IJMS
Vol 32, No 1, March 2007

Original Article

Comparison of the Efficacy of Methadone and Tramadol in Opioid-Assisted Detoxification

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Abstract

Background: A number of drugs are used to control opioid withdrawal symptoms during detoxification. Tramadol, as a partial opioid agonist, has been widely used to manage acute and chronic pains. The present study was designed to assess the effectiveness of tramadol in methadone-assisted detoxification.

Methods: In a double-blind randomized clinical trial 72 opioid-dependent patients as defined by 4th edition of the Diagnostic and Statistical Manual of Mental Disorders were assigned to two groups receiving methadone (15 mg/day) or tramadol (560 mg/day). Patients in both groups received clonidine and oxazepam. The severity of withdrawal symptoms was assessed at the baseline and 7 times every other day onward using the Short Opioid Withdrawal Scale (SOWS).

Results: Mean scores of total withdrawal symptoms on days 13th and 15th were significantly higher in the methadone group than in the tramadol group (16.2±9.5 *vs* 9.5±7.5 and 15.2±10.6 *vs* 8.5±6.9). On day 15th, the patients in methadone group showed significantly more severe psychological symptoms (5.8± 4.1 *vs* 4.3± 4.2). In the methadone group mean score of psychological symptoms was higher on day 15th compared with the first day (15.2±10.6 *vs* 9.7±8.7). Drowsiness and sweating were significantly more in patients in methadone group than in tramadol group.

Conclusion: Tramadol can be used effectively as a substitute drug in opioid-assisted detoxification, particularly in patients with low to moderate dose opioid dependency.
Iran J Med Sci 2007; 32(1): 28-31.

Keywords ● Tramadol ● methadone ● opioids

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Introduction

Dependency is a psychiatric disorder of considerable social, psychological, and biological consequences. The problem prevails in many countries including Iran. According to official reports, there were 1,200,000 to 2,000,000 opioid dependents in the country in 2002; however, unofficial voice put this figure to up to 4 millions.[1]

Many opioid dependents, who volunteer for opioid detoxification avoid treatment programs because of severe withdrawal symptoms.[2] Several methods were used to reduce the severity of such symptoms during the course of treatment.[3] Non-opioid drugs such as clonidine, benzodiazepines, and antispasmodics

were widely used to reduce the withdrawal symptoms.[3,4] Among other drugs, the opioid μ receptor agonists such as methadone and buprenorphine were used both for the substitution of abused opioids and the reduction of withdrawal symptoms.[1,4,5]

Methadone is a synthetic opioid, which has longer half-life and less sedative effects than morphine.[5] The analgesic effect of methadone resembles that of morphine.[5] It produces a dose-dependent effect and withdrawal syndromes, but its detoxification is easier than heroin or morphine.[5] Methadone inhibits substance seeking behavior, therefore, it is widely used for opioid detoxification. The method of detoxification, which is known as methadone-assisted, is based on tapering doses of methadone.[3,5] However, the long half-life of methadone carries a potential risk of cumulative toxicity and subsequent respiratory suppression.[5]

Tramadol, a synthetic analog of 4-phenylpiperidin codeine, is a partial agonist of μ receptors with central analgesic effects via its agonist activity on μ and 5-hydroxy tryptamine-1 (5-HT_1) receptors.[6,7] Tramadol is metabolized via a P450 enzyme (CYP 2D6), and its main demethylated metabolite is excreted by kidneys.[6,7] Like tricyclic antidepressants, tramadol inhibits re-uptake of serotonin and noradrenaline,[8] as well as 5-HT_{2c} receptor.[9] Also tramadol has strong structural similarities to the antidepressant venlafaxine.[8,9] The analgesic duration of tramadol after a single dose oral administration is 6 hours.[6,7]

Because of low risk for dependency and respiratory depression, favorable pain-reducing efficacy, and short half-life tramadol may be useful for management of opioid withdrawal symptoms.[6-7] This study was designed to compare the effects of tramadol and methadone in controlling the withdrawal symptoms during opioid-assisted detoxification.

Patients and Methods

Patients

The study was a double-blind clinical trial conducted in December 2004 to March 2005 recruiting all male patients (20-60 years) referring for the treatment of opium dependence to Noor Hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The protocol of the study was approved by the Board Review of Behavioral Sciences Research Center, Isfahan University of Medical Sciences. It was explained to all participants, and written informed consents were obtained. The subjects who met the criteria of opioid dependence based on the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were enrolled. Those with any medical diseases that prohibit the use of tramadol or methadone, as well as those taking medications that affect the blood levels of methadone or tramadol, or affect the withdrawal symptoms, and those with polysubstance dependency, any major psychiatric disorder including bipolar disorder, psychosis, and major depressive disorder were excluded from the study.

The participants were subjected to methadone equivalent making procedure to determine the dose of methadone, which could prevent withdrawal symptoms. Those who did not have withdrawal symptoms when taking 15 mg/day (n=72) were randomly assigned to a methadone group (group A, n=37) or tramadol group (group B, n=35). Patients in group A and B were given twice a day methadone (15 mg/day) and tramadol (450 mg/day), respectively. In addition, the patients in both groups were given clonidine (0.3 mg/day) and oxazepam (10 to 30 mg/day). The daily doses of methadone and tramadol were reduced by approximately 15% of the respective starting doses to reach a dose of 0 mg/kg on 7th day of the trial. The daily decrements for methadone and tramadol were 2.2 and 65 mg, respectively. Methadone and tramadol were administered in capsules with the same size, shape, and color. Patients in both groups were assessed by Short Opioid Withdrawal Scale (SOWS) every other day starting on the 1st day for a period of 15 days. Short Opioid Withdrawal Scale is a 16 items scale, the validity and reliability of which have been reported.[10-13] The severity of side effects of the treatments was evaluated simultaneously by direct questioning of the patients for somnolence, sweating, dizziness, nausea, vomiting, and constipation.

Statistical analyses

Statistical analysis was carried out by SPSS (version 11.5) software for windows (SPSS Inc., Chicago, Illinois, USA). Baseline comparisons between the two groups were made by using Chi-Square for marital status and unpaired *t* tests for age, duration of abuse, and SOWS**.** Repeated measure analysis of variance (ANOVA) was used to compare SOWS scores on consecutive days. The scores of SOWS and side effects between the two groups were compared by Mann-Whitney U test. Wilcoxon test was used to compare withdrawal scores in each group from baseline to the end of the study.

Results

Fifteen patients in group A and 13 in group B withdrew from the study after the 3rd rating of SOWS. In such cases, the last observed scores of SOWS were used for the following ratings.

The two groups were not significantly different in terms of marital status, age, duration of abuse, and baseline SOWS scores (table 1). There was no significant difference in withdrawal symptoms of each group recorded on alternate days throughout the trial (repeated measures ANOVA, P=0.143).

Table 1: Demographic data and baseline Short Opioid Withdrawal Scale (SOWS) scores of the participants.

Parameters	Group A	Group B
Number and frequency of married patients	32(86.5%)	31(88.6%)
Duration of abuse (years)	12.86±7.05	12.84±4.74
Age (years)	37.21±7.63	36.85±8.23
SOWS score	9.36±8.71	9.68±6.72

The total and mental SOWS scores are shown in tables 2 and 3, respectively. The total SOWS scores of group A at 7th and 8th rating (days 13 and 15 of the study respectively) were significantly higher than those from group B. The mental SOWS score of group A on day 15 was significantly higher than that of group B.

The total SOWS scores of group A on the day 15 were significantly higher than those on the day 1. However, there was no significant difference in the total SOWS on the first and last days from group B (table 2). On the 14th day, the patients in group A had significantly more drowsiness and sweating than those in group B.

Table 2: The total score (mean ±SD) of short opioid withdrawal scale (SOWS) from methadone (group A) and tramadol (group B) patients.

SOWS	group A	group B
SOWS-T_1	9.68(8.71)	9.36(6.72)
SOWS-T_2	8.54(6.56)	8.5 (5.15)
SOWS-T_3	10.04(6.12)	8.77(8.26)
SOWS-T_4	11.18(6.71)	8(5.82)
SOWS-T_5	15.18(8.49)	11.63(8.17)
SOWS-T_6	15.04(8.71)	12.45(5.53)
SOWS-T_7	16.18(9.47)	9.54(7.51)*
SOWS-T_8	15.18(10.62)	8.5 (6.90)*

* Significant difference from group A

Table 3: The mental score (mean ±SD) of short opioid withdrawal scale (SOWS) from methadone (group A) and tramadol (group B) patients.

SOWS	group A	group B
SOWS-M_1	4.97(4.46)	4.11(3.19)
SOWS-M_2	4.48(4.29)	4.71(3.80)
SOWS-M_3	4.78(3.92)	4.11(3.85)
SOWS-M_4	4.56(3.6)	3.8(3.66)
SOWS-M_5	5.35(3.69)	4.77(3.89)
SOWS-M_6	5.40(3.60)	4.97(4.02)
SOWS-M_7	5.86(3.80)	4.74 (4.44)
SOWS-M_8	5.81 (4.12)	4.25(4.22)*

* Significant difference from group A

Discussion

Comparison of consecutive SOWS scores of the two groups through the course of the study showed that patients in both groups had the same rate of changes in the severity of withdrawal symptoms. These findings were consistent with the results of studies, which indicated that tramadol was as effective drug for controlling pain as codeine, pethidine, buprenorphine and morphine.[6-9] Severity of withdrawal symptoms in the methadone group on days 13 and 15 of the study was more intense than of those in the tramadol group. This may be due to the partial agonist activity of the drug, which leads to milder symptoms during the tapering of tramadol. Similarly, it was shown that buprenorphine, a partial μ agonist, reduced the withdrawal symptoms.[14] Lower mental SOWS scores seen towards the end of the study in the tramadol group may be accounted for tramadol inhibition of serotonin and noradrenalin re-uptake, and possible therapeutic effects on depression.[10]

The study showed that in the methadone group, but not the tramadol group, the withdrawal symptoms were significantly more at the end of the study than at the beginning. This phenomenon may be a result of the longer half-life of methadone, which leads to longer withdrawal syndrome and delayed peak.

Having considered the relative low risk of toxicity, dependency, and respiratory suppression,[6-7] and easier availability and better effects on mental withdrawal symptoms, it seems that tramadol can be useful in the treatment of opioids dependency. The findings of the present study should be interpreted in view of the small sample size and the use of subjective method, namely interview, for the assessment of withdrawal symptoms.

Acknowledgement

Authors extend their gratitude to their colleagues at the Substance Treatment Clinic of Noor Hospital, Isfahan University of Medical Sciences.

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