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Evaluation of the Effect of Modafinil on Respiratory and Cerebral Outcomes after Coronary Artery Bypass Graft Surgery

Mojtaba Mansouri MD[1], Gholamreza Massoumi MD[1], Mohamad Kazem Rezaei-Hoseinabadi MD[2]

Original Article

Abstract

BACKGROUND: Pulmonary complications following cardiopulmonary bypass (CPB) pump during coronary artery bypass grafting (CABG) are relatively common and the incidence of cognitive dysfunction is reported as ranging in rate from 30% to 80% in the early postoperative period. The purpose of this study was to assess the effect of modafinil administration on the prevention of pulmonary and cerebral complications and shortening the hospital stay after CABG surgery.

METHODS: This randomized double-blind intervention-controlled clinical trial was performed on 74 patients (37 in the intervention group and 37 in the control group) undertaking CABG surgery. The intervention group was orally treated with doses of 200 mg of modafinil on the day of surgery, and on the morning of the day after surgery, the second dose of modafinil 200 mg was given to patients. The control group underwent a placebo with the same intervals.

RESULTS: Administration of modafinil in intervention group significantly decreased the time to reach consciousness (P = 0.001), ventilator time in intensive care unit (ICU) (P < 0.001), length of stay in ICU (P = 0.009), duration of hospitalization (P = 0.008), and arterial blood carbon dioxide pressure (PaCO2) (P = 0.047). In the intervention group, no patients with delirium, agitation, respiratory depression, non-invasive respiratory ventilation, and endotracheal re-intubation were observed.

CONCLUSION: Modafinil tablet as a respiratory and brain stimulant through the central nervous system (CNS) can improve the quality of breathing and arterial blood gases (ABGs) and also can increase the level of consciousness and shorten the recovery time.

Keywords: Modafinil; Coronary Artery Bypass Grafting; Lung Complications

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Introduction

Pulmonary complications following a cardiopulmonary bypass (CPB) are relatively common during coronary artery bypass grafting (CABG) surgery. Up to 12% of patients experience some degree of acute lung injury and approximately 1% require tracheostomy for long-term ventilation. Risk factors for respiratory failure include old age, diabetes or kidney failure, smoking, chronic obstructive pulmonary disease (COPD), and previous cardiac procedures.[1]

Positive end-expiratory pressure (PEEP) during CPB is considered as a method to prevent atelectasis. Airway opening maneuvers following cardiopulmonary pump have a variable effect on intubation time. Most studies show that they are not effective in reducing long-term ventilation time.[2] In the study conducted by Freitas et al., there was no evidence of the usefulness of using incentive spirometry in reducing pulmonary complications after CABG.[3]

In the study conducted by Zarbock et al. in this field, it has been shown that in patients with endotracheal tube, continuous positive airway pressure (CPAP) for at least 6 hours reduces arterial

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1- Associate Professor, Anesthesiology and Critical Care Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Assistant Professor, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Address for correspondence: Mojtaba Mansouri; Associate Professor, Anesthesiology and Critical Care Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; Email: mansouri@med.mui.ac.ir

oxygen loss, pneumonia, and re-intubation after cardiac surgery.[4,5] Carbon dioxide (CO2) levels in obstructive diseases often lead patients to frequent hospitalizations after acute exacerbation.[6] Since non-invasive ventilation, mortality rates have been greatly reduced and patients' lives are saved, but patient readmissions are increasing.[7]

In a seminal study, Hillis et al.[8] classified central nervous system (CNS) injury into two broad categories: type I (focal injury, stupor, or coma at discharge) and type II (deterioration in intellectual function, memory deficit, or seizures). Cerebral injury can also be broadly classified as stroke, delirium (transient global impairment of cognitive function, reduced level of consciousness, profound changes in sleep pattern, and attention abnormalities), or post-operative cognitive dysfunction as outlined in the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for CABG. The incidence of cognitive dysfunction (type II) is reported as ranging in rate from 30% to 80% in the early postoperative period.[8]

Modafinil, now marketed under the brand name Provigil, is a successful drug used in sleep disorders that acts through the dopaminergic system and also affects the sympathetic nervous system. This effect stimulates the respiratory center due to its effect on the CNS. In addition to stimulating respiration, modafinil also increases the level of consciousness in the brain. Some side effects of modafinil are anxiety, headache, and nausea.[9] In the United States (US), the use of modafinil by neurologists and pulmonary disease specialists, psychiatrists, and ears, nose, throat (ENT) specialists is very common and recognized in medical journals.[10]

A study by Larijani et al. revealed that modafinil administration at the beginning of surgery significantly accelerated recovery from the effects of residual anesthesia, improved consciousness and energy in patients after recovery from general anesthesia, and could be used significantly in these patients.[11]

The goal of this study was to diagnose respiratory and cerebral complications and attempt to decrease these complications.

Materials and Methods

Data source and population: Our study was a randomized double-blind intervention-controlled clinical trial (simple randomization and individual randomization unit) that was performed on 74 patients (37 in the intervention group and 37 in the control group) undertaking CABG surgery. Patients were divided to intervention and control groups with randomized number table (the couple numbers would be in the intervention group and the odd numbers would be in the control group) (Figure 1).

The patients that referred to Shahid Chamran Hospital in Isfahan, Iran, in 2020 (From January to October) and were candidates for CABG surgery were our subjects. The sample size was based on the following sample size formula with the aim of comparing the percentage of consciousness (variable with the most variance) in the two groups studied at 5% error level and 80% test power in both case and control groups.

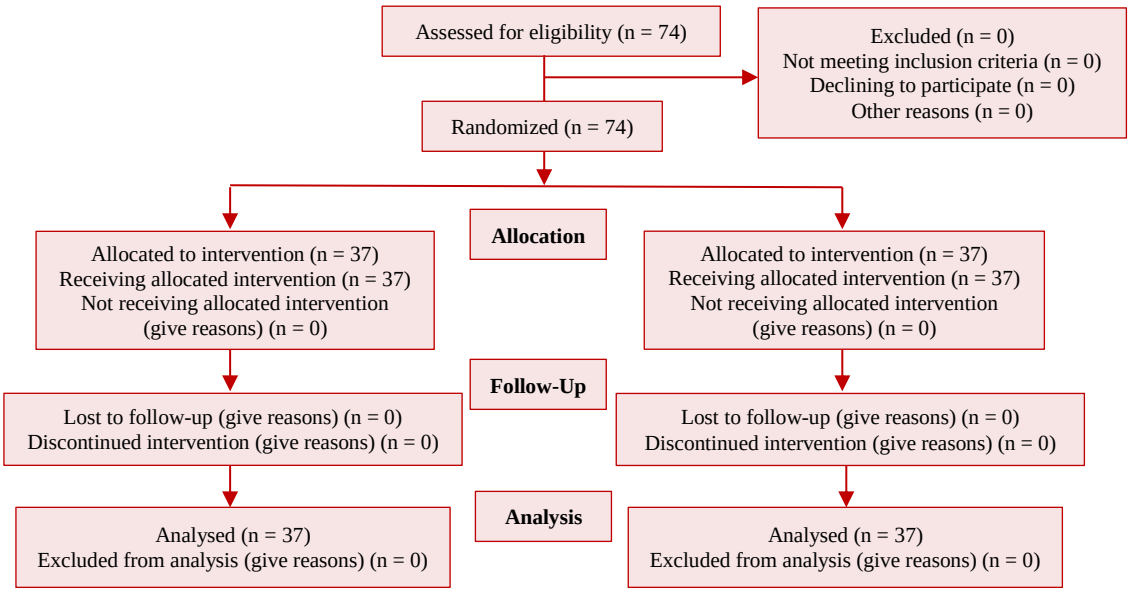

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the two groups of modafinil and control

The inclusion criteria included patients aged 20-80 years with an ejection fraction (EF) greater than 40% with no history of hepatic or renal insufficiency, irregular initial rhythm, and cardiomegaly. Exclusion criteria included need for reoperation due to hemorrhage after entering intensive care unit (ICU) and excessive sensitivity to modafinil. The patients' demographic information including age, sex, weight, drug history, blood pressure, blood glucose, and addiction to narcotics or alcohol was saved in a data collection form.

Additionally, the newest amount of laboratory variables including pressure of CO2 (PaCO2) in arterial blood gas (ABG) before surgery was extracted from the case and recorded.

After complete explanation and obtaining written informed consent from the patients, they were included in the study. After induction of anesthesia and tracheal intubation, surgery started and after separation of the patient from the CPB pump, a simple and individual randomization of modafinil at a dose of 200 mg was given to the intervention group and a placebo was given to the control group orally with a nasogastric tube (NG tube) by a person who had no role in the test.

The intervention group was orally treated with doses of 200 mg of modafinil on the day of surgery, and on the morning of the day after surgery, the second dose of modafinil 200 mg was given to the patients. The control group underwent a placebo with the same intervals. Pressure of CO2 in ABG and level of consciousness were checked in patients, and continued until separation of patient from ventilator.

Outcomes: The patients were followed up to 72 hours after the operation and the daily amounts of including PaCO2 in ABG (mmHg) up to 72 hours after surgery were recorded. The time to reach full consciousness, sedation rate, duration of intubation, frequency of apnea, frequency of respiratory depression, frequency of reintubation with endotracheal tube, arrhythmia frequency, drug side effects, and duration of hospitalization in ICU were extracted and recorded in each patient's profile.

The time to reach full consciousness was evaluated every hour until the patient reached full consciousness and was determined with Richmond criteria that is Richmond Agitation-Sedation Scale (RASS). This criteria consists of 10 stages that the percentage of delirium was determined with it and we used it every day for 72 hours.

Statistical analysis: Quantitative variables were reported as mean ± standard deviation (SD) and qualitative variables as number (%). The effect of intervention on qualitative variables was investigated using Fisher's exact test or chi-square test. Shapiro-wilk test was used to check normality. Student's t-test or Mann-Whitney U test (if the normality assumption was not held) were performed to evaluate the mean difference of quantitative variables in intervention and placebo groups. Changes in blood PaCO2 in the intervention and placebo groups were investigated using repeated measures analysis of variance (ANOVA). The analysis was performed using SPSS software (version 24, IBM Corporation, Armonk, NY, USA) and P-value < 0.05 was considered as significant.

Results

The mean age in the intervention and placebo groups were 61.70 ± 8.54 and 61.92 ± 7.51 years, respectively. The difference in age was not significant (P = 0.91). In the intervention group, 27 (73%) and 10 (27%) were men and women, respectively, and in the placebo group, 24 (65%) were men and 13 (35%) were women, and the difference between the two groups was not significant (P = 0.45) (Table 1).

In the intervention group, no patients with delirium, agitation, respiratory depression, non-invasive respiratory ventilation, and endotracheal re-intubation were observed, but in the placebo group there were 3 (8.1%) patients with delirium, agitation, respiratory depression, non-invasive respiratory ventilation, and 1 (2.7%) with endotracheal re-intubation. No significant differences were observed between intervention and placebo groups (P > 0.05).

In the intervention group, arrhythmia in ICU was observed in 2 (5.4%) patients and in the placebo group, in 3 (8.1%) patients; the difference in the number of arrhythmias in the two groups was not significant (P > 0.999).

Table 1. Frequency distribution of demographic factors in the two groups of modafinil and control

Variable	Intervention group (n = 37)	Placebo group (n = 37)	P
Age (year) (mean ± SD)	61.70 ± 8.54	61.92 ± 7.51	0.91*
Sex [n (%)]			0.45**
Men	27 (73)	24 (65)	
Women	10 (27)	13 (35)	

*T-test; **Chi-square test
SD: Standard deviation

The mean time of consciousness was approximately 5.92 ± 0.76 hours in the intervention group and 6.57 ± 0.83 hours in the placebo group and the difference was significant between two groups (P = 0.001). The mean ventilator time in ICU was approximately 6.50 ± 0.73 hours in the intervention group and 7.40 ± 0.98 hours in the placebo group, which showed a significant difference between the two groups (P < 0.001). The mean duration of ICU hospitalization in the intervention group was approximately 3.00 ± 0.56 days and in the placebo group was approximately 4.00 ± 0.78 days. The difference between the two groups was significant (P = 0.009) (Table 2).

The mean length of hospital stay in the intervention group was approximately 8.60 ± 0.95 days and in the placebo group was approximately 9.20 ± 1.26 days, and the difference between the two groups was significant (P = 0.008). Blood PaCO2 decreased in the intervention group, and this change was significant compared to the placebo group with increasing change (P < 0.001) (Table 2).

Discussion

Administration of modafinil in intervention group significantly decreased time to reach consciousness, ventilator time in ICU, length of stay in ICU, duration of hospitalization, and arterial PaCO2. In the intervention group, no patients with delirium, agitation, respiratory depression, non-invasive respiratory ventilation, and endotracheal re-intubation were observed.

A study by Larijani et al. revealed that modafinil administration at the beginning of surgery significantly accelerated recovery from the effects of residual anesthesia, improved consciousness and energy in patients after recovery from general anesthesia, and could be used significantly in these patients.[11] These results are matched with our findings.

In a study by Parnell et al., modafinil tablets were prescribed in patients with obstructive pulmonary disease and it was concluded that modafinil tablets were prescribed as a respiratory and brain stimulant which through the CNS could improve arterial blood gases, especially for patients with non-invasive ventilation intolerance, and shorten the length of stay in hospital and early discharge[12] and these results was similar with our study.

In 2018, in a study conducted by Carr et al. on patients with obstructive sleep apnea (OSA), 200 mg modafinil or placebo was given to patients before general anesthesia and the duration of recovery was compared between the groups, which showed no significant difference between the two groups in terms of the outcome of length of stay in recovery room, but in modafinil group the respiratory rate increased and mean arterial pressure was lower.[13] The results of this study are consistent with findings of our study.

In 2019, in a study conducted by Oommen et al. on the effectiveness of modafinil, methylphenidate, amantadine, and zolpidem on consciousness in ICU in patients with brain injury, modafinil was associated with the highest increase in the score of consciousness level.[14] The results of this study are consistent with findings of our study.

One of the studies conducted by Bivard et al. resulted in improved quality of life after taking 200 mg modafinil daily;[15] and similar improvement was observed in quality of life after taking 200 mg daily treatment with modafinil.

Table 2. Laboratory test results of patients during the course of disease

Variable	Intervention group [n (%)]	Placebo group [n (%)]	P
Delirium	0 (0)	3 (8.1)	0.240*
Agitation	0 (0)	3 (8.1)	0.240*
Arrhythmia	2 (5.4)	3 (8.1)	> 0.999*
Respiratory depression	0 (0)	3 (8.1)	0.240*
Non-invasive ventilation	0 (0)	3 (8.1)	0.240*
Endotracheal re-intubation	0 (0)	1 (2.7)	> 0.999*
	Mean ± SD	Mean ± SD	
Consciousness (hour)	5.92 ± 0.76	6.57 ± 0.83	0.001**
Mechanical respiration duration (hour)	6.50 ± 0.73	7.40 ± 0.98	0.001**
Duration of stay in ICU (day)	3.00 ± 0.56	4.00 ± 0.78	0.009**
Length of hospital stay (day)	8.60 ± 0.95	9.20 ± 1.26	0.008**
PaCO2 in morning of first day (mmHg)	37.86 ± 4.00	37.19 ± 3.60	< 0.001***
PaCO2 in evening of first day (mmHg)	39.05 ± 4.22	38.57 ± 4.50	
PaCO2 in morning of second day (mmHg)	38.22 ± 3.60	38.86 ± 4.50	
PaCO2 in evening of second day (mmHg)	36.73 ± 4.90	41.84 ± 3.30	

*Obtained by Fisher's exact test; **Obtained by Mann-Whitney test; ***Obtained by repeated measures analysis of variance (ANOVA)
SD: Standard deviation; ICU: Intensive care unit; PaCO2: Partial pressure of arterial carbon dioxide

Another study conducted by Gajewski and Weinhouse reported that with 200 mg of modfinil, to wakefulness and more restful sleep was earned, but modafinil was one of the causes of wakefulness and more restful sleep; and their patients' clinical improvement made it likely that it contributed.[16] In a study conducted by Li et al., the pattern of cognitive enhancing effects in the absence of effects on affective processing suggests a promising potential to enhance cognitive control in clinical populations.[17] Our findings were similar with the results of this study.

Study limitations: The kind of prescription and different doses of modafinil was our limitations. We recommend another study with different doses and different methods for more efficacy.

Conclusion

Our study showed that modafinil significantly decreased cerebral and pulmonary complications and the time of hospitalization. In the intervention group, no patients with delirium, agitation, respiratory depression, non-invasive respiratory ventilation, and endotracheal re-intubation were observed. With these known cerebral and pulmonary complications after surgery, it is important that we can decrease these complications with prescription of modafinil in these patients.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

MM determined the topic and helped in writing the proposal, collecting data, and writing the article. GM helped in writing proposal. MKRHA contributed to writing the proposal, collecting data, and writing the article.

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