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A Study of the Prophylactic and Curative Effect of Melatonin on Postoperative Delirium after Coronary Artery Bypass Grafting Surgery in Elderly Patients

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ABSTRACT

Background: delirium is a common complication after cardiac surgical procedures and is associated with increased morbidity and mortality. Postoperative delirium is associated with an increased length of stay in the intensive care unit, long hospital stay and high hospital charges. **Aim of the Work:** to investigate the effectiveness of melatonin as a preoperative sedative as well as the preventive and the curative effect of melatonin supplementation in elderly patients undergoing coronary artery bypass surgery on postoperative delirium. **Patients and Methods:** this prospective, randomized, controlled, double blind study was conducted on a total of 50 patients allocated into 2 equal groups. It was conducted in Ain Shams University hospitals, in the cardiothoracic surgery unit. **Results:** melatonin has superior sedative effect at 30 min preoperatively compared with placebo (P=0.022). Melatonin succeeded to treat about 56% of delirious patients. The incidence of delirium was 8% in the melatonin group vs. 28% in the control group (P= 0.046). In univariate analysis, predictors of delirium in both groups were age (P= 0.049 in melatonin group, P=0.021 in control group), higher fentanyl dose (P= 0.021 in melatonin group, P=0.047 in control group), lower ejection fraction (P= 0.018 in melatonin group, P=0.008 in control group), longer cardiopulmonary bypass (CPB) times (P= 0.026 in melatonin group, P=0.04 in control group) and longer aortic cross clamping (ACC) times (P= 0.04 in melatonin group, P=0.019 in control group). **Conclusion:** administration of melatonin significantly decreased the incidence of postoperative delirium (POD) after coronary artery bypass grafting in elderly patients and significantly increased preoperative sedation. Advanced age, higher total intraoperative fentanyl dose, lower ejection fraction and longer CPB and ACC times were independent predictors of POD with or without melatonin supplementation.

Keywords: melatonin, postoperative delirium, coronary artery bypass grafting, elderly

INTRODUCTION

Delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, global cognitive impairment, disorientation, the development of perceptual disturbance, attention deficits, decreased or increased psychomotor activity, disordered sleep-wake cycle, and fluctuation in presentation. The term ‘‘delirium’’, from the Latin roots de (meaning ‘‘away from’’) and lira (meaning ‘‘furrow in a field’’) and ium (Latin for singular), literally means ‘‘a going off the ploughed track, a madness’’ [(1)].

Delirium is a common complication in elderly patients after cardiac surgery and is associated with adverse outcomes including prolonged hospital stay and increased mortality [(2)].

The incidence of postoperative delirium ranges from 10 to 46% in general surgical population and reaches 50 to 67% among the patients undergoing cardiac surgery [(3)].

Drugs have been associated with the development of delirium in the elderly. Successful treatment of delirium depends on identifying the reversible contributing factors, and drugs are the most common reversible cause of delirium. Anticholinergic medications, benzodiazepines, and narcotics in high doses are common causes of drug induced delirium [(4)].

Melatonin by virtue of its multiple functions has the potential to take a place in the anesthetic drug armamentarium, because it can be an attractive option for premedication as an anxiolytic and sedative, for the induction of general anesthesia as a hypnotic or as an induction adjuvant and perioperatively for analgesia. Melatonin can also be used postoperatively to store sleep rhythm and prevent delirium [(5)].

AIM OF THE WORK

The aim of this work is to investigate the effectiveness of melatonin as a preoperative sedative as well as the preventive and the curative effect of melatonin supplementation in elderly patients undergoing coronary artery bypass surgery on postoperative delirium.

PATIENTS AND METHODS

Study design and sampling

After approval of the Research Ethics Committee and written informed patient consent,

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this prospective, randomized, controlled, double blind study was conducted on 50 patients allocated into 2 equal groups. This study was conducted at Ain Shams University hospitals, in the Cardiothoracic Surgery unit.

Inclusion criteria Elective coronary artery bypass grafting surgery. Two or three vessel grafts. Age ≥60 years, both sexes. ASA physical status III-IV.

Exclusion criteria: Emergent coronary artery bypass grafting surgery. ASA physical status ≥V. Ejection fraction <40%. Patients with preoperative Mini Mental State Examination (MMSE) score ≤24. History of neuropsychiatric disorders. History of liver cirrhosis or renal failure. History of chronic pulmonary diseases. Uncontrolled systemic disease e.g. uncontrolled diabetes mellitus or systemic hypertension. Serious perioperative or postoperative complications causing unexpected morbidity e.g. sepsis, thromboembolic events, etc. Prolonged postoperative ventilation >8 hours. History of chronic sedative hypnotics use >3 times/week during a month prior to cardiac surgery. Allergy to the study drugs or one of their ingredients**.**

Randomization: Patients who met all the inclusion criteria were randomized to either Group M (Melatonin group) or Group C (Control group) by using computer generated random numbers with closed sealed envelope.

Endpoint: Non occurrence of delirium during the first three postoperative days. The need for further evaluation and treatment of postoperative delirium among delirious patients who did not respond to melatonin.

Methods

All patients were fasted according to standard rules and were seen and examined by an anesthesiologist at the night of the surgery.

All patients were screened at that time by Mini-Mental state examination (MMSE) according to Folstein [(6)] test. The maximum score is 30. Patients with MMSE score ≤ 24 were excluded from the study.

Group M (Melatonin group): received 3 mg melatonin orally at 9 p.m. the night before surgery and another 3 mg melatonin with 15 ml of plain water 30 min before operation and 3 mg melatonin at 9 p.m. in the day of operation after weaning from mechanical ventilation and the first three postoperative days.

Group C (Control group): received a placebo that looked the same and packaged the same way as melatonin at the same times.

The anesthesia residents who administered the drug the night before the surgery and the ICU residents who administered the study drugs and assessed Intensive Care Delirium Screening Checklist (ICDSC) postoperatively were all blinded to the allocation regimen.

On arrival to the preanesthesia room at 9 a.m., sedation was assessed by a five - point clinical global impression (CGI) sedation score for all the patients. The maximum sedation score is 4 and the minimum score is 0.

All patients received their routine cardiac medication until day of surgery. IV antibiotic was started. All Patients were monitored with five lead ECG, invasive arterial blood pressure after radial artery catheterization, oxygen saturation, capnography and a nasopharyngeal temperature probe.

Induction of anesthesia was done with fentanyl (10 μg/kg), thiopental (3-4 mg/kg), midazolam (0.03-0.05 mg/kg) and rocuronium (0.6 mg/kg).

Intubation was done with oral cuffed endotracheal tube size 7-7.5 mm ID for females and 7.5-8 mm ID for males.

Right internal jugular central venous catheter was placed after induction for all patients.

Anesthesia was maintained with isoflurane (0.75- 1%), incremental doses of rocuronium every 30 minutes and increments of fentanyl up to a total dose of 20 μg/kg.

After surgery, patients were transferred to ICU mechanically ventilated, planned for weaning from mechanical ventilation as soon as they reach hemodynamic stability, consciousness and adequate pain control.

Patients of Group M received 3 mg melatonin at 9 p.m. in the same operative day after weaning from mechanical ventilation and the following three postoperative days.

Intensive Care Delirium Screening Checklist (ICDSC) was reported in the same day after operation (Day-0) and in the followed three postoperative days (Day-1, Day-2 and Day-3). All patients were vitally stable and normothermic at the time of evaluation. Patients who had ICDSC score ≥ 4 were considered to have postoperative delirium[(7)]. These patients

received 3 mg melatonin orally at 9 p.m. daily and ICDSC was reassessed daily for up to 3 successive days after delirium development. A psychiatrist was consulted for further management if there was no response to melatonin.

Measured variables: Preoperative variables: hemoglobin level, serum creatinine, BUN, SGOT, SGPT, albumin, ejection fraction and Mini-mental state (MMSE) score. Preoperative sedation score. Total doses of intraoperative narcotics (pre, post and during cardiopulmonary bypass). End tidal concentration of inhalational anesthetics. Number of grafts. Aortic cross clamping time and cardiopulmonary bypass time. Time for weaning from mechanical ventilation. Postoperative delirium: The postoperative delirium was assessed by implementing the Intensive Care Delirium Screening Checklist (ICDSC). Including altered level of consciousness, the ICDSC consists of eight items (rated present or absent), and each patient was given a score from 0 to 8; 4 or greater is considered diagnostic of delirium [7].

Statistical analysis

Using *Power Analysis and Sample Size (PASS) 13*, group sample size of 25 patients per group achieved 80% power to detect a difference of 15% in the reduction of delirium incidence between the two groups with a significant alpha level of 0.05.

Data were analyzed using *Statistical Package for Social Science (SPSS) version 21.0. Chicago, Illinois, USA.* Quantitative data were expressed as mean ± standard deviation. Qualitative data were expressed as number of patients and percentage. The independent-samples t-test was used to compare between means in the two groups. Skewed numerical data are presented as median (range) and independent samples-median test was used to compare between medians in both groups. Chi square test was used to compare proportions between two qualitative parameters. Univariate analysis was used to test the predictors of delirium. *P-value <0.05* was considered significant and *P-value < 0.01* was considered highly significant.

RESULTS

1. Demographic data

Group M and Group C were comparable regarding age, sex weight, American Society of Anesthesiologists Physical Status (ASA-PS) and past medical history, no statistically significant differences between both groups were found (P-value > 0.05) (table 1).

Table (1): Demographic data.

Variable	Group M(n=25)	Group C(n=25)	P-value
Age (years)	66.56±4.79	67.88±4.13	0.303
Weight (Kg)	84.61±10.41	83.88±11.12	0.814
Sex (M/F)	12/13	14/11	0.571
ASA-PS (III/IV)	14/11	13/12	0.777
Medical history (None/DM/HTN/Both	5/6/7/7	3/7/8/7	0.886

Data presented as mean ± SD or number of patients; P-value > 0.05 is considered statistically non-significant;
ASA-PS=American Society of Anesthesiologists Physical status; DM=Diabetes mellitus and HTN=Hypertension.

2. Preoperative variables

The preoperative variables (Hemoglobin "Hb" level, serum creatinine, BUN, SGOT, SGPT, albumin, ejection fraction "EF" and Mini-Mental State Examination "MMSE" score) showed no significant difference between the two groups (P-value> 0.05) (table 2).

Table (2): Preoperaive variables.

Variable	Group M(n=25)	Group C(n=25)	P-value
Hb (gm/dl)	12.66±1.20	12.48±1.17	0.595
Creatinine (mg/dl)	1.01±0.24	0.82±0.17	0.06
BUN (mg/dl)	18.28±4.19	18.84±4.65	0.657
SGOT (mg/dl)	40.28±5.30	38.52±5.29	0.246
SGPT (mg/dl)	41.60±6.53	44.28±7.24	0.176
Albumin (gm/dl)	4.12±0.41	5.78±8.38	0.330
EF (%)	58.40±6.37	59.08±6.43	0.709
MMSE	29(27-30)	29(28-30)	0.773

Data presented as mean± SD or median (range); P-value > 0.05 is considered statistically non-significant
BUN=Blood urea nitrogen; EF=Ejection fraction; Hb=Hemoglobin; MMSE=Mini-Mental State Examination; SGOT=Serum glutamic oxaloacetic transaminase and SGPT=Serum glutamic pyruvic transaminase.

3. Intraoperative and postoperative variables

Isoflurane end-tidal concentration (%), total doses of fentanyl consumed (μg), aortic cross clamping time (min) and bypass time (min) were all recorded intra-operatively (table 3).

Table (3): Intraoperative and postoperative variables.

Variable	Group M (n=25)	Group C (n=25)	P-value
Isoflurane end tidal concentration (%)	1±0.176	1.1±0.16	0.936
Fentanyl consumed (μg)	1250±156.79	1234±140.47	0.706
CPB (min)	66.52±17.42	68.4±23.17	0.747
ACC time (min)	44.4±13.01	41.6±11.06	0.416
Number of grafts	2(2-3)	3(2-3)	0.777
Time for weaning from ventilator (hours)	5.76±1.48	5.60±1.08	0.664

Data presented as mean± SD or median (range); P-value > 0.05 is considered statistically non-significant

ACC= Aortic cross clamping and CPB=Cardiopulmonary bypass.

4. Assessment of sedation

Sedation was assessed by a five point scale at 30 min after the premedication in the morning of the surgery. The results demonstrated that melatonin was associated with higher sedation compared to placebo (P-value = 0.002) (table 4).

Table (4): Sedation score.

Score	Group M(n=25)	Group C(n=25)	P-value
0	19	25	0.022
1	6	0	
2	0	0	
3	0	0	
4	0	0	

Data presented as number of patients; P-value < 0.05 is considered statistically significant

5. Assessment of postoperative delirium (POD)

POD was assessed by using Intensive Care Delirium Screening Checklist (ICDSC) on postoperative days 0, 1, 2 and 3. The cutoff ICDSC score to diagnose delirium was ≥ 4. The results demonstrated that there was a significant decrease in the incidence of delirium among the patients who received prophylactic melatonin (Group M) compared to Group C (P-value < 0.05).The use of prophylactic melatonin had succeeded to decrease the incidence of POD from 28% to 8% (table 5).

Table (5): Delirium data in both groups.

Delirium data	Group M (n=25)	Group C (n=25)	P-value
Incidence of delirium	2 (8%)	7 (28%)	0.046
Number of patients who developed delirium on:			
Day-0	1	5	
Day-1	1	1	
Day-2	0	1	
Day-3	0	0	

Data is presented as number of patients or (%); P-value < 0.05 is considered statistically significant

6. Melatonin as a therapeutic agent in patients who developed delirium in both groups

Assessment of delirium by ICDSC was further extended to another three days in patients who developed ICDSC score ≥ 4 in either group on Day-0, 1, 2 or 3.

All patients in Group M who developed delirium on the same day of surgery or any of the first three postoperative days were cured in response to melatonin therapy "ICDSC score dropped below 4" (table 6).

Three (3) out of seven (7) patients who developed delirium in Group C on the same day of surgery or any of the first three postoperative days were cured in response to melatonin therapy "ICDSC score dropped below 4" (table 6).

Two (2) out of seven (7) patients who developed delirium in Group C on the same day of surgery or any of the first three postoperative days improved but were not cured in response to melatonin therapy "ICDSC score still = 4" (table 6).

Two (2) out of seven (7) patients who developed delirium in Group C on the same day of surgery or any of the first three postoperative days did not respond to melatonin therapy (table 6).

Table (6): Response to melatonin therapy in patients who developed delirium in both groups.

	Group M (n=25)	Group C (n=25)	P-value
Incidence of delirium	2 (8%)	7 (28%)	0.046
Number of patients who were cured after melatonin therapy	2 (100%)	3 (42.9%)	
Number of patients whose ICDSC score improved but were not cured in response to melatonin therapy	0	2 (28.6%)	
Number of patients who did not respond to melatonin therapy	0	2 (28.6%)	

Data is presented as count or (%); P-value < 0.05 is considered statistically significant

ICDSC=Intensive Care Delirium Screening Checklist

7. Univariate analysis of variables in both groups in association with delirium

Univariate analysis of the variables of both groups confirmed that older age ≥ 70 years (P-value = 0.049), longer CPB time ≥ 60 min (P-value = 0.026), longer ACC time ≥ 45 min (P-value = 0.04), lower EF < 55% (P value = 0.018) and higher fentanyl dose > 1200 μg (P-value = 0.021) were independently associated with POD (table7).

Table (7): Univariate analysis of the different independent variables in relation to the incidence of delirium in Group M.

Category	Number	Number with delirium (%)	P-value	OR	95% CI	
					Lower	Upper
Age ≥ 70 years	9	2 (22.2%)	0.049	2.286	1.124	4.198
Male gender	12	0 (0%)	0.175	--	--	--
DM and /or HTN	20	2 (10%)	0.157	--	--	--
EF < 55 %	7	2 (28.6%)	0.018	3.61	1.19	6.834
Fentanyl dose ≥ 1200 µg	20	1 (5%)	0.021	1.211	1.011	4.121
ACC time ≥ 45 min	14	1 (7.1%)	0.04	1.769	1.043	13.866
CPB time ≥ 60 min	16	2 (12.5%)	0.026	1.643	1.036	11.631

Data is presented as number of patients or (%); P-value < 0.05 is considered statistically significant

ACC=Aortic cross clamping; CBP=Cardiopulmonary bypass; CI=Confidence interval; DM=Diabetes Mellitus; EF=Ejection fraction; HTN=Hypertension and OR=Odds ratio.

Table (8): Univariate analysis of the different independent variables in relation to the incidence of delirium in Group C.

Category	Number	Number with delirium (%)	P-value	OR	95% CI	
					Lower	Upper
Age ≥ 70 years	9	5 (55.6%)	0.021	8.75	1.124	4.198
Male gender	14	5 (35.7%)	0.332	--	--	--
DM and /or HTN	22	6 (27.3%)	0.683	--	--	--
EF < 55 %	8	5 (62.5%)	0.008	12.5	1.6	97.647
Fentanyl dose ≥ 1200 µg	19	6 (31.6%)	0.047	2.308	1.219	24.316
ACC time ≥ 45 min	12	6 (50%)	0.019	12.124	1.164	13.68
CPB time ≥ 60 min	15	6 (40%)	0.002	6.025	1.596	60.437

Data is presented as number of patients or (%); P-value < 0.05 is considered statistically significant

ACC=Aortic cross clamping; CBP=Cardiopulmonary bypass; CI=Confidence interval; DM=Diabetes Mellitus; EF=Ejection fraction; HTN=Hypertension and OR=Odds ratio.

DISCUSSION

Delirium after cardiac surgery is a major problem. The exact mechanisms behind delirium are not fully understood. Several predisposing and precipitating risk factors have been identified for delirium. The development of delirium following cardiac surgery is associated with worse outcomes in the perioperative period. Multiple interventions are being explored for the prevention and treatment of delirium. Studies investigating the potential pharmacological interventions to reduce the incidence of delirium are necessary to mitigate this negative outcome [8].

There is growing interest in the perioperative use of melatonin for its potential analgesic, sedative and anxiolytic effects. In the current work, the perioperative use of melatonin was discussed for its potential prophylactic and therapeutic role in delirium in elderly patients.

The results of the present study showed that melatonin succeeded as a prophylaxis against POD in elderly patients undergoing CABG. It reduced the incidence of POD from 28% to 8%. Also melatonin was used as a therapy in patients who developed POD and was successful to treat about 56% of cases. Premedication with melatonin also proved a sedative effect. The correct dosage of melatonin in humans seems largely unknown [9].

Pharmacokinetic studies of orally administered melatonin (3 mg) in critically ill patients showed serum peak after 16 minutes and therapeutic levels were maintained up to 10 hours following administration [10].

A possible clinical effect and an appealing safety profile makes melatonin an interesting new drug for the perioperative setting. Moreover, widely used analgesics, anxiolytics and sedatives are associated with risk of side effects such as respiratory depression, Postoperative delirium (POD) and postoperative nausea and vomiting (PONV). The use of melatonin might decrease the risk of serious complications in the perioperative period [9].

The sedative of melatonin was investigated in the current study. The results demonstrated higher sedation score at 30 min after premedication with melatonin compared to placebo.

These results were consistent with those published by **Pokharel *et al.*** [11] who compared the effects of oral melatonin (3 mg), alprazolam (0.5), a combination of both medications and placebo on preoperative sedation and anxiety. Regarding sedation, they found that the three groups including melatonin (3 mg) are significantly sedated at 30 min and 60 min after premedication. These results matched those of **Sultan** [12] who found significant sedation with melatonin (5 mg) at 30 min after premedication compared to the control group in patients undergoing hip arthroplasty under spinal anesthesia.

In the current study, Melatonin succeeded to decrease the incidence of POD from 28% to 8%. The overall incidence of POD in both groups was 18%.

Artemiou *et al.* [13] had studied the prophylactic role of melatonin in the prevention of POD after cardiac surgery. They had found that the incidence of POD among cardiac surgery patients is 14.6% in both groups with delirium developed in 20.8% in control group vs. 8.4% in melatonin

group. This may indicate the effectiveness of the melatonin dose (3 mg) used in the current study in the prevention of POD as it showed comparable results with the higher dose of 5 mg.

Burkhart *et al.* [14] studied the modifiable and non-modifiable risk factors for POD after elective cardiac surgery with cardiopulmonary bypass (CPB) in patients aged 65 or older and reported the incidence of POD in these patients as 30%.

On the other hand, **Smulter *et al.*** [15] diagnosed delirium in 54.9% in their study upon 142 elderly patients aged 70 or more scheduled for routine cardiac surgery. They targeted older population in their study group.

The incidence of POD reaches up to 50-67% among the patients undergoing cardiac surgery. Wide variations in reported incidence depend on methodological differences between the studies, mainly concerning the implementation of delirium diagnostic tools and the characteristics of the study populations [3].

So, different assessment tools for POD as Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Mini Mental State Examination (MMSE) could be another explanation of higher incidence of POD.

The original validation study of CAM-ICU demonstrated a sensitivity between 95% and 100% and aspecificity between 89% and 93%. The validation of ICDSC was performed in a medical-surgical ICU, yielding a sensitivity of 99% and a specificity of 64%. When comparing these 2 tools, there are some advantages and disadvantages from each method. In general, the CAM-ICU does not depend exclusively on the verbal response, thus being relevant for patients on mechanical ventilation [16]. ICDSC was implemented in the current study as delirium assessment was conducted in the study groups only after extubation.

It is worth noting that all above mentioned studies which aimed at investigating POD in cardiac surgery did not focus on a homogenous operative group in contrast to the present study which was limited to patients undergoing CABG.

Regarding the heterogeneous cardiac surgery populations targeted in different studies, there may be a different factor in every type of cardiac surgery which may play a predominant role in the development of POD. For example aortic manipulation and atherosclerotic microembolization during cannulation and cross-clamping in CABG, whereas air bubbles trapped in the cardiac chambers may play a significant role in the development of delirium in valve surgery [17].In this context, **Artemiou *et al.*** [13] found that CABG and CABG combined with valve surgeries were all confirmed to be associated with an increased risk for the development of POD than the valve surgery alone. However, **Hudetz et al.** [18] had reported more frequent POD in patients undergoing valve surgery with or without CABG compared with CABG alone. This may also attribute to the vast differences in the reported incidence of POD after cardiac surgery and contributes to the multifactorial etiology of delirium.

The efficacy of melatonin in POD was shown in many studies upon patient populations other than cardiac surgery patients. **Al-Aama *et al.*** [19] had found that a low dose of melatonin (0.5mg) decreased the incidence of delirium in elderly patients aged 65 and over admitted through the emergency department to a medical unit (12% vs. 31%).

Also, **Sultan** [12] found in his study upon elderly patients scheduled for hip arthroplasty under spinal anesthesia that perioperative melatonin decreased POD to 9.43% compared to 32.56% in the control group.

Melatonin was used in the current study for treatment of POD in a total of nine (9) patients; two (2) patients in Group M and seven (7) patients in Group C. The success rate of melatonin to treat POD was about 56%. Another two (2) patients in Group C had improved ICDSC score in response to melatonin but they were not fully cured (ICSDC score improved but did not go down below 4). So melatonin succeeded to let ICDSC score go down (with or without total cure) in about 78% of all patients who developed delirium.

These results were comparable to those of **Sultan** [12] who studied the role of melatonin as a therapy in patients who developed POD after hip arthroplasty under spinal anesthesia. In his study, melatonin effectively treated thirty six (36) patients out of a total of sixty two (62) patients who developed delirium in the same day of surgery or any of the first three postoperative days in any of his study groups (the success rate was about 58%).

The results of the current study showed no statistically significant difference in the total doses of fentanyl consumed intraoperatively in the melatonin group compared to placebo.

In agreement with these results, **Artemiou *et al.*** [13] found no statistically significant difference in the total doses of sufentanil*(P-value = 0.286)* or benzodiazepines *(P-value = 0.116)* in the melatonin group when compared to the control group.

Also **Naguib and Samarkandi** [20] evaluated the perioperative effects of melatonin premedication (5 mg) compared to midazolam and placebo in women undergoing laparoscopic gynecological surgeries. There was no significant difference in the intraoperative opioid use or total doses of analgesics consumed in the melatonin, midazolam or placebo groups.

In contrast, **Caumo *et al.*** [21] who studied the narcotic sparing effect of melatonin upon patients undergoing abdominal hysterectomy found that melatonin (5 mg) resulted in reduction of postoperative morphine consumption by 30% compared to the control group in their study.

Also **Ionescu *et al.*** [22] studied melatonin as a premedication in patients undergoing laparoscopic cholecystectomy. The patients received melatonin (3 mg) the night before the surgery and in the morning as a premedication. They found that melatonin lowered the intraoperative fentanyl requirements in comparison to placebo.

A possible explanation for the conflicting results regarding the narcotic sparing effect of melatonin is the enrollment of dissimilar operative groups in different studies, employment of different melatonin doses, adopting different anesthetic techniques and vast differences in operative times especially when comparing cardiac surgery to general surgery.

In the current study, no statistically significant difference in isoflurane end tidal concentration was found between melatonin and placebo. No studies had investigated the influence of melatonin on the requirements of inhalational anesthetics.

In the present study, univariate analysis of various predictors of POD in both Group M and Group C showed statistical significance of older age as an independent variable of POD development. This matched the results of **Kazmierski *et al.*** [23] who revealed that advanced age was independently associated with delirium after cardiac surgery in their study. **Artemiou *et al*.** [13] also found that older age was a predictor of POD in patients undergoing cardiac surgery.

Furthermore, different intraoperative predictors were found in the present study to be associated with POD. The higher the fentanyl dose (≥ 1200 μg), the higher was the risk for developing POD. This correlated with the results of the study done by **Artemiou *et al*.** [13] who found the same correlation for higher sufentanil doses ≥ 15 μg in the control group in patients undergoing cardiac surgery. Also there was a significant association between longer cardiopulmonary bypass (CPB) times ≥ 60 min and aortic cross clamping (ACC) times ≥ 45 min with delirium. Going with similar results, **Andrejaitiene and Sirvinskas** [24] reported that ACC times more than 68 min is associated with the development of POD. **Artemiou *et al.*** [13] also reported this association in the control group.

Interestingly, **Artemiou *et al.*** [13] found that administration of melatonin eliminated the association of the predictors linked to time with delirium (total sufentantil dose, ACC time and CPB time). In other words, they found that the perioperative predictors of POD in the melatonin group were limited to advanced age and higher EuroScore II. This may be due to usage of higher melatonin dose (5mg) or inclusion of wider age group with different types of cardiac surgery in their study.

CONCLUSION

Premedication with melatonin in the current study significantly increases preoperative sedation. Moreover, the administration of melatonin significantly decreases POD in elderly patients undergoing CABG in the current study. Melatonin also has been proved successful as a therapeutic agent in delirious patients. Univariate analysis for risk factors of delirium indicated that advanced age, higher total intraoperative fentanyl dose, lower ejection fraction and longer CPB and ACC times were independent predictors of POD with or without melatonin supplementation.

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