ORIGINAL ARTICLE

The effect of melatonin on cognitive functions following coronary artery bypass grafting: A triple-blind randomized-controlled trial

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Background: Cognitive dysfunction presents one of the chief causes of postoperative morbidity. Melatonin as a neurohormone can improve neurocognitive functioning and sleep disorders. We evaluated the effect of melatonin on the postoperative cognitive function of patients undergoing coronary artery bypass grafting (CABG). **Materials and Methods:** A triple-blind randomized-controlled trial was conducted on 66 CABG candidates in Namazee Hospital (Shiraz, Iran). Patients were assigned equally into two groups receiving melatonin 10 mg or a placebo daily for 4 weeks before surgery and 2 days after surgery in the intensive care unit. The Mini-Mental State Examination (MMSE), Tower of London (ToL), and Wechsler Adults Intelligence Scale-Revised (WAIS-R) cognitive function tests were performed in both groups 4 weeks before surgery (time point 1), 2 days after surgery (time point 2), and 6 weeks after initial administration of melatonin (time point 3). **Results:** The mean change score (time point 3-time point 1) differed significantly between the two groups in the MMSE ($P \leq 0.001$), ToL total score ($P = 0.001$), and WAIS-R general IQ ($P \leq 0.001$), picture completion ($P \leq 0.001$), vocabulary ($P = 0.024$), and digit span ($P = 0.01$). On the other hand, no significant differences were detected in the WAIS-R block design, ToL total time delay, ToL total lab, and ToL total result scores. **Conclusion:** The MMSE and WAIS-R tests revealed that melatonin might have prophylactic effects against postoperative cognitive disturbance in patients undergoing elective CABG.

Key words: Cognitive function, coronary artery bypass graft surgery, melatonin

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is reported in 23%–81% of patients after coronary surgery,[1] adversely affecting the patient's quality of life.[2] Although the pathogenesis of POCD remains unknown, this figure is probably higher among patients with unfavorable demographic characteristics (e.g., higher age) or complicated anesthesia or surgery.[3,4] Some specific drugs, comorbid conditions (cerebrovascular disease and severe heart disease), psychological factors (cognitive impairment history such as dementia and delirium), multi-morbidity, and frailty in the context of hospitalization have been confirmed as other risk factors for developing POCD.[5,6] Well-established tools for evaluating the cognitive functions of patients at risk of POCD include the Mini-Mental State Examination (MMSE), Wechsler Adult Intelligence Scale-Revised (WAIS-R), and Tower of London (ToL) tests.[7,8]

Nonpharmacological factors such as ventilation, oxygenation, hemodynamic changes, and postoperative pain management can affect the establishment or progression of POCD.[3] Furthermore, several medications are used for POCD treatment. Wang *et al.* confirmed the ability of lidocaine to reduce the incidence

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of cognitive dysfunction following surgery.[9] Furthermore, ketamine has been shown to improve cognitive function in POCD patients.[10]

Melatonin is mainly secreted from the pineal gland into the bloodstream and cerebrospinal fluid, interacting with melatonin receptors type 1 and 2. These receptors are located in the central nervous system and various peripheral organs.[11] Geyik *et al*. revealed that in the morning, patients have superior conservation of neurocognitive function due to the greater level of melatonin, leading to reduced ischemia-reperfusion (IR) damage.[12] Compared with oxazepam, melatonin can markedly improve sleep disorders in patients after cardiac surgery.[13] Melatonin has a protective effect on different organs against IR injury due to its antioxidant properties.[14]

Although the positive effect of melatonin on cognitive functions has been shown in a few studies,[15,16] this issue is yet to be investigated following coronary artery bypass grafting (CABG). Hence, we evaluated the effect of melatonin on cognitive functions following CABG using the MMSE, ToL, and WAIS-R tests.

MATERIALS AND METHODS

This triple-blind placebo-controlled study was conducted from March to July 2019. After approval by the Ethics Committee of Shiraz University of Medical Sciences (IR. SUMS. MED. REC.1396.40), the study protocol was registered in the Iranian Registry of Clinical Trials (IRCT20141009019470N77). Written informed consent was obtained from each eligible participant.

Inclusion criteria were all patients aged 40–75 years referred to Namazee Hospital (Shiraz, Iran) for elective on-pump CABG and anesthetized between 8 and 9 am on the day of the surgery. Exclusion criteria were recent myocardial infarction (<3 months), emergency operation, not enough time for melatonin use (<4 weeks), re-operation, renal insufficiency (creatinine >2 mg/dl), immunologic disorders, confirmed cerebrovascular disease or prior stroke by computerized tomography of the brain or patient history, severe pulmonary disease, ejection fraction below 40%, current anticoagulation with warfarin, any concomitant surgery (valvular, etc.), nonsinus rhythm, hepatic insufficiency, alcohol abuse, regular use of benzodiazepines or opioids, psychiatric disease, dementia, pregnancy, breastfeeding, active infection, graft count <2 and more than six, pump time >90 min, aortic and carotid atheromatous (more than 50%), and experiencing adverse effects of melatonin such as daytime drowsiness, headache, or stomach pain.

In this study, the sample size was estimated based on the large effect size of 0.80 of the MMSE test. In the beginning, 10 patients were randomly assigned to the case group and ten to the control group. We figured the mean ± standard deviation in the two groups (case group: 17 ± 0.6; control group: 17.5 ± 0.68), thereby attaining the effect size of 0.8. A power of 80% and an α value of 0.05 were considered based on a pilot study. Thirty-three participants were recruited per group considering a 0.25 drop-out rate to decrease the possibility of error.

After considering the inclusion and exclusion criteria, eligible patients were randomly allocated to either the melatonin group ($n = 33$) or the placebo group ($n = 33$) based on a computer-generated chart with a fixed block size of six. An individual who was not a study investigator supervised the randomization process.

The patients, physicians, research staff, and data analyzers were blinded. Both the patients and the investigators were unaware of the identity of medications as identical medications were distributed. Medications were coded before being given to the study investigators, and coded data were given to the statistician. The statistician was not the individual responsible for the randomization.

The intervention group received two 5 mg tablets of melatonin (Nature Made, USA) every night for 4 weeks before the surgery and also 2 days after surgery in the intensive care unit (ICU), while patients in the control group received a placebo for the same period. Furthermore, cognitive function tests were taken in both groups by a psychologist who was not in charge of this study 4 weeks before surgery (time point 1; the start of treatment), 2 days after surgery (time point 2), and 6 weeks after the first dose of medications was administrated (time point 3).

After arrival in the operating room, all patients received standard monitoring including pulse-oximetry, electrocardiographic, thermometry, invasive and noninvasive blood pressure monitoring, central venous pressure monitoring, capnography, and urine output monitoring.

Patients were anesthetized with midazolam (0.1 mg/kg), sufentanil (0.6–0.7 mg/kg), morphine (0.12–0.15 mg/kg), propofol (0.5–1.5 mg/kg), and pancuronium (0.15 mg/kg). All patients received an intraoperative infusion of propofol (100 μg/kg/min).

After skin preparation and sterilization, surgery began with a median sternotomy approach and 400 IU/kg heparinization; extra-corporal circulation (CPB) was started

by injecting a priming solution of ringer with nonpulsatile flow (between 2.4 and 2.8 l/min/m^2) and moderate hypothermia (32°C -34°C). The cardiopulmonary cannula was applied to the root of the aorta. Myocardial protection was provided by anterograde cold blood cardioplegia during aortic cross-clamping.

All patients underwent the same technique of pump-on CABG performed by the same surgical team. The same cardiac medication regimen was given, and the arterial oxygen pressure was maintained at about 250 mmHg.

During the operation, inotropes (ephedrine and epinephrine), vasopressors (norepinephrine and phenylephrine), and vasodilators (nitroglycerine or sodium nitroprusside) were used as indicated to maintain hemodynamic stability. Heparin was reversed with protamine sulfate by control of the Activated Clotting Time (ACT), and patients were transferred to the ICU postoperatively.

In the period before the operation, we contacted the patients every week and asked them about compliance, adverse events, and complications such as dizziness, headache, severe sleepiness, or abdominal cramps.

Tools

1. A demographic questionnaire was used to assess the patients' characteristics (age, gender, etc.)
2. The MMSE cognitive screening test is a 30-point questionnaire that, in 10–15 min, analyzes several cognitive functions including short and long-term memory, orientation, attention, calculation, and language. In this study, the Iranian version of the MMSE was used; Foroughan *et al*. confirmed this scale's satisfactory reliability and validity (α = 0.78) and reported 90% sensitivity and 84% specificity for the cutoff point of 21[17,18]
3. Five subscales of WAIS-R were extracted to evaluate cognitive function. These included: information, picture completion, vocabulary, digit span, and block design.[19] The validity and reliability of the Persian version of the Wechsler Intelligence Scale were evaluated among the Iranian students by Jazayeri and Poorshahbaz in 2003. The reported reliability coefficients were above 0.95 and concluded that the scale is reliable and valid[20]
4. The ToL neuropsychological screening test (computer form) was used to assess executive functioning, particularly for identifying deficits in planning, arranging, and problem-solving.[21,22] The reliability coefficient of the Persian version of this test was reported as 0.86. Its validity was calculated for the verbal, practical, and total tests as 0.76, 0.74, and 0.80, respectively.[23]

The MMSE and WAIS-R were our primary outcomes, while the ToL test was our secondary outcome. All patients' responses were recorded at the three specified time points.

Statistical analysis

The study data were extracted from 59 fully evaluable datasheets, and statistical analysis was performed using SPSS (version 23; SPSS Inc., Chicago, IL, USA). In this study, normal continuous data were reported as mean ± standard error of the mean. The normality of continuous data was evaluated using the Kolmogorov–Smirnov test and the Q–Q plot. Comparisons between groups were made using repeated measures analysis of variance (ANOVA), the paired *t*-test, and the independent *t*-test. Mauchly's test was used for evaluating the sphericity assumption in repeated measures ANOVA. Categorical variables were presented as numbers and percentages; the Chi-squared or Fisher's exact test was used to estimate the significant values as appropriate.

RESULTS

Among 79 CABG candidates, 20 were excluded from the study for various reasons, such as lack of eligibility, loss of follow-up, and death. Finally, 59 patients completed the study, including 30 in the placebo group and 29 in the intervention group [Figure 1].

The two groups were homogeneous in gender, age, marital status, addiction status, and residential area (urban and rural) [Table 1].

The mean change score (time point 3-time point 1) differed significantly between the two groups in information ($P \leq 0.001$), picture completion ($P \leq 0.001$), vocabulary ($P = 0.024$), digit span ($P = 0.01$), the MMSE ($P \leq 0.001$), and ToL total scores ($P = 0.001$). On the other hand, no significant differences were detected in the WAIS-R block design, ToL total time delay, ToL total lab, and ToL total result scores.

Based on repeated measure ANOVA analysis, when an interaction effect was significant, we relied on each time point independently and performed a *t*-test [Table 2].

Table 1: Baseline characteristics of the participants

	Melatonin	Placebo	Total	*P*
Gender: Male (%)	18 (63.2)	17 (56.7)	35 (59)	0.652
Age (mean±SD)	62.21±7.57	61.87±7.56	62.22±6.36	0.878
Marital status: Married (%)	29 (100)	30 (100)	59 (100)	-
Addiction (%)	6 (21.1)	2 (6.7)	8 (12.2)	0.190
Residential area: Urban (%)	21 (73.7)	20 (66.7)	41 (69.4)	0.604

SD=Standard deviation

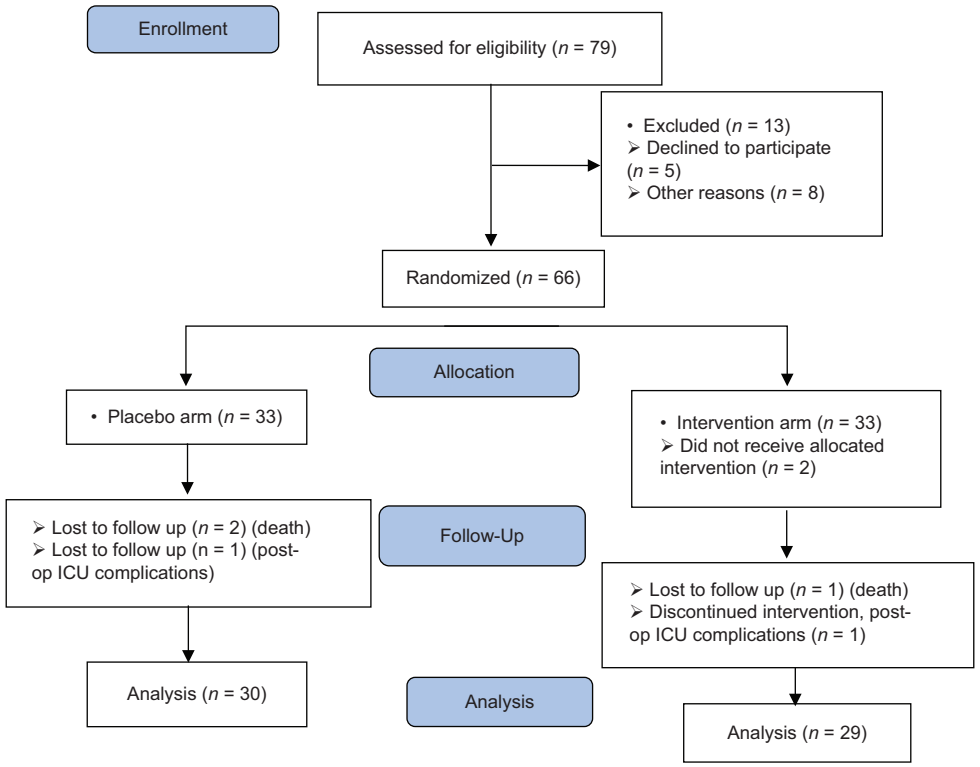
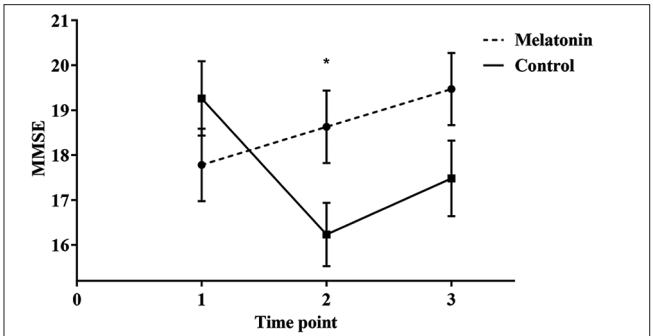


Figure 1: The CONSORT flow diagram of the study. CONSORT = Consolidated Standards of Reporting Trials



*Significant *P*-value ($P = 0.034$)
$P = 0.002$ for time, ≤ 0.001 for time-group interaction, and 0.420 for group.
All the data are presented as mean ± SEM.
Time point 1: four weeks before surgery; time point 2: two days after surgery; time point 3: six weeks after initial melatonin administration.

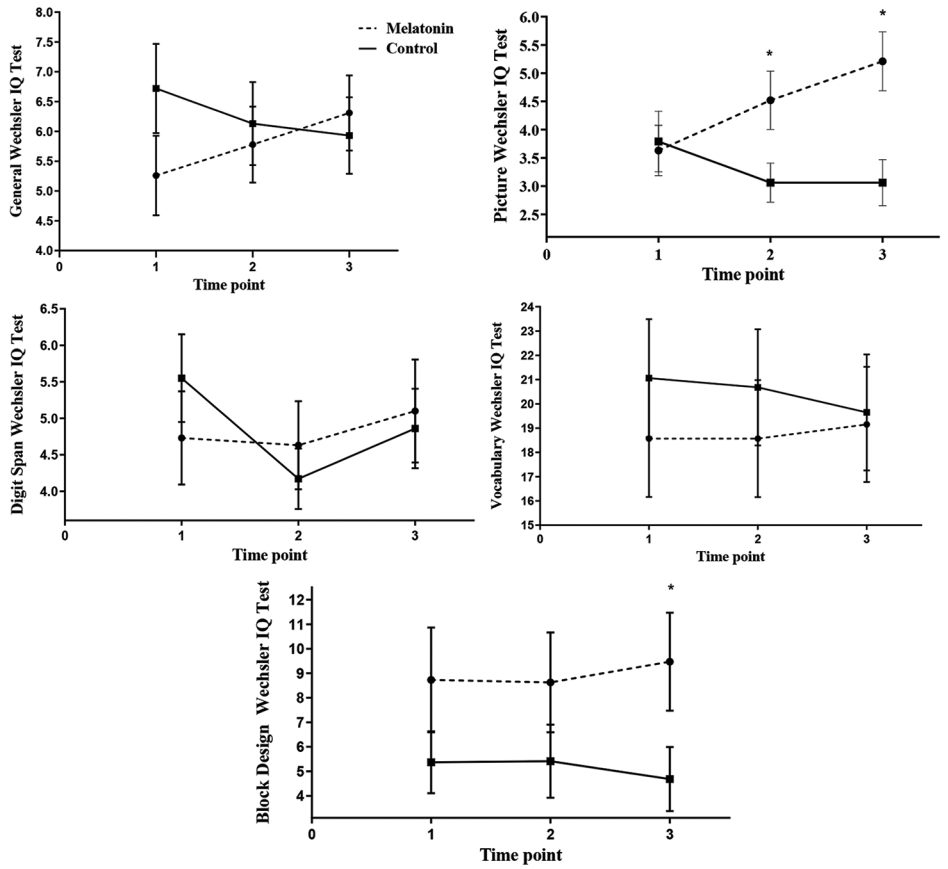
Figure 2: Comparing the results of the MMSE test between the melatonin and control groups. MMSE=Mini-mental state examination

For MMSE, the time effect ($P = 0.002$) and time-group interaction effect were significant ($P < 0.001$), but the group effect was insignificant ($P = 0.420$). The comparison between the two groups showed a significant difference in MMSE scores at time point 2 ($t = 2.18$, df = 47, $P = 0.034$) [Table 2]. Based on the paired *t*-test, in the melatonin group, there were significant differences in this index between time points 1and 3 ($t = -3.77$, df = 18, $P = 0.001$) and between time points 2 and 3 ($t = -2.65$, df = 18, $P = 0.016$). In the control group, a significant difference was detected between time points 1 and 2 ($t = 8.06$, df = 29, $P < 0.001$) and between time points 1 and 3 ($t = 3.75$, df = 28, $P = 0.001$) [Figure 2].

In the general WAIS-R score, the time-group interaction effect was significant ($P < 0.001$). There were no significant differences in independent factors between the two groups at any time point [Table 2]. Within the melatonin group, significant differences were observed between time points 1 and 3 ($t = -4.47$, df = 18, $P < 0.001$) and between time points 2 and 3 ($t = -3.29$, df = 18, $P = 0.004$). Such differences were recorded between time points 1 and 2 ($t = 2.9$, df = 28, $P = 0.007$) and between time points 1 and 3 in the control group ($t = 2.89$, df = 28, $P = 0.007$) [Figure 3].

In the picture subscale of WAIS-R, a significant interaction effect could be seen between the time point and group ($P < 0.001$). Between the melatonin and placebo groups, there were significant differences at time points 2 ($t = 2.43$, df = 46, $P = 0.005$) and 3 ($t = 3.25$, df = 46, $P = 0.001$) [Table 2]. In the melatonin group, significant differences were detected when comparing each pair of time points (1–2: $t = -3.92$, df = 18, $P = 0.001$; 13: $t = -4.96$, df = 18, $P < 0.001$; 2–3: $t = 3.15$, df = 18, $P = 0.006$), though such differences were not seen within the control group [Figure 3].

There was no marked time-group interaction effect ($P = 0.905$) according to the comparison between the two groups in WAIS-R vocabulary score, where the progress of patients in both groups over time was similar ($P = 0.631$). Comparing each time point between the two groups [Table 2] and comparing time point pairs within each group both failed to reveal significant data [Figure 3].



*Significant *P*-value in Picture IQ ($P = 0.005$, $P \leq 0.001$)
*Significant P-value in Block Design IQ ($P = 0.013$)
General IQ $P = 0.595$ for time, ≤0.001 for time-group interaction, and 0.636 for group. Picture IQ $P = 0.138$ for time, ≤0.001 for time-group interaction, and 0.073 for group. Digit Span IQ $P = 0.007$ for time, 0.022 for time-group interaction, and 0.62 for group. Vocabulary IQ $P = 0.592$ for time, 0.90 for time-group interaction, and 0.631 for group.
Block Design IQ $P = 0.978$ for time, 0.024 for time-group interaction, and 0.112 for group.
All data are presented as mean ± SEM.
Time point 1: four weeks before surgery; time point 2: two days after surgery; time point 3: six weeks after initial administration of melatonin.

Figure 3: Comparing the results of the Wechsler test between the melatonin and control groups

A time-group interaction effect was identified ($P = 0.022$) when comparing the digit span scores (WAIS-R) of the two groups. There was no significant difference in scores between the melatonin and control groups at any point in time [Table 2]. There was no significant difference in the scores of this subscale between time point pairs in the melatonin group, but the difference between time points 1 and 2 was significant in the control group ($P = 0.003$) [Figure 3].

In the WAIS-R block design subscale scores, while a time-group interaction effect was seen ($P = 0.024$), the trend of changes among the groups was insignificant during the study time ($P = 0.112$). A comparison between the groups showed a significant difference at time point 3 ($P = 0.013$) [Table 2]. In the melatonin group, there was a significant change in scores of this subscale from time point 2 to 3 ($P = 0.004$), whereas no meaningful changes were found over time in the control group [Figure 3].

In all ToL test parameters, there was no time-group interaction effect ($P = 0.640$) and no meaningful differences between groups at any point in time ($P = 0.313$) [Figure 4]. However, within the melatonin group, the ToL total score changed remarkably between time points 1 and 2 ($t = 3.19$, df = 18, $P = 0.005$). No significant changes were found in this score over time in the control group [Figure 4].

In the ToL total time delay parameter, the pairwise comparison of scores at different time points showed significant differences between time points 1 and 2 in

Table 2: Comparing the results of the mini-mental state examination and Wechsler tests between the melatonin and control groups at the three study time points (mean±standard deviation)

Group	Time point		
	1	2	3
MMSE			
Melatonin	17.78±0.807	18.63±0.806	19.47±0.803
Control	19.2±0.82	16.2±0.70	17.48±0.84
P	0.234	0.034	0.112
WAIS-R			
General			
Melatonin	5.26±0.66	5.78±0.63	6.31±0.63
Control	6.72±0.74	6.13±0.69	5.93±0.64
P	0.231	0.966	0.437
Picture completion			
Melatonin	3.63±0.44	4.52±0.51	5.21±0.52
Control	3.79±0.53	3.06±0.34	3.06±0.40
P	0.772	0.005	0.001
Digit span			
Melatonin	4.73±0.63	4.63±0.60	5.1±0.70
Control	5.55±0.60	4.17±0.41	4.86±0.54
P	0.432	0.717	0.848
Vocabulary			
Melatonin	18.57±2.40	18.57±2.41	19.15±2.37
Control	21.06±2.43	20.68±2.39	19.65±2.39
P	0.784	0.825	0.833
Block design			
Melatonin	8.73±2.13	8.63±2.03	9.47±1.99
Control	5.37±1.26	5.41±1.49	4.68±1.30
P	0.127	0.103	0.013

MMSE=Mini-mental state examination; WAIS-R=Wechsler Adults Intelligence Scale-revised

both the melatonin ($t = 3.50$, df = 18, $P = 0.003$) and control groups ($t = 5.48$, df = 29, $P < 0.001$) [Figure 4].

DISCUSSION

In our study, the progressive improvement in cognitive function (MMSE) in the melatonin group indicates the positive effects of melatonin on cognition, suggesting that melatonin might be able to mitigate the related adverse effects of surgery. This improvement in cognitive function would probably elevate the melatonin group's cognitive level even after discontinuation of the drug.

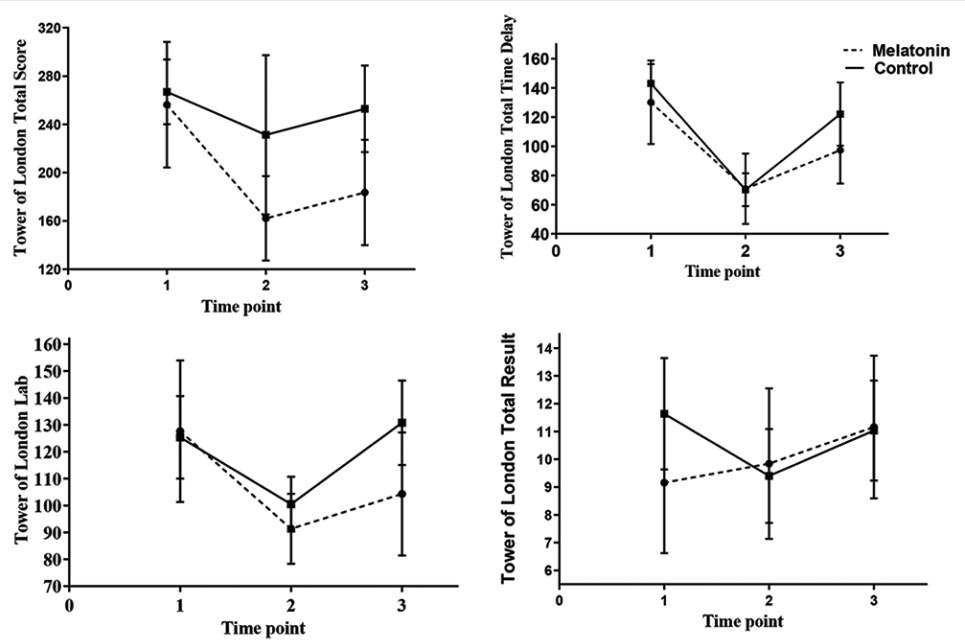
Patients receiving melatonin showed a progressive increase in general IQ scores, which might explain melatonin's positive and valuable effects in such patients. While at time point 1, the general IQ score was lower in the melatonin group relative to the control group, it increased over time; ultimately, the mean information score was higher in the melatonin group than the control group at time point 3. The significant rise in the mean general IQ score between time points 1 and 3 and between time points 2 and 3 in the melatonin group indicates the positive effects of melatonin over time [Figure 3]. The significant difference between the two groups in the change in mean score over time (time point 3-time point 1) in favor of the melatonin group confirms the positive effects of melatonin. Major surgery and anesthesia can disturb the rhythm of melatonin secretion, especially in elderly patients, associated with cognitive dysfunction after surgery.[13,24] Hence, this noteworthy increase in the score of the WAIS-R information subscale could support the routine administration of exogenous melatonin during the perioperative time. In similar studies, WAIS-R was utilized for patients receiving medications like memantine and melatonin, indicating that preoperative administration of these medications could protect patients from the development of POCD following cardiac surgeries.[25,26]

Our research is in line with the study of Fan *et al.*, showing the probable effect of melatonin supplementation before surgery on the prevention of POCD.[27] In a similar study by Dianatkhah *et al.*, melatonin and oxazepam were compared, with the former being superior in terms of improving sleep and Groningen Sleep Quality Score after cardiac surgery. Notably, the researchers reported that delirium was diagnosed in fewer patients in the melatonin group.[13]

In addition, the significant difference in mean score change over time (time point 3-time point 1) between the two groups indicated an improvement in patients receiving melatonin. Alongside the cognitive benefits of melatonin, its antioxidant activity and safety mean that it can induce a cardiovascular protective effect against reperfusion injury during CABG[14,28] without suppressing the cardiovascular responses to acute hypotension.

The exact mechanism by which melatonin induces sleep remains elusive. Melatonin may exert its effects by stimulating GABA receptors or interacting with benzodiazepine receptors. In addition, plasma cGMP may have a role in the circadian rhythm. Administering melatonin stimulates cGMP secretion. The peak level of cGMP is reached during night sleep, which approximately coincides with the melatonin peak level and is associated with sleepiness, indicating the link between melatonin and cGMP in inducing sleep. Moreover, melatonin can induce sleep by its effect on the suprachiasmatic nucleus.[29]

The conservative effect of melatonin on neurocognitive functions has also been shown in a related study where neurocognitive function improved among patients who underwent CABG at 8 am compared with 1 pm, attributed to the higher melatonin plasma level in the morning.[13] In the present study, we limited our study population to patients undergoing CABG in the morning to minimize



Total Score P = 0.240 for time, 0.640 for time-group interaction, and 0.313 for group. Time Delay P≤0.001 for time, 0.275 for time-group interaction, and 0.431 for group.
Lab P = 0.029 for time, 0.527 for time-group interaction, and 0.555 for group.
Total Result P = 0. 390 for time, 0.247 for time-group interaction, and 0.778 for group.
All data are presented as mean ± SEM.
Time point 1: four weeks before surgery; time point 2: two days after surgery; time point 3: six weeks after initial administration of melatonin.

Figure 4: Comparing the results of the Tower of London test between the melatonin and control groups

the confounding impact of plasma melatonin fluctuations during the day.

Sleep disorder is one of the pivotal factors leading to cognitive disorders;[13] melatonin can improve neurocognitive dysfunction after surgery by alleviating sleep disorders.[30] Furthermore, administrating melatonin can improve cognitive disorders like delirium by reducing the catabolism of serotonin and tryptophan through its negative feedback in the signaling cascade.[31] Some operations were scheduled momentarily therefore, inadequate time for data collection before surgery was one of our limitations. We suggest the use of a bigger sample size for future studies. Other psychiatric tests, including the evaluation of stress and sleepiness, should be utilized in future studies.

CONCLUSION

Our findings indicate that 10 mg of melatonin nightly for 4 weeks before CABG and 2 days in the ICU post-CABG improves cognitive function according to the MMSE and WAIS-R tests.

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Conflicts of interest

There are no conflicts of interest.

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