ORIGINAL ARTICLE

Very low dose naltrexone in opioid detoxification: a double-blind, randomized clinical trial of efficacy and safety

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Abstract

Withdrawal syndrome is one of the initial focuses of opioid detoxification. Very low dose naltrexone (VLNTX) has been found to reduce opioid tolerance and dependence in animal and human clinical studies. The aim of this study was to determine the safety and efficacy of VLNTX during early stages of detoxification. In a multi-arm parallel, double-blind, randomized controlled trial, 63 opioid-dependent male participants referring to Imam Reza Rehabilitation Center were allocated to three equal groups using block randomization method. They received 0.125 mg, 0.250 mg of VLNTX or placebo daily for 10 days, together with the routine clonidine-based protocol. Self-reported and observer ratings of withdrawal severity and adverse events were measured on the 1st, 4th and 10th day of treatment. Runny eyes ($p=0.006$), anxiety ($p=0.031$) and dehydration ($p=0.014$) were reduced during the whole 10 days in the 0.125 mg VLNTX-treated group compared to placebo. Only drowsiness ($p=0.043$) and dysphoric mood ($p<0.001$) were reduced in the 0.250 mg VLNTX-treated group. Results of 1st, 4th, and 10th-day assessment showed that most symptoms reductions were for the 0.125 mg VLNTX and the placebo group in the 1st and 4th days, respectively. On the 10th day, there was not any significant difference between 0.250 mg VLNTX-treated group and placebo group. No adverse effect was observed. In the starting days of detoxification, VLNTX can reduce the withdrawal symptoms, but the efficacy declined by passing time. Further studies are needed to test the utility of this new therapeutic approach.

Keywords Naltrexone · Opioid · Metabolic detoxification · Substance withdrawal syndrome

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Introduction

Drug dependency is a major worldwide health problem. One of the most common forms of drug abuse in Iran is opioid usage [1, 2]. Different protocols have been used for opioid detoxification including using clonidine.

For many years, the alpha-2-adrenergic agonist medications have shown to be as effective as methadone taper in managing withdrawal. However, clonidine does not

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consistently control a few numbers of important symptoms, such as anxiety, restlessness, and craving, or does not show reliable efficacy in combination with methadone taper [3]. It has considerable adverse effects such as hypotension and sedation that make it unsuitable for an outpatient setting [4, 5].

Naltrexone, an opioid receptor antagonist, is commonly used after opioid detoxification phase as a safeguard. The therapeutic dose varies between 25 and 100 mg per day. If a non-tolerant individual relapse on opiates, naltrexone will antagonize or ‘block’ the mu receptor activity including central nervous system, respiratory depression as well as euphoria.

It has been shown that concurrent administration of very low doses of naltrexone (VLNTX) (although a wide range of doses from 0.1 to 10 mg has been considered as VLNTX in different studies) with opioid agonists was associated with reduced tolerance and dependence in rodents [5]. It also decreases withdrawal intensity in humans [6, 7]. In a systematic review evaluating opioid antagonists with minimal sedation for opioid withdrawal, the authors concluded that because of variability in abused drugs and doses it is impossible to describe a “standard regime” of antagonists [8]. Besides some studies have examined the effectiveness of VLNTX after completing detoxification phase, and concurrent administration of VLNTX in early detoxification phase has not been studied previously [9, 10].

The objective of this study was to evaluate whether adding VLNTX to clonidine-based treatment would be safe and effective in attenuating the severity of withdrawal symptoms during outpatient opioid detoxification.

Materials and methods

Trial design

This study was designed as a multi-arm parallel, double-blind, placebo-controlled randomized trial in a 10-day duration. Using a computerized random number generator for block randomization (block size: 3), participants were assigned to one of the three parallel groups, in 1:1:1 ratio to receive one of VLNTX regimens (0.125 and 0.250 mg/day) or placebo altogether with routine clonidine-based detoxification protocol (which is an accepted protocol in Mashhad, Iran). These doses were chosen based on other similar studies considering that we administered them concurrently in the detoxification phase. The VLNTX and placebo were in capsule form and identical in size, appearance, smell, and taste. They were prepacked in small plastic bags and consecutively numbered for each participant according to the randomization schedule. Participants and clinical examiner were blinded to the allocated treatments.

Participants and procedures

Sample size calculation was based on the findings of previously performed study (i.e. the percentage of urines negative for benzodiazepines and methadone) [11] $p_1 = 66.7\%$, $p_2 = 100\%$, $\alpha = 0.05$, and $\beta = 0.9$. By considering 25% dropout (due to the high prevalence of dropout in addict patients) final sample size was estimated to be 21 in each arm of the study. The eligible participants were male adults aged 18 or over who were non-methadone treated opium-dependent patients (self-report) seeking outpatient detoxification. Addiction is a major problem among men in Iran and so we restricted our sample to them. Exclusion criteria were documented past medical history of hypersensitivity to naltrexone, cancer, pain syndrome and diabetes. A routine physical examination was performed prior to starting of medications.

The study sample was obtained from opium-dependent referring to Imam Reza Rehabilitation Center (IRRC) who agreed to participate from June 2013 to December 2013. IRRC is a governmental center dedicated to performing detoxification in Mashhad, which is the second populous city in Iran.

Ethics approval of this superiority designed study was obtained from the Ethics Committee Mashhad University of Medical Sciences (88725). This study is registered in Iranian Registry of Clinical Trials (IRCT2013081914404N1). Written informed consent was obtained from participants prior to recruitment and there was no payment for participation.

Treatments

Very Low-Dose Naltrexone: Participants were randomly assigned to one of the three conditions: (1) naltrexone 0.125 mg/day and clonidine based routine treatment ($n = 21$); (2) naltrexone 0.250 mg/day and clonidine based routine treatment ($n = 21$); (3) placebo and clonidine based routine treatment ($n = 21$).

Clonidine: Clonidine flexible dose (0.1–0.2 mg every 6 h) was routinely used for detoxification based on clinical judgment of the clinical toxicologist.

Ancillary Medications: Ancillary medications were available as needed for all participants and included 400 mg Ibuprofen every 4–6 h, up to 40 mg oral Chlordiazepoxide, 20 mg Fluoxetine, 300 mg Gabapentin, Vitamins, and fluids if needed. Need for and use of ancillary medications was determined in a routine clinical fashion by the clinical toxicologist.

In-study assessments

The evaluation was conducted at baseline, and at 1st, 4th and 10th day of the study between 5 and 7 p.m. by a single individual. The study duration was selected based on long clinical expertise, available resources in the clinic and previously reported studies. Drug use was monitored by asking the patient during each visit about consuming it. By starting the study, the usage of all self-administered drugs were stopped. Adverse events, vital signs, and signs and symptoms of withdrawal syndrome including but not limited to tearing, goosebumps, feeling of hyperthermia, anxiety, chilling, craving, dehydration and higher muscle aches and vomiting were noted as reported by participants or observed during each visit. These signs and symptoms were measured based on a Likert scale.

Outcome measures

The primary anticipated outcome measure was a reduction in opioid withdrawal severity score during the 10-day outpatient detoxification process. This score was measured using a previously validated and standardized questionnaire [12]. This questionnaire was designed based on a Likert scale (0–4 points for pain; 0–3 points for nausea, vomiting, sweating, tremor, irritability; and all other signs/symptoms had 0–2 points) and was adjusted separately for subjective and objective items. A secondary measure was the adverse effects rate. Any unknown and acute outcomes were considered as adverse effects and it was assessed through the study period by the clinical toxicologist.

Statistical analysis

All analyses were done based on the intention-to-treat approach. A power calculation based on the severity score of the 10th day showed a power of 91%. Demographic and clinical characteristics were compared using analysis of variance (ANOVA) for continuous variables and χ^2 -test for categorical variables. Changes from baseline of withdrawal syndrome scores were analyzed using one-way repeated measures ANOVA. Data analysis was performed using SPSS version 11.5 with a significance level of $p < 0.05$.

Results

Participants

Eligible participants were recruited from June 2013 to December 2013 (Fig. 1). The mean age of the participants was 27 ± 6 , 28 ± 4 and 31 ± 6 years for 0.125 VLNTX, 0.250 VLNTX, and placebo groups, respectively ($p = 0.15$).

Also, age at starting opium usage was 23 ± 6 , 24 ± 5 and 31 ± 6 years for 0.125 VLNTX, 0.250 VLNTX, and placebo groups, respectively ($p = 0.56$). The last usage of drug abuse in 24% of 0.125 VLNTX group, 28% of 0.250 VLNTX group and 28% of the placebo group was the referral day ($p = 0.92$). Besides, there were no significant differences in clinical measures or in dose and frequency of ancillary medications among the three groups. None of the participants reported any other diseases nor specific medical prescriptions or psychoactive drugs.

Clinical findings

Vital signs Vital signs including systolic and diastolic blood pressure, respiratory rate and temperature were not different in the three groups during the study period. Only pulse rate was significantly higher in the placebo group in all three evaluations (Table 1).

Opioid Withdrawal Total mean severity score (SS-which was calculated based on self-reported and observer-rated scales) for the three groups are presented in Fig. 2. Although the severity score increased in the middle of the study period (day 4) and declined by the end (day 10), this trend was not statistically significant.

Withdrawal symptoms in the 1st day

To characterize the effects of different treatments, individual symptoms were compared between the placebo group and the VLNTX groups. Disregarding the dose, naltrexone intervention groups had lower tearing ($p = 0.03$), goosebumps ($p = 0.018$), feeling of hyperthermia ($p = 0.027$), anxiety ($p = 0.015$), chilling ($p = 0.002$), craving ($p = 0.001$), and dehydration ($p = 0.004$). However, muscle aches ($p = 0.003$), and vomiting ($p = 0.042$) were higher in VLNTX groups compared to the placebo group.

There was no significant difference in pain severity, nausea, congestion in the nose, yawn, sweating, tremor, dysphoria, vomiting, bone pain, stomach pain, diarrhea, insomnia, pain sensitivity, dehydration, dilated pupils, muscle spasm, and drowsiness between the three study groups.

Withdrawal symptoms in the 4th day

On the 4th day, naltrexone-treated participants had higher pain sensitivity ($p = 0.028$), sweating ($p = 0.027$), vomiting ($p = 0.042$), muscle aches ($p = 0.018$), craving ($p = 0.011$), and dysphoric mood ($p = 0.01$) compared to placebo group.

There was no significant difference in pain severity, nausea, congestion in the nose, yawn, tearing, tremor, dysphoria, calf pain, goose bump, stomach pain, diarrhea, feeling of hyperthermia, anxiety, insomnia, chilling, dehydration,

Fig. 1 Flow diagram of study design

dilated pupils, muscle spasm, and drowsiness between the three study groups.

Withdrawal symptoms in the 10th day

On the 10th day naltrexone-treated participants had higher nausea ($p=0.013$), diarrhea ($p=0.029$), chilling ($p=0.018$), and dysphoric mood ($p=0.002$) compared to placebo group.

There was no significant difference in pain severity, congestion in the nose, yawn, sweating, tearing, tremor, vomiting, muscle ache, bone pain, goosebump, stomach pain, the feeling of hyperthermia, anxiety, insomnia, pain sensitivity, craving, dehydration, dilated pupils, muscle spasm, and drowsiness between the three study groups. A more detailed comparison of these three checkpoints between either of VLNTX groups and placebo group is represented in Table 2.

Withdrawal symptoms in the overall 10 days

In the overall 10 days, it was revealed that participants treated with 0.250 mg naltrexone had significantly more symptoms compared to the other two groups including muscle spasm

($p<0.001$), sweating ($p=0.009$), craving ($p=0.016$), dehydration ($p=0.014$), and dilated pupils ($p=0.004$). Participants in 0.125 VLNTX-group had significantly lower symptoms including: tearing ($p=0.006$), anxiety ($p=0.031$), and pain sensitivity ($p=0.011$). However, vomiting ($p=0.002$), calf pain ($p=0.027$), drowsiness ($p=0.043$), and dysphoric mood ($p<0.001$) were higher in this group compared to the other two study groups.

There was no significant difference in pain severity, nausea, congestion in the nose, yawn, tremor, bone pain, goose bump, stomach pain, diarrhea, pyrexia, insomnia, and chilling between the three study groups.

Adverse events

No adverse events were observed in any of the interventional groups during the study period.

Table 1 Vital signs are listed in three groups during 3 days of assessment

	0.125 NTX	0.250 NTX	Placebo	Sig. ^b
SBP^a				
1st day	120 (12)	124 (11)	119 (12)	0.36
4th day	114 (11)	112 (7)	113 (9)	0.81
10th day	123 (11)	122 (11)	122 (9)	0.90
DBP				
1st day	74 (10)	76 (10)	74 (9)	0.77
4th day	78 (8)	73 (9)	78 (8)	0.17
10th day	74 (12)	78 (10)	74 (10)	0.41
PR				
1st day	65 (8)	69 (18)	76 (14)	0.01
4th day	68 (5)	76 (20)	80 (10)	0.01
10th day	72 (5)	73 (23)	83 (11)	0.04
RR				
1st day	10 (1)	10 (1)	10 (2)	0.92
4th day	10 (1)	10 (1)	9 (2)	0.60
10th day	9 (1)	10 (1)	9 (2)	0.29
T				
1st day	37 (0)	37 (0)	37 (0)	0.49
4th day	37 (0)	37 (0)	37 (0)	0.16
10th day	37 (0)	37 (0)	37 (0)	0.91

SBP systolic blood pressure (mmHg), DBP diastolic blood pressure (mmHg), PR pulse rate (beats/min), RR respiratory rate (breaths/min), T Temperature (°C)

^aMean (SD)

^bOne-way ANOVA

Fig. 2 Mean (SE) severity score in 3 days of observation in three interventional groups (n=21 in each group)

Discussion

Effects of adding two different very low doses of naltrexone to the routine clonidine-based opium detoxification protocol in the early phases of this process in comparison to placebo were assessed in this double-blind randomized

controlled trial. Out of 30 different evaluated signs and symptoms of withdrawal syndrome, 20 had significant differences between the three groups.

We found that tearing and anxiety were significantly lower with VLNTX. This was not the case for vomiting, calf pain, drowsiness and dysphoric mood. A previously reported study about post detoxification use of low doses of naltrexone showed no significant difference between 50, 0.5 and 0.05 mg of naltrexone on craving and depression [13].

Rea et al. [13] used VLNTX in post detoxification phase and did not find any significant difference between different doses of VLNTX. Considering the half-life of naltrexone, this discrepancy could be explained by different doses of VLNTX: 0.125 and 0.250 mg was used in this study while Rea et al. [13] had used 50 mg.

Results of this study revealed that approximately all significant differences were seen in the whole 10-day period. Most of the symptoms were significantly improved on the first day and, a few numbers of symptoms were improved on the 10th day. It can be concluded that after the beginning of the detoxification program, the differences between doses gradually vanish. So, controlling the withdrawal symptoms in the first days of the program seems to be of great importance. The previously reported studies had not compared symptoms in different days of detoxification course [6, 10, 14, 15].

During the study period, drowsiness and dysphoric mood were highly reduced by 0.250 mg of VLNTX. Muscle spasm, sweating, and nausea were reduced in the placebo and one of the VLNTX groups, which can put a question mark in front of the efficacy of VLNTX. However, similar to previous reports, we found a significant reduction in craving in 0.125 VLNTX group [6, 10, 15]. This could be interesting as there was a wide variation in these studies regarding methodological aspects. For example, in one of these trials, the starting dose was 0.125 mg and then it was increased daily up to the 6th day [14]. However, in our study, the dose was constant during the whole trial. In another two studies, the patients received naltrexone along with methadone [4, 13], while in our study, the treatment was based on clonidine protocol. Besides, a considerably wide range is considered for naltrexone administration in different studies [10, 16, 17]. For example, in one study, 1–10 mg of naltrexone was considered as low dose naltrexone. The authors of this study found a significant reduction of craving in the intervention group compared to control one [10]. Although several mechanisms have been hypothesized for craving, most of them are studying this symptom in animals [18–20]. On the other hand, the stimulation of NMDA receptors, brain thermoregulation, for yawning; $\alpha(2)$ -agonists, inhibition of calcium currents, hippocampal calcium channel mechanism/involvement of locus coeruleus, and biomechanical reflex mechanism for tremor; 5-HT₃ receptor antagonists, serotonin receptors in the CNS

Table 2 Comparison of statistically significant changes in signs and symptoms in 1st, 4th and 10th day of study in VLNTX treated groups

	0.125 mg NTX		0.250 mg NTX	
	Reduced	Increased	Reduced	Increased
Day 1 of study	Tearing Tremor Goose bumps Feeling of hyperthermia Anxiety Chilling Craving Dehydration	Vomiting Diarrhea	Goose Bumps Diarrhea Feeling of hyperthermia	Muscle Aches Tremor Dehydration
Day 4 of study	Muscle spasm	Vomiting Muscle aches Craving Dysphoric mood	Vomiting Craving	Pain Sensitivity Muscle spasm Sweating Muscle aches Dysphoric mood
Day 10 of study	None	Nausea Chilling Diarrhea Dysphoric mood	Nausea Chilling Dysphoric mood	Diarrhea

and gastrointestinal tract for vomiting; neuroplastic phenomenon, venous stasis or activation of pain fibers for lacrimation; time perception, central immune signaling, hypofunction of the noradrenergic, GABAergic and serotonergic systems for craving are among the suggested mechanism for various withdrawal syndrome in humans. For further information about withdrawal mechanism in animals and humans please refer to supplement Table 1 [21–32] (online appendix).

Most studies did not compare individual symptoms, so the comparison of our findings with other studies would be impossible. The most reduction in symptoms was in 0.125 VLNTX group at the first day, in which 8 symptoms (tearing, tremor of hand, goosebumps, fever, anxiety, craving, chilling, and dehydration) were reduced. On the 4th day, most symptoms were reduced in the placebo group. In the 10th day, 4 symptoms were significantly reduced in the placebo and one of the VLNTX groups. So, based on the results of this study, it is not clear that these doses of VLNTX in combination with clonidine provide sufficient evidence of efficacy.

The maximum severity score was seen on the 4th day and the least one in the last day of assessment in all three groups. Although, there was a mild increase in mean severity score in 0.125 VLNTX-group on the last day. Mannelli et al. [6] showed a reduction in mean severity score by adding VLNTX to methadone in the detoxification program. As in other studies, the participants of this study did not experience any adverse effects [10, 14, 33]. Although naltrexone was prescribed in the early phases of detoxification, having no adverse effects could be explained by the usage of very low doses of this drug.

Although the majority of patients (more than 90%) referring to the rehabilitation center are male but, the

preponderance of male patients (100%) is a limitation of our study. It may seem that there are not so many opium-addicted women in Iran, but cultural issues like stigmatization can prevent them from seeking help. This trial had been done during 10-days in one center. Although this center was the largest one in northeast of Iran, a multicentric trial with longer follow-up is recommended for greater generalizability. Many of our qualitative variables were assessed in Likert scale. It is recommended to measure these variables in visual analog scale to have a more precise evaluation. Finally, the drug's effect may be influenced by the body weight and we did not study that issue. But it is necessary to mention that this study was the first randomized controlled trial for evaluation of VLNTX for reducing the withdrawal symptoms in Iran. Also, most findings were consistent with previous studies, we recommend larger studies in the community to evaluate the effectiveness of this new protocol.

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Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

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