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Original Article

Post-Coronary Artery Bypass Graft Surgery Insomnia: Quetiapine vs Alprazolam

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ABSTRACT

Background: Given that insomnia is common and not always easily handled after coronary artery bypass graft surgery (CABG), this study was conducted to compare the efficacy of quetiapine and alprazolam in post-CABG insomnia.

Methods: In this clinical trial, 90 patients undergoing CABG were selected and randomly divided into 2 groups of 45 patients. The first group received 12.5 mg of oral quetiapine and the second group received 0.5 mg of alprazolam before bedtime (at 10 PM). The patients' insomnia was evaluated and compared using the Insomnia Severity Index (ISI) questionnaire on 3 occasions: 1 month before surgery and then 3 days and 14 days after surgery.

Results: The mean score of insomnia 1 month before surgery and 3 days after surgery had no statistically significant difference in both groups (P =0.89 and P =0.55, respectively). The mean score of insomnia on the 14th postoperative day, which was at the end of the 10-day treatment period, was 15.33 ± 3.87 in the alprazolam group and 13.33 ± 4.71 in the quetiapine group (P >0.05 and P =0.043, respectively). In the quetiapine group, 2 patients experienced drowsiness on the following day and 1 patient developed pruritus; none of them experienced restless leg syndrome or dystonia. Nine patients in the quetiapine group and 3 patients in the alprazolam group had drug noncompliance.

Conclusions: Despite more drug noncompliance, very low-dose quetiapine was more effective than alprazolam in improving the sleep quality of our early postoperative CABG patients.
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KEYWORDS: Alprazolam, Quetiapine fumarate, Sleep initiation and maintenance disorders, Coronary artery bypass, Antipsychotic agents

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Coronary artery bypass graft surgery (CABG) is the most common cardiac surgery; it prevents myocardial ischemia and saves lives. One of the most common problems after CABG is sleep disorders, which can reduce patients' quality of life significantly. [1] Different therapeutic modalities such as medical therapy, acupuncture, and massage therapy are used to alleviate postoperative insomnia. [2, 3]

Alprazolam is a short-acting drug of triazolobenzodiazepines; it is most commonly used to treat stress. It is also used at a dose of 0.25 to 0.5 mg for the treatment of insomnia after CABG. [4]

Quetiapine is a second-generation antipsychotic that demonstrates its efficacy by antagonizing the D2 receptors in the mesolimbic and mesocortical dopamine tracts in the brain. [5] The sedative properties of quetiapine are possibly due to the antagonistic effect on type I histamine receptors and type IIA serotonin receptors. [6]

Antipsychotic medications are usually not prescribed for insomnia owing to their side effects and a lack of clinical studies on these therapeutic aspects. [7] In recent studies, low-dose quetiapine (12.5–50 mg) has been used for the treatment of insomnia in patients with Parkinson's disease and no motor symptoms. [8] Quetiapine has also been associated with increased subjective and objective sleep quality in bipolar patients. [9]

Despite reasonable effects on sleep disturbances, the United States Food and Drug Administration (FDA) has not approved quetiapine because of its side effects. [8] Clinical studies have indicated that the antipsychotic effect of quetiapine usually occurs in the range of 200 to 800 mg/d. [10]

Some studies have reported metabolic derangements with low-dose quetiapine, defined as less than 200 mg for a period shorter than 3 months. [11] Still, no study has to date reported metabolic derangements with very low doses (12.5 mg) of quetiapine for short-time use. [5] On the other hand, benzodiazepine and non-benzodiazepine hypnotics are also associated with known adverse effects such as withdrawal effects, the rapid development of tolerance, and the potential for dependence and abuse. [12]

In this study, we tried to evaluate the effects of the short-term use of very low-dose quetiapine on post-CABG sleep disturbances and compare its effects with those of alprazolam, a well-known sedative and hypnotic.

METHODS

This study is a randomized double-blind clinical trial performed on patients undergoing CABG (clinical trial registration code: IRCT20160716028945N4). The inclusion criteria of the study were CABG patients, no drug sensitivity, no history of mental illness, a lack of dementia, no insomnia complaints, the absence of acute closed-angle glaucoma, and consent to participate in the study. The exclusion criteria were unstable medical problems, allergies or drug side effects, and poor compliance with the medications during a 2-week period after surgery.

The data were collected using the Insomnia Severity Index (ISI) questionnaire, which contains 7 items: difficulty in falling asleep, difficulty in staying asleep, waking up too early, interfering with daily function, sleeping problems noticeable to others by impairing the quality of life, and being worried about sleep problems. Each of the items has 4 points (0 =never and 4 =high). The maximum score is 28, with a score of 0 to 7 indicating no clinically significant insomnia, 8 to 14 subthreshold insomnia, 15 to 21 moderate insomnia, and 22 to 28 severe insomnia. [13] The Persian version of the questionnaire has been approved in terms of validity and reliability. [14]

This study was double-blind. Packages A and B were prepared; they contained

quetiapine (Tranqopine, Tadbir Kalaye Jam Pharmaceutical Company, Iran) at a dose of 12.5 mg and alprazolam (Alprazolam Pursina, Pursina Pharmaceutical Company, Iran) at a dose of 0.5 mg. They were delivered to the principal prescribers while they were unaware of the contents of the packages. The interviewer filling the questionnaire was unaware of the drug prescribed.

After permission was obtained from the Medical Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1396.3.191), 90 patients were enrolled in the study and randomly divided into 2 groups of 45 patients. The sample size was calculated by the following formula:

$$(n = \frac{(z_1 + z_2)^2 (2S^2)}{d^2})$$

Written consent was obtained from all the included patients. All the patients were given a sleep quality questionnaire 1 month before surgery and they were asked to fill it on day 3 and day 14 postoperatively. The drugs were prescribed for 10 days from day 3 to day 13 before bedtime (at 10 PM). The data were entered into SPSS, version 25, and analyzed using the independent *t* test, the paired *t* test, and the analysis of covariance.

RESULTS

In this study, 90 patients undergoing CABG surgery were divided into 2 groups of 45 patients receiving alprazolam and quetiapine. Three patients from the alprazolam group and 9 patients from the quetiapine group (2 because of daytime somnolence and 1 because of pruritus) were excluded due to drug noncompliance and not being cooperative. Forty-two patients in the alprazolam group and 36 patients in the quetiapine group completed the study (Fig. 1). Both groups had no significant difference in age, sex, diabetes mellitus, hyperlipidemia, smoking, and the preoperative ejection fraction. Only hypertension was more prevalent in the preoperative evaluation of the quetiapine group (P =0.03).

The mean ISI score 1 month before surgery in the alprazolam and quetiapine groups was 9.95 ± 2.08 and 9.89 ± 1.98, respectively (P =0.89). The mean ISI score 3 days after surgery was 16.31 ± 3.63 and 16.83 ± 4.01 in the 2 groups, respectively (P = 0.55). The mean ISI score on the 14th postoperative day, which coincided with the end of the 10-day treatment period, was 15.33 ± 3.87 in the alprazolam group and 13.33 ± 4.71 in the quetiapine group (P <0.05 and P =0.043, correspondingly) (Fig. 2 & Table 1).

The mean difference of the insomnia score between day 3 and day 14 was compared between the 2 groups, and the results showed the effectiveness of the treatment. This score was −0.79 ± 1.22 (−5.71 ± 9.04%) in the alprazolam group and −3.25 ± 3.18 (−19.3 ± 18.17) in the quetiapine group. The analysis with repeated measures ANOVA on the above data showed that the mean ISI score changes were significantly more in the quetiapine group (P =0.021), indicating that the quetiapine group had a more effective treatment of insomnia than the alprazolam group. Patients who had diabetes, hyperlipidemia, smoking, and low ejection fractions had a worse sleep quality after surgery (Table 1).

Table 1. Insomnia severity score (mean ± standard deviation) based on study variables

Variables		1 Month Before Surgery		3 Days After Surgery		14 Days After Surgery	
		Insomnia Score	*P*-value	Insomnia Score	*P*-value	Insomnia Score	*P*-value
Drugs	Alprazolam	9.95±2.08	0.89	16.31±3.63	0.55	15.33±3.87	0.043
	Quetiapine	9.89±1.98		16.85±4.01		13.33±4.71	
Age, y	<50	10±2.45	0.34	16.67±5.68	0.99	14±4	0.71
	50-59	10.33±2.09		16.57±3.84		14.93±4.32	
	≥ 60	9.62±1.91		16.52±3.56		14.1±4.5	
Sex	Male	9.74±2.02	0.12	16.11±3.87	0.044	13.66±4.27	0.002
	Female	10.63±1.93		18.25±3.04		17.31±3.52	
Diabetes mellitus	Yes	10.84±1.81	<0.001	18.65±2.88	<0.001	16.52±3.74	<0.001
	No	9.32±1.95		15.17±3.71		13.02±4.22	
Hypertension	Yes	9.48±1.81	0.14	15.93±3.75	0.27	12.48±4.05	0.27
	No	10.18±2.12		16.92±3.81		15.55±4.17	
Hyperlipidemia	Yes	11.23±1.09	0.01	19.31±1.55	0.003	16.23±4.44	<0.001
	No	9.66±2.07		16±3.88		14.04±4.29	
Smoking	Yes	9.92±1.79	0.99	16.15±3.94	0.52	12.73±3.75	0.015
	No	9.92±2.15		16.75±3.75		15.25±4.44	
Ejection fraction (%)	<40	10±2.5	0.42	17.22±4.15	0.7	17±4.03	0.003
	40-49	10±2.37		16.25±4.43		15.75±4.77	
	50-59	10.26±1.97		16.94±3.95		15.03±3.64	
	≥ 60	9.35±1.7		15.87±3.17		11.78±4.24	

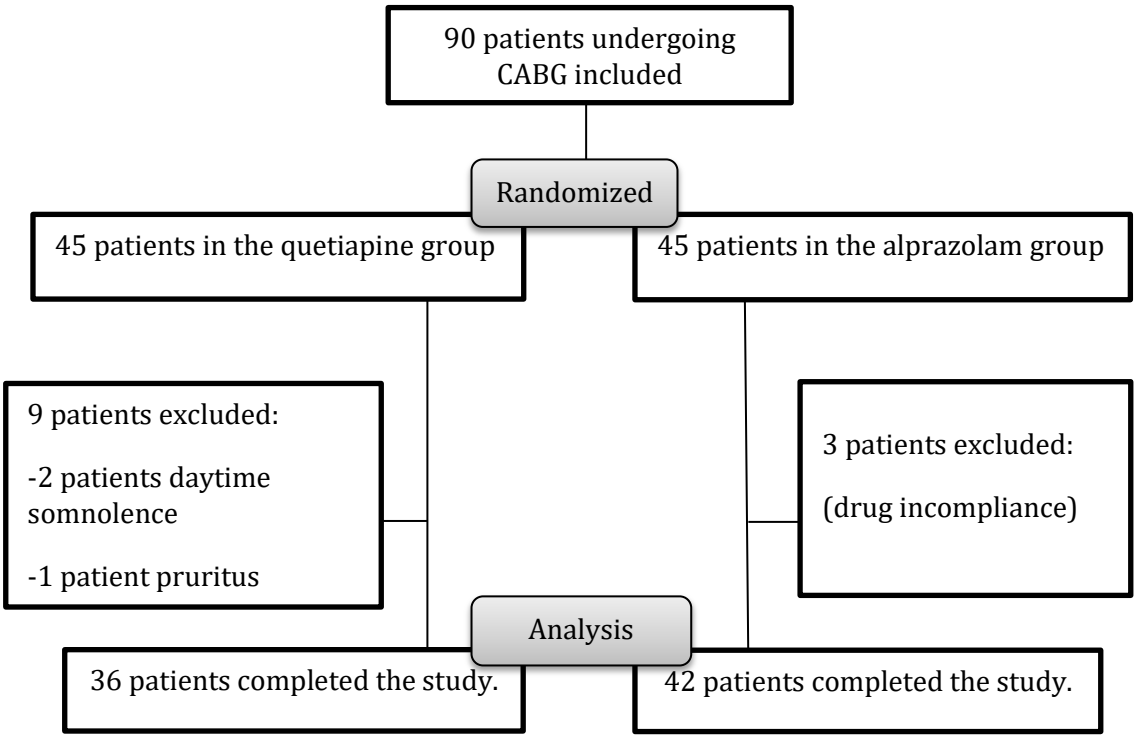

Figure 1. The image depicts the flowchart of the included and excluded patients.

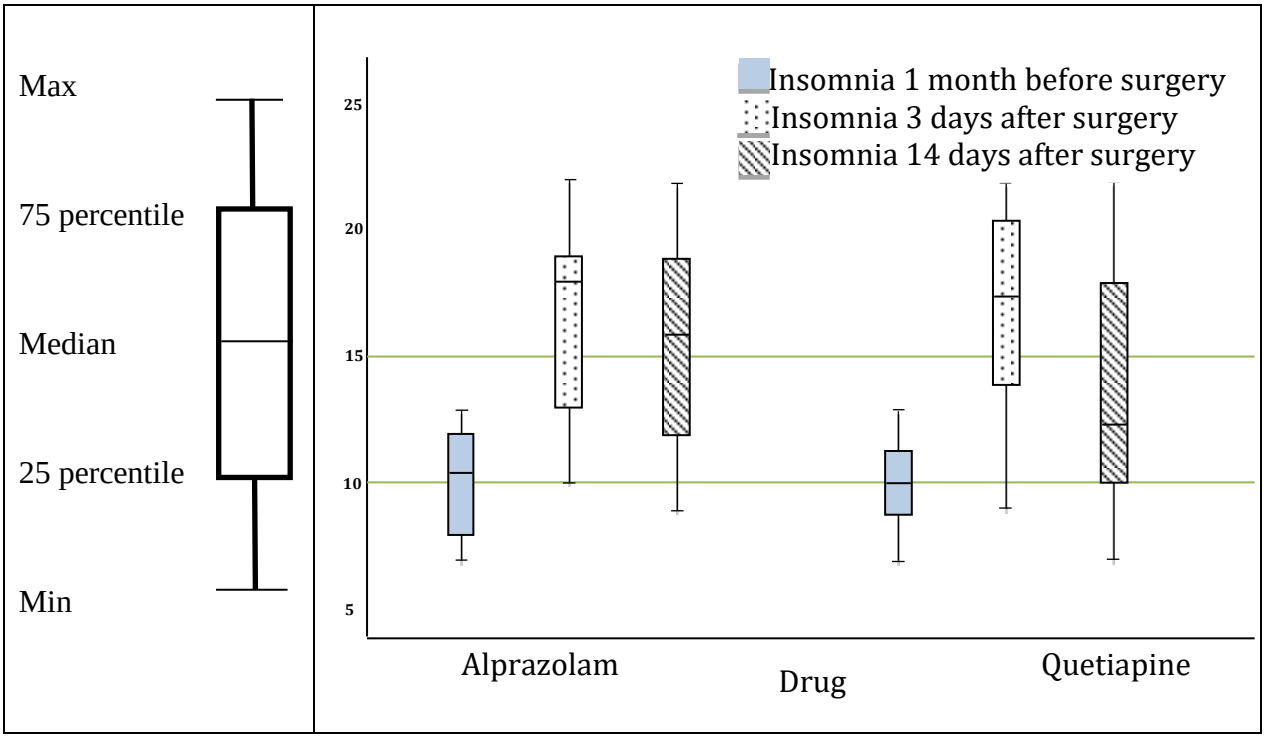

Figure 2. The image illustrates the median, range, and 25–75 percentiles of the insomnia score in the 2 groups.

DISCUSSION

Insomnia in patients undergoing CABG can have harmful effects on psychosocial activities, including anxiety, a lack of concentration, and the disruption of daily activities. [1, 15] Redder et al, [16] in a study on 72 patients, reported that sleep problems were the main problems for up to 8 weeks after CABG inasmuch as they affect the patients' physical and mental state. In a study on 123 patients, Hunt et al [15] found that those reporting a poor sleep quality were 4.8% more likely to report a very poor and poor quality of life postoperatively. Aside from its negative effect on the quality of life, insomnia can aggravate the risk factors of cardiovascular diseases such as hypertension. [17] A meta-analysis showed that short and long sleep duration may increase the risk of cardiovascular diseases. [18] Many strategies have been investigated for treating post-CABG insomnia, but none has thus far proved completely satisfying.

In this study, we sought to evaluate the efficacy of quetiapine on post-CABG sleep disturbances and compare its efficacy with the well-known alprazolam. The groups were uniform in patient characteristics and cardiovascular risk factors except for hypertension. Moreover, both groups had the same postoperative sleep score on the third postoperative day just before the beginning of a 10-day medical treatment; therefore, the differences observed between the 2 groups were probably related to the effect of the type of drug used to treat insomnia. The mean difference of insomnia score between day 3 and day 14 postoperatively had a statistically significant difference between the 2 groups, showing that the patients receiving quetiapine had improved in terms of sleep quality much more than those receiving alprazolam. The higher efficacy

notwithstanding, the patients receiving quetiapine had more drug noncompliance (20% vs 6.6%). We found no study in the literature evaluating the effect of quetiapine on post-CABG sleep quality to compare with our results.

Quetiapine usage even at high doses is FDA approved for psychiatric diseases. [5] Doses as high as 200 to 800 mg may have some important side effects. [10] Although the use of quetiapine for insomnia is not FDA approved, it is widely used for insomnia as an off-label drug. [19] Moreover, other drugs used for insomnia such as benzodiazepine and non-benzodiazepine drugs do not always cause sufficient relief of insomnia, and they are associated with prevalent side effects making patients seek for other medications to relieve their irritating insomnia. [12] We used the lowest dose of quetiapine (12.5 mg) to minimize its side effects if any of them persisted. Studies that have reported side effects with low-dose quetiapine have a different definition of a low dose such as using at least 200 mg for less than 3 months or an average dose of 116 mg for an average period of 44 months, which is on average 10 times more than the prescribed dose in this study. [11] They also have reported that patients who have taken the drug only when needed had no metabolic side effects. [11] Until now, there have been no sufficient data supporting the idea of not using very low-dose quetiapine (12.5 mg) for the short-term treatment of insomnia.

Evaluating the side effects in our patients, we found 2 patients discontinuing the drug for drowsiness on the following day and 1 patient for pruritus, which was relieved by discontinuing the drug. Nonetheless, we were not sure about the cause-and-effect relationship of this side effect. We had no cases of restless leg syndrome or dystonia in our study population. We could not evaluate metabolic side effects because the patients were in the early postoperative period and had many confounding factors such as loss of appetite, sedentariness, and the short-term use of the drug. Metabolic side effects with very low-dose quetiapine, which are important, especially in cardiovascular patients, need to be evaluated precisely in a well-designed study. It is likely that one of the reasons for the superiority of the drug for postoperative usage is the effect of quetiapine on delirium, which is prevalent in the postoperative period of cardiac surgery patients. [20] It may also be a special issue to focus on in future studies. In addition, it should be kept in mind that one of the limitations of the study was more drug noncompliance in the quetiapine group (20% vs 6.6%).

CONCLUSION

Notwithstanding more drug noncompliance, very low-dose quetiapine was more effective than alprazolam in improving the sleep quality of our early postoperative CABG patients.

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