Original Article

Role of Benzodiazepines in the management of agitation due to inappropriate use of naltrexone

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Abstract

Background: Agitation is an early symptom of the acute opioid withdrawal syndrome in addicts that may start by inappropriate use of naltrexone. The current drug interventions are not efficient or need critical care as well. This study compares the clinical role of midazolam and diazepam for the management of agitation due to inappropriate use of naltrexone.

Materials and Methods: In this double-blind randomized controlled clinical trial, 44 agitated addicts, who did not use any type of benzodiazepine, not on systematic central nervous system depressant drugs, without any known hypersensitivity to diazepam, midazolam, or any other component of their formulation and had no evidence for the need of critical care, were enrolled. An i.v. stat dose of 0.1 mg/kg diazepam and 0.1 mg/kg stat dose of midazolam and a 0.1 mg/kg/h infusion of these drugs were administered for different groups of patients, respectively. Agitation scores were recorded at 30, 60, 120 min after the start of drug administration using Richmond Agitation Sedation Scale score.

Results: A significant difference between the mean onset of agitation control in midazolam group (at 67 min) and diazepam group (at 81 min) was recorded. The difference of mean agitation score in the midazolam and diazepam group was only significant at 120 min. There was a negative correlation between agitation score and time elapsed from naltrexone administration to admission.

Conclusion: Midazolam and diazepam may not be considered suitable and perfect pharmacologic agents for the initial controlling of agitation induced by naltrexone.

Key words: Benzodiazepines, naltrexone, psychomotor agitation, substance withdrawal syndrome

Introduction

Nurses routinely encounter by many stressful working conditions.[1,2] A well-defined stress factor for nursing caregiver is the agitation of patients with certain diseases,[3] especially in addicts. This clinical condition (agitation) is also an early symptom of the acute withdrawal syndrome, especially following inappropriate use of naltrexone in addicted people, which may jeopardize health status of the addicts and also their close relatives. Naltrexone is a well-known drug for the prevention of drug re-abuse in addicts, which competitively antagonizes opium euphoria due to its role in μ- and κ-receptor antagonism.[4,5] The drug has a 10-h half-life and should be used 7–10 days after opium quit[4,6] and 10–14 days after the last dose of methadone.[7] Severe withdrawal syndromes will appear if naltrexone is used accidentally or earlier than the above because of acute block of opioid receptor. Agitation, delirium, yawning, severe muscular pain, tachycardia, diarrhea, and vomiting are common in this case,[5,8,9] which may be much more dangerous in geriatric patients and also patients with underlying ischemic heart disease.

In our setting, there are many admissions of addicts referred to the department of clinical toxicology just due to inappropriate use of naltrexone having severe agitation. As it is mentioned before, this agitation is so dangerous that the patient may hurt himself/herself or the health care professionals, and it can be managed by sedation. Clonidine and propofol are believed to have a role in controlling these patients but using propofol needs ICU admission and intubation. It also increases the risk of respiratory infections.[10] In addition, clonidine has a limited efficacy, which is not appropriate for acute and critical status of these patients.[11,12]

Benzodiazepines are among the safest sedative drugs which their efficacy in similar situations are documented elsewhere.[4,5,13,14] Midazolam and diazepam are both available in parental dosage form, and both are used in acute-care settings in our department routinely. Midazolam is a short-acting benzodiazepine with about 2 h half-life,

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which metabolizes in the liver and is used regularly for relieving preoperation anxiety and also agitation in critically ill patients. The onset of action of midazolam is about 2 min and is physically compatible with dextrose 5% and saline on administration. Diazepam is a long-acting benzodiazepine with a 1–2 days half-life.

One of the common causes of agitation in our department is misusing naltrexone in addicted patients. The routine medication in our department is diazepam bolus dose and infusion. Although the different medications have been used for agitation induced by naltrexone in addicted patients, none of them had an acceptable efficacy on admission control of agitation. Therefore this study was conducted to have a comparative evaluation of these two drugs for controlling agitation due to inappropriate use of naltrexone in addict patients.

Materials and Methods

This double-blind randomized controlled clinical trial was carried out in 2005 in the Department of Clinical Toxicology at Noor General Teaching Hospital affiliated with Isfahan University of Medical Sciences (Iran).

Eligible patients were naltrexone used agitated adult addicts who were not given or used any type of benzodiazepines in any dosage form (oral, parenteral, or rectal), not on systematic central nervous system depressant drugs (eg, tricyclic antidepressants, phenothiazines, buterophenones), without any known hypersensitivity to diazepam, midazolam, or any other component of their formulation. Patients who required the endotracheal intubations were excluded. Patients who were discharged from the ward with their own written consent were also excluded from the study due to ethical issues.

Families of eligible patients or their legally eligible companions were informed by one of the investigators about the whole study, and it was optional for the patients to take part in the investigation. So, all the included patients had a written informed consent form, which was signed without any hesitation after the interview. The consent form was in concordance with Helsinki II declaration and also Tehran declaration for ethics in human researches. The study protocol was approved by Isfahan University of Medical Sciences board of human studies.

Using NCSS-PASS (Jerry Hintze, Utah, 2004) the minimum patient number for at least 10% of difference in efficacy scoring of therapy (α =0.05) and for a power of 80%, was calculated as 21 for each arm of the study (diazepam and midazolam). Assuming a dropout of about 20% of patients (eg, if they met the exclusion criteria) the total patient number needed for the study was at least 48. In this study, 51 patients were included, from which 42 completed full course of study. Patients were randomly allocated in 2 groups (A and B), using the random number table after primary supportive measures. Group A received an intravenous stat dose of 0.1 mg/kg diazepam and group B received 0.1 mg/kg stat dose of midazolam and 0.1 mg/kg/h of the drugs was infused in dextrose water 5% as the maintenance dose.

Patients were kept blinded using two types of coded vials, code 1 for midazolam vials and code 2 for diazepam vials. Agitation was evaluated and scored by an attending physician who was unaware of the type of treatment groups. The patient's agitation score was measured using Richmond Agitation Sedation Scale.[15] Each patient was evaluated individually and was scored on admission at 30, 60, and 120 min. Direct observation and judgment were needed to confirm and add up the results using the following definitions to describe the severity of agitation: Mildly agitated (score 1–3), patient was quite calm and there was no need for any physical restriction; moderate agitation (score 4–6), patient was more or less calm, muscular fasciculation was faded but he/she needed physical restriction; severe agitation (score 7–9), patient was slightly sleepy after benzodiazepine administration with muscular fasciculation, and physical restriction was needed. Finally, very severe agitation (score 10) was observed when the patient was completely cooperative and had frequent involuntary organ movement and was firmly restricted to the bed.

Mann–Whitney *U* test, Student's *t* test, and *t* paired test were performed for statistical analysis using SPSS 11 statistical software.

Results

From 42 eligible patients (38 male and 4 female), 26 had taken naltrexone as 50 mg oral tablet and 3 patients were not sure about the naltrexone dosage form strength, but drug utilization was documented. All the patients had been admitted in less than 4 h after taking naltrexone. An 82% of the patients had a history of less than 10 years addiction. A 72.8% of the patients had used opioid less than 10 h of admission and 27.3% of them 11–15 h before admission in hospital [Table 1].

Both groups had the agitation score of 10 on admission and 30 min after administrating benzodiazepines. Comparing the mean agitation scores in midazolam and diazepam groups did not show a significant difference at 0, 30, and 60 min after medication administration.

However, the difference was significant at 120 min (P = 0.04, Table 2).

The difference between the mean onset of action in the midazolam group (at 67 min) and diazepam group (at 81 min) was statistically significant (P = 0.04). None of the patients required endotracheal intubation. Correlation between the agitation score and naltrexone dose was not significant (P = 0.020).

There was a negative and significant correlation (R^2= - 0.09 P=0.02) between agitation score and time interval from opioid used to taking naltrexone [Figure 1]. Furthermore, there was a negative correlation between agitation score and time elapsed from naltrexone administration to admission.

Discussion

Since many years, addict patients are considered as special population of ill people who need particular nursing care.[16] Nurse practitioners in the emergency wards all round the world are more or less familiar with the agitated addicts with withdrawal syndrome[17] who need special nursing care. Drug therapy is still considered as part of the treatment in these patients. To the best of our knowledge, this is the first comparative study on efficacy of midazolam and diazepam for controlling the agitation precipitated following naltrexone misuse. The results [Tables 1 and 2] showed that diazepam cannot reduce agitation, and its mean onset of action is lower than midazolam, so midazolam acts more efficiently for controlling agitation, but on the base of our data and other studies,[4,9] none of the drugs are suitable choices for controlling agitation because agitation management is important during first minutes that it is severe and patients may hurt himself/herself, companions, or medical staff.

Although propofol is a suitable alternative to benzodiazepines in severe acute withdrawal syndrome but has side effects, such as hypoventilation, causing atelectasis and respiratory arrest.[10,18] Interestingly, the agitation was controlled by the injection of thiopental in both groups.

Our results indicate that, there is no relationship between naltrexone dose and the agitation score in the study patients. However, elongation of time elapsed between opioid usage and taking naltrexone, leads to a better response to treatment and lower agitation score, because of reduction

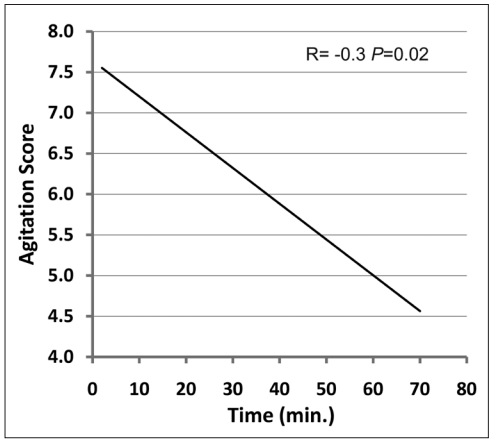

Figure 1: Correlation between agitation scores and time elapsed from the last dose of opioid utilization

Table 2: Comparison of the mean agitation score in midazolam and diazepam groups

Time	Midazolam	Diazepam	*P* value
	Agitation score Mean (±SD)	Agitation score Mean (±SD)	(*t* test)
T_0	10 (1.9)	10 (2.1)	NS
T_{30}	10 (2.2)	10 (1.5)	NS
T_{60}	9 (1.7)	8.5 (1.3)	NS
T_{120}	7.5 (1.7)	6.3 (2.1)	0.04

NS, Not significant

Table 1: Intoxication and toxicologic characteristics of the study patients

		Diazepam		Midazolam	
		Male (19)	Female (2)	Male (19)	Female (2)
Naltrexone dose	50 mg	8	2	14	2
	25 mg	6	0	5	0
	Unknown	2	0	1	0
Time elapsed from naltrexone administration and hospital admission	1 h	4	0	5	0
	2 h	9	2	6	1
	3 h	6	0	6	1
	4 h	1	0	3	0
Addiction period	1–5 years	8	2	5	1
	6–10 years	3	0	12	1
	11–15 years	3	0	2	0
	>15 years	1	0	1	0
Time of the last usage of narcotic drug	1–5 h before	9	1	8	1
	6–10 h before	5	1	6	1
	11–15 h before	6	0	6	0
	>15 h before	0	0	0	0

of naltrexone half-life. Based on our data [Tables 1 and 2] it is clear that severity of agitation depends on the amount of undetoxified opioid and it is in concordance with the results from other studies.[5,19]

Only one patient responded to treatment very quickly, but it was confirmed that he had received a single dose of morphine in another clinic prior to the admission. It seems that that co-administration of benzodiazepines and a dose of morphine were effective in the management of agitation due to naltrexone inappropriate usage in that patient. Further clinical studies are needed to clear this theoretically logic issue.

A limitation of our study was the different number of males and females in the study sample. Sex differences may influence the substance use disorders, response to opioid withdrawal, and rate of the response to the treatment or required dose of the drugs.[14,20,21] Also the type of the opioid that addicts had used was not mentioned in this study. Opioids such as heroin and morphine have generally a short half-life, whereas methadone has a long one, and this issue can affect onset and severity of symptoms of withdrawal and also rate of the response to agitation treatment.[12,22]

Further studies are needed to test the efficacy of combination therapy of benzodiazepines with opioid agonists, and also other sedative drugs, such as ultra–short-acting barbiturates (eg, thiopental) for controlling and management of agitation in these patients. Regarding the increased reports of acute opioid withdrawal, which are precipitated by naltrexone, adequate patient counseling and family awareness seem to be necessary.

In conclusion, the present study showed that despite the induction of sedation by midazolam and diazepam in their usage for the agitation due to inappropriate use of naltrexone, these agents are not drugs of choice in this issue.

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Conflict of interests

Authors had no conflict of interest – including personal or financial relationships with organizations that might inappropriately influence, or be perceived to influence the work.

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