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Original Article

Role of Oral Premedication in Balanced Anesthesia: Comparative Evaluation of Melatonin and Clonidine on Perioperative Hemodynamic Stability and Recovery Characteristics

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ABSTRACT

Background: Balanced anesthesia aims to optimize perioperative physiological stability while minimizing adverse drug effects and facilitating rapid postoperative recovery. Oral premedication forms an integral component of this strategy by reducing anxiety, improving patient comfort, attenuating stress responses, and enhancing overall perioperative management. Melatonin and clonidine possess distinct pharmacological properties that may contribute to balanced anesthesia through different mechanisms. This study compared their overall perioperative performance with emphasis on haemodynamic stability, recovery characteristics, and postoperative safety in adult patients undergoing elective surgery under general anesthesia.

Methods: This prospective, randomized, comparative study included 60 ASA physical status I–II adult patients undergoing elective surgery under general anesthesia with endotracheal intubation. Participants were randomly assigned to receive either oral melatonin 6 mg or oral clonidine 0.2 mg 90 minutes before induction. Perioperative heart rate, systolic, diastolic and mean arterial pressures were recorded from baseline until 10 minutes after intubation. Recovery time, Ramsay Sedation Scores, and postoperative adverse effects were also evaluated.

Results: Both oral premedicants contributed to perioperative haemodynamic control and satisfactory postoperative recovery. Clonidine demonstrated superior attenuation of heart rate and blood pressure responses throughout airway instrumentation, while melatonin maintained acceptable haemodynamic stability with fewer postoperative adverse effects. Early postoperative sedation was greater in the clonidine group, whereas recovery time remained comparable between groups. Nausea was observed only in the melatonin group, while transient bradycardia and postoperative sedation occurred more frequently following clonidine administration.

Conclusions: Both oral melatonin and oral clonidine represent useful premedicants within a balanced anesthesia protocol. Clonidine provides superior perioperative haemodynamic control, whereas melatonin demonstrates a more favourable postoperative safety profile. Selection between these agents should therefore be

individualized according to patient characteristics, cardiovascular risk, and recovery priorities.

Keywords: Balanced anesthesia, Premedication, Melatonin, Clonidine, Hemodynamic stability, Recovery characteristics.

INTRODUCTION

Balanced anesthesia is based on the principle of combining multiple pharmacological interventions to achieve adequate hypnosis, analgesia, muscle relaxation, autonomic stability, and rapid postoperative recovery while minimizing drug-related adverse effects. Oral premedication represents an important component of this multimodal strategy because it reduces preoperative anxiety, improves patient comfort, facilitates smooth induction of anesthesia, and attenuates the physiological stress response associated with surgery. An ideal oral premedicant should therefore provide effective anxiolysis and mild sedation while preserving cardiovascular stability and promoting early postoperative recovery without excessive respiratory depression or prolonged sedation (1,2).

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced primarily by the pineal gland that regulates circadian rhythm and the sleep–wake cycle. In addition to its physiological role, melatonin possesses anxiolytic, sedative, analgesic, antioxidant, and anti-inflammatory properties that have generated considerable interest in perioperative medicine. Experimental and clinical evidence suggests that melatonin modulates γ-aminobutyric acid (GABA)-mediated neurotransmission and reduces sympathetic nervous system activity, thereby contributing to improved perioperative haemodynamic stability and enhanced postoperative recovery. Owing to its favourable safety profile and minimal impairment of cognitive and psychomotor function, melatonin has emerged as a promising oral premedicant in modern balanced anesthesia (3).

Several clinical studies have demonstrated the beneficial perioperative effects of melatonin. Previous randomized trials have shown that preoperative melatonin administration attenuates haemodynamic responses during laryngoscopy and endotracheal intubation while improving perioperative patient comfort and maintaining favourable recovery characteristics. These findings suggest that melatonin may serve as an effective alternative to conventional sedative premedication, particularly in ambulatory surgery and enhanced recovery pathways (4,5).

Clonidine, a selective partial α_2-adrenergic receptor agonist, is another widely used oral premedicant that provides sedation, anxiolysis, analgesia, and sympatholysis through inhibition of central sympathetic outflow. By decreasing circulating catecholamine release and enhancing baroreceptor sensitivity, clonidine improves perioperative haemodynamic stability while reducing anaesthetic and opioid requirements. However, its pharmacological actions may also increase the likelihood of dose-dependent bradycardia, hypotension, and postoperative sedation, necessitating careful patient selection. Previous randomized clinical trials have consistently demonstrated the effectiveness of oral clonidine in attenuating cardiovascular responses during airway manipulation and improving perioperative stability (6,7).

Although both melatonin and clonidine have independently shown favourable perioperative effects, comparative evidence evaluating their overall contribution to balanced anesthesia remains limited. Most available studies have focused on individual outcomes such as haemodynamic response or postoperative sedation rather than integrating perioperative cardiovascular stability, recovery characteristics, and overall safety into a single clinical assessment. Therefore, the present prospective randomized comparative study was undertaken to evaluate the role of oral melatonin (6 mg) and oral clonidine (0.2 mg) as premedicants in balanced anesthesia by comparing their effects on perioperative haemodynamic stability, postoperative recovery characteristics, and overall safety in adult patients undergoing elective surgical procedures under general anesthesia.

MATERIALS AND METHODS

Study Design and Setting

This prospective, randomized, comparative study was conducted at Apollo BGS Hospitals, Mysore, India, over a period of 12 months (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 before enrolment.

Study Population

A total of **60 adult patients** scheduled for elective surgical procedures under general anaesthesia with endotracheal intubation were enrolled. Participants were randomly allocated into two equal treatment groups:

- **Group M (n = 30):** Oral melatonin 6 mg administered 90 minutes before induction of anaesthesia.
- **Group C (n = 30):** Oral clonidine 0.2 mg administered 90 minutes before induction of anaesthesia.

Eligibility Criteria

Inclusion Criteria

Patients fulfilling all of the following criteria were included:

- Age between 18 and 45 years.
- American Society of Anesthesiologists (ASA) physical status I or II.
- Mallampati airway grade I or II.
- Elective surgery requiring endotracheal intubation under general anaesthesia.
- Written informed consent.

Exclusion Criteria

Patients were excluded if they had:

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

Randomization and Blinding

Patients were randomized using a computer-generated randomization sequence into two equal groups. Drug administration was performed by an anaesthesiologist who was not involved in subsequent intraoperative observations or postoperative assessments. The investigator responsible for data collection remained blinded to treatment allocation throughout the study, thereby minimizing observer bias.

Anaesthetic Management

All patients received a standardized anaesthetic technique.

Routine monitoring included:

- Electrocardiography (ECG)
- Pulse oximetry
- Non-invasive blood pressure (NIBP)

An 18-gauge intravenous cannula was inserted and Ringer's lactate infusion was initiated.

All patients received intravenous:

- Midazolam 1 mg
- Fentanyl 2 µg/kg

Anaesthesia was induced with propofol (2 mg/kg) mixed with preservative-free lignocaine, followed by vecuronium bromide (0.1 mg/kg). Following three minutes of ventilation with 100% oxygen, direct laryngoscopy using an appropriately sized Macintosh blade was performed, and tracheal intubation was completed within 15 seconds.

Anaesthesia was maintained with oxygen (33%), nitrous oxide (66%), and sevoflurane (1%) under controlled mechanical ventilation. Additional doses of vecuronium were administered according to neuromuscular requirements. Intravenous paracetamol (1 g) was administered intraoperatively for analgesia. Neuromuscular blockade was reversed with glycopyrrolate and neostigmine before extubation.

Study Outcomes

Unlike the previous two analyses that evaluated either haemodynamic efficacy or postoperative safety separately, the present manuscript assessed the overall contribution of oral premedication to balanced anaesthesia by integrating intraoperative haemodynamic control with postoperative recovery.

Primary Outcomes

- Heart rate (HR)
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Mean arterial pressure (MAP)

These variables were recorded at:

- **T0:** Baseline
- **T1:** 90 minutes after drug administration (pre-induction)

- **T2:** During laryngoscopy and intubation
- **T3:** 1 minute after intubation
- **T4:** 3 minutes after intubation
- **T5:** 5 minutes after intubation
- **T6:** 10 minutes after intubation.

Secondary Outcomes

The following variables were also evaluated to assess perioperative recovery:

- Duration of intubation.
- Duration of surgery.
- Recovery time.
- Ramsay Sedation Score at the first and fourth postoperative hours.
- Drug-related adverse events including nausea, bradycardia, and postoperative sedation.

Statistical Analysis

The calculated minimum sample size was 23 patients per treatment group. To improve study power and compensate for potential dropouts, 30 patients were enrolled in each group. Statistical analyses were performed using IBM SPSS Statistics version 17.0. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were summarized as frequencies and percentages. Between-group comparisons 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 perioperative 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. Summary of perioperative haemodynamic parameters

Parameter	Melatonin	Clonidine	Overall Comparison
Heart Rate	Controlled	Better control	Clonidine superior
SBP	Controlled	Better control	Clonidine superior
DBP	Controlled	Better control	Clonidine superior
MAP	Controlled	Better control	Clonidine superior

Table 3. Recovery profile

Variable	Melatonin	Clonidine	p-value
Recovery time (min)	1.82 ± 0.64	1.93 ± 0.66	0.537
First-hour Ramsay Sedation Score	1.96 ± 0.18	2.36 ± 0.89	0.019
Fourth-hour Ramsay Sedation Score	2.00 ± 0.00	2.00 ± 0.00	NS

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 role of oral melatonin and oral clonidine as components of balanced anesthesia by integrating perioperative haemodynamic stability, postoperative recovery characteristics, and overall safety into a single clinical assessment. The principal findings demonstrate that both agents contributed positively to perioperative management; however, each exhibited distinct clinical advantages. Oral clonidine

provided superior attenuation of haemodynamic responses during laryngoscopy and endotracheal intubation, whereas oral melatonin was associated with fewer postoperative adverse effects and comparable recovery characteristics. These findings suggest that selection of an oral premedicant should be individualized according to the patient's cardiovascular status, recovery goals, and overall perioperative risk.

Balanced anesthesia emphasizes the use of complementary pharmacological agents to minimize surgical stress while facilitating smooth recovery. An effective oral premedicant should reduce anxiety, provide appropriate sedation, suppress sympathetic activation, preserve cardiovascular stability, and avoid excessive postoperative complications. In the present study, both melatonin and clonidine fulfilled many of these objectives. The established sympatholytic action of clonidine through central α_2-adrenergic receptor stimulation has been well documented and remains one of the principal reasons for its incorporation into balanced anesthesia protocols (8).

The superior haemodynamic stability observed with clonidine in the present study is consistent with previous investigations evaluating its perioperative use. Ghignone and colleagues demonstrated that clonidine significantly improves perioperative cardiovascular stability while reducing anaesthetic requirements. Likewise, Khare and colleagues reported favourable perioperative outcomes with oral premedication strategies that support the importance of adequate anxiolysis and haemodynamic control during general anaesthesia. Together, these findings reinforce the role of clonidine in minimizing sympathetic responses associated with airway manipulation and surgical stimulation (9,10).

Although melatonin did not suppress haemodynamic responses to the same extent as clonidine, it nevertheless provided satisfactory cardiovascular stability while demonstrating an excellent postoperative safety profile. The favourable recovery characteristics observed in the present study are consistent with the pharmacological properties of melatonin, which promotes physiological sleep and anxiolysis without producing excessive residual sedation. Reviews of clonidine pharmacology and autonomic regulation further support the concept that the differing mechanisms of action of these two agents explain their distinct clinical profiles, allowing clinicians to tailor premedication according to individual patient requirements (11,12).

Recovery quality represents an essential component of balanced anesthesia. Despite greater early postoperative sedation in the clonidine group, recovery time remained comparable between the two treatment groups, indicating that improved haemodynamic control was achieved without delaying emergence from anaesthesia. Conversely, melatonin produced only mild postoperative sedation and fewer cardiovascular adverse effects, making it particularly attractive for ambulatory surgery, enhanced recovery protocols, elderly patients, and individuals in whom rapid neurological recovery is desirable. The pharmacological basis for these observations is consistent with current understanding of centrally acting sedative agents and perioperative drug selection (13).

From a clinical perspective, the findings of the present study suggest complementary rather than competing roles for melatonin and clonidine within balanced anesthesia. Clonidine may be preferred in patients at increased risk of perioperative haemodynamic instability or excessive sympathetic activation, whereas melatonin may be advantageous in patients where preservation of rapid recovery and minimization of cardiovascular adverse effects are priorities. Previous randomized studies evaluating melatonin have similarly reported favourable postoperative recovery, improved patient comfort, and minimal residual sedation, supporting the present observations and reinforcing its value as a safe oral premedicant (14,15).

The present study has several strengths, including its prospective randomized design, standardized anaesthetic protocol, and comprehensive evaluation of both intraoperative and postoperative outcomes. 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. Additional outcomes such as postoperative analgesic consumption, patient satisfaction, sleep quality, cognitive recovery, and discharge readiness were not evaluated. Future multicentre randomized controlled trials involving larger and more diverse patient populations are warranted to further define the role of oral melatonin and clonidine within contemporary balanced anesthesia and enhanced recovery protocols.

CONCLUSION

Both oral melatonin and oral clonidine are effective premedicants that contribute to balanced anesthesia by improving perioperative management through different mechanisms. Oral clonidine provides superior haemodynamic stability during laryngoscopy and endotracheal intubation, whereas oral melatonin offers a favourable postoperative safety profile with fewer cardiovascular adverse effects and comparable recovery. Selection between these agents should therefore be individualized according to patient characteristics, perioperative cardiovascular risk, and recovery goals, allowing clinicians to optimize balanced anesthesia while maintaining patient safety.

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