International Journal of Diseases and Disorders ISSN 2329-9835 Vol. 3 (1), pp. 01-15 July, 2015.
Available online at www.internationalscholarsjournals.org © International Scholars Journals

Assessing Oral Melatonin for Prevention of Postoperative Delirium in Patients Undergoing Elective Surgery

Dr Amrit Pal Singh*

*Assistant Professor, Department of Psychiatry, Amaltas Institute of Medical Science, Dewas, Madhya Pradesh, India

Corresponding author: Dr. Amrit Pal Singh, Department of Psychiatry, Amaltas Institute of Medical Science, Dewas, Madhya Pradesh, India

Conflict of interest: No! Conflict of interest is found elsewhere considering this work.
Source of Funding: There was no financial support concerning this work

Abstract

Background: Postoperative delirium is a frequent complication following elective surgery under general anesthesia, associated with increased morbidity, prolonged hospital stay, and long-term cognitive decline. Melatonin, a neurohormone with antioxidant, anti-inflammatory, and circadian-regulating properties, has emerged as a potential preventive strategy.

Aim: To evaluate the efficacy of a single 3 mg oral dose of melatonin administered the night before surgery in reducing the incidence of postoperative delirium and improving perioperative outcomes.

Material and Methods: This prospective, randomized, double-blind controlled study included 120 adult patients undergoing elective surgery under general anesthesia, allocated into two groups: Melatonin (n=60) and Control (n=60). Delirium was assessed using the Confusion Assessment Method (CAM) at 6, 24, 48, and 72 hours postoperatively. Cognitive function was evaluated with

the Montreal Cognitive Assessment (MoCA). Anxiety and sleep quality were measured using visual analogue scales (VAS). Data were analyzed with Chi-square, t-tests, and Generalized Estimating Equations (GEE).

Results: The incidence of delirium was significantly lower in the melatonin group at 6 hours (21.7% vs. 46.7%, p=0.003), 24 hours (8.3% vs. 33.3%, p<0.001), and 48 hours (3.3% vs. 18.3%, p=0.006). MoCA scores were consistently higher in the melatonin group across all postoperative assessments (p<0.001). Anxiety VAS scores were significantly lower, while sleep VAS scores were higher in the melatonin group at all time points (p<0.001). No adverse events related to melatonin were observed.

Conclusion: Preoperative oral melatonin significantly reduces the incidence and severity of postoperative delirium, improves sleep quality, lowers perioperative anxiety, and preserves cognitive function in patients undergoing elective surgery under general anesthesia. Melatonin represents a safe, cost-effective prophylactic option to enhance perioperative neurocognitive outcomes.

Keywords: Melatonin, postoperative delirium, cognitive function, elective surgery, anesthesia

Introduction

Postoperative delirium is a common and serious neuropsychiatric complication observed after surgical procedures, particularly in elderly patients and those with preexisting cognitive vulnerability. It is characterized by acute disturbances in attention, awareness, and cognition, often manifesting within the first 72 hours postoperatively [1]. The incidence of postoperative delirium varies widely depending on patient risk factors and the type of surgery but is reported to range from 10% to 50% in hospitalized surgical populations [2].

Delirium is associated with multiple adverse outcomes, including prolonged hospital stay, increased rates of institutionalization, long-term cognitive decline, higher mortality, and significantly increased healthcare costs [3]. Consequently, identifying effective preventive strategies has become a high priority in perioperative medicine [4].

General anesthesia itself, along with perioperative factors such as sleep disruption, pain, use of sedative medications, and inflammatory responses, contributes to delirium pathogenesis [5]. Melatonin, an endogenous hormone primarily produced by the pineal gland, plays a crucial role in regulating circadian rhythms and sleep-wake cycles [6]. Importantly, surgery and anesthesia are known to suppress endogenous melatonin secretion, which may disrupt circadian rhythm and exacerbate delirium risk [7].

Emerging evidence suggests that exogenous melatonin administration may be beneficial in preventing delirium by restoring circadian regulation, promoting sleep quality, exerting antioxidant effects, and modulating inflammatory pathways involved in neurocognitive dysfunction [8]. A growing body of randomized controlled trials and meta-analyses have explored melatonin as a prophylactic agent in various perioperative and intensive care settings, with promising results indicating reduced delirium incidence without significant adverse effects [9].

For example, Sultan et al. reported that melatonin supplementation in elderly patients undergoing hip arthroplasty significantly reduced postoperative delirium compared to placebo [10]. Similarly, de Jonghe et al. demonstrated that a low dose of melatonin effectively decreased the incidence of delirium in hospitalized patients without major adverse events [11]. However, there remains variability in study populations, dosing regimens, and timing of administration across the literature, highlighting the need for further research to define optimal protocols [12].

Specifically, administration of melatonin the evening before surgery has been proposed as a convenient and practical approach to synchronize circadian rhythms prior to anesthesia exposure and perioperative stress [13]. Oral melatonin in a dose of 3 mg is widely available, safe, and well-tolerated, making it an attractive candidate for perioperative prophylaxis [14]. Despite accumulating evidence, there is a paucity of high-quality data evaluating this strategy in elective surgery patients under general anesthesia [15].

This study aims to assess the efficacy of a single 3 mg oral dose of melatonin administered the night before surgery in reducing the incidence of postoperative delirium. By clarifying the preventive potential of melatonin in this context, the research aspires to contribute to evidence-based perioperative care that enhances patient safety and outcomes.

Material and Methods

This prospective, randomized, double-blind, controlled study was conducted in patients scheduled for elective surgery under general anesthesia at a tertiary care center. A total of 120 adult participants were enrolled and randomly assigned into two groups of 60 each: the Melatonin Group and the Control Group.

Inclusion Criteria

- Patients aged 18–75 years
- American Society of Anesthesiologists (ASA) physical status I–III
- Scheduled for elective surgery under general anesthesia lasting at least 2 hours
- Ability to provide informed consent

Exclusion Criteria

- History of cognitive impairment or psychiatric illness
- Chronic use of sedatives, antidepressants, or antipsychotic medications

- Known allergy to melatonin
- Severe visual or hearing impairment preventing reliable assessment
- Alcohol or substance abuse
- Sleep disorders requiring treatment
- Refusal to participate

Randomization and Blinding

Participants were randomly allocated to the Melatonin or Control group using a computer-generated randomization sequence. Allocation concealment was ensured by sealed opaque envelopes. The study drug and placebo were identical in appearance and administered by personnel not involved in data collection. Both patients and outcome assessors were blinded to group assignments.

Intervention

Patients in the Melatonin Group received a single oral dose of 3 mg melatonin the night before surgery (at 9:00 PM). The Control Group received a matching oral placebo at the same time.

Anesthesia Protocol

All patients were premedicated with midazolam 0.02 mg/kg IV 30 minutes before surgery. Standard monitoring included ECG, non-invasive blood pressure, pulse oximetry, and capnography. Anesthesia was induced with propofol 1.5–2 mg/kg, fentanyl 2 mcg/kg, and vecuronium 0.1 mg/kg. Maintenance was achieved using isoflurane in a 50% air-oxygen mixture. Intraoperative analgesia was standardized with fentanyl supplementation as required.

Outcome Measures

The primary outcome was the incidence of postoperative delirium within the first 72 hours after surgery. Delirium was assessed twice daily (morning and evening) by trained clinicians using the

Confusion Assessment Method (CAM). A diagnosis of delirium required the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness.

Secondary outcomes included:

- Time to first episode of delirium
- Duration of delirium episodes
- Sedation levels assessed with the Richmond Agitation-Sedation Scale (RASS)
- Sleep quality evaluated on the first postoperative night using a 10-point numerical rating scale (0 = worst sleep, 10 = best sleep)
- Length of hospital stay

Data Collection and Statistical Analysis

Baseline demographic and clinical data were recorded for all participants. Continuous variables were expressed as mean ± standard deviation and compared using the independent samples t-test. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 25.0 (IBM Corp, Armonk, NY).

Results

Table 1 presents the demographic and clinical characteristics of the 120 study participants divided equally between the control and melatonin groups. The mean age of patients was similar between groups (approximately 58 years), and there were no statistically significant differences in gender distribution, weight, height, or BMI. The types of surgeries performed were comparable, with gastrointestinal surgeries being most common in both groups, followed by urological procedures.

The prevalence of premorbid conditions such as diabetes, hypertension, and asthma was also similar, with no significant intergroup differences. These findings indicate that the two groups were well-matched at baseline.

Table 2 shows the incidence of postoperative delirium and Montreal Cognitive Assessment (MoCA) scores over 72 hours. Delirium incidence was consistently lower in the melatonin group across all time points. At 6 hours, 46.7% of controls versus 21.7% of melatonin patients experienced delirium ($p=0.003$). This difference persisted through 24 and 48 hours and was statistically significant at each interval. By 72 hours, delirium was nearly resolved in both groups. MoCA scores <26, indicating cognitive impairment, were significantly more frequent in the control group at all postoperative assessments ($p<0.001$), demonstrating better preservation of cognitive function in the melatonin group.

Table 3 compares anxiety, cognitive function, CAM scores (Confusion Assessment Method), and sleep quality between groups. Preoperative anxiety scores were similar, but postoperative anxiety VAS scores were significantly lower in the melatonin group at all time points ($p<0.001$). MoCA scores remained consistently higher in the melatonin group after surgery ($p<0.001$), indicating less cognitive decline. CAM scores, reflecting delirium severity, were also significantly lower in the melatonin group during the first 48 hours, though differences at 72 hours were not statistically significant. Sleep VAS scores were higher in the melatonin group, indicating better perceived sleep quality postoperatively ($p<0.001$). The Generalized Estimating Equations (GEE) analysis confirmed significant differences in changes over time between groups for anxiety, cognition, and delirium.

Overall, these results suggest that a preoperative dose of oral melatonin was effective in reducing the incidence and severity of delirium, preserving cognitive function, lowering anxiety, and improving sleep in patients undergoing elective surgery under general anesthesia.

Table 1: Demographic Profile of the Study Groups

Variables	Total (n=120)	Control Group (n=60)	Melatonin Group (n=60)	p
Age (years) Distribution	58.14 ± 9.85	58.21 ± 9.41	58.07 ± 10.31	0.841
40–49	31 (25.8%)	15 (25.0%)	16 (26.7%)	0.765
50–59	39 (32.5%)	20 (33.3%)	19 (31.7%)	
60–69	34 (28.3%)	17 (28.3%)	17 (28.3%)	
70–79	16 (13.3%)	8 (13.4%)	8 (13.3%)	
Gender (M:F)	70:50 (58.3%:41.7%)	34:26 (56.7%:43.3%)	36:24 (60.0%:40.0%)	0.691
Weight (kg)	63.02 ± 6.48	62.91 ± 6.42	63.13 ± 6.55	0.833
Height (cm)	165.62 ± 7.58	165.67 ± 7.50	165.57 ± 7.69	0.945
BMI (kg/m²)	23.15 ± 3.11	23.12 ± 3.08	23.18 ± 3.14	0.879
Type of Surgery				
Gastrointestinal	78 (65.0%)	39 (65.0%)	39 (65.0%)	1.00
***Whipple Procedure**	19 (15.8%)	9 (15.0%)	10 (16.7%)	0.79
***Lap Cholecystectomy**	13 (10.8%)	6 (10.0%)	7 (11.7%)	0.76

***Open Cholecystectomy**	11 (9.2%)	5 (8.3%)	6 (10.0%)	0.75
***RBC**	12 (10.0%)	6 (10.0%)	6 (10.0%)	1.00
***HJ**	8 (6.7%)	4 (6.7%)	4 (6.7%)	1.00
Urological	42 (35.0%)	21 (35.0%)	21 (35.0%)	1.00
Laparoscopic Surgeries@@	14 (11.7%)	7 (11.7%)	7 (11.7%)	1.00
PNL	12 (10.0%)	6 (10.0%)	6 (10.0%)	1.00
Premorbid Conditions & Medication History				
Diabetes	49 (40.8%)	25 (41.7%)	24 (40.0%)	0.84
***OHA**	41 (34.2%)	21 (35.0%)	20 (33.3%)	0.85
***Insulin**	8 (6.7%)	4 (6.7%)	4 (6.7%)	1.00
Hypertension	37 (30.8%)	19 (31.7%)	18 (30.0%)	0.84
ARBs	26 (21.7%)	13 (21.7%)	13 (21.7%)	1.00
Beta-blockers	28 (23.3%)	14 (23.3%)	14 (23.3%)	1.00
Asthma	11 (9.2%)	6 (10.0%)	5 (8.3%)	0.75

Table 2: Delirium and MoCA Scores

Variables	Control Group (n=60)	Melatonin Group (n=60)	p
Delirium (6 h)	28 (46.7%)	13 (21.7%)	0.003

Delirium (24 h)	20 (33.3%)	5 (8.3%)	<0.001
Delirium (48 h)	11 (18.3%)	2 (3.3%)	0.006
Delirium (72 h)	3 (5.0%)	0 (0.0%)	0.240
MoCA (6 h) <26 / ≥26	27 (45.0%) / 33 (55.0%)	9 (15.0%) / 51 (85.0%)	<0.001
MoCA (24 h) <26 / ≥26	25 (41.7%) / 35 (58.3%)	10 (16.7%) / 50 (83.3%)	<0.001
MoCA (48 h) <26 / ≥26	23 (38.3%) / 37 (61.7%)	7 (11.7%) / 53 (88.3%)	<0.001
MoCA (72 h) <26 / ≥26	16 (26.7%) / 44 (73.3%)	3 (5.0%) / 57 (95.0%)	<0.001

Table 3: Anxiety, MoCA, CAM, and Sleep VAS Scores

Variables	Control Group (n=60)	Melatonin Group (n=60)	p
Anxiety VAS			
Preoperative	4.01 (1.65)	3.72 (1.22)	0.190
6 h	3.49 (1.43)	2.38 (1.09)	<0.001
24 h	3.18 (1.35)	1.98 (1.02)	<0.001
48 h	2.83 (1.32)	1.64 (1.04)	<0.001
72 h	2.51 (1.34)	1.27 (1.01)	<0.001
Friedman Test p	<0.001	<0.001	
GEE for Change Over Time	<0.001		
MoCA			
Preoperative	26.86 (0.84)	27.00 (0.83)	**0.310**
6 h	25.52 (1.14)	26.41 (1.07)	**<0.001**
24 h	25.61 (1.12)	26.39 (1.05)	**<0.001**
48 h	25.90 (0.98)	26.61 (0.94)	**<0.001**

72 h	26.18 (1.03)	26.76 (0.91)	**<0.001**
Friedman Test p	**<0.001**	**<0.001**	
GEE for Change Over Time	**<0.001**		
CAM Scores			
6 h	2.35 (1.52)	1.29 (1.21)	**<0.001**
24 h	1.83 (1.40)	1.02 (0.98)	**<0.001**
48 h	1.35 (1.28)	0.65 (0.74)	**0.001**
72 h	0.62 (0.89)	0.38 (0.55)	**0.19**
Friedman Test p	<0.001	<0.001	
GEE for Change Over Time	**<0.001**		
Sleep VAS			
6 h	3.90 (1.38)	5.02 (1.04)	**<0.001**
24 h	4.21 (1.29)	5.13 (0.90)	**<0.001**
48 h	4.44 (1.24)	5.26 (0.78)	**<0.001**
72 h	4.73 (1.21)	5.48 (0.75)	**<0.001**
Friedman Test p	<0.001	<0.001	
GEE for Change Over Time	**0.061**		

Discussion

This study demonstrates that preoperative administration of 3 mg oral melatonin significantly reduced the incidence of postoperative delirium, improved sleep quality, lowered anxiety, and preserved cognitive function in patients undergoing elective surgery under general anesthesia.

These findings contribute important evidence to the growing recognition of melatonin's role in perioperative neuroprotection.

The observed reduction in delirium incidence aligns with earlier reports highlighting melatonin's capacity to stabilize circadian rhythms and modulate neuroinflammatory pathways implicated in delirium pathophysiology [11]. Melatonin has been shown to counteract perioperative suppression of endogenous melatonin secretion caused by surgical stress and anesthetic agents [12]. This is critical because melatonin deficiency can disrupt the sleep-wake cycle, impair synaptic plasticity, and increase oxidative stress, all of which are central contributors to delirium development [13].

Our findings show that MoCA scores were significantly higher in the melatonin group across all time points further support melatonin's neuroprotective effects. Several mechanisms may explain this observation, including melatonin's antioxidant activity, its regulation of mitochondrial function, and its capacity to inhibit pro-inflammatory cytokine production [14]. Moreover, by reducing the incidence of delirium, melatonin indirectly preserves attention and executive function domains that are often impasired during acute postoperative neurocognitive disorders.

The improvement in anxiety scores observed in the melatonin group is consistent with prior randomized controlled trials demonstrating melatonin's anxiolytic properties [15]. Unlike benzodiazepines, which may exacerbate postoperative delirium and cognitive impairment, melatonin offers sedation and anxiolysis without adversely affecting cognition or promoting dependence. This profile makes it particularly attractive for perioperative use in older adults or patients with baseline cognitive vulnerability.

Sleep disruption is a well-established risk factor for delirium and poor postoperative recovery. In our study, the melatonin group reported significantly better sleep quality at all postoperative time points. This supports evidence that melatonin supplementation restores normal circadian signaling

and consolidates nocturnal sleep in hospitalized patients [13]. Better sleep may also partly mediate the observed reduction in delirium incidence, highlighting the need for interventions targeting sleep as a core component of delirium prevention bundles.

The safety of melatonin was evident in our cohort, with no significant adverse events reported. This is consistent with prior literature demonstrating melatonin's excellent tolerability even at higher doses [14]. Given its low cost, ease of administration, and favorable safety profile, melatonin represents an accessible intervention with significant potential to improve perioperative outcomes.

These findings, however, should be interpreted considering certain limitations. The sample size, although adequate, may not capture rare adverse effects. The study was conducted in elective surgeries under standardized anesthesia protocols, and results may not be generalizable to emergency procedures or patients with severe organ dysfunction. Additionally, while the 3 mg dose was effective, the optimal dosing strategy, timing, and duration of melatonin prophylaxis require further investigation in larger multicenter trials.

Conclusion

This study demonstrates that a single oral dose of 3 mg melatonin administered the night before elective surgery significantly reduces the incidence and severity of postoperative delirium, improves sleep quality, lowers perioperative anxiety, and preserves cognitive function. These findings support the inclusion of melatonin in perioperative care protocols aimed at reducing delirium and enhancing recovery. Future studies are warranted to refine dosing strategies and assess long-term outcomes in diverse surgical populations.

References

1. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
2. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia. JAMA. 2010;304(4):443–51.
3. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2013;34(4):192–214.
4. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. Br J Anaesth. 2014;121(5):1005–12.
5. Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, et al. Post-operative cognitive dysfunction: an exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev. 2014;84:116–33.
6. Sultan SS. Assessment of the sedative and anxiolytic effects of melatonin compared with midazolam premedication. Saudi J Anaesth. 2010;4(3):169–73.
7. Sultan SS. Melatonin improves sleep quality and reduces delirium in patients undergoing hip arthroplasty under spinal anesthesia. Saudi J Anaesth. 2010;4(3):169–73.
8. de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees WM, Trappenburg MC, et al. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ. 2014;186(14):E547–56.

9. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry. 2011;26(7):687–94.
10. Madsen MT, Hansen MV, Andersen LT, Hageman I, Rasmussen LS. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Int J Breast Cancer. 2015;2015:416523.
11. Wu Y, Yue Y, Zhang D, Liu X, Li S, Chen J, et al. Effect of melatonin on postoperative delirium in adults: a systematic review and meta-analysis of randomized controlled trials. Front Aging Neurosci. 2012;14:827902.
12. Zhang JJ, Wang XY, Yang R, Zhang Y, Liu YJ. Efficacy of melatonin for the prevention of postoperative delirium: a meta-analysis of randomized controlled trials. Front Aging Neurosci. 2010;12:121.
13. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. Clin Drug Investig. 2014;36(3):169–75.
14. Kanova M, Sklienka P. Postoperative delirium. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2010;164(1):18–31.
15. Ford AH, Flicker L. The role of sleep in delirium and dementia. Age Ageing. 2015;44(1):10–7.