Received: 22.1.2005 **Accepted: 1.6.2005**

Original Article

Tramadol versus methadone for the management of acute opioid withdrawal: an add-on study

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ABSTRACT

BACKGROUND: Opioid agonists such as methadone have been used widely in controlling opioid withdrawal symptoms. Tramadol, a partial opioid agonist, also has been prescribed to manage acute and chronic pain. We sought to compare the efficacy of tramadol and methadone in reducing the severity of opioid withdrawal symptoms.

METHODS: In a double blind clinical trial 70 opioid dependent patients who used daily opium equal to 15 mg methadone randomly were assigned in two groups. In one group, methadone was started at 15 mg/day while in the other group 450 mg/day tramadol was prescribed. Both drugs were tapered in a week and placebo was prescribed in the 2nd week. The severity of withdrawal symptoms were assessed five times by short opioid withdrawal scale (SOWS). Data were analyzed by Repeated Measures Analysis of Variance, Mann-Whitney U, and Wilcoxon tests.

RESULTS: There were statistically significant differences between two groups in the severity of anxiety (P = 0.015), irritability (P = 0.044), palpitation (P = 0.018), agitation (P = 0.037), and dysphoria (P = 0.044) that all were more common in methadone group. Comparison of side effects revealed statistically significant differences in sweating (P = 0.003) and drowsiness (P = 0.019) between two groups that were more frequent in methadone group.

DISCUSSION: Tramadol was more efficacious in controlling opioid withdrawal symptoms with lower side effects.

KEYWORDS: Methadone, tramadol, opioid withdrawal

JRMS 2006; 11(3): 185-189

Opioid dependence is an overt social problem in Iran [1]. Formal reports revealed that there were 1,200,000 opium dependent patients in Iran in year 2000 while informal evaluations estimate a prevalence of about 4,000,000 substance dependents and abusers [1]. Detoxification is usually considered the first step of treatment of these patients which aims to overcome physical dependency [2]. During rapid opioid detoxification (ROD) usually the opioid is tapered in two weeks to reach complete withdrawal state [2]. In addition to opioid, many drugs such as clonidine, benzodiazepines, and antispasmodics have been used to help in controlling opioid withdrawal symptoms and cease the physiologic and psychologic stress in patient [3]. In recent years, methadone has been widely used for ROD [2]. Levomethadyl acetate and buprenorphine are the other opioid agonists which have been used for this purpose [1-3]. Some of the side effects of methadone such as respiratory depression and prolonged washout period, besides its legal prescribing limitations of methadone restrict the use of methadone [2,3].

Tramadol, a synthetic analog of 4-phenylpiperdin codeine, is a partial agonist of μ receptor with central analgesic effect via its agonism on μ and 5-HT_1 receptors [4-6]. Tramadol is metabolized via P450 ($2D_6$) enzyme and the main M_1 demethylated metabolite is excreted by kidney [4-6]. Like tricyclic antidepressants, tramadol inhibits reuptake of serotonin and noradrenalin [7]. It has inhibitory

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effect on $5HT_{2c}$ receptor too [8]. Also, tramadol has strong structural similarity to the antidepressant venlafaxine [7].

The tramadol effect on $5HT_3$ receptor in spinal cord reduces the pain [9]. Analgesic Duration of tramadol after a single dose oral administration is 6 hours [5,6].Tramadol blocks acetylcholine α_7 nicotinic receptor which is involved in sensory gating [10] and also has some anticholinergic effects by type III muscarinic receptor inhibition [11]. Inhibitory effect of tramadol on NMDA glutamate receptor may induce some analgesic effect [12].

After acute administration of tramadol, activity of natural killer cells and IL_2 production will be enhanced that may indicate tramadol as a good choice in treatment of pain in immunocompromised patients [13].

Sobey reported a retrospective detoxification chart review of 59 patients with tramadol in comparison with 85 patients detoxified with clonidine on rates of leaving against medical advice (AMA) and control of withdrawal symptoms. Patients detoxified with tramadol had 23% risk of leaving AMA and scored an average of 0.24 points lower on a 0-3 point withdrawal symptom scale compared with patients detoxified with clonidine. This preliminary study indicates that tramadol is more effective in managing withdrawal than clonidine, and may be especially useful in outpatient detoxification [14]. The results of another study were consistent with previous pilot reports that indicated few clinical differences between parenteral buprenorphine and oral tramadol protocols when used in the management of acute heroin withdrawal [15]. Because of the low risk of dependency and respiratory depression, good effects on reducing pain and short half life it may be useful for management of opioid withdrawal symptoms. This study has been designed to compare the effects of tramadol and methadone in controlling opioid withdrawal symptoms.

Methods

The protocol of this study was approved by the ethics committee of the board review of Behavioral Sciences Research Center, Isfahan University of Medical Sciences. After complete description of the study for all eligible subjects a written informed consent was obtained.

In winter 2005, all male patients referred to Noor hospital (affiliated to Isfahan University of Medical Sciences) for treatment of opium dependence who met the criteria of opioid dependence based on Fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) aged between 20 to 60 years were considered. The exclusion criteria were presence of any medical disease that prohibit using tramadol and methadone, taking extra medications, polysubstance dependency, and presence of any major psychiatric disorder (bipolar disorder , psychosis and major depressive disorder).

Since the precise amount of daily opium taken by each patient was not clear, all of them underwent methadone equivalent evaluation and only those patients who had not objective signs of opioid withdrawal when used 15 mg of methadone for one day were selected. These patients were randomly assigned into two groups for a double blind clinical trial. In the beginning day of the trial, patients in "group A" took 15 mg/day of methadone while in "group B" patients received 450 mg/day of tramadol which is an equivalent to 15 mg/day of methadone [16]. Both groups also were treated with 0.3 mg/day of clonidine and 10 to 30 mg/day oxazepam.

The above mentioned doses of opioids were given by same number of capsules with identical shape and size twice daily for three stabilization days. The doses of methadone and tramadol were reduced by 15% decrements every day to reach 0 at 7^{th} day of trial. Patients in both groups took placebo during the second week of the study. Neither patients, nor researchers knew the contents of capsules.

Patients in both groups were assessed with interview based Short Opioid Withdrawal Scale (SOWS) at the 1^{st}, 3^{rd}, 5^{th}, 7^{th}, and 14^{th} days of the trial by the second author who was well familiar with questionnaire. Assessments were performed before prescribing the morn-

ing doses of opioids. SOWS is a 16 items scale with acceptable validity and reliability [17-20]. The 16 items of SOWS are diarrhea, stomach cramps, palpitation, agitation, irritability, dysphoria, anxiety, craving, muscle cramp, muscle tension, yawing, coldness, nausea, aches and pains, runny eyes, and sleep problems. Each item was assessed on 0–3 Likert scale.

Also, the severity of side effects of medications was evaluated simultaneously by direct questioning about somnolence, sweating, dizziness, nausea, vomiting and constipation.

Statistical analysis was carried out by SPSS 11.5 software for windows (SPSS Inc., Chicago, Illinois, USA). Baseline comparisons between 2 groups were analyzed by chi-square and T testS. The principal analysis for each scale was a repeated measure analysis of variance (time × treat interaction). Regarding non-nominal nonparametric variables, the scores of SOWS and side effects between two groups were compared by Mann-Whitney U test while Wilcoxon test was used to compare withdrawal scores in each group from baseline to the end of study.

Results

Of total 167 referred patients, 70 patients were eligible for this study that 36 were randomly assigned in "group A" (methadone) and 34 in group B (tramadol). Fourteen patients in group A and 12 in group B were dropped out through the course of study. There was no significant difference between these two groups regarding baseline characteristics of two groups (table 1).

Repeated measures Analysis of Variance showed no statistically significant difference between total SOWS scores of treatment methods at different intervals (P = 0.143) while such comparisons for dysphoria, anxiety, agitation, irritability, and palpitation subscales of SOWS revealed statistically significant differences (P = 0.044, P = 0.015, P = 0.037, P = 0.044, P = 0.018 respectively).

Table 1. Baseline characteristics of patients.

	Group A n = 36 % (n)	Group B n = 34 % (n)
Married	86.1 % (31)	85.3 % (29)
Elementary education	44.4 % (16)	50.0 % (17)
High school diploma	38.8 % (14)	35.3 % (12)
University degree	16.6 % (6)	14.7 % (5)
	Mean (SD)	Mean (SD)
Duration of dependency (year)	12.86 (7.05)	12.85 (4.74)
Age (year)	37.21 (7.63)	36.85 (8.23)
SOWS scores at 1st day	11.97 (9.86)	10.28 (7.20)

Mean final total SOWS scores at day 14th ($SOWS_5$) were 15.18±10.62 for group A and 4.22 ± 4.20 for group B that Mann-Whitney U test revealed a significant difference between two groups (P = 0.01). Table 2 contains only the Mann-Whitney U test comparison results of subscale mean ranks of five times consecutive SOWS assessments of two groups which showed significant differences. The other items that did not show differences between two groups were not shown here.

Comparison between subscales of SOWS scores at 1st and 7th day assessments in group A by Wilcoxon test showed significantly more irritability on the 7th day (P = 0.047) while, in group B , this comparison showed significantly more abdominal cramp (P = 0.015), insomnia (P = 0.027), and craving to opium (P = 0.026). There were no significant differences between two groups' scores of other subscales.

Comparison of total SOWS scores at 1st and 14th days by Wilcoxon test, showed significant reduction of SOWS scores in group B (P = 0.016) and no significant difference within group A (P = 0.52). Wilcoxon test also revealed significantly higher scores of feeling sick (P = 0.028), insomnia (P = 0.03), and agitation (p<0.0001) at day 14th compared to the beginning of the study in group A. This comparison in group B showed no significant difference between the first day and the 14th in all subscales.

Table 2. Comparison of subscale mean ranks of five times consecutive SOWS assessments of the two groups.

Symptom	Time of sows	Mean rank A	Mean rank B	Level of significance
Dysphoria	$Sows_1$	37.49	35.46	0.328
	$Sows_2$	38.34	34.56	0.21
	$Sows_3$	37.17	35.84	0.387
	$Sows_4$	40.19	32.6	0.086
	$Sows_5$	28.2	16.18	0.002
Agitation	$Sows_1$	37.49	35.46	0.326
	$Sows_2$	36.36	36.64	0.476
	$Sows_3$	37.57	35.37	0.31
	$Sows_4$	39.04	33.81	0.243
	$Sows_5$	29.11	15.89	0
Anxiety	$Sows_1$	39.14	33.71	0.113
	$Sows_2$	35.32	37.74	0.297
	$Sows_3$	37.11	35.86	0.387
	$Sows_4$	41.18	31.56	0.01
	$Sows_5$	26.03	18	0.008
Irritability	$Sows_1$	37.93	34.99	0.262
	$Sows_2$	36.64	36.36	0.486
	$Sows_3$	37.53	35.41	0.318
	$Sows_4$	40.92	31.83	0.039
	$Sows_5$	26.7	18.3	0.009
Palpitation	$Sows_1$	37.09	35.87	0.351
	$Sows_2$	38.24	34.66	0.131
	$Sows_3$	35.96	37.07	0.368
	$Sows_4$	37.96	34.97	0.168
	$Sows_5$	24.55	20.45	0.038

SOWS: Short Opioid Withdrawal Scale
$P<0.05$

Side effects scores at 7th day of trial revealed no significant difference between two groups. At 14th day, patients in group A had significantly more drowsiness and sweating than group B ($P = 0.0195$ and $P = 0.003$ respectively).

Mann-Whitney U test did not reveal a significant difference between total SOWS scores of dropped out patients of two groups at different assessments.

Discussion

There were the same rates of changes in the severity of withdrawal symptoms on days 1, 3, 5, 7, and 14 of the study in two groups. These findings were consistent with the results of studies which indicate that tramadol is just as effective as codeine, pethidine, buprenorphine and morphine in control of pain [1-6]. One study also reported its efficacy in reducing heroin withdrawal symptoms [21]. Thus, tramadol could be considered as a potential substitute for low doses of methadone (15 mg/day or less) to manage opioids withdrawal syndrome.

On the other hand, higher anxiety, agitation, irritability, and dysphoria scores (mental dimension of opioid withdrawal syndrome) in patients who received methadone during the study were probably related to the effects of tramadol on 5-HT_1 receptors and antidepressant-like effects of tramadol.

Higher rates of irritability, anxiety, and opium craving in methadone group at 7th and 14th days also indicated more effects of tramadol in the management of psychological dimension of opioid withdrawal

Drowsiness and sweating rates of patients received methadone were more than those received tramadol which could be due to longer half-life of methadone along with less affinity of tramadol to opioid receptors and its lack of affinity to GABA receptors.

Because of the relative lack of respiratory depression and toxicity, lower dependency potential, and its antidepressant–like effects, tramadol can be used during ROD to reduce symptoms of opioids withdrawal especially in cases of low dosage of opium using.

This study had several limitations. First, clinical trials on substance dependent patients in an outpatient setting usually are confronted with problems such as patient noncompliance. Second, this study was not sufficiently powered statistically to determine the optimal method because of small sample size. Third, only one subjective assessment tool was used to evaluate the severity of withdrawal syndrome. Finally, the follow up period, especially for methadone group, was short.

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