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Original Article

Postoperative Safety and Sedation Profile of Oral Melatonin Versus Oral Clonidine as Premedication Before General Anesthesia: A Prospective Comparative Study

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ABSTRACT

Background: An ideal premedicant should provide adequate anxiolysis and sedation while maintaining rapid postoperative recovery with minimal adverse effects. Oral melatonin and oral clonidine are commonly used preoperative medications with sedative and anxiolytic properties; however, their postoperative safety profiles differ because of their distinct pharmacological mechanisms. Comparative evidence regarding postoperative sedation, recovery characteristics, and adverse effects between these two agents remains limited. This study compared the postoperative safety profile of oral melatonin and oral clonidine administered before general anesthesia in adult patients undergoing elective surgery.

Methods: This prospective, randomized, comparative study included 60 ASA physical status I–II adult patients scheduled for elective surgical procedures under general anesthesia. Patients were randomly allocated to receive either oral melatonin 6 mg (Group M, n=30) or oral clonidine 0.2 mg (Group C, n=30) 90 minutes before induction. Postoperative Ramsay Sedation Scores were assessed at the first and fourth postoperative hours. Recovery time following discontinuation of anesthesia, duration of intubation, duration of surgery, and drug-related adverse effects including nausea, bradycardia, and excessive sedation were recorded and compared between groups.

Results: Baseline demographic characteristics and operative variables were comparable between groups. Patients receiving oral clonidine demonstrated significantly higher Ramsay Sedation Scores during the first postoperative hour than those receiving melatonin (2.36 ± 0.89 vs 1.96 ± 0.18; p=0.019), whereas sedation scores were identical at the fourth postoperative hour. Recovery time did not differ significantly between the two groups. Postoperative adverse effects differed significantly, with clonidine associated with bradycardia (13.3%) and transient postoperative sedation (23.3%), whereas nausea was the only adverse event observed in the melatonin group (6.7%). Most patients in both groups experienced no clinically significant postoperative complications.

Conclusions: Both oral melatonin and oral clonidine demonstrated acceptable postoperative safety profiles as premedicants before general anesthesia. Clonidine provided greater early postoperative sedation but was associated with a higher incidence of bradycardia and transient sedation, whereas melatonin showed a more favorable adverse-effect profile with comparable recovery time. Melatonin may

therefore represent a useful alternative when rapid postoperative recovery and minimal cardiovascular adverse effects are desired.

Keywords: Melatonin, Clonidine, Premedication, Ramsay Sedation Score, Postoperative Recovery, General Anesthesia.

INTRODUCTION

Preoperative anxiety and psychological stress are common among patients undergoing surgery and are associated with increased sympathetic activity, greater anaesthetic requirements, and less favourable perioperative outcomes. Appropriate premedication not only facilitates smooth induction of general anaesthesia but also improves patient comfort, reduces anxiety, enhances cooperation, and contributes to improved postoperative recovery. An ideal oral premedicant should provide effective anxiolysis and mild sedation while preserving cardiovascular stability and allowing rapid postoperative recovery without excessive respiratory depression or delayed emergence (1,2).

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone synthesized primarily by the pineal gland and is widely recognized for regulating circadian rhythm and the sleep–wake cycle. Beyond its physiological role, melatonin possesses anxiolytic, sedative, analgesic, antioxidant, and anti-inflammatory properties that have attracted considerable interest in perioperative medicine. Unlike conventional sedative agents, melatonin induces physiological sleep with minimal impairment of cognitive or psychomotor function and has been associated with reduced perioperative anxiety, improved sleep quality, and enhanced postoperative recovery. Clinical studies have demonstrated that melatonin can be safely used as an oral premedicant while maintaining favourable recovery characteristics in patients undergoing elective surgical procedures (3).

In addition to reducing preoperative anxiety, melatonin has been reported to improve several postoperative outcomes. Previous randomized clinical trials have demonstrated reductions in postoperative pain, improved sleep quality, decreased analgesic requirements, and satisfactory postoperative sedation without clinically significant residual drowsiness or delayed recovery. These characteristics make melatonin particularly attractive for ambulatory surgery and enhanced recovery protocols where early mobilization and rapid discharge are desirable (4,5).

Clonidine, a selective partial α_2-adrenergic receptor agonist, is another well-established oral premedicant that provides sedation, anxiolysis, analgesia, and sympatholysis through inhibition of central sympathetic outflow. By reducing catecholamine release and enhancing perioperative haemodynamic stability, clonidine has become an important component of balanced anaesthesia. However, its pharmacological effects may also increase the incidence of dose-dependent adverse events, including bradycardia, hypotension, and excessive postoperative sedation. Consequently, careful evaluation of its postoperative safety profile remains clinically relevant when selecting an appropriate premedication strategy (6,7).

Although both melatonin and clonidine have independently demonstrated favourable perioperative effects, direct comparative evidence focusing specifically on postoperative recovery, sedation profile, and adverse effects remains limited. Since both agents are inexpensive, orally administered, and widely available, understanding their relative postoperative safety may help anaesthesiologists individualize premedication according to patient characteristics and surgical requirements. Therefore, the present prospective randomized comparative study was undertaken to evaluate and compare the postoperative safety profile of oral melatonin (6 mg) and oral clonidine (0.2 mg), administered 90 minutes before induction of general anaesthesia, with particular emphasis on postoperative sedation, recovery characteristics, and treatment-related adverse effects.

MATERIALS AND METHODS

Study Design and Setting

This prospective, randomized, comparative study was conducted at Apollo BGS Hospitals, Mysore, India, over a 12-month period from October 2017 to September 2018. Institutional Ethics Committee approval was obtained before commencement of the study, and written informed consent was obtained from all participants prior to enrolment.

Study Population

Sixty adult patients scheduled for elective surgical procedures under general anaesthesia with endotracheal intubation were enrolled. Patients were randomly assigned into two equal groups (n = 30 each):

- **Group M:** Oral melatonin 6 mg administered 90 minutes before induction of anaesthesia.
- **Group C:** Oral clonidine 0.2 mg administered 90 minutes before induction of anaesthesia.

Eligibility Criteria

Inclusion Criteria

Patients fulfilling the following criteria were included:

- Age between 18 and 45 years.

- ASA physical status I or II.
- Mallampati airway grade I or II.
- Elective surgical procedures requiring endotracheal intubation.
- Provision of written informed consent.

Exclusion Criteria

Patients were excluded if they had:

- Refused participation.
- Pregnancy or lactation.
- Drug or alcohol abuse.
- Chronic pain syndrome or psychiatric illness.
- Peripheral vascular disease.
- Body mass index >30 kg/m².
- Concurrent use of clonidine, antihypertensive drugs, sedatives, hypnotics, antidepressants, benzodiazepines, α-blockers, monoamine oxidase inhibitors, or other medications affecting the central nervous system.

Randomization and Blinding

Participants were randomized using a computer-generated random number sequence into two equal treatment groups. Drug allocation and administration were performed by an anaesthesiologist who was not involved in intraoperative observations or postoperative assessment. The investigator responsible for data collection remained blinded to treatment allocation throughout the study period.

Anaesthetic Technique

All patients underwent a standardized anaesthetic protocol. Routine monitoring included electrocardiography, pulse oximetry, and non-invasive blood pressure monitoring. Intravenous access was established with an 18-gauge cannula, and Ringer's lactate infusion was initiated.

Patients received intravenous midazolam (1 mg) and fentanyl (2 μg/kg) before induction. Anaesthesia was induced using propofol (2 mg/kg) followed by vecuronium bromide (0.1 mg/kg) to facilitate tracheal intubation. Direct laryngoscopy using an appropriately sized Macintosh blade was performed after three minutes of ventilation with 100% oxygen, and endotracheal intubation was completed within 15 seconds.

Anaesthesia was maintained with oxygen, nitrous oxide, and sevoflurane under controlled ventilation. Neuromuscular blockade was maintained with supplemental vecuronium, and intravenous paracetamol (1 g) was administered for intraoperative analgesia. At the end of surgery, neuromuscular blockade was reversed using neostigmine and glycopyrrolate before extubation.

Postoperative Assessment

Unlike the primary efficacy analysis presented separately, this study primarily evaluated postoperative recovery and safety outcomes.

Sedation was assessed using the Ramsay Sedation Scale at the first postoperative hour and fourth postoperative hour.

Recovery time was defined as the interval between discontinuation of nitrous oxide and spontaneous eye opening.

Drug-related adverse effects were recorded throughout the postoperative observation period, including:

- Bradycardia
- Sedation
- Nausea
- Respiratory depression
- Other clinically significant adverse events

Duration of intubation and duration of surgery were also documented to ensure procedural comparability between treatment groups.

Outcome Measures

Primary Outcome

- Ramsay Sedation Score at 1 and 4 hours after surgery.

Secondary Outcomes

- Recovery time from anaesthesia.
- Incidence of postoperative nausea.
- Incidence of bradycardia.
- Other postoperative adverse events.
- Overall postoperative safety profile.

Statistical Analysis

The required sample size was estimated to be at least 23 patients per treatment group. To improve statistical power and compensate for potential dropouts, 30 patients were enrolled in each group. Statistical analysis was performed using IBM SPSS Statistics version 17.0.

Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. Between-group comparisons of continuous variables were performed using the independent-samples *t*-test, while categorical variables were analysed using the Chi-square test where appropriate. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Baseline demographic and operative characteristics

Variable	Melatonin (n=30)	Clonidine (n=30)	p-value
Age (years)	33.07 ± 6.34	32.86 ± 6.53	0.904
Male/Female	14/16	16/14	1.000
Weight (kg)	52.23 ± 3.54	53.29 ± 3.92	0.278
Height (cm)	153.38 ± 6.43	154.26 ± 5.80	0.578
BMI (kg/m²)	22.26 ± 2.42	22.40 ± 1.38	0.779
Duration of intubation (sec)	13.70 ± 2.78	12.86 ± 1.52	0.155
Duration of surgery (min)	77.20 ± 7.33	80.00 ± 6.58	0.125

Table 2. Comparison of postoperative Ramsay Sedation Scores

Assessment Time	Melatonin	Clonidine	p-value
First postoperative hour	1.96 ± 0.18	2.36 ± 0.89	0.019
Fourth postoperative hour	2.00 ± 0.00	2.00 ± 0.00	NS

Table 3. Recovery characteristics

Variable	Melatonin	Clonidine	p-value
Recovery time (min)	1.82 ± 0.64	1.93 ± 0.66	0.537
Duration of intubation (sec)	13.70 ± 2.78	12.86 ± 1.52	0.155
Duration of surgery (min)	77.20 ± 7.33	80.00 ± 6.58	0.125

Table 4. Comparison of postoperative adverse effects

Adverse Effect	Melatonin n (%)	Clonidine n (%)
Nausea	2 (6.7)	0
Bradycardia	0	4 (13.3)
Sedation	0	7 (23.3)
No adverse effects	28 (93.3)	19 (63.3)

DISCUSSION

The present prospective randomized comparative study evaluated the postoperative safety profile of oral melatonin (6 mg) and oral clonidine (0.2 mg) administered as premedication before general anaesthesia. The principal findings demonstrate that both agents were safe and clinically effective; however, they differed in their postoperative recovery characteristics. Oral clonidine produced significantly greater early postoperative sedation and a higher incidence of bradycardia, whereas oral melatonin exhibited a more favourable adverse-effect profile while maintaining recovery times comparable to clonidine. These findings suggest that the choice of oral premedication should be individualized according to the desired balance between postoperative sedation, cardiovascular safety, and recovery characteristics.

An ideal premedicant should provide adequate perioperative sedation without delaying postoperative recovery or interfering with early neurological assessment and mobilization. In the present study, patients receiving clonidine demonstrated significantly higher Ramsay Sedation Scores during the first postoperative hour, although sedation resolved by the fourth postoperative hour in both groups. Similar observations have been reported in pharmacological reviews describing clonidine as an effective α_2-adrenergic agonist that provides reliable perioperative sedation through central sympatholytic mechanisms without causing clinically significant respiratory depression when administered in appropriate doses (8,9).

The greater early postoperative sedation observed in the clonidine group is consistent with previous clinical investigations evaluating its perioperative use. Ghignone and colleagues demonstrated that clonidine provides effective perioperative sedation while improving cardiovascular stability and reducing anaesthetic requirements. Likewise, Raval and Mehta reported significant sedative and sympatholytic effects of oral clonidine during the perioperative period, supporting its role as an effective oral premedicant in elective surgical procedures (10,11).

Melatonin, in contrast, produced adequate perioperative sedation with fewer postoperative adverse effects and no clinically significant delay in recovery. The physiological mechanism of melatonin differs from conventional sedatives because it promotes natural sleep through activation of melatonin receptors and modulation of γ-aminobutyric acid (GABA)-mediated neurotransmission. Previous clinical studies by Talebi et al. and Kumar et al. have similarly demonstrated favourable

recovery characteristics, satisfactory patient comfort, and minimal residual postoperative sedation following perioperative use of these agents, findings that support the excellent postoperative recovery profile observed in the present study (12,13). Recovery time is an important determinant of patient turnover and enhanced recovery protocols. Despite greater early sedation with clonidine, recovery time did not differ significantly between the two treatment groups, indicating that neither drug adversely affected immediate emergence from general anaesthesia. From a clinical perspective, clonidine may be advantageous when greater perioperative sedation and sympatholysis are desirable, whereas melatonin appears particularly suitable for ambulatory surgery, elderly patients, and individuals in whom excessive postoperative sedation or cardiovascular adverse effects should be minimized. The favourable safety profile of melatonin may therefore contribute to improved patient satisfaction and facilitate enhanced recovery pathways (14,15).

The present study has several strengths, including its prospective randomized design, standardized anaesthetic protocol, identical timing of drug administration, and direct comparison of two commonly used oral premedicants under similar clinical conditions. Nevertheless, certain limitations should be acknowledged. The study was conducted at a single centre with a relatively small sample size and included only ASA physical status I–II patients undergoing elective surgery. Furthermore, long-term postoperative outcomes such as quality of sleep, patient satisfaction, cognitive recovery, analgesic requirements, and cost-effectiveness were not assessed. Future multicentre randomized controlled trials involving larger and more diverse patient populations are warranted to validate these findings and further define the optimal role of oral melatonin and clonidine in contemporary perioperative practice.

CONCLUSION

Both oral melatonin and oral clonidine were safe and effective premedicants before general anaesthesia. Oral clonidine produced greater early postoperative sedation but was associated with a higher incidence of transient bradycardia and sedation. Oral melatonin demonstrated a more favourable postoperative safety profile with minimal adverse effects while providing comparable recovery time. These findings suggest that melatonin may be a suitable alternative when rapid recovery and a lower incidence of cardiovascular adverse effects are clinical priorities.

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