Journal of Pharmaceutical Research International

31(6): 1-11, 2019; Article no.JPRI.52677
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparing Methadone and Tincture of Opium for the Management of Opioid Withdrawal among Subjects with an Opioid Use Disorder

Mohammad Jamalian[1], Milad Nasrollahzadeh[1], Amir Mohammad Kazemifar[2*] and Hasan Solhi[1]

[1]Department of Forensic Medicine and Poisoning, Arak University of Medical Sciences, Arak, Iran.
[2]Department of Internal Medicine, Qazvin University of Medical Science, Qazvin, Iran.

Authors' contributions

This work was carried out in collaboration among all authors. Author MJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MN and AMK managed the analyses of the study. Author HS managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2019/v31i630349
Editor(s):
(1) Dr. R. Deveswaran, Associate Professor and Head, Drug Design and Development Centre, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, India.
Reviewers:
(1) Heba Atia Yassa, Assiut University, Egypt.
(2) Vaishali Waindeskar, All India Institute of Medical Sciences (AIIMS) Bhopal, India.
(3) Euclides Mauricio Trindade Filho, State University of Health Sciences of Alagoas, Brazil.
Complete Peer review History: http://www.sdiarticle4.com/review-history/52677

Original Research Article

Received 12 September 2019
Accepted 19 November 2019
Published 16 December 2019

ABSTRACT

Introduction: Drug addiction is associated with complications such as mortality, monetary burden, and various socioeconomic problems at the individual to the community level. Methadone and Tincture of Opium (TOP) are the most commonly used drugs to help addicts maintain their drug withdrawal process and eventually permanent withdrawal. Desirable clinical experiences have been reported in the use of these two agents in the management of opioid withdrawal. The purpose of this study was to compare the efficacy of methadone and TOP using Khomree method for detoxification of drug abuse.

Materials and Methods: This study was a randomized double-blind clinical trial among opium addicts (at least one year of use) referred to Arak University of Medical Sciences. Seventy subjects were enrolled in the study according to inclusion and exclusion criteria and then randomly divided into two groups (n = 35, treated with methadone) and group 2 (n = 35, treated with TOP).

**Corresponding author: E-mail: amkazemifar@qums.ac.ir;*

Furthermore, patients were evaluated for withdrawal symptoms on days 1, 3, 7, 14 and 28 after treatment. Finally, the results were analyzed using SPSS 18 software.

Results: Severity of sweating (group 1: P = 0.0001, group 2: P =0. 005), runny nose (P = 0.001), lacrimation (P = 0.001), chord reflex (P = 001.0), fecal excretion (group 1: P = 0.001, group 2: P = 0.01, muscle twitches (P = 0.001), drooling (P = 0.001) warming sensation (P = 0.0001) and substance seeking (group 1: P = 0.0001, P = 0.008) in both groups were significantly improved during 28 days of treatment.

Conclusion: Methadone and TOP detoxification are both effective in opioid withdrawal syndrome and the effect of methadone and TOP in opiate withdrawal are not preferable. However, further studies are recommended.

Keywords: Opium; methadone; Tincture of Opium (TOP).

1. INTRODUCTION

Addiction is one of the problems of human society and imposes significant costs on governments and international communities [1]. In addicts, withdrawal or reduction in consumption may result in symptoms, including severe muscle cramps, diarrhoea, abdominal cramps, nasal congestion, lacrimation, thinning hair, yawning, sweating, pupil dilation, insomnia or restless sleep, Depression, anxiety, tachycardia, hypertension, or hyperthermia (hypothermia or hyperthermia). The purpose of addiction treatment is to reduce patient discomfort and to reduce disorders that can occur in the social, and occupational issues, as well as functional areas of the individual [2,3].

Various medications such as clonidine, lofexidine, methadone, buprenorphine and naltrexone are prescribed by specialists for the treatment of addiction [4-6]. One of these drugs is methadone. Methadone is an industrial drug used orally and injectable. As a standard, methadone can be used for the treatment of addiction for two purposes including detoxification and maintenance of treatment [7].

In some societies, the cost of using methadone has been an obstacle to its spread. One answer to this is the Tincture of Opium (TOP) as an alternative treatment [8]. TOP is a solution containing 10 g of morphine in 1 litre of 20% alcohol. Its fluidity makes it easy for medical measurements per square centimetre and also reduce the process [9]. TOP as traditional medicine is prevalent in some parts of Southeast Asia and is culturally accepted and its cost is another advantage over methadone [10].

Regarding the risks, complications, and likelihood of recurrence of symptoms in routine methadone or opium and TOP [11,12], thus, it is always necessary to introduce alternative therapies to reduce withdrawal symptoms in addicts along with reduced recurrence rates [11-13]. In the standard method, the concentration and volume of methadone and /or TOP both decrease gradually by 10% over approximately 1 month, with an interval of 10% every 3 days. It has been found that this decrease is associated with high recurrence at the end of detoxification. On the other hand, the traditional method, unlike the standard method, is characterized by providing 2 weeks of required volume and concentration of methadone for the individual and decreasing the methadone concentration on long days but many days, but without a decrease in volume over many days. In this method, unlike the first method, the decrease in methadone concentration during one month of use was very gradual and daily. Also boiling water added to the volume of daily consumption. As a result, the containers have an initial volume, but lower methadone or opioid tincture levels than the previous day. This treatment seems to be able to reduce the risk of recurrence due to lower daily methadone concentrations and a more appropriate psychological effect on the person due to the more gradual decrease in methadone concentration than the first method, as well as lack of volume loss on consecutive days because of the lack of volume reduction. This case itself can help the regular follow-up of the treated person and his or her longing for finishing their treatment. There are currently no appropriate alternatives for relapse and failure of standard treatment with methadone or TOP [14]. The purpose of this study was to compare the effect of methadone and tincture of opium on the detoxification of drug abuse using Khomree method.

2. MATERIALS AND METHODS

The study was designed as a randomized, double-blind, clinical trial and the study population included addicted patients (diagnosed

with opium addiction) referred to the centre for addiction studies in Arak University of Medical Sciences, Iran. Patients of both sexes, ranging in age from 20 to 60 years, were randomly selected based on inclusion and exclusion criteria. After obtaining informed consent, patients were included in the study. The primary criterion for confirming opioid dependence or addiction was based on DSM-IV criteria.

Inclusion criteria included: 1. People with opium addiction, 3. Informed consent, 3. Consumption of at least 1 year, 4. Age 20 to 60 years, 5. Having no personal history of mental disorders, 6. Consumption of less than 2.3 g of opium per day, 7. Not taking drugs and other substances at the same time, 8. No major underlying disease such as lung disease, diabetes, liver disease, etc., 9. No contraindications to methadone use

Exclusion criteria were: 1. Failure to follow up the next control, 2. Patient's unwillingness to continue the study.

Demographic and clinical checklists were then completed for all patients included in the study. This checklist contains basic information such as age, sex, duration of addiction (year), daily opium intake (grams), number of cigarettes consumed per day, desire to quit, previous quit, frequent quit, successful quit, failed attempts to quit.

Patients' clinical information checklist included: severity of sweating (0: mild, 1: moderate, and 2: severe), pupil size (mm), drooling rate (0: mild, 1: moderate, and 2: severe), yawning rate (Increased than before or not), heart rate, respiratory rate, deep tendon reflexes, nausea, vomiting, bowel movements, insomnia (having or not), 24-hour sleep duration, muscle twitches, muscle pain, reflex Cholera, temperature changes (with or without), daytime warming, daytime colds, drug-seeking, lacrimation (0: mild, 1: moderate and 2: severe), runny nose (0: mild, 1: moderate and 2: severe), severity of social and occupational dysfunction (0: mild, 1: Moderate and 2: Severe), satisfaction with prior ejaculation in married people.

Patients were randomly divided into two groups, including the methadone detoxification group (group 1) and the TOP group (group 2) using Khomree method

2.1 Sample Size

The sampling method was random based on inclusion and exclusion criteria. Sample size was calculated as 35 for each group (70 patients; α = 0.05).

$$\alpha = 0.05$$
$$p_1 = 0.048$$
$$p2 = 0.5$$
$$\beta = 0.2$$

$$n_1 = n_2 = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2} = 35$$

2.2 Analysis

Data were analyzed using SPSS software version 18 (SPSS Inc., Chicago, IL) and descriptive statistical methods to determine the frequency of variables. At the same time to analyze quantitative variables of Student t-test (comparison between two groups in each patient follow-up phase). Chi-square was used for qualitative variables. Due to the non- non-normal distribution of the data, the Friedman test was employed to analyze the changes in variables instead of Repeated Measures Analysis.

In addition to the numerical variables, pain intensity or discomfort, some other variables including nausea, muscle twitches, muscle pain, a daytime warming sensation, daytime cold sensation, sneezing and drug demand were evaluated based on the VAS criteria. (Visual Analogue Scale). P-value <0.05 was considered as significant level.

3. RESULTS

The mean age of the subjects was 36.83±8.65 years. Of the 70 evaluated patients, 59 were men (84.2%) and 11 were women (15.7%). In the methadone group, 6 women (17.1%) and 29 men (82.8%) were included. There were 5 women (14.2%) and 30 men (85.7%) in the TOP group. Sex distribution between the two groups was not significant (P> 0.05). Mean age of group 1 and 2 patients was 36.05±37.9 and 37.61±7.98 years, respectively, which was not found to be significant (P=0.261).

The baseline clinical information on substance use, in general, is given in Table 1. Based on this information, the mean of the previous quit, and failed attempts to quit were 3.1±2.44 and 2.75± 1.99. times, respectively, which were significantly higher than the average crack failure times.

Subjects were evaluated in 5 stages (on days 1, 3, 7, 14 and 28) for clinical signs and symptoms

of drug withdrawal as well as social and occupational performance.

The severity of sweating in subjects was evaluated in Table 2 as non-sweating, with mild and severe sweating. The severity of sweating was significant between the two groups in all 5 stages of the clinical study.

On day 1, most patients in group 1 (65%, 24 subjects) and (50%, 18 subjects) were without sweating followed by no sweating and mild sweating on day 28 (group 1: 62.5%, 23 subjects, group 2: 45%. 17 subjects).

The analysis of sweating intensity changes over the 28 days showed that the sweating intensity decreased significantly in both groups (Group 1: P = 0001.0, Group 2: P = 005.0).

In assessing the severity of nasal runoff, subjects with no runny nose and mild to the severe runny nose were considered. The intensity of nasal drainage was significant between the two groups at the 4th and 5th stages of clinical examination (day 14: P = 001.0 and day 28: P = 001.0). On day 14, most patients in groups 1 (30 subjects; 80%) and 24 subjects, 5.67%) exhibited no runny nose and on day 28, most patients in both groups 1 (5.67%) and 2 (5.67%) had no runny nose.

Analysis of changes in the severity of runny nose over the 28 days showed that the severity of this symptom was significantly decreased in both groups, and this difference was significantly different between the two groups (both groups: P = 0.001).

The patients' yawning rates in Table 3 were considered as no increase and increase. Yawning rate was not found to be significantly different among two groups (day 1: P = 0.612; day 3: P = 0.622; day 7: P = 0.1; day 14: P = 0.489; day 28: P = 0.155). Analysis over the 28 days showed no significant change in the yawning rate in both groups (Group 1: P = 0.5; Group 2: P = 0.76).

Insomnia rates in individuals were considered as cases with or without insomnia (Fig 1). Insomnia was significantly different between the two groups at stages 2 and 5 of the clinical trial (day 3: P = 0.001; day 28: P = 0.002). On day 3, most patients in groups 1 and 2 considered as with and without insomnia (28, 77.5%; 21, 60%) patients with and without insomnia, and on day 28, most patients in groups 1 and 2 had (19, 55%; 29, 80%) were with and without insomnia. Analysis of the changes in insomnia rate over the 28 days showed that insomnia decreased significantly in both groups (both groups: P = 0.0001).

Table 1. Basic clinical information on drug use of all subjects understudy

Variable	Mean±SD
Duration of addiction (year)	13.26±6.71
Amount of opium consumed per day (g)	2.72±1.06
Smoking consumed per day (number of threads)	11.9±6.49
Frequently decided to leave the addiction	4.2±2.7
Frequency of the Previous quit	3.1±2.44
Frequency of successful quit	0.73±0.8
Frequency of quitting	2.57±1.99

Table 2. Frequency of sweating intensity

Patient review days	Group (%)	Sweat intensity			P-value
		No	Mild	Severe	
Day 1	Group 1 (35 cases)	(65) 24	(30) 10	(5) 1	0.005
	Group 2 (35 cases)	(50) 18	(37.5) 13	(12.5) 3	
Day 3	Group 1 (35 cases)	(32.5) 11	(62.5) 23	(5) 1	0.001
	Group 2 (35 cases)	(57.5) 21	(42.5) 14	(0) 0	
Day 7	Group 1 (35 cases)	(65)24	(30) 10	(5) 1	0.009
	Group 2 (35 cases)	(72.5) 27	(22.5) 7	(5) 1	
Day 14	Group 1 (35 cases)	(32.5) 11	(62.5) 23	(5) 1	0.001
	Group 2 (35 cases)	(67.5) 25	(30) 10	(2.5) 0	
Day 28	Group 1 (35 cases)	(27.5) 9	(62.5) 23	(10) 3	0.001
	Group 2 (35 cases)	(7.5) 2	(47.5) 17	(45) 16	

Table 3. Changes in the yawning rates

Patient review days	Group (%)	Yawning rate changes		p-value
		Increase than before	No increase compared to before	
Day 1	Group 1 (35 cases)	(30) 10	(70) 25	0.612
	Group 2 (35 cases)	(22.5) 7	(77.5) 28	
Day 3	Group 1 (35 cases)	(25) 8	(75) 27	0.622
	Group 2 (35 cases)	(32.5) 11	(67.5) 24	
Day 7	Group 1 (35 cases)	(45) 16	(55) 19	>0.05
	Group 2 (35 cases)	(25) 8	(75) 27	
Day 14	Group 1 (35 cases)	(32.5) 11	(67.5) 24	0.489
	Group 2 (35 cases)	(42.5) 15	(57.5) 20	
Day 28	Group 1 (35 cases)	(25) 8	(42.5) 14	0.155
	Group 2 (35 cases)	(75) 27	(57.5) 21	

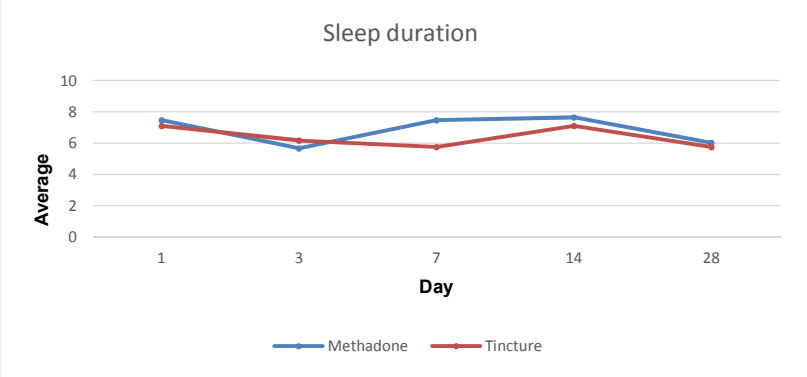

Fig. 1. Changes in average sleep duration (hours) in 5 steps

The level of deep tendon reflexes was evaluated in subjects in Fig. 2 as having normal reflex and abnormal reflex respectively. DTR levels in all 5 stages of clinical study (day 1: P = 0.001; day 3: P = 0.001, day 7: P = 0.003; day 14: P = 0.001; day 28: P = 0.001) between the two groups was meaningful (On day 28, group 1 and 2: 27 [75%] and 27 [75%] patients with and without normal reflex; on day 28, group 1 and 2: 31 [85%] and 21 [60%] patients with or without natural reflexes). Analysis of DTR changes over the 28 days showed that DTR levels were normal in both groups (P = 0.001).

The severity of lacrimation in the subjects was assessed as mild, severe, and severe lacrimation (Table 4). The severity of lacrimation in stages 2, 4 and 5 of patients (day 3: P = 0.001, day 14: P = 0.006, day 28: P = 0.001) was significant between the two groups. On day 3, most patients in groups 1 and 2 with 29 (5.77%) and 16 (45%) patients showed lack of lacrimation or mild lacrimation and on day 28, most patients in groups 1 and 2, (28 [77.5%] and 16 [45%]) exhibited lack of lacrimation or moderate lacrimation.

The severity of drooling was evaluated in subjects with no discharge and mild to severe discharge. There was a significant difference between the two groups in the severity of drooling in stages 4 and 5 of the clinical trial (day 14: P = 0.001 and day 28: P = 0.001). On day 14, most patients in groups 1 and 2 (29 [80%] and 24 [67.5%] patients) were categorized as without drooling, or mild drooling; on day 28, groups 1 and 2 had both 24 (67.5%) patients without drooling, or with mild drooling. Analysis of changes in drooling over the 28 days showed a significant decrease in both groups (both groups: P = 0.001).

The severity of social and occupational dysfunction was considered as non-disordered and mild to severe. The severity of the disorder was significant between the two groups in all 5 stages of the study (day 1: P = 0.005, day 3: P = 0.001, day 7: P = 0.001, day 14: 0.006, P = 28: 0.001). So that on day 1 most patients in group 1 and 2 (27 [75%] and 20 [57.5%]) showed to be as without or with mild dysfunction; on day 28, most patients in group 1 and 2 (31 [85%] and 16 [45%] were found as without or severe

dysfunction. Analysis of changes in the severity of dysfunction over the 28 days showed that the severity of dysfunction in group 1 was significantly reduced (P = 0.001) and in group 2, there was no significant change (P = 52.0).

Mean pupil size in 5 stages was evaluated in Fig. 3, which was significantly higher in group 1 than the control group (all 5 stages: P = 0.001). Analysis over the 28 days showed that the mean pupil size in group 1 had a significant decrease (P = 0.0001), despite the decrease in pupil size in group 2, no significant changes were observed (P = 0.217).

Heart rate changes during 28 days were not significant in either group (P = 4.0). Mean respiratory rate was significant between the two groups in the 5 stages of the study (P = 0.001), with a significant difference between days 1 and

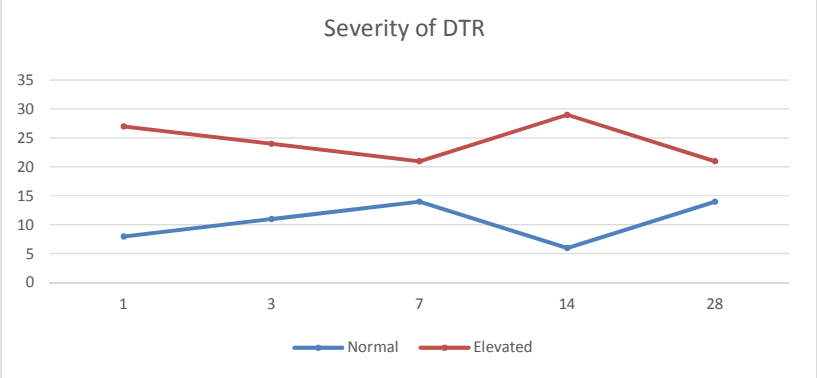

Fig. 2. Changes in severity of the DTR in 5 steps

Table 4. Frequency of lacrimation severity

Patient review days	Groups (%)	lacrimation severity			p-value
		No	Mild	Severe	
Day 1	Group 1 (35 cases)	(77.5) 28	(17.5) 5	(5) 1	0.025
	Group 2 (35 cases)	(57.5) 21	(42.5) 14	(0) 0	
Day 3	Group 1 (35 cases)	(77.5) 29	(17.5) 5	(5) 1	0.001
	Group 2 (35 cases)	(17.5) 6	(45) 16	(37.5) 13	
Day 7	Group 1 (35 cases)	(77.5) 28	(22.5) 7	(0) 0	0.094
	Group 2 (35 cases)	(57.5) 20	(42.5) 15	(0) 0	
Day 14	Group 1 (35 cases)	(77.5) 28	(17.5) 5	(5) 2	0.006
	Group 2 (35 cases)	(42.5) 15	(45) 16	(7) 5	
Day 28	Group 1 (35 cases)	(77.5) 28	(22.5) 8	(0) 0	0.001
	Group 2 (35 cases)	(17.5) 1	(45) 16	(37.5) 13	

Table 5. Frequency of severity of social dysfunction

Patient review days	Group (%)	The severity of occupational and social dysfunction			p-value
		No	Mild	Severe	
Day 1	Day1 (35 cases)	(75) 27	(22.5) 8	(0) 0	0.005
	Day2 (35 cases)	(42.5) 15	(57.5) 20	(0) 0	
Day 3	Day1 (35 cases)	(77.5) 29	(17.5) 5	(5) 1	0.001
	Day2 (35 cases)	(42.5) 15	(37.5) 13	(20) 7	
Day 7	Day1 (35 cases)	(77.5) 29	(17.5) 5	(5) 1	0.001
	Day2 (35 cases)	(42.5) 15	(57.5) 20	(0) 0	
Day 14	Day1 (35 cases)	(77.5) 28	(22.5) 7	(0) 0	0.001
	Day2 (35 cases)	(32.5) 11	(47.5) 17	(20) 7	
Day 28	Day1 (35 cases)	(85) 31	(10) 3	(5) 1	0.001
	Day2 (35 cases)	(27.5) 6	(37.5) 13	(45) 16	

14 in group 1 and day 28 in group 2. Changes in respiratory rate during 28 days were not significant in both groups (P = 5.0). In Table 6, the mean of vomiting frequency was evaluated and there was a significant difference between the two groups in 5 stages (every 5 stages: P = 0.001). The mean was significantly higher in group 1 on days 1 and 3, and on days 7, 14 and 28 in group 2 as compared to other groups.

Analysis of vomiting frequency over the 28 days showed that the mean vomiting frequency in group 1 was significantly reduced (P= 0.092), while it was unchanged in group 2 (P = 0.466). Table 6: Average vomiting frequency. The mean frequency of excretion in the 5 stages (every 5 stages: P = 0.001) was significantly higher in group 1 than in group 2. According to the analysis of excretion changes over the 28 days, excretion changes were significant in both groups of patients (Group 1: P = 0.001, Group 2: P = 0.0001). Except for stage 3, mean sleep duration patients in other stages were significantly different between the two groups (day 1: P = 0.001, day 3: P = 0.006, day 7: 0.094, day 14: p=0.001, day 28: p=0. 004). This mean was significantly higher in group 1 on days 1, 7, 14 and 28 as compared to group 2, while this rate was significantly higher in group 2 on day 3 than group 1. Based on the analysis of sleep duration changes during 28 days, sleep duration in group 1 showed a significant decrease (P = 0.001), while group 2 did not show any significant change (P = 0.5).

The intensity of the variables of muscle twitches, muscle pain, feeling hot or cold in the day, sneezing, nausea, and drug-seeking was measured based on the VAS. Mean VAS in muscle twitches in the 5 stages of patient was higher in group 2 as compared to group 1 (stage 1: P = 0.014, stage 2: 0.001, stage 3: 0.001, stage 4: 0.002, stage 5: 0.004). Table 7 shows the mean changes of VAS in terms of muscle twitches and showed a significant decrease in both groups during the 28 days (P = 0.001).

Mean VAS in terms of sneezing rate in 5 stages was significantly higher in group 2 compared to group 1 (all stages: P =0. 001). Mean VAS changes in sneezing rate were not significant in both groups during 28 days. (Group 1: P = 0.1, Group 2: P = 0.52). Mean VAS in nausea was significantly higher in group 2 than in group 1 (all stages: P = 0.001). Analysis of VAS means changes in nausea during the 28 days showed that changes (P = .0001.0) were not significant in group 2 as compared to group 1 (P = 0.114).

Mean VAS was evaluated for muscle pain (Table 8). Muscle pain was significant between the two groups only at the 2nd (day 3; P = .001) and 5th (day 28; P = .001) stages. This mean was significantly higher in group 2 as compared to group 1. Mean VAS changes in muscle pain over the 28 days were not significant in both group (group 1: P = 0.11, group 2: P = 0.4).

The mean VAS for the warm feeling (all 5 steps: P = .001) was significantly higher in group 2 than in group 1. Analysis of VAS mean changes in warm feeling over the 28 days showed a significant difference in both groups during the study (both groups: P = 0.0001). Mean VAS in cool feeling was significantly higher in group 2 than in group 1 on day 5 (all 5 steps: P = 0.001). Analysis of changes over the 28 days showed that this mean was significantly higher in groups 1 and 2 (P = 0.985, P = 0.7, respectively). As indicated in Fig. 4, the mean VAS was significantly different between the two groups in the level of drug-seeking (all 5 steps: P = 0.001). Except for day 3, the mean was significantly higher in group 2 compared to group 1. This was significantly higher in the remaining days in group 1 as compared to group 2.

Table 6. Average vomiting frequency

Patient review days	Group	Vomiting frequency (Mean±SD)	p-value
Day 1	Group 1 (35 cases)	15.02±1.0	0.001
	Group 2 (35 cases)	2.05±0.0	
Day 3	Group 1 (35 cases)	1.2±1.0	0.001
	Group 2 (35 cases)	37.1±0.0	
Day 7	Group 1 (35 cases)	26.07±0.0	0.001
	Group 2 (35 cases)	4.12±0.0	
Day 14	Group 1 (35 cases)	15.02±0.0	0.001
	Group 2 (35 cases)	5.17±0.0	
Day 28	Group 1 (35 cases)	0	0.001
	Group 2 (35 cases)	5.17±0.0	

Table 7. Mean VAS for muscle twitches

Patient review days	Group	Muscle twitches (Mean±SD)	p-value
Day 1	Group 1 (35 cases)	97.1±1.1	0.014
	Group 2 (35 cases)	18.32±1.2	
Day 3	Group 1 (35 cases)	08.1±2.1	0.001
	Group 2 (35 cases)	43.95±1.2	
Day 7	Group 1 (35 cases)	97.1±1.1	0.001
	Group 2 (35 cases)	36.92±1.2	
Day 14	Group 1 (35 cases)	08.1±2.1	0.002
	Group 2 (35 cases)	29.5±1.2	
Day 28	Group 1 (35 cases)	15.95±1.0	0.004
	Group 2 (35 cases)	36.92±1.2	

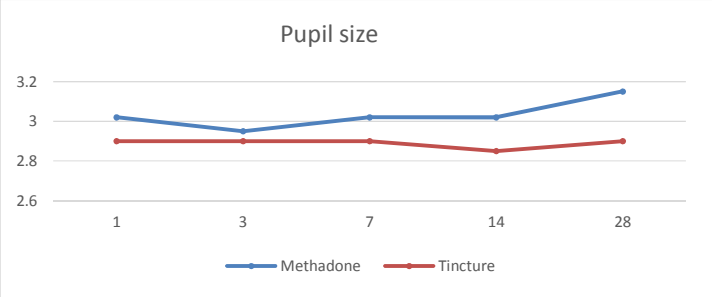

Fig. 3. Average pupil size changes in 5 steps

Table 8. Mean VAS for muscle pain

Patient review days	Group	Muscle Pain (Mean±SD)	p-value
Day 1	Group 1 (35 cases)	21.75±2.1	0.055
	Group 2 (35 cases)	12.82±1.2	
Day 3	Group 1 (35 cases)	2.2±1.1	0.001
	Group 2 (35 cases)	37±2.3	
Day 7	Group 1 (35 cases)	91.85±1.1	0.138
	Group 2 (35 cases)	37±2.3	
Day 14	Group 1 (35 cases)	1.5±2.1	0.071
	Group 2 (35 cases)	34.8±1.2	
Day 28	Group 1 (35 cases)	2.2±1.1	0.001
	Group 2 (35 cases)	37±2.2	

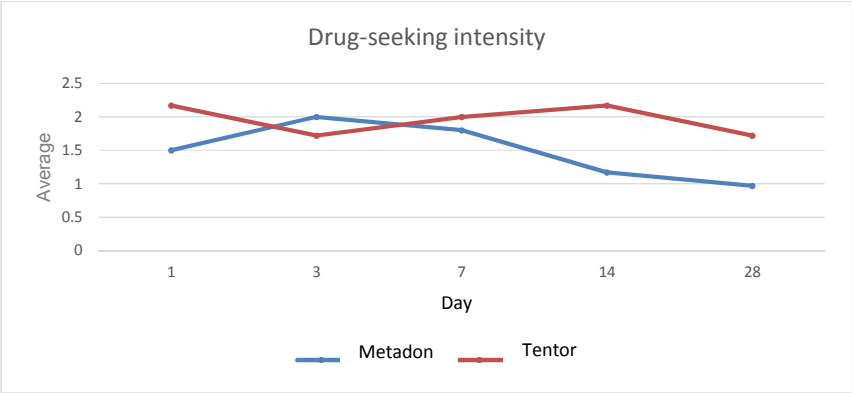

Fig. 4. VAS-based drug-seeking intensity during the 5 steps

Table 9. Frequency of ejaculation satisfaction in married patients

Patient review days	Group(%)	The value of satisfaction with ejaculation			p-value
		More satisfaction than before	Less satisfaction than before	Unchanged	
Day 1	Group 1 (21cases)	(4.7) 1	(28.5) 6	(66.6) 14	0.164
	Group 2 (19cases)	(0) 0	(36.8) 7	(63.1) 12	
Day 3	Group 1 (21cases)	(9.5) 2	(28.5) 6	(61.9) 13	0.63
	Group 2 (19cases)	(5.2) 1	(31.5) 6	(63.1) 12	
Day 7	Group 1 (21cases)	(0) 0	(28.5) 6	(71.4) 15	0.252
	Group 2 (19cases)	(5.2) 1	(26.3) 5	(68.4) 13	
Day 14	Group 1 (21cases)	(0) 0	(33.3) 7	(66.6) 14	0.7
	Group 2 (19cases)	(5.2) 1	(28.5) 6	(63.1) 12	
Day 28	Group 1 (21cases)	(4.7) 1	(23.8) 5	(71.4) 15	0.73
	Group 2 (19cases)	(5.2) 1	(21) 4	(73.6) 14	

Analysis of mean VAS changes in drug-seeking over the 28 days showed a significant decrease in both groups of patients (group 1: P = 0.0001, group 2: P = 0.008).

Satisfaction with ejaculation was evaluated in Table 9 and was considered as more or less satisfied, and unchanged. The unchanged response was predominant in most of the two groups in all 5 stages, however, there was no significant difference in patient satisfaction in the five stages between the two groups. Also, changes in this variable were not significant in any of the two groups during the 28 days (group 1: P = 0.23.0, group 2: P = 0.78).

4. DISCUSSION

Drug addiction is characterized by complications such as mortality, rising costs, and various socioeconomic problems at the individual to community level (1-3). Methadone is one of the most commonly used drugs to help addicts maintain their drug withdrawal process and eventually permanent withdrawal. Evidence indicates that favourable clinical experiences of methadone use in improving withdrawal symptoms [15]. This study aimed to compare the effect of methadone and tincture of opium on the drug abuse detoxification. Our findings indicated that the variables of sweating, runny nose, DTR, lacrimation, drooling, faecal excretion, muscle twitches, daytime warming, and drug demand were all significantly different in both groups. However, changes in yawning, heart rate, respiratory rate, sneezing frequency, muscle pain, cold feeling, and ejaculation satisfaction were not significant in either group. Our results also showed that changes in some variables, including social and occupational performance, pupil size, vomiting frequency, sleep and nausea, were significant as compared to the TOP group with unchanged rates. Clausen, et al. [15] intending to examine mortality reductions in opioid maintenance treatment, showed that this treatment was capable of reducing mortality by 0.5%, while mortality was higher in addicts who have not received maintenance treatment [15]. In the present study, one of the most significant changes was related to the improvement of symptoms in both groups. Alongside these symptoms, there was a smaller group of symptoms, with no significant changes. Another group of symptoms showed significant changes only in the methadone group. Overall, based on our results, none of the patients' symptoms in any of the two groups intensified during the study.

A study by Amatol, et al. [16] aimed at investigating the effectiveness of tapered methadone in the management of opioid withdrawal, were showed that change of methadone administration method and slow tapering with temporary substitution of long-acting opioids could be much more effective in reducing withdrawal severity. The method is conventional [16]. Improvement in social and occupational dysfunction, muscle twitches and daytime cooling was seen in the methadone group as compared to the TOP group, indicating the superiority of methadone treatment with Khomree method. It can be said that methadone and Laudanum can be almost equally effective in reducing the withdrawal symptoms, although this effect may be significant in the opiate methadone by using Khomree method.

Somogyi, et al. [17] evaluated the effectiveness of a range of TOP doses for managing opioid withdrawal.

Withdrawal scores were found to be low for all patients (range 9–23%). Dose-dependent changes in both systolic and diastolic Blood pressure were observed (P = 0.021 and P = 0.01). Flexible dosing of TOP would reduce the withdrawal symptoms, but these changes were not found to be clinically significant [17].

Gossop, et al. [18] also conducted a study aimed at the withdrawal symptoms of methadone during the 21-day detoxification procedure. The authors of this study reported that the peak of withdrawal symptoms was at the end of the program and gradually diminished. Also, the results of this study could not prove the effectiveness of methadone in inducing withdrawal scores [18].

However, due to the lack of studies in this field, future studies are needed to compare methadone and TOP use with its standard method, as well as the combination of the stated goals to reach a definitive conclusion.

5. CONCLUSION

Although it may be slightly more considerable to improve opioid withdrawal symptoms and other clinical conditions in the methadone-treated groups, however, due to the lack of statistically significant differences as well as the improvement of some of the most significant clinical symptoms, such as sensation of drug-seeking in both groups, it can be concluded that methadone and TOP are both effective in opiate withdrawal and the two treatments are not preferable to each other.

CONSENT AND ETHICAL APPROVAL

By giving full explanations and obtaining informed consent, patients entered the study and could be excluded at any time. The research team was committed to considering all the provisions of the Helsinki Declaration and the Research Ethics Declaration of the University of Medical Sciences. This research project (No. 2027) has been approved by the Ethics Committee of the Research Council of Arak University of Medical Sciences with a code of ethics, 21-171-93.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Botvin GJ. Griffin KW, Paul E. Preventing Tobacco and Alcohol use among elementary school students through life skills training. Journal of Child & Adolescent Substance Abuse. 2003;11(5): 290-299.
2. Sadock BJ, Sadock VA, Ruiz P. Comprehensive textbook of psychiatry 9th ed. Philadelphia lippincott Williams Wilkins. 2009;11(5):1367-8.
3. Bagheri Yazdi A, Shams Alizadeh N, Abedin A, Vazirian M. Guidelines for the Prevention and treatment of substance abuse (Especially Doctors). Salman Publishing. 2005;23(12):77-102.
4. Ekhtari A, Behzad A, Sadeghi M, Mirbah H. Guide to recognition and treatment of addiction in Iran. Arjomand Publications. 2002;132(24):107-95.
5. Rasoolian B. Opium (in addition to methadone abandonment and introducing newer drug abuse drugs). Timurzadeh Cultural Publishing Institute, Tabib Publishing. 2004;9(12):116-9.
6. Horspool MJ, Seivewright N, Armitage CJ, Mathers N. Post treatment ontcomes of buprenophine detoxification in community setting: A systemic Review. European addiction research. 2008;1(4):179-185.
7. Caplehorn JR, Bell J. Correction of error: Methadone dosage and retention of patients in maintenance treatment. Med J Aust. 1993;159(9):640-9.
8. Jumi Hayaki, Bradley J. Anderson b, Michael D. Stein. Drug use expectancies among no abstinent community cocaine users. Drug and Alcohol Dependence. 2009;9(4):109–115.
9. Dahmardehei M, Rafaiee R. Opium syrup distribution, limitation and challenges. Zahedan J Res Med Sci (ZJRMS). 2012; 14(6):48.
10. Solhi H, Sadeghi-Sedeh B, Emami P, Jamalian M, Kazemifar AM. Does Ingestion of Tincture of Opium Notably Raise Blood Alcohol Concentration? Addiction & Health. 2014;6(34):100-104.
11. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. 2000;22(3):179-90.
12. Maxwell JC, Pullum TW, Tannert K. Deaths of clients in methadone treatment

in Texas: 1994-2002. Drug Alcohol Depend. 2005;78(1):73-81.
13. Pashaei T, Moeeni M, Roshanaei Moghdam B, Heydari H, Turner NE, Razaghi EM. Predictors of treatment retention in a major methadone maintenance treatment program in iran: A survival analysis. J Res Health Sci. 2014; 14(4):291-5.
14. Nosyk B, Li L, Evans E, Urada D, Huang D, Wood E, Rawson R, Hser YI. Utilization and outcomes of detoxification and maintenance treatment for opioid dependence in publicly-funded facilities in California, USA: 1991-2012. Drug Alcohol Depend. 2014;14(3):149-57.
15. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. Drug Alcohol Depend. 2008;94(1-3):151-7.
16. Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2013;2(21): 560-0.
17. Somogyi AA, Larsen M, Abadi RM, Jittiwutikarn J, Ali R, White JM. Flexible dosing of tincture of opium in the management of opioid withdrawal: Pharmacokinetics and pharmaco-dynamics. Br J Clin Pharmacol. 2008;66(5):640-7.
18. Gossop M, Griffiths P, Bradley B, Strang J. Opiate withdrawal symptoms in response to 10-day and 21-day methadone withdrawal programmes. The British Journal of Psychiatry. 1989;154(3):360.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/52677