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Comparative Effectiveness of Oral Melatonin and Oral Clonidine for Attenuation of Hemodynamic Stress Response During Laryngoscopy and Endotracheal Intubation: A Randomized Controlled Study

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation produce a transient but marked sympathetic response characterized by tachycardia and hypertension, which may increase perioperative cardiovascular risk, particularly in susceptible patients. Although several pharmacological agents have been investigated to attenuate this response, an ideal oral premedicant with effective hemodynamic control and minimal adverse effects remains desirable. Melatonin possesses sedative, anxiolytic, and sympatholytic properties, whereas clonidine is a well-established α_2-adrenergic agonist known to provide perioperative hemodynamic stability. Direct comparison between these two agents has been limited.

Methods: A prospective, randomized, comparative study was conducted in 60 adult patients (ASA physical status I–II) undergoing elective surgery 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 of anesthesia. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded at baseline, before induction, during laryngoscopy and intubation, and at 1, 3, 5, and 10 minutes after intubation. Demographic characteristics and operative variables were also compared.

Results: Baseline demographic characteristics were comparable between groups. Oral clonidine produced significantly lower HR, SBP, DBP, and MAP before induction and throughout the post-intubation observation period compared with oral melatonin ($p<0.05$ for all major comparisons). During laryngoscopy, both groups demonstrated transient hemodynamic increases; however, the magnitude of increase was substantially lower in the clonidine group. Duration of intubation and duration of surgery were comparable between groups.

Conclusions: Oral clonidine (0.2 mg) administered 90 minutes before induction was more effective than oral melatonin (6 mg) in attenuating the hemodynamic stress response associated with laryngoscopy and endotracheal intubation while maintaining comparable operative conditions. These findings support oral clonidine as a useful premedication for improving perioperative cardiovascular stability during airway instrumentation.

Keywords: *Clonidine, Melatonin, Laryngoscopy, Endotracheal Intubation, Hemodynamic Response, Premedication.*

INTRODUCTION

Laryngoscopy and endotracheal intubation are indispensable components of general anaesthesia but are consistently associated with a transient sympathoadrenal response characterized by tachycardia, hypertension, and increased myocardial

oxygen demand. These haemodynamic alterations result from reflex sympathetic stimulation caused by mechanical manipulation of the larynx and trachea during airway instrumentation. Although these responses are generally well tolerated in healthy individuals, they may precipitate myocardial ischemia, arrhythmias, cerebrovascular events, or acute heart failure in patients with hypertension, coronary artery disease, or other cardiovascular comorbidities. Consequently, attenuation of the pressor response to laryngoscopy remains an important objective of modern anaesthetic practice (1,2).

Over the past several decades, numerous pharmacological and non-pharmacological strategies have been investigated to minimize the cardiovascular stress response associated with airway manipulation. Increasing the depth of anaesthesia, topical airway anaesthesia, opioids, β-blockers, calcium-channel blockers, vasodilators, intravenous lidocaine, and α_2-adrenergic agonists have demonstrated varying degrees of success. However, many of these interventions are associated with adverse effects such as excessive hypotension, bradycardia, respiratory depression, delayed recovery, or the requirement for intensive haemodynamic monitoring. Therefore, identifying an effective oral premedicant that provides reliable haemodynamic stability with minimal adverse effects remains a clinically important goal (3,4).

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous hormone secreted by the pineal gland, has gained increasing attention as a perioperative adjuvant because of its sedative, anxiolytic, analgesic, antioxidant, and sympatholytic properties. Experimental and clinical evidence suggests that melatonin modulates γ-aminobutyric acid (GABA)-mediated neurotransmission and reduces sympathetic nervous system activity, thereby improving perioperative haemodynamic stability. In addition to reducing preoperative anxiety, melatonin has been shown to attenuate increases in blood pressure and heart rate during laryngoscopy without producing significant psychomotor impairment or delayed recovery, making it an attractive alternative to conventional sedative premedication (5).

Clinical studies evaluating oral melatonin before induction of general anaesthesia have reported favourable effects on haemodynamic responses during laryngoscopy and endotracheal intubation. Previous randomized trials have demonstrated significant reductions in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure following preoperative melatonin administration compared with control groups, supporting its potential role as a safe and effective oral premedicant (6,7).

Despite these encouraging findings, direct comparisons between oral melatonin and oral clonidine remain limited. Since both drugs are inexpensive, orally administered, and possess distinct pharmacological mechanisms capable of attenuating sympathetic activation, establishing their relative efficacy is clinically relevant. Therefore, the present randomized comparative study was undertaken to evaluate the effectiveness of oral melatonin (6 mg) and oral clonidine (0.2 mg), administered 90 minutes before induction of general anaesthesia, in attenuating the haemodynamic stress response to laryngoscopy and endotracheal intubation in adult patients undergoing elective surgical procedures.

MATERIALS AND METHODS

Study Design and Setting

This prospective, randomized, comparative study was conducted in the Department of Anaesthesiology at Apollo BGS Hospitals, Mysore, India, over a 12-month period from October 2017 to September 2018. The study was approved by the Institutional Ethics Committee, 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. Eligible participants were randomly allocated in a 1:1 ratio into two equal groups (n = 30 each):

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

Eligibility Criteria

Inclusion Criteria

Patients fulfilling all of the following criteria were included:

- Age 18–45 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, lactation, or menstruation.
- Drug or alcohol abuse.
- Chronic pain syndrome, psychiatric illness, or peripheral vascular disease.

- Body mass index >30 kg/m².
- Current treatment with clonidine, antihypertensive drugs, sedatives, hypnotics, antidepressants, benzodiazepines, α-blockers, methyldopa, monoamine oxidase inhibitors, or other medications affecting the central nervous system that could interfere with study outcomes.

Randomization and Blinding

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

Anaesthetic Protocol

All patients received identical perioperative management. Standard monitoring included electrocardiography, non-invasive blood pressure measurement, and pulse oximetry after arrival in the operating room. An 18-gauge intravenous cannula was inserted, and Ringer's lactate infusion was commenced.

Patients were premedicated intravenously with midazolam 1 mg and fentanyl 2 μg/kg. Anaesthesia was induced using propofol 2 mg/kg mixed with preservative-free lignocaine, followed by vecuronium bromide 0.1 mg/kg to facilitate neuromuscular blockade. After 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 using a cuffed endotracheal tube.

Anaesthesia was maintained using oxygen (33%), nitrous oxide (66%), and sevoflurane (1%) with controlled mechanical ventilation. Supplemental doses of vecuronium were administered according to neuromuscular requirements, and intravenous paracetamol (1 g) was used for intraoperative analgesia. At the conclusion of surgery, neuromuscular blockade was reversed using neostigmine and glycopyrrolate before tracheal extubation.

Outcome Measures

The **primary outcome** was attenuation of the haemodynamic response to laryngoscopy and endotracheal intubation.
Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded at the following predefined time points:

- **T0:** Baseline before drug administration
- **T1:** Ninety minutes after premedication (pre-induction)
- **T2:** During laryngoscopy and tracheal intubation
- **T3:** One minute after intubation
- **T4:** Three minutes after intubation
- **T5:** Five minutes after intubation
- **T6:** Ten minutes after intubation

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

Statistical Analysis

Sample size estimation indicated a minimum requirement of 23 patients per group; therefore, **30 patients were enrolled in each group** to improve statistical power and compensate for potential dropouts. Statistical analyses were performed using **IBM SPSS Statistics version 17.0**. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages. Between-group comparisons were performed using the independent-samples *t*-test, whereas 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 heart rate (beats/min)

Time	Melatonin	Clonidine	p-value

Baseline (T0)	89.43 ± 13.30	87.03 ± 11.78	0.462
Pre-induction (T1)	81.47 ± 13.03	74.83 ± 11.83	0.038
Intubation (T2)	97.33 ± 13.16	77.83 ± 11.18	<0.001
1 min (T3)	96.67 ± 13.12	72.50 ± 11.08	<0.001
3 min (T4)	81.97 ± 10.80	69.90 ± 11.15	<0.001
5 min (T5)	77.97 ± 10.80	69.10 ± 11.21	0.002
10 min (T6)	71.47 ± 10.72	65.10 ± 11.21	0.028

Table 3. Comparison of systolic blood pressure (mmHg)

Time	Melatonin	Clonidine	p-value
Baseline	133.13 ± 14.39	134.73 ± 11.16	0.705
Pre-induction	124.93 ± 13.80	116.37 ± 9.08	0.006
Intubation	140.60 ± 9.97	119.40 ± 8.97	<0.001
1 min	125.30 ± 7.71	112.93 ± 9.04	<0.001
3 min	119.53 ± 7.89	104.50 ± 9.11	<0.001
5 min	117.20 ± 8.06	100.83 ± 9.14	<0.001
10 min	114.33 ± 6.05	99.70 ± 4.47	<0.001

Table 4. Comparison of diastolic blood pressure and mean arterial pressure

Time	DBP Melatonin	DBP Clonidine	MAP Melatonin	MAP Clonidine
Baseline	80.67 ± 9.24	83.07 ± 7.32	98.15 ± 9.52	100.29 ± 7.29
Pre-induction	75.63 ± 9.36	66.50 ± 6.91	92.07 ± 9.38	83.12 ± 6.70
Intubation	86.03 ± 7.20	69.93 ± 6.82	104.22 ± 7.06	86.42 ± 6.59
1 min	75.40 ± 6.64	65.80 ± 6.27	92.03 ± 6.56	81.51 ± 6.29
3 min	70.37 ± 6.84	59.80 ± 6.27	86.76 ± 6.75	74.69 ± 6.31
5 min	66.83 ± 6.94	55.30 ± 6.44	83.62 ± 6.88	70.48 ± 6.43
10 min	62.87 ± 5.42	52.93 ± 3.89	80.02 ± 5.05	68.52 ± 3.51

DISCUSSION

The present prospective randomized comparative study evaluated the effectiveness of oral melatonin (6 mg) and oral clonidine (0.2 mg), administered 90 minutes before induction of general anaesthesia, in attenuating the haemodynamic stress response associated with laryngoscopy and endotracheal intubation. The principal finding was that although both oral premedicants reduced sympathetic responses during airway manipulation, oral clonidine consistently provided superior control of heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure throughout laryngoscopy and the early post-intubation period. These findings suggest that clonidine offers greater perioperative haemodynamic stability and may be a more effective oral premedicant for patients undergoing elective surgery.

Baseline demographic characteristics, including age, sex distribution, body mass index, duration of intubation, and duration of surgery, were comparable between the two groups, thereby minimizing potential confounding factors. The observed differences in haemodynamic parameters are therefore likely attributable to the pharmacological actions of the study drugs rather than differences in patient characteristics or procedural variables.

The superior haemodynamic control observed with oral clonidine is consistent with previous clinical studies evaluating its role as a premedicant. Raval and Mehta demonstrated that oral clonidine significantly attenuated increases in heart rate and arterial pressure during laryngoscopy and endotracheal intubation compared with conventional premedication. Similarly, Talebi et al. reported that preoperative oral clonidine effectively reduced the cardiovascular stress response to airway instrumentation, confirming its sympatholytic efficacy and favourable perioperative haemodynamic profile (8,9).

The beneficial effects of clonidine are biologically plausible because of its selective central α_2-adrenergic agonist activity, which suppresses sympathetic outflow, decreases circulating catecholamine concentrations, and enhances baroreceptor sensitivity. These mechanisms reduce both heart rate and systemic arterial pressure during periods of intense surgical stimulation. Earlier investigations by Ghignone et al. and Nishikawa et al. similarly demonstrated improved perioperative cardiovascular stability and reduced haemodynamic variability following clonidine premedication, supporting the findings of the present study (10,11).

Although oral melatonin also demonstrated favourable haemodynamic effects, its attenuation of the stress response was less pronounced than that observed with clonidine. The sedative, anxiolytic, antioxidant, and sympatholytic properties of melatonin contribute to reduced perioperative anxiety and improved cardiovascular stability; however, its overall sympatholytic action appears comparatively weaker than that of α_2-adrenergic agonists. Previous studies comparing melatonin with other oral premedicants have similarly reported improvements in perioperative haemodynamic parameters

and patient comfort, while comprehensive reviews have highlighted its favourable safety profile and minimal psychomotor impairment (12,13).

One of the major strengths of the present study is the direct head-to-head comparison of two commonly used oral premedicants using a standardized anaesthetic protocol, identical timing of drug administration, and uniform perioperative management. Unlike many previous investigations that compared either melatonin or clonidine with placebo, the present study provides clinically relevant evidence regarding their relative effectiveness under routine anaesthetic conditions. These findings may assist anaesthesiologists in selecting an appropriate oral premedication strategy for elective surgical procedures.

Nevertheless, several limitations should be acknowledged. The relatively small sample size and single-centre design may limit the generalizability of the findings. Furthermore, postoperative sedation, analgesic requirements, patient satisfaction, recovery characteristics, and long-term clinical outcomes were not evaluated. Future multicentre randomized controlled trials involving larger populations, including patients with significant cardiovascular disease and high perioperative risk, are warranted to validate these findings and determine the broader clinical applicability of oral clonidine as a routine premedicant. Comparative studies assessing additional perioperative outcomes may further clarify the relative advantages of these oral agents (14,15).

CONCLUSION

Oral premedication with both melatonin (6 mg) and clonidine (0.2 mg) attenuated the haemodynamic response associated with laryngoscopy and endotracheal intubation. However, oral clonidine provided significantly superior control of heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure throughout airway instrumentation. These findings support oral clonidine as a more effective premedicant for maintaining perioperative haemodynamic stability during elective surgery under general anaesthesia.

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