Original Article

Comparison the Effects of Gabapentin and Oxazepam on Sleep Quality, Anxiety, and Pain in Unstable Angina Patients Admitted to Coronary Care Unit of Hazrat Rasool Akram Hospital

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Abstract

Background: This study aimed to compare the efficacy of gabapentin and oxazepam on sleep quality, the severity of anxiety, and pain level in patients admitted to the coronary care unit (CCU). **Materials and Methods:** This double-blind randomized clinical trial was done on the patients with unstable angina (UA) admitted to the CCU of Hazrat Rasool Akram Hospital in Tehran. A total of 56 patients were entered the study and randomly divided into two groups of 26. The first group was given a gabapentin capsule at a dose of 300–1200 mg/day, and the second group was given 10–20 mg of oxazepam tablets per day until hospitalization in the CCU. On the first and 4th days of hospitalization, Groningen sleep quality score (GSQS), Beck Anxiety Inventory, and severity of pain experienced by Visual Analogue Scale were recorded, and the mean frequency of chest pains was calculated in 24 h during the first 4 days. The amount of drug (morphine) prescription in CCU also compared between the two groups. **Results:** There was no significant difference in GSQS scores between both groups. The mean score of Beck's anxiety scale did not differ significantly between the two groups. However, the incidence of chest pain was significantly lower in the gabapentin-receiving group than in the oxazepam-receiving group (<0.001). The days that the patients experienced chest pain were significantly less in the gabapentin-receiving group than in the oxazepam-receiving group (<0.001). **Conclusion:** The results of our study showed that gabapentin compared to oxazepam could significantly reduce chest pain in patients with UA.

Keywords: *Anxiety, coronary care unit, gabapentin, oxazepam, sleep quality, unstable angina*

Introduction

Cardiovascular disease is one of the leading causes of death in developed countries[1] and many people referred to the emergency wards every year because of these problems. Chest pain is the second leading complaint in North America.[2] Of 5.3 million patients who come to the emergency wards each year with a complaint of chest pain, about a third are hospitalized with a diagnosis of unstable angina (UA) or nonST-elevation myocardial infarction as the most common cause of heart disease.[3] Myocardial infarction is the most common cardiovascular disease and is the second-most common disease in developed and developing countries,[9] so that in Iran, the first cause of 138,007 deaths (45.3%) is cardiovascular disease, and the half of these mortalities are due to the myocardial infarction.[10] UA, called a coronary event, accounts for 3%–10% of emergency ward visits.[3] Cardiovascular disease is responsible for 38 of all global deaths, meaning one in every 2.6 deaths.[4] Of this mortality rate, UA morbidity is 25%–30%.[5] American Heart Association statistics in 2008 showed that in 2004, 15,800,000 people in the United States suffered from cardiovascular disease, and 452,300 died of it.[6] According to 2005 statistics, 2500 Americans have been admitted to the CCU due to cardiovascular disease in this year.[7] In Iran, the number of cardiovascular diseases is high, and according to the Ministry of Health and Medical Education, 46% of deaths in Iran are due to circulatory diseases.[4]

By 2020, for the first time in human history, these diseases are expected to become the first cause of death and disability in the world and killing 25 million people worldwide each year.[8,9] In addition to high mortality, cardiovascular disease imposes huge costs on the health care systems

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of countries. In the United States, the direct and indirect costs of cardiovascular disease in 2008 estimated about $ 4753 billion, and in Iran, it was annually 15 billion Rials,[10] and it approximately $ 50 million is spent on treatment and purchase of medical equipment. In addition to these problems, acute cardiovascular disease has psychological effects due to hospitalization in the cardiology and CCU sections, such as pain, anxiety, and sleep disorders.

Sleep disorders are more common in patients admitted to the CCU, and these patients experience sleep disturbances as changes in the REM stage, during sleep and disturbances in biological systems at night.[8]

Decreased rest and sleep can exacerbate cardiovascular attacks and can lead to more sympathetic system activity, resulting in increased blood pressure and heart rate. Low sleep quality increases pain and there is a direct link between reduced sleep and pain intensity. In patients in CCU, it is difficult to sleep, especially due to medical interventions, monitoring, and ambient sound, while these patients require more sleep.[9]

The influence of such factors as individual and social characteristics of each person in the prevalence of physical problems in heart disease have been well studied, but very few studies have been conducted on the psychological problems of these patients.[10,11]

Among these, anxiety is one of the most common and important psychological reactions of patients with heart problems, which has a very negative effect on the course of the disease and the stage of physical and mental recovery of patients, and sometimes even lasting after the acute course of the disease.[11-14] According to a group of North American researchers, anxiety levels in patients with heart disease are 26 times higher than in psychiatric patients, which can be due to fear of death, acute ischemia, arrhythmia, and stroke. A high level of anxiety is observed in the first 48 h. After hospitalization, anxiety increased the complications of the disease by 4.9% compared to patients with lower anxiety.[15,16] Anxiety also increases blood pressure, the onset of deadly dysrhythmias, impairs the blood coagulation system, weaken the immune system, and delays wound healing, which is very dangerous for patients with acute myocardial infarction and exacerbates ischemia and cardiac necrosis. Given the above-mentioned facts, anxiety reduction is important in cardiac patients.[15-17] In patients admitted to CCU due to UA pectoris, the prevalence of anxiety is 2.8.[18] Delirium syndrome also has a significant prevalence in cardiac CCU, and the elderly are at higher risk for developing the syndrome. Various countries have reported a 10%–40% increase in the incidence of delirium in the CCUs. Patients who experienced delirium during hospitalization were 62 times more likely to die than patients without delirium.[19] The duration of hospitalization of these patients also increases on average from 5 to 10 days.[20] Pharmacological treatments are widely used in known cases of delirium, but its effect on the outcome of the treatment has not been clearly established.[19]

Oxazepam, a benzodiazepine drug, is commonly used to treat the symptoms of patients who have experienced chest pain. Benzodiazepines can reduce anxiety, pain, and high cardiovascular activity. Benzodiazepines exacerbate the effects of GABA on the central nervous system and also environmentally reduce catecholamines. These drugs may also dilate the heart, prevent dysrhythmia, and prevent platelet aggregation, although further studies are needed.[21]

Benzodiazepines, on the other hand, have a number of side effects, including central nervous system depression, psychomotor retardation, memory loss, emotional problems, lack of restraint, dependence symptoms, withdrawal symptoms (autonomic instability, insomnia, sensory irritability, and in severe cases seizures and delirium tremens). Elders (who make the majority of patients with acute heart diseases) may be more likely to have drug interactions, psychomotor retardation, cognitive impairment, and behavioral dysfunction. Benzodiazepine use in the elderly has been linked to an increased risk of fall and pelvic or bone fractures and increased motor accidents.[22]

The tendency to use benzodiazepine substitutes is increasing. Recently, gabapentin, a gabaergic drug, has been used to treat the psychological complications of physical problems and some cardiac conditions, which was first introduced as an anticonvulsant drug. It has therapeutic effects in neuropathic pain in diabetic patients,[23] reduction of pain after mastectomy,[24] thoracic surgery[25] and coronary artery bypass graft surgery[26] and increase sleep quality by increasing slow-wave sleep[27] and also has anti-anxiety effects.

The effect of gabapentin on patients admitted to the CCU, who commonly have sleep problems, anxiety, and pain, as well as those exposed to delirium, has not been studied. In addition, due to the common side effects of benzodiazepines used for this purpose and with considering the numerous problems that affect patients with cardiovascular disease and the lack of a comprehensive study on the effects of a single drug in the treatment of these problems, in the present study the effects of gabapentin compared with oxazepam in terms of the effect on sleep quality, the severity of anxiety, and severity of pain and the incidence of delirium.

Materials and Methods

This double-blind randomized clinical trial was done on population included the patients with UA admitted to the CCU of Hazrat Rasool Akram Hospital in Tehran and it was approved by the ethics committee of Iran University of Medical Sciences with the code of IR. IUMS.FMD. REC.1398.239. The participants were explained about the research and if they filled the consent form and they were

included in the study. Sample size with 95% confidence level, the error of 5%, and power of 80% was calculated as 56.

After obtaining informed consent, samples were sent to random form (pairing and individualizing the relevant codes) and were divided into two intervention and control groups. All patients learned how to use gabapentin capsules correctly and got informed about the importance and possible side effects (drowsiness, dizziness). A total of 56 patients entered the study and were randomly divided into two groups of 28 people [Figure 1]. The first group was given a gabapentin capsule at a dose of 300–1,200 mg/day, and the second group was given 10–20 mg of oxazepam tablets per day until hospitalization in the CCU.

The inclusion criteria included hospitalization in CCU with definitive diagnosis of UA, age of 18–60 years, minimum literacy of reading and writing, being alert, interviewable, and fluent in Persian.

Exclusion criteria include Class III-IV heart failure, cardiogenic shock, or the need or performing invasive cardiovascular procedures other than diagnostic angiography without coronary artery disease (Axis I acute psychiatric disorder, major depression, bipolar disorder, psychotic disorders, etc.) and other personality disorders in Axis II in the case group during the study, drug and alcohol dependence in the study duration, use of psychotropic drugs, history of sleep disorders, history of head trauma leading to decreased level of consciousness or anesthesia, epilepsy and major neurological diseases, mental retardation, incomplete filling of the ethical questionnaire and inappropriate answering to more than 15% of questions, patient withdrawal of interview or completing the questionnaire or participating the study for any reason, no willingness for continuing to cooperate at each stage of the study, the patient's death and discharge from the CCU before 4 days of clinical trial the individuals were excluded from the study.

The drugs were ostensibly similar, and to the end of the study alone the pharmacist was aware of the type of medication for each patient, so the study was double-blind and researcher and patient were not aware of the type of medicine used.

Our sampling method was nonprobability convenience sampling. Biological information of each person including demographic information (age, gender, body mass index), risk factors (family history, hyperlipidemia, hypertension, diabetes mellitus, smoking), basic laboratory data (blood lipid index, serum creatinine, fasting blood sugar), cardiac parameters (sinusoidal or arrhythmic rhythm) and performing or not performing diagnostic coronary angiography to record the matching of the two groups of case and control were recorded. Both groups of patients were treated with the standard UA treatment, which may include aspirin, clopidogrel, beta-blockers, angiotensin receptor blockers (ARBs), or angiotensin converting enzyme inhibitors (ACEI) heparin, warfarin.

On the first and 4th day of hospitalization, Groningen's sleep quality score (GSQS), Beck Anxiety Inventory, and Visual

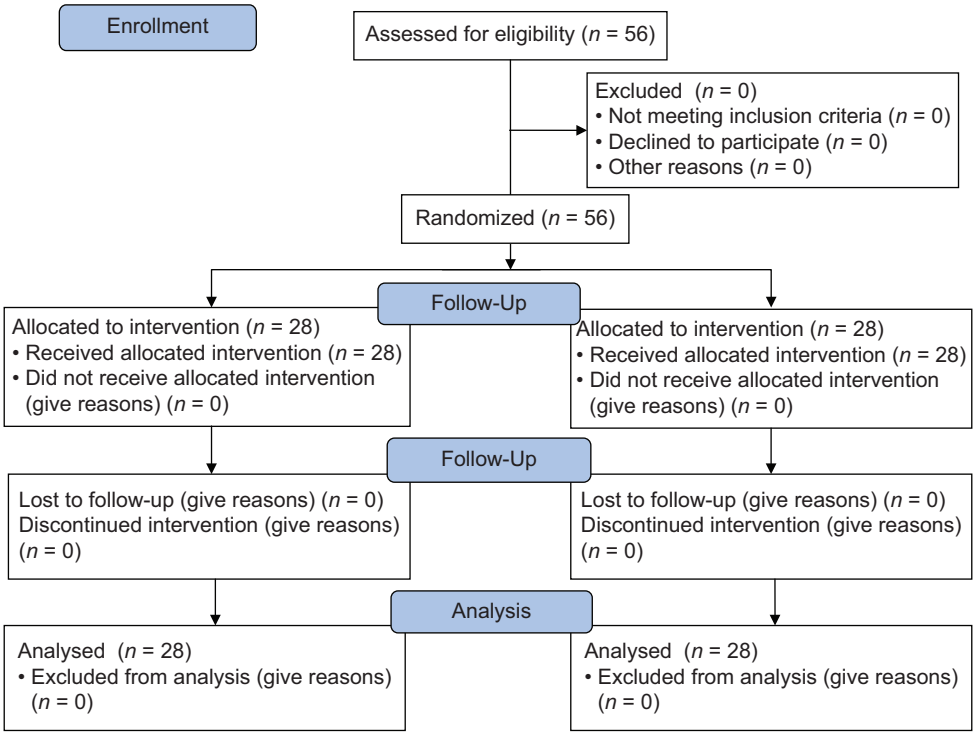

Figure 1: Consort flowchart

Analogue Scale were completed. The average frequency of chest pains was calculated in 24 h during the first 4 days of hospitalization. Moreover, the amount of drug (morphine) prescribed to the patient was compared during the 4 days of hospitalization at the CCU in the two groups.

After collecting the data, all the data were analyzed in the SPSS software version 21 (SPSS Inc., Chicago) using descriptive statistics and Inferential (paired *t*-test and independent *t*-test).

Results

At the beginning of the study, 58 volunteers entered the study. Of these, 6 were excluded from the study due to their history of psychiatric disorders and use of sleeping pills, as well as lack of proper completion of the questionnaire. Finally, this study was performed on 52 volunteers qualified for inclusion criteria with a mean age of 58.1 ± 7.7. These individuals were randomly divided into two groups of 26. Gabapentin was given in the first group and oxazepam in the second group. None of the eligible subjects in the study had a psychiatric disorder of axis I or II, a history of drug or alcohol use, psychiatric and hypnotic medication use, sensitivity to gabapentin or oxazepam, a history of seizure, head trauma, and mental retardation. Of the 52 patients, 30 were male (57.7%) and 22 (42.3%). Table 1 compares the demographic information between the two groups studied.

As can be seen in Table 1, there was no significant difference between the two groups in terms of baseline data, so it can be concluded that the two groups are homogeneous in terms of baseline data. On the other hand, the mean morphine consumption in the intensive care unit was 6.25 ± 1.25 mg in the exazepam group and 0 in the gabapentin group, which was a significant difference between the two groups ($P < 0.001$).

As observed in Table 2, the two groups receiving gabapentin and oxazepam did not differ significantly in terms of GSQS scores. On the other hand, the mean score of Beck's anxiety scale did not differ significantly between the two groups. However, the incidence of chest pain was significantly lower in the gabapentin-receiving group than in the oxazepam-receiving group (<0.001). On the other hand, the days when a person experienced chest pain were less in the gabapentin-receiving group than the oxazepam-receiving group, which was also had a significant difference (<0.001).

In our study, drug complications were also investigated using a checklist in two groups. Our results showed that no complications were observed in either oxazepam or gabapentin.

Table 1: Demographic characteristics in Gabapentin and Exazepam groups

Variables	Gabapentin (*n*=26)	Oxazepam (*n*=26)	*P*
Age (years), mean±SD	58.9±7.7	57.3±7.7	0.857 (*t*=0.739, *F*=0.03)
Sex, *n* (%)			
Male	15 (57.7)	15 (57.7)	0.402 (df=1)
Female	11 (42.3)	11 (42.3)	
Smoking, *n* (%)	10 (38.5)	9 (34.6)	0.770 (df=1)
BMI (kg/m^2), mean±SD	30.5±4.8	30.9±5.8	0.335 (*t*=0.270, *F*=0.946)

SD: Standard deviation, BMI: Body mass index

Table 2: Scores of questionnaires related to sleep, anxiety, and pain in the group of gabapentin and oxazepam

Variable	Group	Mean±SD	*t*	*F*	*P*
GSQS	Gabapentin	8.15±2.7	0.922	0.419	0.326
	Oxazepam	7.34±3.1			
Days of maximum pain	Gabapentin	4.03±1.2	−5.658	2.540	<0.001
	Oxazepam	6.23±1.6			
Chest pain episodes	Gabapentin	1.31±0.6	0.626	−7.939	<0.001
	Oxazepam	3.00±0.9			
Beck anxiety score	Gabapentin	24.9±12.2	0.472	1.598	0.639
	Oxazepam	23.5±9.3			

SD: Standard deviation, GSQS: Groningen sleep quality score

Discussion

The aim of the present study was to evaluate and compare the effectiveness of gabapentin and lorazepam on pain, anxiety, and sleep quality of patients with UA hospitalized in the intensive care unit (CCU).

The results of our study, which were performed mainly on the elderly with the mean age of 58.1 ± 7.7 years without a history of psychiatric disorder, showed that gabapentin consumption did not make a significant difference in improving the quality of sleep or reducing patients' anxiety compared to oxazepam. Oxazepam and gabapentin were not significantly different in terms of reducing anxiety symptoms and improving sleep quality. The results of our study showed that the two groups receiving gabapentin and oxazepam did not differ significantly in terms of GSQS scores. On the other hand, the mean Beck's anxiety scores did not differ significantly between the two groups.

However, the incidence of chest pain was significantly lower in the gabapentin-receiving group than in the oxazepam-receiving group. On the other hand, in the group receiving gabapentin, the patients experienced chest pain in the fewer days than the group receiving oxazepam, which was also significant. The results also showed that in CCU, the mean consumption of morphine was 1.25 ± 6.25 mg in the exazepam group and in the gabapentin group, it was 0, which the difference between the two groups was significant suggesting the gabapentin is more effective in reducing pain than oxazepam.

This difference in pain relief can be investigated in the mechanism of action of the two drugs. Gabapentin is structurally similar to gamma butyric acid. However, in the body, it is not converted to gamma-aminobutyric acid or its agonists. It does not inhibit or eliminate gammabutyric acid reabsorption. Furthermore, the mechanism by which gabapentin exerts its analgesic or anticonvulsant effect on humans has not yet been determined. It was originally developed to treat epilepsy but is now available for a variety of uses, including pain relief, especially for neurological pain (such as headaches and low back pain). In one study, a review of the analgesic effect of gabapentin on fibromyalgia was reviewed. This study provided good evidence for recommendation of taking gabapentin daily at doses of 1200–2400 mg to reduce pain in people with fibromyalgia.[27]

A study conducted by Talebi *et al*. for investigation the effect of preoperative gabapentin use in reducing pain and nausea after laparoscopic cholecystectomy. In that double-blinded, randomized, two-way clinical trial, 70 patients aged 6–20 years were selected with the American Society of Anesthesiologists Class I, II and divided into two groups. An hour before the operation, 300 mg oral gabapentin capsules were given to a group, placebo was given to the second group. Patients underwent similar general anesthesia. Nausea and intensity of pain were measured on a ten-point Visual Analog Scale, and vomiting was measured every 2 h to 6 h after surgery and then every 4 h for the next 12 h based on its frequency. The findings showed that the mean pain intensity in the two groups of placebo and gabapentin was statistically significant. There was also a significant difference in the need for additional drugs in the gabapentin group. The mean severity of nausea in the gabapentin group was clearly lower as well as the frequency of vomiting that was clearly lower.[28] The results of our study also showed that the mean of drug usage in the CCU was significantly lower in the gabapentin group.

On the other hand, the results of the above study showed that gabapentin had no complications, which is consistent with the results of our study.

A study by Han C *et al*. aimed at examining the use of gabapentin in pain management after knee arthroplasty surgery was done on 859 people. Visual analog scores 40 h after surgery, the degree of knee flexion, and the drug complications were evaluated. Significant reductions in morphine intake were observed at 4, 24, and 40 h in the gabapentin group. Furthermore, the rate of pruritus was lower in these patients compared with the control group. Evidence in this study showed that gabapentin is usually effective in reducing drug use and postoperative pruritus.[29] The results of this study are consistent with the results of our study.

Another study by Ucak A *et al*.was conducted aimed at investigating the effect of gabapentin on severe pain after coronary artery bypass grafting in 40 patients that were randomly divided into two groups. The first group received 1.2 g daily gabapentin, 2 days before and 2 days after surgery, and the second group was taking placebo. The study investigated the pain level at rest and when coughing, the amount of morbidities, and the amount of tramadol used. The amount of pain in groups 1, 2, and 3 was significantly lower than in group 2, but the pain level after 1–3 months was slightly lower and relatively similar in each case.[22]

A study was conducted by North *et al*. on the effect of gabapentin on the pain and sleep of fibromyalgia patients. The study included people who were diagnosed of the disease and had given up gabapentin due to the complications. These individuals were given a widely distributed gabapentin pack for 5 weeks. Of the 34 people included in the study, four were able to make full use of the package. The patients claimed pain relief in the 4th week, and a remarkable improvement was observed in sleep quality. Finally, they found that gabapentin reduced pain symptoms, increased quality of life, and improved sleep quality and quantity.[30] The results of our study showed that gabapentin was not significantly different from oxazepam in improving sleep quality.

Another study by Megna Jl *et al*. was conducted to investigate the effect of gabapentin on the restlessness of 11 hospitalized patients due to mental disorders. At 6 months before and after taking gabapentin, they were taking Brief Psychiatric Rating Scale (BPRS), Corrigan Agitated Behavior Scale (CABS), and Clinical Global Impression (CGI)-Severity. By analyzing the statistical data, it was observed that the BPRS test scores finally reached to 3.5 from 9.5, they concluded that with the use of gabapentin, CGI increased from 4.34 to 25 and CABS test from 40 to 2.33. Finally, it was found that there was a significant reduction in symptoms of anxiety and restlessness in the patients.[31]

The results of our study showed that there was no significant difference between oxazepam and gabapentin in post-CCU anxiety reduction. This can be due to the anti-anxiety properties of benzodiazepines, which can also reduce anxiety.

The main limitation of our study was the lack of use of placebo and also the choice of only one center to examine patients and small sample size and follow-up period, and future studies are recommended to be implemented with higher sample size and use of placebo.

Conclusion

The results of our study showed that gabapentin compared to oxazepam could significantly reduce chest pain in the patients of UA.

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Conflicts of interest

There are no conflicts of interest.

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