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Original Article

Effect of Melatonin on Delirium After on-Pump Coronary Artery Bypass Graft Surgery: A Randomized Clinical Trial

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Abstract

Background: Patients undergoing cardiac surgery are particularly prone to delirium. This study aimed to evaluate the effect of melatonin administration on the inhibition of postoperative delirium in patients undergoing open-heart surgery.

Methods: This study was conducted as a double-blind randomized clinical trial in Golestan Hospital. Ahvaz, Iran, (September 2018 to March 2019). Sixty patients undergoing elective on-pump coronary artery bypass graft surgery were enrolled in the study, and they were randomly divided into a group receiving 3 mg of melatonin and a group receiving a placebo. The main outcomes were delirium occurrence and delirium intensity up to 48 hours after extubation. The data were analyzed using SPSS, version 22, (SPSS, Chicago, IL). Group comparisons were performed using the *t* test and the Chi-square test. Statistical significance was defined as a P value of less than 0.05.

Results: On the first postoperative day, delirium developed in four (13.3%) patients in the melatonin group and 11 (36.6%) patients in the control group; the difference between the groups was statistically significant (P=0.037). On the second postoperative day, delirium developed in three (10%) patients in the melatonin group and 14 (46.6%) patients in the control group, with the difference in the incidence of delirium between the groups constituting statistical significance (P=0.029). The severity of delirium between group was significant on the first and second postoperative days (P=0.003).

Conclusion: Melatonin may be effective in reducing the severity of delirium after cardiac surgery. The effect of melatonin as a delirium prevention agent should be considered in patients admitted in the cardiovascular intensive care.

Trial Registration Number: IRCT20180909040979N3.

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Keywords ● Melatonin ● Delirium ● Thoracic surgery

What's Known

- Patients undergoing cardiac surgery are particularly prone to delirium due to the complexity of the operation, cardiopulmonary bypass, macro- and microemboli, reperfusion, and postoperative complications. The prevalence of delirium after open-heart surgery is about 50% to 67%, while it is between 10% and 46% in noncardiac surgery.

What's New

- Melatonin may be effective in reducing the severity of delirium after cardiac surgery. The effect of melatonin as a delirium prevention agent should be considered in patients admitted to the cardiovascular intensive care unit.

Introduction

Delirium is characterized by a disturbance in the level of consciousness and cognitive or perceptual function that lasts for hours and days and fluctuates over time.[1, 2] Delirium is an acute disturbance of consciousness and cognition, which develops over a short time in the context of an acute medical condition.[3] Advances in surgical techniques have made it possible to perform

cardiac surgery even in the elderly.[4-6] Old age can be effective in increasing postoperative delirium.[4] The occurrence rate of delirium ranges from 11% to 33% on admission, and its frequency during hospitalization is between 3% and 56% among aging patients in emergency units or medical and surgical wards in general hospitals.[4] With the rise in the number of aged people, further increases in delirium appear likely. Delirium occurs after major surgeries within the first three days.[7]

Contrary to popular belief about delirium, only 4% of the patients with delirium were fully recovered at discharge and 80% had remaining defects for up to six months postoperatively in a previous investigation.[8] Therefore, delirium is not always transient and, in some cases, may be associated with structural brain damage, resulting in persistent cognitive impairment.[8]

Delirium can lead to increased morbidity and mortality, the need for longer mechanical ventilation, risk of injury to patients or staff, the risk of falling out of bed, unwanted extubation, and increasdlength of intensive care unit (ICU) stay, contributing to increased treatment costs.[9]

Delirium may be affected by several etiological factors such as age; type of surgery and anesthesia; hypoxia and hypercapnia; severe pain; opioid use; long-term lack of sleep; previous trauma to the head; a history of impaired cognitive status before surgery; alcohol consumption; diabetes; systemic infection; and sodium, potassium, or glucose disturbances before surgery.[9]

Patients undergoing cardiac surgery are particularly prone to delirium due to the complexity of the operation, cardiopulmonary bypass, macro- and microemboli, reperfusion, and postoperative complications.[9, 10] The prevalence of delirium after open-heart surgery is about 50% to 67%, whereas it ranges between 10% and 46% in noncardiac surgery.[4]

One of the main mechanisms of delirium is the disruption of melatonin levels following heart surgery.[10] A serotonin-produced hormone in the pineal gland, melatonin (N-Acetyl-5-methoxytryptamine) is secreted with the circadian rhythm into the circulatory and cerebrospinal fluid and adjusts the cycle of sleep and awakening.[11-13] Delirium and perioperative sleep disorders are possibly linked, either as predisposing factors or as symptoms of one another.[11]

To our knowledge, there is a dearth of data on the role of exogenous melatonin in the inhibition of delirium after heart surgery. Hence, we conducted the present study to evaluate the effect of melatonin administration on the inhibition of delirium following on-pump coronary artery bypass graft (CABG).

Patients and Methods

This randomized double-blind clinical trial was conducted from September 2018 to March 2019 in Golestan Hospital, Ahwaz, Iran. A convenience sample of 60 patients were assessed by dividing them in to two groups of intervention and control. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, approved all the procedures of this study (IR.AJUMS.REC.1398.199 and the RCT code was IRCTID: IRCT20180909040979N3).

Written informed consent for participation in the study was obtained from all the patients after they received clear explanations about the objective and potential risks and benefits of the study. During the study period, 120 patients undergoing elective on-pump CABG were eligible to participate in the trial. After the initial screening, 90 patients agreed to participate and provided informed consent. Among them, 30 patients did not meet the inclusion criteria: five patients had an ejection fraction below 30%, 10 underwent off-pump CABG, five had allergies, five were on antipsychotic drugs, and five suffered from renal disease. Ultimately, 60 patients were enrolled in the study and were assigned to two groups of melatonin and placebo, 30 patients in each group (figure 1).

The inclusion criteria consisted of being at least 30 years of age, being a candidate for elective on-pump CABG, being in anesthesia class II–III anesthetic risk, having a minimum ejection fraction of 30%, and being admitted to Golestan Hospital (September 2018–October 2019). The exclusion criteria constituted the presence of melatonin contraindications, allergy to the drug or its compounds, the chronic or recent use of melatonin or hypnotic drugs, receiving barbiturates or antipsychotics, a history of liver or kidney disease or chronic pulmonary disease, a history of neurological or psychological diseases, alcohol consumption, inability to communicate verbally, and the occurrence of serious and life-threatening events during or after.

Randomization

The participants were randomized 1:1 to receive either melatonin or a placebo. To ensure that both the patients and the investigators were blind to the treatment group before the study begins, we utilized a computer-generated allocation-concealment process before recruiting the patients. The eligibility criteria were electronically confirmed in a web-based case-report form and subsequently randomization was

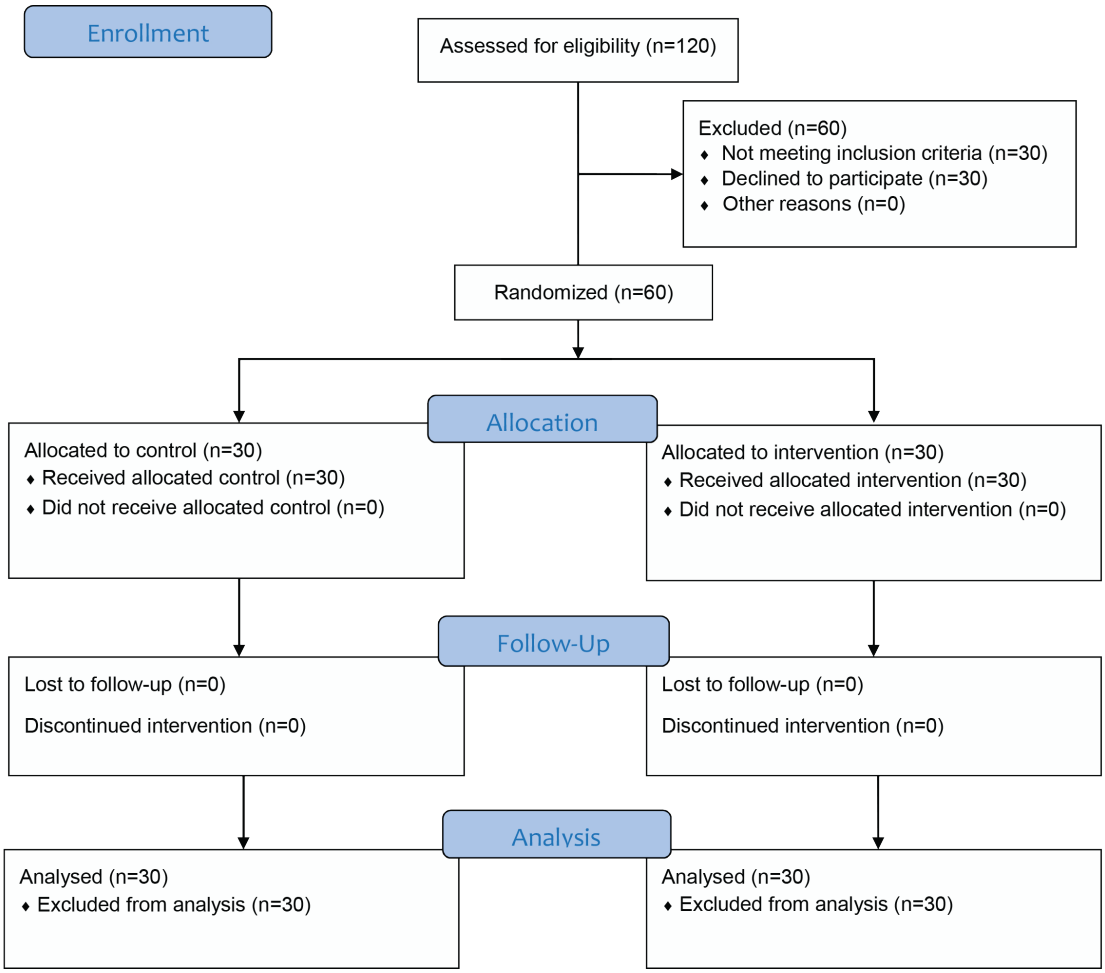

Figure 1: The figure illustrates the CONSORT flowchart diagram.

performed. Then, randomization was performed centrally without stratification. The sequence was generated with the aid of using an unbiased statistician, and the use of a random range generator with a 1:1 allocation the use of random block sizes of two.

Intervention

The patients in the melatonin group received 3 mg of melatonin (prolonged-release tablets; Webber Naturals®, Canada) the evening before the operation and 3 mg on the morning of surgery. The treatment was continued until second postoperative day with 3 mg of melatonin. In the control group, the patients received a placebo. The placebo capsules were filled with cornstarch powder (Beijing, China). A reliable intravenous line was inserted to allow the hydration of the patients using Ringer's lactate solution (Iran Injection and Pharmaceutical Products Company, Iran), 10 mL/kg. Next, necessary monitoring, including pulse oximetry, invasive and noninvasive blood pressure control, electrocardiography, and capnometry was established and the patients underwent general anesthesia with the same drugs: 0.1–0.2 mg/kg of midazolam (Caspian Tamin, Iran), 0.5–1 μg/kg of sufentanil (Aburaihan, Iran), 1 mg/kg of ketamine (Rotexmedica, Germany), and 0.5 mg/kg of cisatracurium (Rosamed, Iran). Additionally, isoflurane 1% (Piramal Critical Care, USA) in 50% oxygen, 0.1 μg/kg/h of sufentanil, 0.1 mg/kg/h of midazolam, and 0.1 mg/kg/h of cisatracurium were used to maintain general anesthesia. After the induction of anesthesia, a central venous catheter (Arrow, USA) was inserted. For the initiation of cardiopulmonary bypass, 400 u/kg of heparin (Alborz Darou, Iran) was injected to all the patients. The heparin dosage was adjusted based on the target activated clotting time (ACT) of 450 to 480 seconds.[14] After the bypass was cut off, protamine (Exir Darou, Iran) was administered to reverse heparin. Cardiac surgery and postoperative management were standardized.

After surgery, all the patients were admitted to the cardiovascular ICU, where a standard protocol was implemented for sedation, analgesia, and mechanical ventilation management. The patients were extubated if they were responsive

and cooperative, had PO_2 levels of 80 to 100, had an oxygenation index (PO_2/FiO_2) of greater than 300, and were hemodynamically stable. The patients were sedated in the ICU with propofol (B.BRAUN, Germany; 0.5 mg/kg/h) until extubation. Analgesia was provided with an intravenous morphine infusion (Darou Pakhsh, Iran) at 2 mg/h and 0.3 µg/kg/h of dexmedetomidine (Pfizer, USA).

Primary and Secondary Outcomes

Delirium occurrence was assessed based on the Confusion Assessment Method for Intensive Care Unit (CAM-ICU), and delirium intensity was assessed based on the Memorial Delirium Assessment Scale (MDAS) for up to 48 hours after extubation every 12 hours. For the monitoring of delirium in both ventilated and extubated patients, The CAM-ICU was used. This is a tool according to the Diagnostic and Statistical Manual of Mental Disorders criteria and includes a four-step algorithm.[15] Patients are adjudged delirious (CAM-positive) if they manifest the standard features of delirium.[15] All the cardiovascular ICU nurses were educated and well-qualified in the application of the CAM-ICU and MDAS in both ventilated and non-ventilated patients.[16] The mechanical ventilation time and the ICU length of stay comprised the secondary outcomes.

Statistical Analysis

The statistical analyses were performed using SPSS Software, version 22.0, (SPSS, Inc, Chicago, IL, USA). The quantitative variables were described as mean±SD and the qualitative variables as frequencies and percentages. The continuous variables were compared using the unpaired *t* test or a nonparametric equivalent (Mann–Whitney *U* test). Group comparisons were performed using the *t* test and the Chi-square tests. Statistical significance was defined as a P value of less than 0.05.

Results

During the study period, from September 2018 to March 2019, a total of 120 patients undergoing elective on-pump CABG surgery were eligible to participate in the trial. After the initial screening, 90 patients agreed to participate and provided informed consent. Among them, 30 patients did not fulfill the inclusion criteria. Ultimately, 60 patients were enrolled in the study and were assigned to two groups of melatonin and placebo (n=30 per group). As is shown in table 1, there were no statistically significant differences between the two groups in terms of demographic characteristics (P>0.05).

Primary Outcomes

Delirium based on the CAM-ICU was not established in each of the groups on the day of surgery. On the first postoperative day, delirium developed in four (13.3%) patients in the melatonin group (age>70 y) and 11 (36.6%) patients in the control group (four patients with an age range of 50–70 and seven patients aged over 70 years); the difference in the incidence of delirium between the groups was statistically significant (P=0.037). On the second postoperative day, delirium developed in three (10%) patients in the case group (>70 y) and 14 (46.6%) patients in the control group (four patients with an age range of 50–70 and 10 patients aged over 70 years), with the difference in the incidence of delirium between the two groups failing to constitute statistical significance once again (P=0.029). The patients developed only hyperactive delirium (table 2).

The difference between the melatonin and control groups with regard to the severity of delirium and based on the MDAS was statistically significant (P=0.003).

Secondary Outcomes

The average time required for mechanical ventilation after surgery was 6±1.26 hours in the group treated with melatonin and 6.56±2.1 hours in the control group, and the difference between the groups was statistically significant (P=0.032). The mean duration of admission to ICU in the melatonin group and the control group was 3.83±1 days and 4±1.7 days, respectively, which was statistically significantly different (P=0.04).

No serious adverse events were detected during the follow-up period in the patients treated with melatonin.

Discussion

The results of the current study showed that melatonin administration reduced the incidence (based on the CAM-ICU) and severity (based on the MDAS) of delirium after CABG. In the melatonin group, delirium occurred more frequently among older patients. Accordingly, older age was strongly associated with the development and severity of delirium.

Martinez and others conducted a randomized clinical trial on 850 adult patients hospitalized in the ICU.[17] The patients, hospitalized for 72 hours, were randomly divided into two groups of melatonin and placebo. The patients in the melatonin group received 4 mg of melatonin and those in the control group received a placebo for

Table 1: Preoperative characteristics of the melatonin and control groups

Variable		Melatonin Group (n=30)	Control Group (n=30)	P value
Age (y), mean±SD		60.26±9.50	62.9±8.08	0.251*
<50 n (%)		4 (13.3%)	3 (10%)	0.626**
50–70 n (%)		21 (70%)	19 (63.3%)	
>70 n (%)		5 (16.6%)	8 (26.6%)	
Sex	Male	20 (66.6)	22 (73.3)	0.58**
	Female	10 (33.3)	8 (26.6)	
EuroSCORE (%), mean±SD		2.63±2.65	2.86±2.83	0.48*
Diabetes n (%)		12 (40)	13 (43)	0.79**
Hypertension n (%)		26 (86.6)	29 (96.6)	0.16**
Hyperlipidemia n (%)		21 (70)	26 (86.6)	0.56**
Smoking n (%)		10 (33.3)	12 (40)	0.59**
Alcohol consumption n (%)		0 (0)	0 (0)	0.07**
Opium addiction n (%)		4 (13.3)	6 (20)	0.49**
Aortic cross-clamp time (min) (mean±SD)		55.11±38.61	49.47±30.73	0.53*
≤60 min n (%)		25 (83.3%)	23 (76.6%)	0.52**
>60 min n (%)		5 (16.6%)	7 (23.3%)	
Cardiopulmonary bypass time (min) (mean±SD)		79.50±5.3	77.43±6.8	0.32*
≤120 min n (%)		25 (83.3%)	23 (76.6%)	0.52**
>120 n (%)		5 (16.6%)	7 (23.3%)	

*Group comparisons were performed using the *t* test, ***Group comparisons were performed using the Chi-square test

Table 2: Comparisons of delirium occurrence based on the Confusion Assessment Method for Intensive Care Unit between the melatonin and control groups

Days After Surgery	Melatonin Group (n=30) n (%)	Control Group (n=30) n (%)	P value*
Day of surgery	0 (0)	0 (0)	0.09
First day after surgery	4 (13.3)	11 (36.6)	0.03
Second day after surgery	3 (10)	14 (46.6)	0.02

A P value <0.05 was considered statistically significant, *Comparisons were performed using the Chi-square test

14 days. The patients were studied in terms of the severity and duration of delirium, sleep quality, participation in physical therapy sessions, morbidity and mortality, and care costs. Martinez and colleagues concluded that melatonin was effective as a preventive agent of delirium in their patient population hospitalized in the ICU. Their results were in line with the results of the present investigation, although our study had a smaller sample size, lower melatonin dose, and shorter time of evaluation. Additionally, the incidence and severity of delirium were diminished both in their study and ours.

De Junge and others, in a double-blind randomized clinical trial, examined 378 hip-fracture operations to assess the impact of melatonin on reducing postoperative delirium.[18] They compared the patients in two groups of case and placebo. The participants received 3 mg of melatonin 24 hours before surgery for 5 days. De Junge and colleagues reported that the incidence of delirium was 29.6% in the melatonin group and 25.5% in the placebo group (P=0.02) and concluded that melatonin did not reduce the severity and duration of delirium. Their study is concordant with ours insofar as melatonin was found to reduce the incidence of delirium. Nonetheless, in contrast to our study, they found no decrease in the severity and duration of delirium, probably due to dissimilar measurement criteria.

Al-Aama and others examined 72 patients aged 65 years and older with a history of surgery to investigate the efficacy of melatonin administration in reducing delirium.[19] The patients were randomly selected and divided into two groups of case and control to receive 0.5 mg of melatonin or a placebo for 14 days. The researchers reported that the incidence of delirium in the melatonin group and the placebo group was 3.6% and 19.2%, respectively (P=0.015). The results of their study are also consistent with our findings, except that melatonin injection was used to reduce delirium and the patients were treated for longer periods and with different drug doses.

In a double-blind clinical trial, Ford and others studied 210 candidates for heart surgery to assess the effect of melatonin on the prevention of delirium.[20] The patients were randomly divided into two equal groups: a group treated with 3 mg of melatonin for up to 7 days

and a group treated with 3 mg of a placebo. The severity and duration of delirium, the symptoms of depression, and the length of hospitalization were studied in a 3-month period. Their results revealed that melatonin significantly reduced postoperative delirium.

Artemiou and others studied two successive groups of 250 consecutive patients who had various types of cardiac surgery in a prospective clinical observational study.[21] The patients were randomly selected and divided into two groups of case and control. The melatonin group received prophylactic melatonin treatment. The patients received 5 mg of melatonin the evening before the surgery, and the treatment was continued three days after surgery. The incidence of delirium was 8.4% in the melatonin group and 20.8% in the control group (P=0.001). Artemiou and others reported that the use of melatonin significantly decreased the incidence of delirium after cardiac surgery as well as the effect of different risk factors existing in the patients who did not receive melatonin therapy. Moreover, they concluded that melatonin administration was able to shorten the mechanical ventilation time and the ICU length of stay. The results of their study are consistent with our findings.

In a meta-analysis of 16 trials (1634 patients), Ng and others found that the incidence of delirium was not significantly lower in the patients who received melatonin (odds ratio [OR]: 0.55, 95% confidence interval [CI]: 0.24 to 1.26; P=0.16).[22] Further, the certainty of the evidence was low and the trial sequential analysis proved inconclusive. However, the authors reported that the patients randomly assigned to receive melatonin had a significantly shorter length of stay in the ICU (mean difference: 1.84 days [2.46±1.21 d], 95% CI; P<0.001). This result is consistent with our findings concerning the length of ICU stay. Ng and others observed no differences between the patients who received melatonin and those who did not as regards the need for physical restraints (OR: 0.65, 95% CI: 0.31 to 1.37; P=0.26) and the need for sedative agents (OR: 0.86, 95% CI: 0.48 to 1.55; P=0.62).[22]

Regarding the type of the procedure, in our study, CABG was the only surgery associated with the development of postoperative delirium. Other researchers have also reported a higher occurrence of delirium in patients experiencing valve placement and complex surgery with valve replacement and CABG compared with patients undergoing isolated CABG.[23] The reason for the higher incidence rate may be the embolization of the air that is surrounded by the cardiac chambers during valve surgery.

To the best of our knowledge, there is currently a paucity of information on the role of exogenous melatonin in the inhibition of delirium after heart surgery. The fact that we investigated this issue may be considered among the strong points of the current study. Nevertheless, our investigation has some limitations as well. Firstly, we did not perform baseline psychiatric screening tests in relation to preoperative psychological illnesses, which are strong prognosticators of postoperative delirium. Secondly, we conducted the CAM-ICU assessment in the cardiovascular ICU and did not extend it to the cardiac surgical level; hence, our results can be applied only to early postoperative delirium. Thirdly, we did not evaluate complications such as postoperative bleeding as a cause of delirium.

Conclusion

Melatonin may be effective in reducing the incidence and severity of delirium after cardiac surgery. Further studies with larger sample sizes and treatments of patients with different doses of melatonin may provide answers to other questions in this field. We also recommend that the effect of melatonin as a delirium prevention agent be investigated in patients admitted to the cardiovascular ICU.

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Conflict of Interest: None declared.

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