antiserotonergic substances contained in ginger or the flavonoids contained in Rheum palmatum or the tannin contained in Acacia arabica.

Conclusion

Due to the better efficacy of Hab-o Shefa in comparison to datura extract in controlling morphine withdrawal symptoms, the use of TIM combination drugs could result in lower drug side effects and higher efficacy. In complementary future studies, clinical trials will be performed on the natural combination of Hab-o Shefa in controlling withdrawal symptoms of opioids.

Acknowledgments

This study was the result of a PhD thesis which is registered under the same title in Shahed University registry system (Number: 118 967 Date: Sep 20, 2011). The authors wish to thank the Department of Traditional Medicine of the Medical School of Shahed University, Department of Traditional Medicine of Medical School of Tehran and Shahid Beheshti Universities for their kind guidance and consultation in better performing this study.

References

1. Aghili MH. Gharabadin Kabir. 2th edition, Tehran Medical University.2005;899-901.
2. Aghili MH. Makhzanol Advieh. 1th edition, Tehran Bavardaran. 2001; 243-55.
3. Ansari A. Ekhtiarate Badieli. 1th edition. Tehran Pakhshe Razi. 1992; 308-54.
4. Arzani MA. Gharabadin Ghaderi. 2th edition. Tehran Medical University.2009; 18-19.
5. Assadi SM, Hafezi M, Mokri A. Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: A randomized, double blind,

- controlled clinical trial. *Journal of Substance Abuse Treatment*. 2004; 27: 75-82.
6. Chandler JM, Robie PW, Schoolar JC, Desmond MM. (1975 Mar) The effects of methadone on maternal-fetal interactions in the rat. *Journal of Pharmacology Experimental Therapeutics* 1975. 192:549-54.
 7. Ekhtiari H, Mokri A. How can we design a study to evaluate treatment efficacy of a new proposed herbal medicine for opioid dependence. *Tehran: Quarterly Addiction*. 2012; 7: 42-46.
 8. Ghafari F, Naseri M. Emaddodin shirazi. formulator of two new formulation of opium(papaversomniferum). *Proceeding of International Medicinal and Aromatics*. 2010; 9-15.
 9. Khalili M, Naseri M. Effect of oral datura seeds on control of behavioral withdrawal syndrome in rats. *Medical Daneshvar* 2008; 16: 25-32.
 10. Mokri A. Brief overview of the status of drug abuse in Iran. *Archives of Iranian Medicine*. 2002; 5: 190-184.
 11. Nadery S, Sefatian S, Binazadeh M. (2008) *Comprehensive textbook of addiction treatment*. 1th Edition. Tehran Iranian National Drug Control Headquarters. 2008; 570-599.
 12. Naseri M. Clinical pharmacology of Traditional Iranian Medicine. *Tehran Monthly Medicinal Journal of Razi*. 1994; 12: 6-10.
 13. Naseri M. Traditional Iranian Medicine and its development using the WHO guidelines. *Daneshvar Medical Journal*. 2009; 52: 5-71.
 14. Nazari SM, Naseri M, Ghafari F. Opium and Treatment of Opium Addiction in Traditional Iranian Medicine. *Medical History*. 2012; 3: 133-150
 15. Nazem Gahan MA. *Ghrarabadin Hakim Aazam*. 2th edition. Tehran Medical University .2003; 51-52.
 16. Shirazi E. *Resaleh Fionieh*. 1th edition. Tehran Almai.2009; 134-49.
 17. Tonekaboni M.M. *Tohfatomomenin*. 1th edition. Tehran Nashre Shahr 2007; 384-439.
 18. Vajda JA, Ding MG, Oei TP. Methadone dependence in the rat. *Psychopharmacological* 1975; 42: 255-61.