Role of Melatonin in Reducing Post-Operative Delirium in Coronary Artery Bypass Graft Surgery

Syed Jawad Rehmani, Syed Aqeel Hussain Shah, Umer Khan, Tanveer Ahmed Khan, Komail Abid, Muhammad Ali Memon

Department of Adult Cardiac Anesthesia, Armed Forces Institute of Cardiology/National Institute of Heart Diseases/
National University of Medical Sciences (NUMS) Rawalpindi, Pakistan

ABSTRACT

Objective: To determine the role of melatonin in the reduction of postoperative delirium in On pump Coronary artery bypass graft (CABG) patients.

Study Design: Quasi experimental study.

Place and Duration of Study: Department of Cardiac Anesthesia and Intensive Care Department, Armed Forces Institute of Cardiology and National Institute of Heart Diseases, Rawalpindi Pakistan, from Oct -Dec 2023.

Methodology: Two hundred ten patients, irrespective of gender, between the ages of 30 and 60 years, who undergone On pump CABG, were recruited. Non-randomly, the patients were divided into two groups: the Experimental-Group (received melatonin) and the Control-Group (did not receive melatonin). Impact of Melatonin on Delirium was assessed by Confusion Assessment Method for Intensive care Unit (CAM-ICU) and outcomes were compared with standard treatment Control-Group

Results: Among 210 patients, 179(85.2%) were male and 31(14.8%) were female. Occurrence of delirium after 24 hours post-operative CABG surgery in group receiving melatonin was 21(20.6%) whereas 47(43.5%) in control group which was clinically significant ($p<0.001$). Delirium after 48 hours of surgery was found to be 18(17.6%) in Experimental-Group whereas, occurrence in control group was twice 44(40.7%) which showed the significant difference in reduction of delirium in patients who received Melatonin ($p<0.001$).

Conclusion: Melatonin slightly reduced the occurrence of delirium in postoperative on pump CABG patients.

Keywords: Cardiac Anesthesia, Coronary artery bypass, Delirium Management, Melatonin, Prevention

INTRODUCTION

Melatonin, a pineal gland hormone, was recently identified as a reprogramming approach to prevent many diseases for its predominant hypnotic effects, anti-inflammatory activity, and even the prevention of delirium.[1] It alleviates cognitive impairment and protects against neurodegenerative diseases but also reduces neuro inflammation.[2] In its role as a cardio protective medication, melatonin has shown to decrease heart dysfunction and improve left ventricular ejection fraction in humans.[3] Hospitalized patients frequently experience delirium, which is characterized as an acute disruption in attention and overall cognitive function. It is a common postoperative complication in CABG.[4] It may lead to morbidities, longer mechanical ventilation time, the risk of injuries to patients or staff, the possibility of falling out of bed, unwanted extubation, and prolonged stays in the Intensive Care Unit (ICU), all contributing to escalated treatment costs.[5]

Correspondence: Dr Syed Jawad Rehmani, Department of Adult Cardiac Anesthesia, AFIC/NIHD, Rawalpindi, Pakistan

Patients undergoing cardiac surgery are particularly susceptible to delirium due to the complexity of the operation, cardiopulmonary bypass, reperfusion, and postoperative complications.[6] Following heart surgery, the incidence of delirium was reported to be 13.3% in Pakistan whereas globally it is ranging from 8-50%.[4,5] Previous study suggested that a low left ventricular ejection fraction, atrial fibrillation, and cardiopulmonary bypass may predispose patients to post-cardiac surgery delirium.[6]

Patients with delirium have a 12-month mortality rate of 10% to 26%, which is comparable to the fatalities of patients who have myocardial infarction and sepsis.[7] One of the main mechanisms behind delirium is the disruption of melatonin levels following CABG.[1] Preventing Post-Operative Delirium (POD) can significantly contribute to patient recovery after cardiac surgery.[8,9]

Exogenous Melatonin causes drug interaction with antidepressant and monoamine oxidase inhibitor.[10] Despite evidence that melatonin may reduce POD, research into its effectiveness in CABG patients was limited and yields inconsistent results. In

Pakistan, research investigating the efficacy of Melatonin in mitigating the occurrence of delirium following CABG remains unexplored.

This study aimed to evaluate the effect of melatonin in reducing the occurrence of post-operative delirium in patients undergoing CABG. Based on the results of this study, we can establish clinical guidelines for Pakistani population regarding role of Melatonin in minimizing post CABG delirium and improving in hospital outcomes.

METHODOLOGY

This was a Quasi-experimental study conducted at department of Adult Cardiac Anesthesia and Intensive Care Department Armed Forces Institute of Cardiology and National Institute of Heart Diseases, Rawalpindi, from Oct -Dec 2023 after approval from Institutional Ethical Review Board (IERB) (letter#. 9/2/R&D/2023/285;Dated: 13th Sep 2023).

Sample size was calculated to be 144 (n=72 in each group) by using WHO calculator, based on the post-operative Delirium prevalence of 13.3% in Melatonin group and 36.6% in control group with 95% confidence level and 5% margin of error.[11] However, data was collected using non probability consecutive sampling from 210 patients.

Inclusion Criteria: Patients who were between the age of 30 and 60 years, underwent On pump CABG with least a 30% ejection fraction, anesthetic risk classes II or III, which indicate a moderate to high risk of problems during the surgical operation, were included.

Exclusion Criteria: Patients who had a known allergy to melatonin or its compounds, those who had used melatonin or hypnotic drugs in the past or had a chronic or recent use of these substances, History of barbiturates or antipsychotics use recently, those with liver or kidney disease., neurological or psychological diseases or any known malignancies as well as emergency cases with prolonged sedation history were excluded from the study.

After taking informed consent sampling was done using non-probability consecutive sampling technique. These patients were divided into two groups without randomization, keeping in mind of inclusion and exclusion criteria. The participants of Experimental-Group received melatonin along with standard treatment whereas participants of control group received standard treatment regimen without melatonin. 5mg of melatonin dose was administered on the evening before the operation and another 5mg on the morning of the surgery. The melatonin treatment was continued until the second postoperative night. On the other hand, patients in the control group received a standard treatment protocol. Cardiac surgery and postoperative management followed standardized procedures. After the surgery, all patients received a standard protocol for sedation, analgesia, and mechanical ventilation management (Figure-1).
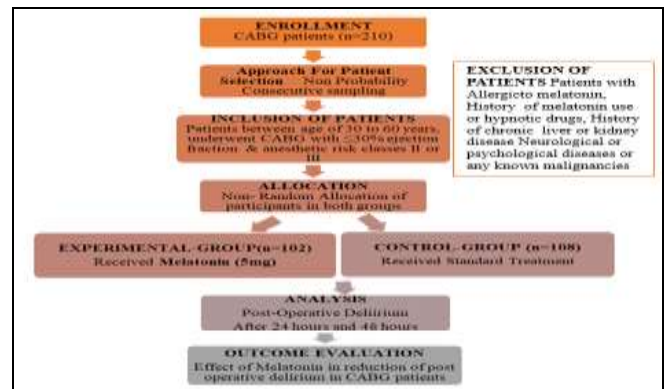

Figure-1: Patient Flow Diagram

The occurrence of delirium was assessed using the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) at 12 hours and then 48 hours after extubating. The CAM-ICU showed the best validity of the evaluated scales to identify delirium in ICU patients as in Figure-2.[1,4]

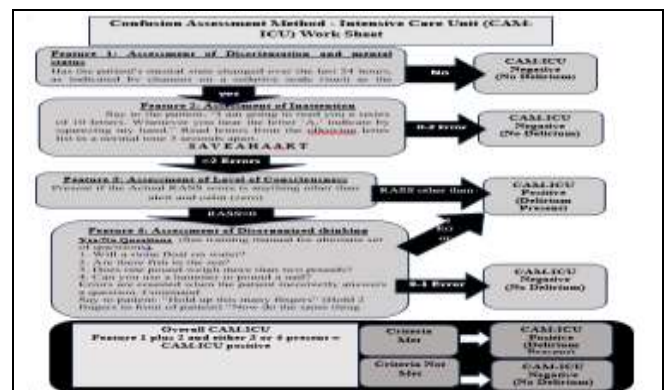
Figure-2: Confusion Assessment Method - Intensive Care Unit (CAM-ICU) Work Sheet For Assessment of Delirium In On Pump CABG Patients.

For statistical analysis we used SPSS Software, version 22.0, (SPSS, Inc, Chicago, IL, USA). The qualitative variables of this study like delirium after 24 & 48 hours of surgery, gender, Comorbid, addiction and study groups were presented as frequencies and

percentages. The normality of continuous variables, including age, blood pressure, pulse oximetry, aortic clamping time, CPB time, mechanical ventilation duration, and ICU stay duration, was assessed using the Kolmogorov-Smirnov test. Since none of the parameters followed a normal distribution, the median and interquartile range were reported. The Mann-Whitney U test was used to evaluate median differences in continuous variables between the study groups. The optimal association between Melatonin intervention and delirium was investigated using Chi-square & McNemar, to analyze difference in incidence of delirium with and without Melatonin. A *p*-value ≤0.05 was considered statistically significant

RESULTS

Our study included two groups experimental and control groups with 210 eligible patients, out of which 179(85.20%) were male and 31(14.80%) were females. Among these patients 64(30.5%) had Diabetes Mellitus and 160 (76.2%) had Hypertension. Other risk factors like smoking 90(42.9%) and addiction to alcohol, Sheesha or any other kind were 48(22.9%). Preoperative factors like PO2, Systolic blood pressure and diastolic blood pressure were found to 96.00(96.00-97.00) %, 163.00(155.00-165.00) mmHg, 90.00(85.00-90.00) mmHg respectively. Median Aortic cross clamping time was 60.00(45.00-72.75) minutes and the median CBP time was 75.00(72.00-85.00) minutes. (Table-I)

Overall occurrence of delirium after 48 hours of

CABG surgery in group receiving melatonin was 18(17.6%) whereas 44(40.7%) among patients in control group after 48 hours. Decrease of frequency of delirium in Experimental-Group was significant (*p*<0.001). Post-operative outcomes like mechanical ventilation was 10.00(9.00-12.00) hours and 9.00(8.00-12.00) hours in experimental and control group respectively whereas ICU stay time was significantly lower in experimental than control group [24.00(24.00-48.00)hours vs. 48.00(24.00-48.00) hours respectively; *p*=0.003] as represented in Table II.

From Experimental-Group 21 patients (20.6%) and 47(43.5%) from control group developed delirium (Figure-3) after 24 hours; the increase in delirium frequency in the control group was statistically significant (*p*<0.001)

After adjusting for confounders, the melatonin group (aOR = 0.42, *p*=0.03), smoking (uOR = 1.83, *p*=0.04), and ICU stay (aOR = 0.89, *p*=0.001) are

significant predictors of delirium after 24 hour. After adjusting for confounders, HTN (aOR = 3.00, *p*=0.03), and ICU stay (aOR = 0.89, *p*=0.001) are significant predictors of delirium after 48 hours. Other variables including age, diabetes, smoking, mechanical ventilation time and procedural factors were not to be found as predictors.
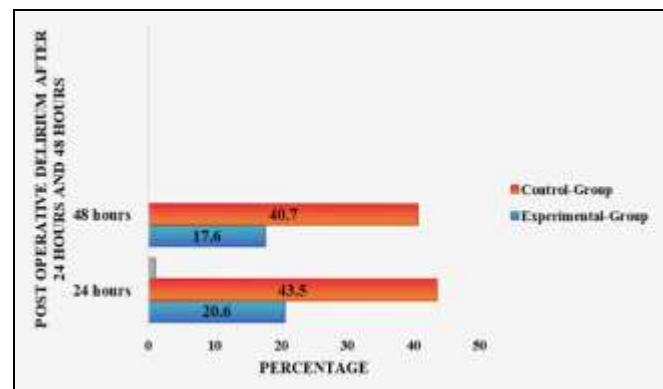

Figure-3: Post-Operative Delirium In ONCAB Patients (n=210)

Table-I: Demographics, Comorbid and Pre-Operative/Intra-Operative and Post-Operative Characteristics of Participants (n=210)

Variables			Frequency (%)
Gender		Male	179(85.2.0%)
		Female	31(14.8%)
Comorbid	Diabetes Mellitus	Yes	64(30.5%)
		No	146(69.5%)
	HTN	Yes	160(76.2%)
		No	50(23.8%)
	Smoking	Yes	90(42.9%)
		No	120(57.1%)
	Addiction (ANY)	Yes	48(22.9%)
		No	162(77.1%)
Age (year)		Median(IQR)	55.00(50.00-59.00)
Pre-Operative Parameters			Frequency (%)
ECG		Atrial Fibrillation	79(37.6%)
		Sinus Ryhtm	131(62.4%)
			Median(IQR)
Pulse Oximetry (%)			96.00(96.00-97.00)
Systolic BP (mmHg)			163.00(155.00-165.00)
Diastolic BP (mmHg)			90.00(85.00-90.00)
Intra Operative Parameters			Median(IQR)
Aortic Cross clamping Time(minutes)			60.00(45.00-72.75)
Cardiopulmonary Bypass Time (minutes)			75.00(72.00-85.00)
Post-Operative Parameters			
Mechanical Ventilation(hours)			10.00(8.00-12.00)
ICU stay(hours)			34.00(24.00-48.00)
Outcome			Frequency (%)
Delirium after 24 hours		Yes	68(32.4%)
		No	142(66.6 %)
Delirium after 48 hours		Yes	62(29.5%)
		No	148(70.5%)

HTN=Hypertension; ICU=Intensive Care Unit

Table II- Comparison of Demographics, Co Morbid and Pre-Operative/Intra- Operative and Post-Operative Characteristics Among Study Groups (n=210)

Variables			Experimental-Group Frequency (%) (n=102)	Control-Group Frequency (%) (n= 108)	*p*-value
Gender		Male	82(80.4 %)	97(89.8 %)	0.05
		Female	20(19.6%)	11(10.2%)	
Comorbid	Diabetes Mellitus	Yes	28(27.5%)	36(33.3%)	0.35
		No	74(72.4%)	72(66.7%)	
	HTN	Yes	73(71.6%)	87(80.6%)	0.12
		No	29(28.4%)	21(19.4%)	
	Smoking	Yes	52(51.0%)	38(35.2%)	0.02
		No	50(49.0%)	70(64.8%)	
	Addiction (If Any)	Yes	24(23.5%)	24(22.2%)	0.82
		No	78(76.5%)	84(77.8%)	
			Median(IQR)		
Age(years)			55.00(50.00-59.00)	56.00(51.00-59.00)	0.35
Pre-Operative Parameters					
Pulse Oximetry(%)			96.00(96.00-97.00)	96.00(96.00-97.00)	0.96
Systolic BP (mmHg)			160.50(155.00-165.00)	165.00(18.00-165.00)	0.33
Diastolic BP (mmHg)			90.00(85.00-90.00)	90.00(85.00-90.00)	0.09
Intra Operative Parameters					
Aortic Cross clamping Time(minutes)			55.00(45.00-75.00)	60.00(45.00-70.50)	0.78
Cardiopulmonary Bypass Time (minutes)			75.00(71.00-85.00)	75.00(73.50-84.00)	0.38
Post-Operative Parameters					
Mechanical Ventilation(hours)			10.00(9.00-12.00)	9.00(8.00-12.00)	0.02
ICU stay(hours)			24.00(24.00-48.00)	48.00(24.00-48.00)	0.003
Outcome			**Frequency (%)**		
Delirium after 24 hours		Yes	21(20.6%)	47(43.5%)	0.001
		No	81(79.0%)	61(56.5%)	
Delirium after 48 hours		Yes	18(17.6%)	44(40.7%)	0.001
		No	84(42.9%)	64(59.3%)	

HTN=Hypertension; ICU=Intensive care unit

Table-III: Unadjusted and Adjusted Odds Ratios for Risk Factors Associated with Delirium at 24 and 48 Hours Post-Surgery

Variable	Delirium after 24 hour				Delirium after 48 hour			
	uOR (95% C.I)	*p*-value	aOR (95% C.I)	*p*-value	uOR (95% C.I)	*p*-value	aOR (95% C.I)	*p*-value
Group	0.33(0.18-0.62)	0.001	0.42(0.19-0.93)	0.03	0.31(0.16-0.59)	0.001	-	-
Age	0.97(0.93-1.01)	0.20	-	-	0.98(0.98-1.02)	0.35	-	-
HTN	1.96(0.93-4.12)	0.07	-	-	2.67(1.17-6.09)	0.01	3.00(1.09-8.22)	0.03
Diabetes	1.25(0.67-2.34)	0.46	-	-	1.01(0.53-1.92)	0.97	-	-
Smoking	1.83(1.02-3.28)	0.04	-	-	1.14(0.62-2.07)	0.66	-	-
ACC Time (minutes)	0.98(0.96-1.00)	0.16	-	-	0.99(0.97-1.01)	0.47	-	-
CPB Time (minutes)	0.98(0.96-1.01)	0.42	-	-	0.99 (0.96-1.01)	0.76	-	-
Ventilation time (hours)	0.98(0.89-1.09)	0.79	-	-	1.02(0.91-1.13)	0.71	-	-
ICU stay (hours)	0.89(0.86-0.92)	0.001	0.89(0.87-0.92)	0.001	0.89(0.86-0.92)	0.001	0.89 (0.86-0.92)	0.001

uOR= unadjusted odds ratio; aOR= adjusted odds ratio; HTN= Hypertension; ACC=Aortic cross clamp; CPB= Cardiopulmonary time; ICU=Intensive Care Unit

DISCUSSION

According to our findings, after 24 hours following on pump CABG surgery, 21(20.6%) and 47(43.5%) patients experienced delirium in group receiving Melatonin and control group respectively, a difference that was clinically significant (*p*<0.001). After 48 hours of operation, delirium was observed in 18(17.6%) in the Experimental-Group, while it occurred twice in 44(40.7%) of patients in Control-Group However, a previous study by Zadeh FJ *et al.,* found that there was a statistically significant

difference (p=0.03) between the groups on the first postoperative day, with delirium occurring in 4 patients (13.3%) in the Melatonin group and 11 patients (36.6%) in Control-Group.Three patients (10%) in the Melatonin group and fourteen patients (46.6%) in the Control-Group experienced delirium on the second postoperative day; this difference in delirium occurrence was statistically significant (p=0.02).[12]

Another study depicted the occurrence of delirium in patients who received Melatonin (10.9%) was comparable to our study (17.6%) after 48 hours.[14] The results of the current study showed that melatonin significantly reduced the occurrence of delirium in individuals who had on pump CABG surgery. Our findings are consistent with the meta analysis, which found that persons who had heart surgery were much less likely to experience delirium while taking melatonin at doses of 3 and 5 mg.[15] According to Kasnavieh FH *et al.,* the occurence of delirium in patients after open-heart surgery was 68.6% at 24 hours and reduced to 31.4% at 72 hours in the Control-Group. In comparison, the melatonin group reported a reduction in delirium from 35.7% at 24 hours to 5.7% after 72 hours. In contrast, our study reported, delirium reduced from 20.6% at 24 hours to 17.6% at 48 hours in the Experimental-Group, but in the co Control-Group, it declined from 43.5% at 24 hours to 40.7% at 48 hours.[16] Up to 50% of older patients may experience postoperative delirium, one of the most common surgical problems in older population.[17]

A Pakistani study found that 20(11.4%) of the 176 patients had post-operative delirium and melatonin was not used in this study to prevent delirium.[18] However, our research revealed that 68(31.9%) out of 210 patients had delirium after CABG.

Another study with 250 patients undergoing elective or urgent heart surgeries found a significant difference in delirium between 2 groups. Group 1, receiving prophylactic perioperative melatonin (5mg), had an 8.4% occurrence of delirium compared to 20.8% in the Control-Group (p=0.001).[14] These results were in line with a current study which found that after 48 hours, 17.6% and 40.7% out of 210 patients experienced delirium in Melatonin group and Control-Group respectively (p=0.001).

Melatonin is an endogenous hormone that is in pharmacological use for fixing sleep disorders and circadian rhythm.[19] This natural compound is also considered to be cardioprotective which may contribute to better surgical outcomes.[20,21] Our study showed that after 24 hours of surgery there was a significant decrease in delirium (p<0.001) when compared with control and two days later, the occurrence rates of delirium were even lower in Melatonin group (from 20.6% to 17.6% respectively (p<0.001). Similar findings were published by Thakur *et al.,* who found that the melatonin group had a considerably decreased occurrence of delirium at 6, 24, and 48 hours (23.5%, 8.6%, and 2.5%).[22]

No association of aortic clamping time, and cardiopulmonary bypass time was established. However, post-operative outcome like ICU stay time was significantly reduced improving the recovery outcomes (p<0.001).Comparable results were observed in study conducted by Mahrose *et al.* where Experimental-Group had lower ICU stays compared to Control-Group (p<0.001).[14]

This study intended to investigate the effectiveness of melatonin in reducing post-operative delirium in ONCAB patients. Melatonin has been shown to dramatically lower the occurrence of delirium in patients after cardiac surgery so this study aimed to validate its possible advantages in enhancing postoperative outcomes in patients undergoing coronary artery bypass grafting.

This study concluded that Melatonin may help reduce the frequency of delirium after heart surgery, consistent with previous research that supported these results. Better recovery outcomes and shorter ICU stays were also emphasized by this study about Melatonin. With regard to lowering postoperative delirium in on pump CABG patients, current study collectively showed that melatonin was an effective treatment option for reducing post-operative delirium.

LIMITATIONS OF THE STUDY

This is a unicentric study and more data is required from various establish facilities. As our experimental design lacks randomization, the results obtained may be different from actual experimental results. Furthermore, age associated confounding and use of melatonin needs to be established as it is a predisposition and its use as intervention needs to be investigated further.

CONCLUSION

Melatonin slightly reduced the occurrence of delirium after cardiac surgery mitigating the risk factors associated with delirium. There was sufficient evidence to safely

conclude that interventions with Melatonin decreased the occurrence of POD in on pump CABG patients. Moreover, it is also effective in saving cost of prolonged hospitalization and ICU stay.

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

SJR & SAHS: Study design & concept, drafting the manuscript, approval of the final version to be published

UK & TAK: Study design & concept, data acquisition, critical review, approval of the final version to be published

KA & MAM: Data acquisition, data analysis, data interpretation, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Gunata ME, Parlakpinar HA, Acet HA. Melatonin: A review of its potential functions and effects on neurological diseases. Re Rev Neurol (Paris) 2020; 176(3): 148-165.
https://doi.org/10.1016/j.neurol.2019.07.025

2. Zhou Q, Lin L, Li H, Wang H, Jiang S, Huang P et al. Melatonin reduces neuroinflammation and improves axonal hypomyelination by modulating M1/M2 microglia polarization via JAK2-STAT3-telomerase pathway in postnatal rats exposed to lipopolysaccharide. Mol Neurobiol 2021; 58(12): 6552-6576.
https://doi.org/10.1007/s12035-021-02568-7

3. Artemiou P, Bily B, Bilecova-Rabajdova M, Sabol F, Torok P, Kolarcik P, et al., Anaesthesiology and Intensive Care Melatonin treatment in the prevention of postoperative delirium in cardiac surgery patients. Kardiochir Torakochirurgia Pol 2015; 12(2): 126-33.
https://doi.org/10.5114/kitp.2015.52853

4. Mattimore D, Fischl A, Christophides A, Cuenca J, Davidson S, Jin Z, et al. Delirium after Cardiac Surgery-A Narrative Review. Brain Sci 2023; 13(12): 1682.https://doi.org/10.3390/brainsci13121682

5. Siddique A, Siddique MU, Javaid R, Khan MA. Frequency of Delirium Associated with Dexmedetomidine and Propofol in Post CABG Patients: A Comparative Study. Pak Armed Forces Med J 2022; 72 (SUPPL-3): S595-598.https://doi.org/10.51253/pafmj.v72iSUPPL-3.9562

6. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 2004 ; 127(1): 57-64.
https://doi.org/10.1016/S0022-5223(03)01281-9

7. Khaing K, Nair BR. Melatonin for delirium prevention in hospitalized patients: A systematic review and meta-analysis. J Psychiatr Res 2021; 133: 181-190.
https://doi.org/10.1016/j.jpsychires.2020.12.020

8. Greaves D, Psaltis PJ, Davis DH, Ross TJ, Ghezzi ES, Lampit A, et al. Risk factors for delirium and cogniti decline following coronary artery bypass grafting surgery: a systematic review and meta-analysis. J Am Heart Assoc 2020 ; 9(22): e017275.
https://doi.org/10.1161/JAHA.120.017275

9. Shin HW, Kwak JS, Choi YJ, Kim JW, You HS, Shin HJ, et al. Efficacy and safety of perioperative melatonin for postoperative delirium in patients undergoing surgery: a systematic review and meta-analysis. J Int Med Res 2024; 52(5): 03000605241239854.
https://doi.org/10.1177/03000605241239854

10. Barnes J, Sewart E, Armstrong RA, Pufulete M, Hinchliffe R, Gibbison B, et al. Does melatonin administration reduce the incidence of postoperative delirium in adults? Systematic review and meta-analysis. BMJ open 2023 ; 13(3): e069950.
https://doi.org/10.1136/bmjopen-2022-069950

11. Zadeh FJ, Janatmakan F, Shafaeebejestan E, Jorairahmadi S. Effect of melatonin on delirium after on-pump coronary artery bypass graft surgery: a randomized clinical trial. Iran J Med Sci 2021 ; 46(2): 120.
https://doi.org/10.30476%2Fijms.2020.82860.1146

12. Evans AS, Weiner MM, Arora RC, Chung I, Deshpande R, Varghese R, et al. Current approach to diagnosis and treatment of delirium after cardiac surgery. Ann Card Anaesth 2016 1; 19(2): 328-337.
https://doi.org/10.4103/0971-9784.179634

13. Wang CM, Zhou LY. Melatonin and melatonergic agents for the prevention of postoperative delirium: A meta-analysis of randomized placebo-controlled trials. Asian J Surg. 2022 ; 45(1): 27-32.
https://doi.org/10.1016/j.asjsur.2021.04.04

14. Mahrose R, ElSerwi H, Maurice A, Elsersi M. Postoperative delirium after coronary artery bypass graft surgery: dexmedetomidine infusion alone or with the addition of oral melatonin. Egypt. J. Anaesth 2021; 37(1): 62-68.
https://doi.org/10.1080/11101849.2021.1885956

15. Han Y, Tian Y, Wu J, Zhu X, Wang W, Zeng Z, Q et al.Melatonin and its analogs for prevention of post-cardiac surgery delirium: a systematic review and meta-analysis. Front. Cardiovasc. Med. 2022; 9: 888211.
https://doi.org/10.3389/fcvm.2022.888211

16. Kasnavieh FH, Rezaeipandari H, Hadadzadeh M, Vakili M, Biouki FH. Effect of melatonin on incidence rate of delirium in elderly patients undergoing open-heart surgery without a pump: a clinical trial. Elderly J Health. 2019 .
https://doi.org/10.18502/ehj.v5i1.1197

17. Yan E, Veitch M, Saripella A, Alhamdah Y, Butris N, Tang-Wai DF, et al. Association between postoperative delirium and adverse outcomes in older surgical patients: a systematic review and meta-analysis. J. Clin. Anesth 2023; 90: 111221.
https://doi.org/10.1016/j.jclinane.2023.111221

18. Mahboob S, Khan SA, Alam U, Amjad Q. Incidence and risk factors of delerium after cardiac surgery. Pak Armed Forces Med J 2018 ; 68(Suppl-1): S64-68
https://pafmj.org/PAFMJ/article/view/3269

19. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013; 21(12): 1190-1222.
https://doi.org/10.1016/j.jagp.2013.09.005

20. Grover S, Dua D, Sahoo S, Chakrabarti S, Avasthi A. Effectiveness of melatonin in the management of delirium: A retrospective study. J MENT HEALTH HUM BE 2019 ; 24(2): 78-84.
https://doi.org/10.4103/jmhhb.jmhhb_56_19

21. Randhawa PK, Gupta MK. Melatonin as a protective agent in cardiac ischemia-reperfusion injury: Vision/Illusion?. Eur. J. Pharmacol 2020; 885: 173506.
https://doi.org/10.1016/j.ejphar.2020.173506

22. Thakur T, Saini V, Grover S, Samra T. Role of oral melatonin in prevention of postoperative delirium in patients undergoing elective surgery under general anesthesia: A Randomized controlled trial Indian J. Psychiatry 2024; 66(5): 457-462.
https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_965_23

ADULT CARDIAC SURGERY & ANAESTHESIA

....