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Cardioprotective Effect of Preoperative Oral Melatonin in Coronary Artery Bypass Grafting Surgery Using on Pump Technique

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ABSTRACT

Background: Myocardial infarction that occurs during surgery for cardiac patients is still a difficult issue that raises morbidity and mortality. Clinical investigations demonstrate that nocturnal melatonin secretion is lowered in individuals with Alzheimer's disease, coronary heart disease, and stroke, although the pathophysiologic implications of altered melatonin secretion remain unclear.

Aim: The current study aimed to evaluate the protective role of melatonin in improving the degree of cardiac injury in patients undergoing bypass surgery.

Patients & Methods: This is a randomized control clinical study, which took place in Suez Canal University Hospital in the routine surgical theaters. Following the departmental research committee approval and informed patient's consent, 74 patients, undergoing CABG surgery were randomly allocated to one of the two groups using a table of random numbers: group M received 10 mg melatonin orally for two nights pre-operative as a study group, and group C received placebo orally for two nights pre-operative as a control group.

Results: Our result presented a substantial difference between the control and melatonin groups in post-cardiopulmonary bypass heart rate, cardiac injury enzymes as cTnI and CK MB levels, new wall motion abnormalities, cardiac systolic function EF %, and post-operative ventilation time.

Conclusion: Administration of oral melatonin hormone 10 mg for two nights pre-operative can decrease myocardial I/R injury and improve outcome after CABG surgery by increasing cardiac systolic function EF%, decreasing cardiac wall motion abnormalities, decreasing cardiac injury biomarkers (CK -MB and troponin I) and decrease post-operative ventilation duration.

Keywords: Melatonin, Coronary, Pump Technique, anesthesia.

INTRODUCTION

Myocardial infarction which occurs during surgery for cardiac patients is still a difficult issue that raises morbidity and mortality. The aortic cross-clamping-unclamping generates a worldwide myocardial ischemia-reperfusion sequence during surgery while on cardiopulmonary bypass (CPB). The myocardium must be safeguarded against acute ischemia-reperfusion damage (IRI) to be able to maintain cardiac contractile function, delay the onset of heart failure, and enhance clinical outcomes in CHD patients [(1)].

The term "cardioprotection" is employed in this article to refer solely to safeguarding the myocardium against the harmful effects of acute IRI. Since its inception, cardioprotection research has continually fallen short of developing a treatment approach that may successfully shield the myocardium against acute IRI in a clinical environment [(2)]. The incapability to adequately transfer many of these intriguing medicines into interventions that truly enhance patient outcomes rather than a lack of possible cardioprotective techniques identified in the preclinical experimental setting is what has led to the failure [(3)].

Increased levels of cardiac troponin I (cTnI) are an independent predictor of adverse outcomes. It is possible to measure the frequency and severity of peri-operative myocardial damage and infarction using serum cardiac enzymes including CK-MB, Troponin-T, and Troponin-I [(4)].

The "Third universal definition of myocardial infarction" recently published guidelines for defining MI relevant to CABG. Type 5 MI, which refers to myocardial infarction associated with CABG, is characterized as an increase in cardiac biomarker values >10 times 99th percentile URL in patients with baseline cardiac Troponin values that are normal (99th percentile URL), accompanied by either new left bundle branch block or new pathological Q waves (LBBB) or fresh graft or new native coronary artery blockage that has been verified by an angiogram. TEE can be used to image new regional wall motion abnormalities or new loss of viable myocardium [(5)].

Additionally, melatonin has intricate impacts on neuroimmunomodulation and antioxidant defense mechanisms [(6)]. Melatonin has been shown to have cardioprotective qualities in lean mice, where it protected the heart from myocardial ischemia/reperfusion damage when administered at physiological or pharmacological dosages pre- or post-ischemic insult [(7)].

The current study looked at how melatonin might reduce the severity of heart damage in patients following bypass surgery.

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PATIENTS & METHODS

The Suez Canal University Hospital's standard operating rooms were used for this investigation, which was a randomized controlled clinical experiment. Seventy-four patients undergoing CABG surgery at Suez Canal University Hospital were randomly allocated to one of the two groups using a table of random numbers after departmental research committee permission and informed patient consent.

Patients who have emergency CABG, heart blocks that are more severe than the first degree, low ejection fractions of less than 35%, concurrent heart valve replacement or repair, esophageal strictures or varices, or concurrent hepatic or renal insufficiency are not included in the study. as well patients with severe cerebrovascular disease, a history of stroke, or severe pulmonary disease.

As a study group, group M was given 10 mg of melatonin orally for two nights before surgery. Group C served as the control group and took a placebo orally for two nights before surgery.

Before being enrolled in the study, all individuals were provided informational sheets outlining the investigation and requested to complete and sign a consent form.

Technique:

The night before surgery, two for two nights, group M (the study group) received 10 mg of melatonin orally, whereas group C (the control group) received a placebo orally, 30 minutes before bedtime. All patients received 2.5 mg of intravenous midazolam 30 minutes before entering the operating room. After cannulation, monitoring devices (Datex-OhmedaTM) were used, including a central venous line after intubation, invasive blood pressure monitoring, a pulse oximeter, a capnograph, and a 3-lead ECG. According to each patient's needs and CVP guidance, intravenous fluid was administered to all patients. Propofol 1-2 mg/kg, cis-atracurium 0.15 mg/kg, and fentanyl 3-5 mcg/kg were used to induce anesthesia after at least three minutes of pre-oxygenation with 100% oxygen. Then, using a Macintosh laryngoscope and an appropriate size endotracheal tube, patients were mechanically ventilated with 100% oxygen until intubation after 2 minutes and with a BIS value of 60 to 40%. Isoflurane was used to maintain anaesthesia, with its end tidal concentration varied to maintain BIS between 60 and 40% while oxygen flow rate was maintained at 2 litres per minute in a totally closed circuit with co2 absorbent and cis-atracurium 0.03 mg/kg guided neuromuscular monitor (TOF).

Hemodynamics (heart rate and mean arterial blood pressure) remained within 25% of baseline values. After the induction of anesthesia, the TEE probe was placed, the evaluation was done while the patient was hemodynamically stable before the incision, and all patients' LV functions were recorded on CD before and after the CPB.

Intra-operative measurements:

After induction of anesthesia, cTnI blood samples were taken 4, 8, 12, and 24 hours after aortic unclamping, and CKMB blood samples were taken after induction of anesthesia. TEE recordings of new wall motion abnormalities and LV functions were made. The duration of all medicines, the cross-clamping time, the anesthetic induction and duration, and the bypass time were all noted.

Post-operative outcome data.

Clinical endpoints included:

1- Cardiac events using TEE:
2- ECG changes.
3- CK-MB peaks were observed 4, 8, 12, 24, and 48 hours after surgery. Diagnosis of perioperative myocardial infarction was done with cut-off values of 32 and 7 microg/L for CK-MB and cTnI.
4- Ventilator dependence 48 h postoperatively, intra-aortic balloon pump (IABP), doses of dopamine ≥5μg/kg/min; any dose of epinephrine, norepinephrine, dobutamine, or milrinone.

Ethics approval and consent to participate:

Both the institutional review board and the local committee of ethics approved the protocol of this research in the Faculty of Medicine of Suez Canal University. It was performed based on the Helsinki Declaration. Written consent for being informed was collected from all participants before their involvement in this study.

Statistical analysis

Using the Windows 8 operating system, IBM SPSS Statistics® 22 was used to conduct the statistical study. The two study groups' continuous variables were compared using the Student T-test, and categorical and dichotomous variables were compared using the Chi-squared test. When p 0.05, the level of statistical significance was deemed to be at 95%.

RESULTS

Table (1): Demographic and clinical characteristics between both study groups

	Melatonin group (n=37)	Control group (n=37)	P-value
Age (years)	54.32±7.6	54.22±7.6	0.972(NS)
Male/Female	25/12	29/8	0.295(NS)
BMI (kg/m^2)	29.9±3.6	28.2±3.1	0.042(NS)
ASA (II/III)	11/26	16/21	0.227(NS)
Smoking	20(54.1%)	23(62.2%)	0.480(NS)
Diabetes	19(51.4%)	14 (37.8%)	0.242(NS)
Hypertension	11(29.7%)	9(24.3%)	0.601(NS)

This table shows that both groups are matched regarding (age, gender, BMI, ASA classifications, smoking, presence of diabetes, and hypertension) basic demographic and clinical characteristics.

Table (2): Intraoperative data in both study groups:

	Melatonin group (n=37)	Control group (n=37)	P-value
Baseline HR	72.16±9.76	75.35±9.76	0.164(NS)
Incision HR	73.89±12.135	77.00±10.12	0.235(NS)
Sternotomy HR	73.11±10.684	77.68±9.384	0.055(NS)
Heart rate 30 min after CPB	**71.76±7.11**	**67.16±7.95**	**0.011***
Baseline (MAP)	98.8±14.5	99.1±8.5	0.897(NS)
Incision (MAP)	81.62 ± 12.4	78.49 ± 6.9	0.186(NS)
Sternotomy (MAP)	78.4±12.7	77.41±7.7	0.685(NS)
After CPB 30min(MAP)	**67.1±12.4**	**61.9±7.5**	**0.031***
Duration of anesthesia (min)	230±25.6	223.38±24.8	0.262(NS)
Duration of surgery(min)	202.97±24.67	193.38±24.8	0.100(NS)
CBP duration (min)	100±22.73	93.38±24.8	0.236(NS)
Aortic cross-clamp duration (min)	82.16±23.59	73.38±24.8	0.123(NS)

This table shows that intraoperative heart rate values are non-substantially different between both groups at all time points except at 30 min after CPB where the mean heart rate is 71.76±7.11 in the melatonin group and 67.16±7.95 in the control group, heart rate after 30 min of CPB was substantially lower in the control group than in the melatonin group. At 30 min after CPB where mean of mean blood pressure (MAP) is substantially lower in the control group (61.9±7.5) than in the melatonin group (67.1±12.4).

Table (3): Level of biomarkers for myocardial injury

		melatonin group (n=37)	Control group (n=37)	P-value
CK-MB level microg/L	**Baseline**	**69.6±79.3**	**95.7±83.6**	**0.174(NS)**
	After CPB(4 hr)	**78.7±79.5**	**99.8±85.8**	**0.275(NS)**
	After CPB(8 hr)	**92.3±91.7**	**106.8±85.8**	**0.486(NS)**
	After CPB(12 hr)	**90.7±77.96**	**118.8±85**	**0.142(NS)**
	After CPB(24 hr)	**83.3±61.2**	**135.4±92.6**	**0.006***
	48 hours postop	**77.35±56.4**	**103.1±71.5**	**0.089(NS)**
Troponin I level microg/L	**Baseline**	**0.4±0.22**	**0.39±0.21**	**0.916(NS)**
	After CPB(4 hr)	**0.44±0.19**	**0.88±1.97**	**0.184(NS)**
	After CPB(8 hr)	**0.44±0.14**	**0.57±0.23**	*** 0.006**
	After CPB(12 hr)	**0.39±0.1**	**0.54±0.2**	*** 0.000**
	After CPB(24 hr)	**0.35±0.09**	**0.53±0.19**	*** 0.000**
	48 hours postop	**0.32±0.1**	**0.46±0.19**	*** 0.000**

This table shows that myocardial injury biomarker (CK-MB) values are non-substantially different between both groups at all time points except at 24 hours after CPB where the mean of CK-MB is substantially lower in the melatonin group(83.3±61.2) than in the control group(135.4±92.6). Myocardial injury biomarker (Troponin I) values are non-substantially different between both groups but show a substantial decrease in troponin I level at 8, 12, 24, and 48 hours after CPB), (0.44±0.14, 0.39±0.1, 0.35±0.09, 0.32±0.1) for melatonin group vs (0.57±0.23, 0.54±0.2, 0.53±0.19, 0.46±0.19) for the control group.

Table (4): Clinical indicators of myocardial injury and wall motion abnormalities using TEE

		melatonin group (n=37)	control group (n=37)	P-value
No WMAs N(%)	**Before CPB**	**27(73%)**	**20(54.1%)**	**0.091(NS)**
	After CPB	**33(89.2%)**	**20(54.1%)**	**0.001***
	Postoperative	**33(89.2%)**	**20(54.1%)**	**0.001***
Hypokinesia N(%)	**Before CPB**	**7(18.9%)**	**11(29%)**	**0.278(NS)**
	After CPB	**4(10.8%)**	**11(29%)**	**0.043***
	Postoperative	**4(10.8%)**	**13(35.1%)**	**0.013***
Akinesia/ dyskinesia N(%)	**Before CPB**	**3(8.1%)**	**6(16.2%)**	**0.286(NS)**
	After CPB	**0**	**6(16.2%)**	**0.011***
	Postoperative	**0**	**4(10.8%)**	**0.040***

This table shows no substantial difference between both groups in all readings of wall motion before CPB but after CPB there is a substantial difference between both groups regarding hypokinesia and akinesia abnormalities(4(10.8%) pts for the melatonin group vs 11(29%) pts for control one p-value=0.043) (0 pts for melatonin group vs 6(16.2%) pts for control one p- value=0.011). The number of patients noticed to have pre-CPB wall motion abnormalities (hypokinesia seen pre-CPB = 7(18.9%) pts vs hypokinesia seen pot CPB = 4(10.8%) pts in melatonin group) (akinesia seen pre-CPB = 3(8.1%)pts vs akinesia seen pot CPB = 6(16.2%)pts in melatonin group) were decreased after revascularization in both groups but more decreased in the melatonin group.

Table (5): pre and post-CPB and post-operative ejection fraction (EF %) measured by TEE.

	Melatonin group (n=37)	Control group (n=37)	P-value[1]
After induction	**50 ± 5**	**49 ±5**	**0.609(NS)**
After CPB	**56 ± 8#**	**52 ±9**	**0.047***
Postoperative	**57 ±6#**	**54 ± 4#**	**0.033***
P-value[2]	**0.0002***	**0.0001***	

This table shows that although there was no statistically substantial difference between both groups regarding the mean of ejection fraction (EF%) after induction of anesthesia, their means were substantially higher in the melatonin group intra-operatively after bypass and postoperatively (0.56 ±0.08# in the melatonin group vs 0.52 ±0.09 in control one after CPB with p value=0.047*) (0.57 ±0.06# in melatonin group vs 0.54 ±0.04# in control one postoperative reading with p value=0.033*). On the other hand, the mean of change in ejection fraction after bypass compared to after induction was substantially bigger in the melatonin group. However, the means of change in ejection fraction postoperatively compared to after induction were non-substantially different between both groups.

Table (6): General postoperative outcomes in both study groups:

	Melatonin group N 37	Control group N 37	P-value
Substantial Arrhythmias post-CPB N (%)	**0**	**0**	
Ventilation time (hrs)	**10.49±6.1**	**20.16±6.5**	**0.000***
Inotrope and vasoactive drugs need N(%)	**23 (62.2%)**	**25 (67.6%)**	**0.4(NS)**
Postoperative MI/CHF N(%)	**0**	**0**	**-**
Need for IABP N(%)	**0**	**0**	**-**

This table shows that the incidence of substantial arrhythmias and new pathological Q wave was non-substantially different between both groups before and after bypass. The incidence of postoperative adverse cardiac events and the need for inotrope and vasoactive drugs were non-substantially different between both groups. However, postoperative \ventilation time was substantially lower in the melatonin group (10.49±6.1 hrs).

DISCUSSION

In this study, we investigated how melatonin can reduce the severity of heart damage in patients following bypass surgery. We conducted this study to assess the cardioprotective benefits of preoperative oral melatonin and to reduce myocardial injury and infarction after CABG surgery.

The CK-MB peaks were seen 4, 8, 12, 24, and 48 hours after surgery, allowing the diagnosis of perioperative myocardial damage. At 48 hours, the diagnosis of perioperative myocardial infarction was made with 100% sensitivity using cut-off values of 32 and 7 microg/L for CK-MB and cTnI, respectively. After myocardial reperfusion, our study found a substantially higher mean ejection fraction% in the melatonin-treated group (0.56 0.08) compared to the placebo-controlled group (0.52 0.05).

Dominguez *et al.* [8] demonstrated the significance of melatonin serum levels in predicting heart failure in individuals with hypertensive cardiomyopathy, and it also demonstrated the link between melatonin and LV remodeling during the chronic phase of post-MI. These results support the hypothesis that melatonin plus secondary preventive therapy may work synergistically to protect against LV remodeling. that concurred with our findings.

Zhang *et al*. [9] concluded that melatonin treatment (30 mg/kg, 3, 6, 12, 18, and 24 hours after cecal ligation and double puncture (CLP)) facilitated myocardial cytochrome-c-oxidase (CcOX) activity and blood lactate level, attenuated heart dysfunction with a higher left ventricular ejection fraction (LVEF%) and promoted 48-hour survival of the rats compared to the control group. These results were consistent with ours

In 2017, **Ekeloef *et al.*** [10] published the findings of another clinical study, which demonstrated that giving 48 ST-elevation myocardial infarction (STEMI) patients intravenous melatonin at a dose of 0.1 mg/ml or intracoronary melatonin at a dose of 0.1 mg/ml failed to improve LV function, decreased infarct size, or improve clinical outcomes. The timing of melatonin administration can impact its cardioprotective effects.

Our research demonstrates that the intraoperative heart rate was considerably lower in the control group (67.167.95) than in the melatonin group (71.767.11) after 30 minutes of CPB.

In a study on the hearts of rats published in 2013, **Diez *et al.*** [11] discovered that ventricular tachycardia incidence was high at the start of reperfusion and that the severity of the arrhythmias gradually decreased in hearts handled with melatonin. The action potential duration at the start of reperfusion was shortened by melatonin. Myocardial arrhythmia can be improved by melatonin. These trials supported our findings since there were no post-CPB substantial tachycardias or arrhythmias in the melatonin-treated groups. However, we did see substantial bradycardia and cardiac stunning in the placebo group (67.167.95), which required the administration of cardiac support medications.

Cardiac troponin I is recognized as a particular indicator of acute myocardial infarction and as a measure of the success of reperfusion following thrombolytic treatment.

In comparison to the placebo-controlled group (0.570.23) microg/L, the melatonin-treated group had a substantially lower plasma level of cTnI (0.440.14) microg/L [12].

In this study, which **Dwaich *et al***. [12] presented in 2016, 45 patients who were experiencing elective CABG were randomly assigned to 3 study groups: a placebo-controlled group (C), a low-dose melatonin treatment group taking a 10 mg capsule once a day (M1), and a high dose melatonin treatment group taking a 20 mg capsule once a day (M2) (M2). The ejection fraction (EF%) substantially increased in the M1 and M2 groups as opposed to the control group, while the heart rate (HR) substantially decreased ($P<0.05$). The plasma levels of the cardiac Troponin-I (CTnI), interleukin-1beta (IL-1), inducible nitric oxide synthase (iNOS), and caspase-3 enzymes were also substantially lower in the melatonin groups (groups M1 and M2) as opposed to the control group ($P< 0.05$). When as opposed to the M1 group, the M2 group's changes in these metrics were more substantial ($P<0.05$). These results proposed that melatonin supplementation may have dose-dependent beneficial effects in reducing the severity of the myocardial ischemic-reperfusion injury.

The results of our study are following the study of **Rodriguez *et al.*** [8] which found that the intravenous administration of 51.7 mol melatonin at 60 min before reperfusion and the use of an intracoronary bolus of 8.6 mol melatonin at the beginning of reperfusion in 146 individuals with STEMI substantially reduced infarct size in the melatonin-induced myocardial infarction. Additionally, they discovered that melatonin administered roughly 2.5 hours following the onset of chest discomfort could lower the infarct size by about 40% as determined by cardiovascular magnetic resonance. According to a study by **Rodriguez *et al.*** [13], the use of melatonin in conjunction with secondary preventive care may have supplementary protective benefits on LV remodeling.

Declaration of conflict of interest

There was no disclosure of any possible conflicts of interest related to the research.

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CONCLUSION

The administration of oral melatonin hormone 10 mg for two nights pre-revascularization can decrease myocardial I/R injury and Improve outcome after CABG surgery by increasing cardiac systolic function EF%, decreasing and improving cardiac wall motion

abnormalities, decreasing cardiac injury biomarkers (CK -MB and troponin I) and decrease post-operative ventilation duration.

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