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ARTICLE

Opium tincture versus methadone syrup in management of acute raw opium withdrawal: A randomized, double-blind, controlled trial

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ABSTRACT

The aim of this study was to evaluate the effectiveness of opium tincture versus methadone syrup in the management of acute withdrawal syndrome in opium dependent patients during the detoxification period. In this double-blind randomized controlled study, a total of 74 adult male raw opium dependent patients were treated with opium tincture or methadone syrup 2 times daily for 5 consecutive days. Detoxification was initiated by tapered dose reductions to reach abstinence. At the end of the 10th day, the medications were discontinued. The Objective Opioid Withdrawal Scale was used to assess withdrawal symptoms every day. Significant decreases on the Objective Opioid Withdrawal Scale were found for both treatment methods during the study period ($p < .0001$). However, there was no significant difference between groups on the total Objective Opioid Withdrawal Scale, and adverse effects existed. Opium tincture can be considered as a potential substitute for methadone syrup for suppression of raw opium withdrawal symptoms, with minimal adverse effects.

KEYWORDS

Detoxification; methadone; opium tincture; withdrawal

Introduction

Opiate dependence is a major social and health concern in many parts of the world that continues to grow.[1] More than 50% of the world's opiate users (7.8 million) are found in Asian countries, and despite rapid change, raw opium continues to be smoked or eaten by traditional means in many third world countries.[2,3] Easy availability of the opium and also the misconception among some people about the beneficial effects of opium consumption in the prevention or amelioration of diabetes mellitus, hypertension, and the occurrence of cardiovascular disease, as well as treatment of conjunctivitis, diarrhea, the common cold, and insomnia increase the prevalence of its consumption in these regions.[3–5] Opiates, especially smoked or ingested raw opium, have been the dominant substance of abuse in Iran for decades[6–8] and the major drug of abuse among treatment seekers in Iranian urban de-addiction centers is opium (varying between 50 and 97%).[9]

Detoxification, which is a short-term management of opium withdrawal, is usually considered the first step of treatment in these patients which aims to bring the patient into an opium-free state and overcome physical dependency. This is a frequently requested treatment modality for management of opium dependence. During rapid opioid detoxification, the opioid is commonly tapered in about 2 weeks to reach a complete withdrawal state.[10,11]

Various pharmacological agents, such as methadone, clonidine, and buprenorphine, are used for opioid detoxification, and each of these drugs has its clinical *strengths and limitations.*[12] In many countries, methadone, which is a μ-opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine, is the principal pharmacotherapy utilized in the treatment of opioid dependence to treat the signs and symptoms of opioid withdrawal.[13] Although methadone has been widely used for opioid detoxification and its efficacy in improving the physical and psychological health of patients who are in treatment has been demonstrated,[13–15] some studies have found methadone-associated QT interval prolongation and Torsades de Pointes in methadone users.[16–18] Also, other issues related to the use of methadone include its prolonged

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washout period (10 days), respiratory depression, and high abuse potential, besides its legal prescribing limitations restrict the use of methadone.[3] Moreover, in some parts of the world, including southeast Asia, the cost of methadone is a barrier to its widespread use. On the other hand, as heroin is the most commonly used opiate worldwide (about 75% of global opiate users),[19] another important issue is the fact that methadone-aided detoxification protocols are mainly designed to overcome the withdrawal signs and symptoms of heroin addicts. Therefore, there is a need to investigate alternative opioid pharmacotherapies that will be effective in the treatment of opium dependence and locally acceptable.[20] One response to this problem has been the use of opium tincture (OT), which is a preparation of opium in alcohol and water, that in pharmaceutical preparation is standardized to contain 1% morphine, as a less expensive substitution treatment.[21] OT is perceived to be a traditional medicine in some parts of southeast Asia, and so appears to be a culturally acceptable alternative to medications, such as methadone, in some parts of this region as a traditional medicine for opioid detoxification and relieving opioid withdrawal symptoms.[14,21,22] In recent years, maintenance therapy with OT has been introduced in Iran as a new strategy to treat drug use problems among injecting drug users.[21] However, there are few studies regarding the use of OT in the management of opioid withdrawal in opium addicted patients. Furthermore, all of these studies were open labeled.[14,20] Therefore, considering the importance of withdrawal signs and symptoms through the detoxification period in opium addicted patients, and few studies which have been carried out in this regard, this study was conducted to evaluate the effectiveness of OT versus methadone syrup in management of acute opioid withdrawal in raw opium addicted patients during the detoxification period.

Materials and methods

This double-blind randomized-controlled prospective trial was performed at the Zare Hospital in Sari-Mazandaran-Iran, between April and October 2013.

After the approval of Mazandaran University of Medical Sciences Research Affairs and ethical committee, 97 adult male outpatients, aged 18−60, with a confirmed diagnosis of opium dependence by a psychiatrist using the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) criteria, were invited to participate in the study and undergo opium detoxification. Opium dependence was confirmed with urine laboratory test.

Seventeen patients were excluded from the study. Exclusion criteria consisted of clinically significant physical illnesses (e.g., tuberculosis, acquired immune deficiency syndrome [AIDS], renal failure, acute hepatic failure, diabetes, thyroid disease, and history of seizure disorders), any psychiatric illnesses (including psychotic disorders, bipolar mood disorders, major depressive disorder, acute suicidal ideation, anxiety disorders like generalized anxiety disorder [GAD], post-traumatic stress disorder [PTSD], and panic disorder), and using other drugs or substances except nicotine (e.g., other opioids, monoamine oxidase [MAO] inhibitors, doxepin, anti-spastic drugs, beta blockers, known inducers or inhibitors of CYP3A and CYP2D6, cannabinoids, amphetamines, and alcohol). Also, six patients were excluded because they were unwilling to follow researcher instructions or had received maintenance therapy with other opioids (e.g., buprenorphine, codeine derivatives). In order to assess the physical health of volunteers, some laboratory tests, including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), white blood cell (WBC), red blood cell (RBC), hemoglobin (Hgb), and hematocrit (Htc), were measured at baseline (before entering the study). Moreover, physical examination was undertaken by a psychiatry resident. To match the participants with the inclusion and exclusion criteria, the urine test was applied at baseline to investigate presence of morphine, cannabis, and methamphetamine in urine samples of the patients.

Informed consents were obtained from 74 eligible patients who were included in the study. They were assigned to two groups by simple randomization. Each patient received either OT (group A) or methadone syrup (group B) by a nurse who was blind to the study groups, according to the computer generated list. The patients' severity of dependence has been assessed by Addiction Severity Index (ASI), and they were categorized to mild, moderate or severe blocks. ASI is a semi-structured interview designed to address patients' status in several functional domains: alcohol and drugs, employment, self support, medical and psychiatric health, family relations, and illegal activity. The Persian version of this scale is validated by Lavasani et al.[23] For patients in group A and B, OT (45, 90,

and 135 mg/day) and methadone syrup (15, 30, and 45 mg/day), was administered according to their blocks, respectively. The total dose of OT or methadone syrup divided into two equal doses and administered twice a day for all patients. Appearance, color, and odor of both medications were matched by pharmaceutical industry experts.

These starting doses were maintained for five consecutive days under double-blind conditions in which neither the patient, nor the medical staff (attending physician, resident, and nurse), were aware of the study group assignment. Thereafter, detoxification was initiated by tapered dose reductions (20% every day) over a period of 5 days, to reach abstinence. At the end of 10th day the medications were discontinued.

The Objective Opioid Withdrawal Scale (OOWS) was used to assess withdrawal symptoms. This scale is a valid and reliable indicator of the severity of the opiate withdrawal syndrome over a wide range of common signs and symptoms.[24] The OOWS assesses 13 observable physical signs, rated as "present" or "absent" by a psychiatry resident who was an independent observer (score 1 for each item if present). The items in this scale include yawning, rhinorrhea, piloerection, perspiration, lacrimation, mydriasis, tremors, hot and cold flushes, restlessness, vomiting, muscle twitches, abdominal cramps, and anxiety. The OOWS was completed at the all 10 days of the study by the investigator. Assessments were done by a resident who was blind to group assignment before prescribing the morning doses of medicines. Safety was assessed according to serious adverse event criteria recording of spontaneously reported adverse events, daily monitoring of vital signs, and repeated physical examination.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 16 software (SPSS Inc. Chicago, IL). Data were analyzed by analysis of variance (ANOVA) and independent samples *t*-test, Mann–Whitney *U*-test, and Wilcoxon test. Significance levels were set at p-value $< .05$.

Results

A total of 97 patients who were referred for detoxification treatment to the hospital were screened during the study period. Of these, 17 patients did not meet the inclusion criteria and six patients declined to participate in the study. In total, 74 patients completed the present study and data from all these patients were analyzed (Figure 1).

The patient's demographic characteristic and incidence rate of adverse events by detoxification methods are presented in Table 1. In patients who received methadone syrup or OT, the most prevalent adverse effects were perspiration (67.5%) and sleepiness (65.7%), respectively. Tension was the lowest adverse effect by either of the two detoxification methods. There was no statistically significant difference between the two groups regarding these demographic characteristic and adverse effects details.

The mean of the OOWS scores and comparison of their time profiles between these two treatment methods are shown in Figure 2. Statistical analysis revealed that significant decreases were found in the OOWS scores in both treatment methods up to day 10 ($p < .0001$).

As shown in Figure 2, no statistically significant differences were found between OOWS scores of the treatment methods at different intervals ($p > .05$). Statistical analysis using Mann–Whitney *U*-test did not reveal a significant difference between total OOWS scores (pooled data) of two treatment methods (Figure 3).

Also, no significant differences were observed in adverse effects such as headache, dizziness, sleepiness, misbalance, constipation, nausea, seizures, perspiration, tension, and respiratory depression between the two treatment methods (Table 1).

Discussion

The effectiveness of OT versus methadone syrup was evaluated in the management of acute opioid

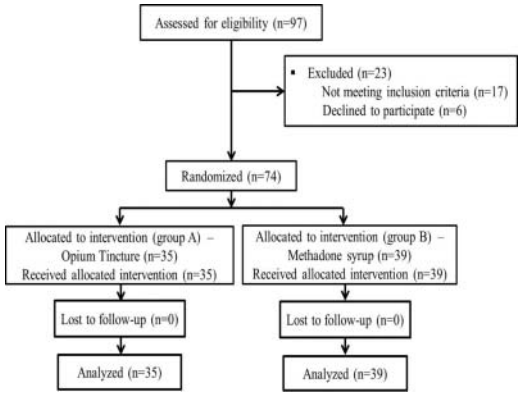

Figure 1. Flowchart of the study.

Table 1. Patient demographics and adverse effects incidence rate by detoxification treatment methods.

Characteristics		Detoxification Methods		*p*-Value
		Opium Tincture	Methadone Syrup	
Demographics	Age (years), mean ± *SD*	41 ± 12.9	39 ± 12.4	.56
	Married, *n* (%)	28 (80.3)	28 (71.8)	.45
Addiction duration (years), mean ± *SD*		4.7 ± 1.4	4.8 ± 2.1	.86
ASI score	Low, *n* (%)	6 (17.2)	8 (20.5)	.86
	Moderate, *n* (%)	19 (54.3)	22 (56.4)	
	Severe, *n* (%)	10 (28.5)	9 (23.1)	
Adverse effects	Headache, *n* (%)	19 (54.3)	22 (56.4)	.65
	Dizziness, *n* (%)	13 (37.1)	14 (35.9)	.63
	Sleepiness, *n* (%)	22 (62.8)	26 (66.6)	.81
	Misbalance, *n* (%)	11 (31.4)	12 (30.7)	.59
	Constipation, *n* (%)	21 (60.0)	25 (64.1)	.63
	Nausea, *n* (%)	14 (40.0)	14 (35.8)	.38
	Respiratory depression, *n* (%)	12 (34.2)	15 (38.4)	.83
	Perspiration, *n* (%)	20 (57.1)	26 (66.6)	.34
	Tension, *n* (%)	9 (25.7)	10 (25.6)	.99

withdrawal in raw opium addicted patients during the detoxification period. The major finding of this study was that the both OT and methadone syrup were equally effective in tapered doses and were associated with decreases in opioid withdrawal syndrome. Also, differences in opioid withdrawal signs and symptoms were not statistically significant between the two treatment groups. The efficacy of methadone with tapered dose reductions in management of opioid withdrawal syndrome in the current study is consistent with the results of other studies using a dose reduction regimen of this medication to control opiate withdrawal.[11,12,14] It has been shown that in opioid addicted patients, methadone is superior to a placebo for management of opioid withdrawal symptoms.[25] Opioid detoxification, which is the first step of treatment in opioid addicted patients, remains a critical area of focus. There is no consensus on the optimal pharmacological treatment strategy for reaching complete abstinence from all opiates.[26] Each patient is evaluated individually, and usually a combination of interventions is used.[22] Although methadone has been widely used for opioid detoxification, a Cochrane review with aim to evaluate the effectiveness of tapered methadone compared with other detoxification treatments in managing opioid withdrawal on completion of detoxification found that the medications used for detoxification are similar in terms of overall effectiveness.[27] Moreover, several studies have found acute methadone intoxication, as well as chronic methadone maintenance therapy, to be associated with significant cardiac effects; specifically, QT interval prolongation and Torsade's de Pointes in its users. Thus, patients who use this

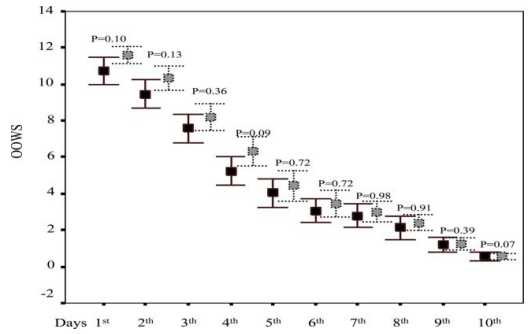

Figure 2. Comparisons of the time profiles of OOWS scores in OT (solid lines) and methadone syrup (dashed lines) treatment methods, before (first day) and following drug intake.

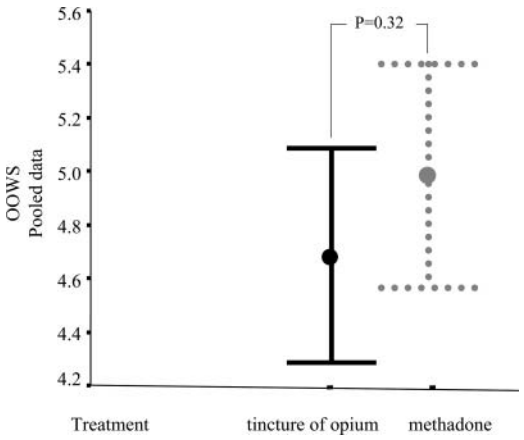

Figure 3. A comparison of the time profiles of total OOWS scores (pooled data), between OT (solid lines) and methadone syrup treatment (dashed lines) methods.

medication may need closer medical supervision.[26,28,29] However, the effect of methadone is dose dependent,[30] and to the best of the authors' knowledge, raw opium has not been studied enough for this side effect. Although, given that this condition can be caused by morphine, and morphine is the main active ingredient in opium, OT overdose is unlikely to cause this side effect.[31]

Considering the equal effectiveness of both methadone syrup and OT in management of opioid withdrawal signs and symptoms in the current study, it seems that OT is a potential substitute for methadone syrup for the suppression of withdrawal syndrome, with minimal adverse effects. The first report of the use of OT for opiate maintenance pharmacotherapy was in a group of 18 opioid-dependent subjects in France and showed a successful use of OT on biopsychosocial status of heroin intravenous (IV) drug users.[32] In an open label study in northern Thailand, 15 opium dependent patients were prescribed 3.33−10 mg morphine equivalents OT 12 hourly compared to methadone 5−20 mg 12 hourly for opiate detoxification. It was seen that the OT group did not do better.[14] Ray et al. believes that it may be due to a lower dose of tincture opium used, which was inadequate to satisfactorily suppress withdrawal syndrome.[3]

In another open label study to evaluate the clinical effectiveness of using different dosages of OT (6.66-, 13.3-, and 20-mg morphine equivalents, twice daily) in the management of opioid withdrawal among 45 opium-dependent patients, Somogyi et al. demonstrated that withdrawal scores were low in all three groups. Also a dose-dependent change in systolic and diastolic blood pressure was seen between three groups on day 5 of maintenance of OT, but these changes were not clinically significant. They concluded that a flexible dose of OT with minimal adverse effects can suppress withdrawal symptoms in opioid-dependent patients.[20] In contrast, in another open label parallel group study carried out by Jittiwutikarn et al. to evaluate and compare the effectiveness of oral OT and methadone in suppressing of opioid withdrawal symptoms in 15 former heroin users (receiving methadone 5−20 mg every 12 hours) and 15 opium smokers (receiving 3.33−10 mg morphine equivalents of OT every 12 hours) in northern Thailand, showing that OT was inferior to methadone in withdrawal symptoms management.[14] One possible explanation for the inadequate efficacy of OT in suppression of withdrawal symptoms in this study may be the lower dose of OT (3.33−10 mg every 12 hours) prescribed for patients compared with the doses of OT in the current study (45, 90, and 135 mg/day). These lower doses of OT may lead to lower serum morphine concentration and therefore the lower efficacy. However, in the current study, the morphine plasma concentration was not measured during the study period.

In another study in Myanmar for detoxification, OT (as a cheap local product, produced by the Myanmar Pharmaceutical Industry) along with chlorpromazine tablets was found to be satisfactory in suppressing withdrawal syndrome over a period of 10 to 14 days. Those dependent only on opium have shown good outcome in treatment setup. Nataparan indicates that OT which has been made available to many people, has generally found to be equally effective compared to methadone.[33] In another study, it was shown that those dependent only on opium have shown good outcome in treatment setup in a general hospital psychiatry unit. Chandrasena believes that their motivation to give up the habit because of social stigma and financial reasons was an important issue. At the 6-month follow-up in this study, 84% of the participants were not using opium.[34] Considering that these studies were open labeled, double-blind design was considered necessary in the current study to minimize the potential *biases in patient selection and* assessments. In a study by Alam Mehrjerdito, the therapeutic effectiveness of OT among a community-recruited sample of women who were simultaneously dependent on opium smoking and non-prescribed use of benzodiazepines were evaluated, patients underwent 6 months of treatment with OT and were followed for 6 months after treatment. Initial and monthly evaluations were conducted by ASI and random urine specimen collection. The result has been shown that OT can prevent non-prescribed use of benzodiazepines among opium-dependent women.[35]

OT is a preparation of opium in alcohol and water that in pharmaceutical preparation is standardized to contain 1% morphine. Distribution of OT has begun since 2011 in Iran; however, it was not welcomed by patients. In a study by Dahmardehei et al., the reasons for patients' unwillingness to use OT from addiction therapists' point-of-view was evaluated and has shown that positive morphine tests, high tariff, liquidity, bitter taste, bad and sharp smell, having alcohol, and

nausea and vomiting were the main reasons for the unwillingness of patients to use OT.[36] OT which was provided for treatment of opium dependence among opium smokers in Thailand since 1996, was also used for heroin users for 5–9 months in nine villages. Natpratan from Ministry of Public Health, Chiang Mai, Thailand stated that this was a successful attempt to control drug abuse as well as HIV infections.[33] In a multi-center, double-blind, randomized study by Madlung-Kratzer et al. to evaluate the efficacy and safety of slow-release oral morphine (SROM) compared with methadone for detoxification from maintenance therapy in 202 male and female opioid dependents, both pharmacological modalities were well tolerated, and detoxification with tapered dose reductions of SROM was not inferior to methadone.[11] Previous studies have shown that the most common side effects of methadone are constipation, sweating, urinary retention, and dose-related orgasm dysfunction in men.[37] In the present study, a relatively lower rate of headache, sleepiness, constipation, respiratory depression, and perspiration observed in patients treated with OT compared to patients treated with methadone syrup. While a relatively higher rate of dizziness, misbalance, and nausea were observed in patients treated with OT compared to patients treated with methadone syrup. However, there was no statistically significant difference between the two groups, which is consistent with Jittiwutikarn et al.'s findings that showed there were no significant changes over time for any objective measure in patients who received oral OT or methadone to control opioid withdrawal.[14]

A variety of exclusion criteria suggested by methadone and OT protocol applied in this study may lead to low external validity. Also this study had a short follow-up period. Future studies will need to extend the follow-up period. Dose size and dosing frequency investigation is suggested for rapid and gradual detoxification in raw opium addicted patients.

In conclusion, this study proved that opium-dependent patients can be detoxified by tapered dose reductions of methadone syrup or OT over a period of 10 days in order to reach abstinence. It was shown that both OT or methadone syrup was equally effective in tapered doses and was associated with decreases in opioid withdrawal syndrome. Therefore, cost effectiveness may be an advantage of OT over methadone in this regard. However, odor and taste modification of OT, as well as tablet preparation of raw opium by pharmaceutical industry experts, may lead to a better patients' acceptance. Although further studies for optimal dose and duration with OT in management of acute opioid withdrawal in raw opium and other opioids addicted patients during detoxification period are warranted.

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