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Possible effects of melatonin on reperfusion injury following coronary artery bypass graft surgery

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Original Article

Abstract

BACKGROUND: Although coronary artery bypass graft (CABG) surgery has been reported to be one of the most effective internentions in terms of myocardial salvage, reperfusion itself can cause additional damage to the myocardium. Since there is strong evidence that free radicals are the principal offender in ischemia-reperfusion (I/R) injury, it has been suggested that treatment with antioxidant agents can be protective. Investigations have shown that melatonin secretion is partially disturbed in CABG patients. The aim of this study was to evaluate the protective effect of melatonin as an antioxidant agent on I/R injury.

METHODS: 164 elective CABG candidates participated in this randomized clinical trial during the preoperative period. The candidates were randomized to receive 3 mg of melatonin tablets (physiologic dose) from 3 days before surgery until the day of discharge. Cardiac biomarkers [troponin and creatine kinase myocardial band (CKMB)] were assessed once before surgery (24 hours before surgery), and 8 and 24 hours after surgery.

RESULTS: Finally, 130 patients, 65 (50%) patients in the melatonin group and 65 (50%) in the control arm finished our study. Mean age of melatonin and control groups was 59.90 ± 9.59 and 60.80 ± 8.00 years, respectively; moreover, 47 (72.30%) in melatonin and 45 (69.23%) in control group were men. No significant difference was seen in baseline cardiac biomarkers between two groups (P > 0.05). In both groups, cardiac biomarkers (CKMB and troponin) elevated after surgery in comparison to their preoperative values. There was no statistically significant difference between the control and melatonin groups regarding the 8-hour and 24-hour troponin and CKMB when adjusted for interacting factors (P > 0.05).

CONCLUSION: Although physiological concentration of melatonin is protective against I/R injury, substitution of endogenous melatonin with the oral supplement which creates physiologic concentration may not prevent I/R injury. In order to have antioxidant effect, pharmacologic doses of melatonin should be employed.

Keywords: Melatonin; Coronary Artery Bypass Graft Surgery; Ischemia Reperfusion Injury

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Introduction

Coronary artery bypass graft (CABG) surgery is one of the wellknown interventions in the history of cardiac surgeries.[1] Although this intervention has been reported to be highly effective regarding myocardial salvage, reperfusion itself can act as a double-edged sword. Ischemia-reperfusion (I/R) injury is the result of restoration of blood flow to the previously ischemic myocardium. This process is associated with additional harm to the myocardium beyond that generated by ischemia alone.[2,3]

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Myocardial I/R injury is a multifactorial process, involving partially reduced oxygen species, free radicals (oxidative stress), and calcium overload.[2] This process can result in denaturation of proteins, modification of deoxyribonucleic acid (DNA) as well as oxidation of membrane lipids, all of which can ultimately lead to myocardial cell death. The extent of injury can be determined by measuring serum troponin and creatine kinase myocardial band (CKMB).[2,4,5] Since there is strong evidence that free radicals are the principal offender in I/R injury, it has been suggested that treatment with antioxidant agents can protect myocardium from I/R injury.[6] Melatonin is a kind of natural hormone mainly secreted by the epiphysis into the blood circulation. In addition to its main role in regulating circadian rhythm, it possesses some antioxidant effects.[6] There is some evidence that melatonin secretion is partially disturbed in perioperative period, but melatonin substitution has not been studied in these patients.[7] The aim of this study was to evaluate the protective effect of 3 mg melatonin on I/R injury.

Materials and Methods

Patients, setting, and intervention: 164 elective CABG candidates participated in this clinical randomized double-blind study during the preoperative period. All the candidates signed the informed consent forms. The protocol of the study has been approved by the Ethics Committee for Human Research at Tehran University of Medical Sciences, Tehran, Iran. Subjects taking antioxidant or anti-inflammatory medications, or concomitant valvular surgery were excluded from our study. Patients were randomized to each group using permuted-block randomization method. Subjects in melatonin group received 3 mg of melatonin tablets (Nature Made, Canada) 3 days before the procedure until the day of discharge, while the control group received nothing. All the candicates underwent operation with the same technique (on pump) and same surgical team. Additionally, patients received the same cardiac medication regimen, including angiotensin-converting enzyme (ACE) inhibitors, betablockers, vasodilator agents, statins, aspirin, and heparin.

There was no source of founding and this clinical trial has been registered in Iranian Registry of Clinical Trials (IRCT) with the allocated number of IRCT201303148698N1.

Evaluation of cardiac biomarkers: Cardiac biomarkers (troponin and CKMB) were assessed once before surgery (24 hours before surgery), and 8 and 24 hours after surgery.

Measurement of CKMB: CKMB was analyzed using standard enzyme-based biochemical analysis. (CKMB Cobas LOT 176907)

Measurement of troponin: High-sensitivity troponin T (hs-TnT) was analyzed using standard enzyme-based biochemical analysis (Troponin T hs Cobas LOT 179491).

Statistical analysis: Continuous variables were presented as mean ± standard deviation (SD) when the data were normally distributed, or median with interquartile range (IQR) boundaries when they were not. Normality assumption was checked with Kolmogorov-Smirnov test. Continuous variables were compared between groups using Student's t-test or Mann-Whitney U test. Categorical variables were expressed through frequency and percentage and were compared between two groups using chi-square test or Fisher's exact test (if needed). Cardiac biomarkers (CKMB and troponin) were analyzed between three times using repeated measures analysis of covariance (ANCOVA) with a Greenhouse-Geisser correction. P-values less than or equal to 0.05 were considered as statistically significant. SPSS software (version 20.0, IBM Corporation, Armonk, NY, USA) was applied to do the analyses.

Results

164 CABG candidates were enrolled in our study. Of this total, 10 (6%) patients were excluded from the study because of postoperative complications (4 in melatonin vs. 6 in the control group), and 24 (14%) were excluded because of high baseline cardiac biomarkers. Therefore, the statistical analysis was performed on 130 patients: 65 (50%) subjects in the melatonin group and 65 (50%) in the control arm (Figure 1). Mean age of melatonin and control groups was 59.90 ± 9.59 and 60.80 ± 8.00 years, respectively; moreover, 47 (72.30%) in melatonin and 45 (69.23%) in control group were men. There was no statistical significant difference regarding age and sex between groups ($P > 0.05$). None of the patients in meltonin or control group died or needed re-operation during their hospital stay. There was no significant difference in the baseline and demographic characteristics of the patients in terms of gender, age, and body mass index (BMI) (Table 1). The risk factors [such as smoking, diabetes, hypertension (HTN), and family history] and perioperative parameters [such as laboratory data, atrial fibrillation (AF), intra-aortic balloon pump (IABP), blood product using, and blood transfusion in intensive care unit (ICU)] showed no significant differences between the two groups.

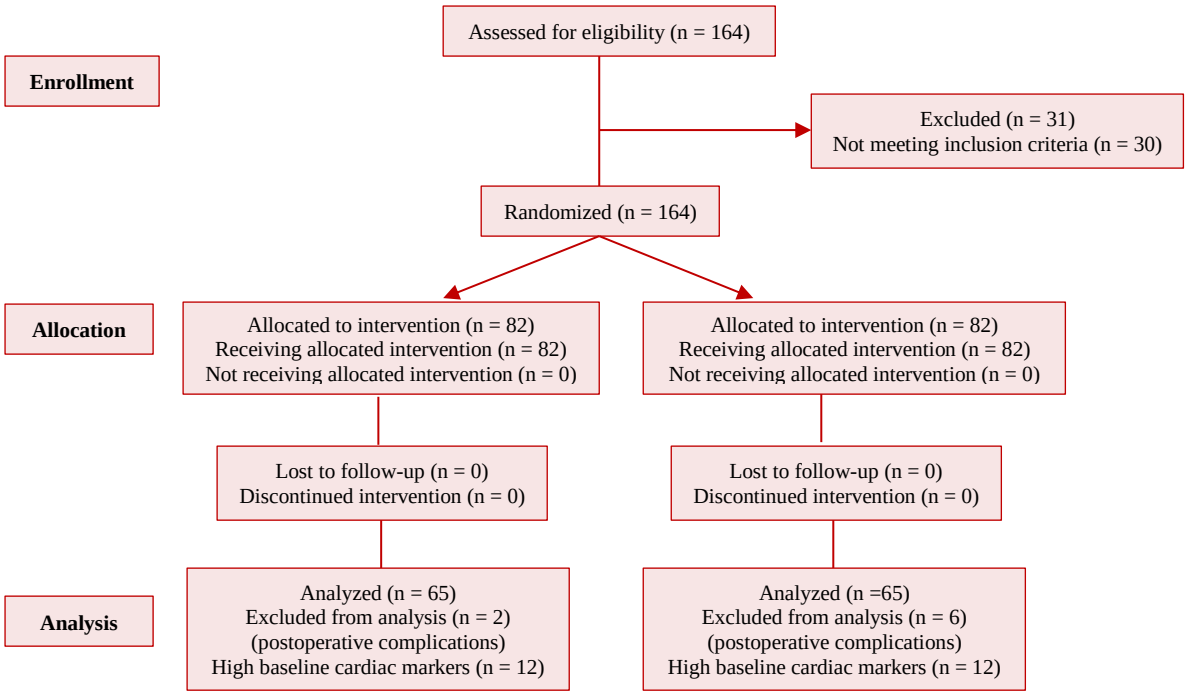

Figure 1. Consort flowchart

However, two groups were different in terms of serum creatinine (Cr) (0.89 mg/dl in melatonin vs. 0.94 mg/dl in the control group), dyslipidemia (38 in melatonin vs. 24 in the control group), pump time (80 minutes in melatonin vs. 60 minutes in the control group), cross-clamp time (50 minutes in melatonin vs. 34.5 in the control group), and sinus rhythm (50 in melatonin vs. 36 in the control group) (Table 2). Since atorvastatin exhibits some antioxidant actions, the administration of atorvastatin was compared between two groups, and there was no significant difference between groups, regarding the atorvastatin administration (Table 3).

Cardiac biomarkers (CKMB and troponin) were analyzed using repeated measures ANCOVA adjusted for pump time, cross-clamp time, atorvastatin, dyslipidemia, Cr, and sinus rhythm. There was no significant difference in baseline cardiac biomarkers between two groups.

Table 1. Comparison of demographics and cardiovascular disease (CVD) risk factors in coronary artery bypass graft (CABG) patients

	Melatonin (n = 65)	Control (n = 65)	P
Demographics			
Age (year)	59.90 ± 9.59	60.80 ± 8.00	0.613
Sex (men)	47 (72.30)	45 (69.23)	0.458
BMI (kg/m^2)	27.00 ± 4.50	28.20 ± 3.82	0.152
CAD risk factors			
Smoking			0.205
Never	43 (66.15)	45 (69.23)	
Current	11 (16.92)	11 (16.92)	
Former	11 (16.92)	9 (13.84)	
Diabetes	16 (24.61)	17 (26.15)	0.863
Dyslipidemia	38 (58.46)	24 (36.92)	0.018
HTN	32 (49.23)	29 (44.61)	0.721
Family history of CVD	14 (21.53)	8 (12.30)	0.118

Continuous and categorical variables were reported as mean ± standard deviation (SD) and number (percent), respectively. Independent t-test and chi-square test were imployed for continuous and categorical variables, respectively.
BMI: Body mass index; CAD: Coronary artery disease; HTN: Hypertension; CVD: Cardiovascular disease

Table 2. Comparison of perioperation factors in coronary artery bypass graft (CABG) patients

Pre-operation lab data	Melatonin (n = 65)	Control (n = 65)	P
WBC (ng/l)	7478.7 ± 1945.7	8165.0 ± 1779.4	0.108
Hb (mg/dl)	13.80 ± 1.53	13.10 ± 1.74	0.051
FBS (mmol/l)	105.30 ± 35.10	96.50 ± 22.10	0.210
BUN (mg/l)	39.10 ± 17.40	37.50 ± 12.60	0.649
Cr (mg/dl)	0.89 (0.74-0.99)	0.94 (0.84-1.03)	0.022
TC (mg/dl)	147.10 ± 37.10	134.20 ± 36.10	0.125
HDL (mg/dl)	37.90 ± 10.90	37.10 ± 9.01	0.734
LDL (mg/dl)	87.40 ± 31.30	83.60 ± 30.30	0.585
TG (mg/dl)	127.0 (94.0-185.0)	108.0 (80.5-157.0)	0.088
Troponin (ng/l)	11.80 ± 1.02	12.12 ± 1.26	0.825
CKMB (ng/ml)	1.65 ± 0.24	2.29 ± 0.31	0.438
Perioperation parameters			
Pump time (minute)	81.0 (70.0-93.0)	60.0 (50.0-80.0)	< 0.001
Cross-clamp time (minute)	50.0 (42.0-56.2)	34.5 (27.7-50.7)	< 0.001
Sinus rhythm	59 (90.76)	39 (60.00)	< 0.001
AF	0 (0)	1 (2.22)	0.828
IABP	0 (0)	0 (0)	-
Blood product using	12 (18.46)	10 (15.38)	0.753
ICU blood transfusion	25 (38.46)	22 (33.84)	0.577

Continuous and categorical variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) and number (percent), respectively. Independent samples t-test and Mann-Whitney U test were employed for normally and non-normally distributed data, respectively. Chi-squre test (or Fisher's exact test) was used for categorical variables.

WBC: White blood cell; Hb: Hemoglobin; FBS: Fasting blood sugar; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CKMB: Creatine kinase myocardial band; Cr: Creatinine; TC: Total cholesterol; TG: Triglyceride; AF: Atrial fibrillation; IABP: Intra-aortic balloon pump; ICU: Intensive care unit

Table 3. Comparison of using medication in coronary artery bypass graft (CABG) patients

Medications Atorvastatin	Melatonin (n = 65)	Control (n = 65)	P
None	5 (7.69)	6 (9.23)	0.910*
20 mg	28 (43.07)	25 (38.46)	
40 mg	32 (49.23)	34 (52.30)	

Data are reported as number (percent)

* Chi-square test was used

In both groups, cardiac biomarkers (CKMB and hs-TnT) were elevated after surgery in comparison with their preoperative values. There was no significant difference between the melatonin and control groups regarding the 8-hour and 24-hour troponin and CKMB when adjusted for interacting factors (P > 0.05) (Tables 4 and 5).

Discussion

The aim of the present study was to evaluate the possible effect of substitution of endogenous melatonin on I/R injury after CABG. Several publications have reported that patients with different stages of cardiovascular disease (CVD) have decreased melatonin concentration in comparison with age-matched individuals with no cardiac pathology.

Similarly, patients with cardiac syndrome X (CSX) have a decreased nocturnal melatonin concentration in comparison with healthy subjects.[8] One study has also shown that low nocturnal levels of melatonin can be predictive for the development of cardiac events in patients with ST elevation acute coronary syndrome (ACS).

Table 4. Mean adjusted melatonin on troponin and creatine kinase myocardial band (CKMB) between groups in coronary artery bypass graft (CABG) patients

	Melatonin (n = 65)			Control (n = 65)			P*
	Baseline	After 8 hours	After 24 hours	Baseline	After 8 hours	After 24 hours	
Troponin (ng/l)	11.80 ± 1.02	476.90 ± 44.50	285.90 ± 31.30	12.12 ± 1.26	396.90 ± 55.10	255.50 ± 38.80	0.461
CKMB (ng/ml)	1.65 ± 0.24	28.50 ± 2.62	18.80 ± 10.90	2.29 ± 0.31	21.80 ± 3.33	12.53 ± 5.05	0.316

Data are reported as mean ± standard error (SE)

Adjusted for pump time, cross-clamp time, atorvastatin, dyslipidemia, creatinine (Cr), and sinus rhythm

* Repeated measures analysis of covariance (ANCOVA) with a Greenhouse-Geisser correction was used.

CKMB: Creatine kinase myocardial band

Table 5. Crude and adjusted analysis of covariance (ANCOVA) for mean difference in coronary artery bypass graft (CABG) patients

	Melatonin		Control		P	
	Mean difference (mean ± SD)	Median (IQR)	Mean difference (mean ± SD)	Median (IQR)	Crude	Adjusted*
Troponin (ng/l)	475.9 ± 299.9	425.3 (247.3-600.1)	397.2 ± 370.4	316.2 (138.1-434.1)	0.007	0.220
CKMB (ng/ml)	29.0 ± 33.2	18.5 (14.0-34.4)	18.6 ± 14.7	15.5 (8.2-20.2)	0.017	0.091

*Adjusted for pump time, cross-clamp time, atorvastatin, dyslipidemia, creatinine (Cr), and sinus rhythm
SD: Standard deviation; IQR: Interquartile range; CKMB: Creatine kinase myocardial band

Some of these beneficial effects are associated with antioxidant effect of melatonin.[9] Melatonin is a potent antioxidant which can act as an intracellular free radical scavenger.[6] Melatonin ability in scavenging free radicals is higher than well-known antioxidants such as glutathione, vitamin C, and vitamin E.[6] With respect to extraordinary high antioxidant effect of melatonin, several animal studies have been designed to evaluate the protective effect of melatonin on I/R injury and most of them have demonstrated promising results. In addition to its radical scavenging effect, melatonin stimulates several antioxidant enzymes and down-regulates pro-inflammatory as well as pro-oxidative enzymes.[10-12] Furthermore, melatonin can decrease cytosolic calcium in cardiomyocytes and promotes the efficiency of the mitochondrial electron transport chain.[6,13,14] Via these combined beneficial actions, melatonin can act as a protective agent against I/R injury. It has also been hypothesized that I/R injury during CABG might be partly due to decresed melatonin secretion in the perioperative period.[15,16]

Many factors have been suggested to inhibit melatonin production during CABG. Some medications which are commonly prescribed in the perioperative period can disturb melatonin secretion.[17] For example, benzodiazepines (BDZs), which are frequently used as hypnotic, can disturb the nocturnal secretion of melatonin and the circadian rythme by interacting with the gamma-aminobutyric acid (GABA) receptor. Additionally, studies have shown that narcotics can supress the circadian rhythm of melatonin. Beta blockers are another class of medications which can decrease melatonin secretion by acting on adrenergic receptors located in the pineal gland.[16,18,19] Moreover, it seems that the reduction of plasma concentration of melatonin is caused by the consumption of this hormone as an antioxidant in order to neutralize the oxidative stress induced by the surgery.[20]

In an investigation which was operated by Sokullu et al., two groups of patients were compared with each other, those who underwent operation at night, when the peak plasma concentration of melatonin is present, and those who underwent operation in the morning.

The findings of this study showed that high plasma levels of melatonin were directly related to low levels of I/R injury markers.[13]

The aim of this study was to evaluate the protective effect of substitution of endogenous melatonin on I/R injury after CABG. In our study, we did not detect any protective effect of melatonin on I/R injury with respect to cardiac biomarkers.

One study has shown that in spite of the critical illness, the bioavailability of melatonin after oral administration is satisfying and the intestinal absorption is comparable to that of normal volunteers.[21]

Gogenur et al. have evaluated the effect of perioperative melatonin on cardiac morbidity and markers of myocardial ischemia in patients undergoing surgery for abdominal aortic aneurysm. In this clinical trial, patients received either 50 mg melatonin or placebo intra-operatively by infusion over a 2-hour period, and 10 mg melatonin or placebo orally for the first three nights after surgery. A significant reduction in cardiac morbidity was seen in the melatonin group. In aforementioned study, 19% of patients who received melatonin had increased troponin levels when compared with 50% of patients in placebo group.[22] In another study, thirty patients undergoing CABG were randomized to receive either 10 mg of melatonin tablet or placebo at night for 1 month before the operation. The activated nuclear factor erythroid 2-related factor 2 (Nrf2) was measured once before aortic clumps and once 45 minutes after the surgery. Melatonin administration before the surgery was associated with a significant increase in both plasma levels of Nrf2 and melatonin concentration.[23]

In all above-mentioned studies, a pharmacologic dose (above 10 mg) of melatonin has been employed to reduce the massive cardiac damage that occurs during I/R injury. Although physiological concentration of melatonin is

protective against I/R injury as shown in Sokullu et al.'s research, creating physiologic concentration with exogenous melatonin may not prevent I/R injury.[13] On the other hand, supraphysiologic or pharmacologic doses of melatonin (from 10 mg to as high as 10 mg/kg) are needed to reduce the damage that occurs during I/R injury. Indeed the reason is the fact that the physiological concentrations of all endogenous antioxidants are not enough to prevent tissue damage caused by such an inordinate oxidative stress.[23-25]

Studies which have examined the different doses of melatonin have found that congesting an oral dose of 0.1 to 0.3 mg can produce plasma concentration similar to those occurring with nocturnal melatonin secretion, and has a physiologic effect. Furthermore, this dose determines the dose range that researchers have to employ if they want to investigate the physiologic effects of melatonin.[26]

This study encountered some limitations. In this study, total antioxidant capacity was not measured before and after the intervention in order to see to what extent the administration of the supplement has changed the total antioxidant capacity. Additionally, lack of placebo group in this study can adversely affect the results, and should be mentioned as a limitation of this study.

Conclusion

Although physiological concentration of melatonin is protective against I/R injury, substitution of endogenous melatonin with oral supplement, which creates physiologic concentration, may not prevent I/R injury. To have antioxidant effect, pharmacologic doses of melatonin should be employed.

Lack of placebo group in this study can be mentioned as a limitation.

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None.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

AHT conceived the presented idea, developed the theory and the design, and supervised the findings of this work. MD carried out the research, and wrote the article. PG contributed to the design and implementation of the research. AS supervised the findings of this work. MD contributed to the interpretation of the results and statistical analysis.

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