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Original Research

Comparison of Oral Clonidine, Melatonin, and Pregabalin for Attenuation of Haemodynamic Responses to Laryngoscopy and Tracheal Intubation in General Anaesthesia.

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Abstract

Background: Direct laryngoscopy and tracheal intubation trigger sympathetic activation, producing transient tachycardia and hypertension. Oral clonidine, melatonin, and pregabalin possess sympatholytic, anxiolytic, or antinociceptive properties that can modify this response. *Objectives:* To compare the effectiveness of oral clonidine, melatonin, and pregabalin in attenuating haemodynamic responses to laryngoscopy and tracheal intubation. *Methods:* This prospective comparative observational study was conducted from January 2021 to September 2021 in a tertiary-care teaching hospital. Seventy-five adults aged 20-45 years with American Society of Anesthesiologists physical status I or II undergoing elective surgery under general anaesthesia were included. Twenty-five patients each received clonidine 100 µg 60 minutes before surgery, melatonin 6 mg 120 minutes before surgery, or pregabalin 150 mg 90 minutes before surgery. Heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were recorded at baseline, before induction, after induction, immediately after intubation, and at 3, 5, and 10 minutes. *Results:* The groups were comparable in age and sex. Immediately after intubation, mean heart rate was 103.12, 64.28, and 89.32 beats/min in the clonidine, melatonin, and pregabalin groups, respectively. Corresponding systolic pressures were 150.72, 111.28, and 129.92 mmHg, while mean arterial pressures were 115.76, 82.88, and 103.36 mmHg. Intergroup differences were significant for heart rate, diastolic pressure, and mean arterial pressure at all post-intubation assessments; systolic pressure differed significantly through 3 minutes. No clinically important respiratory or haemodynamic adverse effects were documented. *Conclusion:* All three oral premedicants attenuated the intubation response to varying degrees. Melatonin provided the greatest early haemodynamic stability, followed by pregabalin and clonidine.

Keywords: *Clonidine; haemodynamic response; laryngoscopy; melatonin; pregabalin; tracheal intubation.*

Introduction

Direct laryngoscopy and placement of an endotracheal tube are brief but intense nociceptive stimuli. Stimulation of the epipharyngeal, laryngeal, and tracheal structures activates sympathetic pathways and increases circulating catecholamines. The resulting response is typically characterized by tachycardia, elevated systolic and diastolic pressures, increased mean arterial pressure, and a higher myocardial oxygen demand. Shribman et al. demonstrated that tracheal intubation adds a substantial cardiovascular and catecholamine response beyond laryngoscopy alone.[1] The response commonly begins within seconds, reaches its maximum during the first minute, and then declines over several minutes when airway instrumentation is uncomplicated. In healthy young adults, these changes are usually transient; however, their magnitude and duration remain clinically relevant during induction of general anaesthesia.

The pressor response assumes greater importance in patients with reduced cardiovascular or cerebrovascular reserve. Rapid increases in heart rate and arterial pressure can disturb the balance between myocardial oxygen supply and demand, precipitate dysrhythmia, and contribute to myocardial ischaemia. Edwards et al. documented myocardial ischaemic episodes in relation to tracheal intubation and extubation.[2] Accordingly, attenuation of sympathetic activation is a routine objective of balanced anaesthesia. Opioids, local anaesthetics, beta-blockers, vasodilators, alpha-2 agonists, and other adjuvants have been studied, but their efficacy and adverse-effect profiles vary. Clonidine has shown useful haemodynamic control through central alpha-2 adrenergic agonism, reduced sympathetic outflow, sedation, and analgesic-sparing effects.[3] Its oral administration is simple, although excessive hypotension, bradycardia, and sedation remain dose-related concerns.

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Melatonin is an endogenous indoleamine involved in circadian regulation. As a premedicant, it offers anxiolytic and sedative effects without the characteristic cognitive impairment associated with conventional sedatives. Its perioperative actions also include antinociceptive, anti-inflammatory, and sympathomodulatory effects.[4] Oral melatonin has variable bioavailability, although immediate-release preparations generally reach peak concentrations within a clinically practical preoperative interval.[5] Pregabalin binds to the alpha-2-delta subunit of voltage-gated calcium channels and reduces excitatory neurotransmitter release. Despite its structural relationship to gamma-aminobutyric acid, it does not act directly at GABA receptors. Its anxiolytic, analgesic, and anticonvulsant properties, rapid absorption, predictable pharmacokinetics, and negligible hepatic metabolism support its use as an oral anaesthetic adjunct.[6]

Comparative evidence involving all three agents within one clinical cohort is limited. Their distinct mechanisms and dosing intervals create a practical question regarding which drug provides the most stable peri-intubation profile. Therefore, the objective of this study was to compare oral clonidine, melatonin, and pregabalin for attenuation of changes in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure during laryngoscopy and tracheal intubation in adults undergoing elective surgery under general anaesthesia.

Materials and Methods

Study design and setting

A prospective comparative observational study was conducted in the Department of Anaesthesiology, Father Muller Medical College, a tertiary-care teaching institution in Mangaluru, Karnataka, India, from January to September 2021. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[7]

Participants

Adults aged 20-45 years, weighing 40-65 kg, of either sex, with American Society of Anesthesiologists physical status I or II and scheduled for elective surgery under general anaesthesia with tracheal intubation were eligible. Exclusion criteria were age outside the specified range; ASA physical status III or IV; anaemia; hypertension; diabetes mellitus; cardiac, renal, respiratory, or psychiatric disease; current antiepileptic, sedative, or anxiolytic therapy; pregnancy or lactation; allergy to study or anaesthetic drugs; Mallampati class III or IV; and anticipated difficult intubation. Cases requiring more than three attempts or more than 20 seconds for airway instrumentation were excluded.

Sample size and group exposure

The calculation used a two-sided 95% confidence level, 90% power, expected means of 92.06 and 86.27, and standard deviations of 3.37 and 5.97, yielding 15 participants per group. The target was increased to 25 per group, giving a total sample of 75. Exposure groups reflected the oral premedication prescribed by the treating anaesthetist: Group A received clonidine 100 µg 60 minutes before surgery, Group B received melatonin 6 mg 120 minutes before surgery, and Group C received pregabalin 150 mg 90 minutes before surgery.

Perioperative procedure and measurements

After written informed consent, preanaesthetic assessment and routine investigations were completed. Participants fasted for 6-8 hours and received ranitidine 150 mg on the preceding night according to institutional protocol. In the operating room, electrocardiography, pulse oximetry, non-invasive blood pressure, and end-tidal carbon dioxide monitoring were instituted. An 18-gauge intravenous cannula was secured, and Ringer's lactate was started. Glycopyrrolate 0.01 mg/kg and fentanyl 2 µg/kg were administered intravenously. After three minutes of preoxygenation, anaesthesia was induced with propofol 2 mg/kg and succinylcholine 2 mg/kg. Tracheal intubation was performed with an appropriately sized cuffed tube. Anaesthesia was maintained with isoflurane, nitrous oxide 66%, oxygen 33%, and vecuronium 0.1 mg/kg. Heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were recorded at baseline, before induction, after induction, immediately after intubation, and at 3, 5, and 10 minutes. Neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg.

Statistical analysis

Data were analysed using SPSS software. Continuous variables were summarized as mean and standard deviation, and categorical variables as frequency and percentage. One-way analysis of variance was used for between-group comparisons of continuous variables, with Bonferroni post hoc testing after a significant omnibus result. Categorical variables were compared using the chi-square test. A two-sided p value below 0.05 was considered significant. Where the source output provided only a threshold, significance is reported as $p<0.05$.

Ethical considerations

Necessary Permissions were obtained before starting the study. Written informed consent was obtained from every participant, and confidentiality was maintained.

Results

All 75 enrolled patients were included in the analysis, with 25 participants in each exposure group. The overall mean age was 36.97 ± 7.75 years. Mean age did not differ significantly among Group A, Group B, and Group C (38.04 ± 8.55, 38.20 ± 7.05, and 34.68 ± 7.36 years, respectively; p=0.195). The study included 38 (50.7%) men and 37 (49.3%) women, and sex distribution was comparable across groups (p=0.688) (Table 1).

Table 1. Demographic characteristics of the study groups

Characteristic	Group A	Group B	Group C	Total	p value
Age, years, mean ± SD	38.04 ± 8.55	38.20 ± 7.05	34.68 ± 7.36	36.97 ± 7.75	0.195
Female, n (%)	11 (44.0)	12 (48.0)	14 (56.0)	37 (49.3)	0.688
Male, n (%)	14 (56.0)	13 (52.0)	11 (44.0)	38 (50.7)	0.688

Group A: clonidine 100 µg; Group B: melatonin 6 mg; Group C: pregabalin 150 mg. Age was compared using one-way ANOVA; sex was compared using the chi-square test.

Heart-rate trajectories differed across the three groups. Immediately after intubation, the mean heart rate was highest in Group A at 103.12 beats/min, compared with 64.28 beats/min in Group B and 89.32 beats/min in Group C. At 3 minutes, the corresponding values were 98.28, 67.88, and 84.16 beats/min. Intergroup differences were statistically significant at each post-intubation assessment through 10 minutes ($p<0.05$) (Table 2).

Table 2. Mean heart rate across peri-intubation time points

Time point	Group A	Group B	Group C	p value
Baseline	80.04	86.16	72.40	NR
Before induction	88.24	62.68	74.88	NR
After induction	93.24	63.32	75.20	NR
Immediately after intubation	103.12	64.28	89.32	<0.05
3 minutes	98.28	67.88	84.16	<0.05
5 minutes	93.28	69.80	81.56	<0.05
10 minutes	88.12	71.36	78.48	<0.05

Values are means in beats/min. NR: exact intergroup p value not reported in the source output.

The immediate systolic pressor response was also most marked in Group A. Mean systolic pressure immediately after intubation was 150.72 mmHg in Group A, 111.28 mmHg in Group B, and 129.92 mmHg in Group C. At 3 minutes, values were 127.28, 119.12, and 126.24 mmHg, respectively. The intergroup comparison was significant immediately and at 3 minutes after intubation, whereas differences at 5 and 10 minutes were not statistically significant (Table 3).

Table 3. Mean systolic blood pressure across peri-intubation time points

Time point	Group A	Group B	Group C	p value
Baseline	109.96	136.44	115.52	NR
Before induction	118.88	111.24	122.40	NR
After induction	120.08	110.36	112.48	NR
Immediately after intubation	150.72	111.28	129.92	<0.05
3 minutes	127.28	119.12	126.24	<0.05
5 minutes	120.32	121.84	122.96	NS
10 minutes	115.52	126.36	119.76	NS

Values are means in mmHg. NR: exact intergroup p value not reported; NS: not statistically significant.

For diastolic blood pressure, Group B maintained the lowest value immediately after intubation. Mean diastolic pressures at that point were 99.56 mmHg in Group A, 68.32 mmHg in Group B, and 90.16 mmHg in Group C. Significant intergroup differences persisted at 3, 5, and 10 minutes ($p<0.05$) (Table 4).

Table 4. Mean diastolic blood pressure across peri-intubation time points

Time point	Group A	Group B	Group C	p value
Baseline	73.12	88.00	80.40	NR
Before induction	76.48	67.28	82.16	NR
After induction	85.32	66.88	81.76	NR
Immediately after intubation	99.56	68.32	90.16	<0.05
3 minutes	84.48	73.12	87.92	<0.05
5 minutes	77.24	75.44	85.12	<0.05
10 minutes	75.64	78.28	82.88	<0.05

Values are means in mmHg. NR: exact intergroup p value not reported in the source output.

Mean arterial pressure followed a similar pattern. Immediately after intubation, mean arterial pressure was 115.76 mmHg in Group A, 82.88 mmHg in Group B, and 103.36 mmHg in Group C. At 10 minutes, the respective values were 89.68, 94.00, and 95.24 mmHg. Intergroup differences were significant at all post-intubation assessments ($p<0.05$) (Table 5).

Table 5. Mean arterial pressure across peri-intubation time points

Time point	Group A	Group B	Group C	p value
Baseline	85.52	104.16	92.08	NR
Before induction	87.96	81.84	95.44	NR
After induction	90.84	81.28	92.00	NR
Immediately after intubation	115.76	82.88	103.36	<0.05
3 minutes	97.00	88.48	100.72	<0.05
5 minutes	91.56	91.48	97.76	<0.05
10 minutes	89.68	94.00	95.24	<0.05

Values are means in mmHg. NR: exact intergroup p value not reported in the source output.

No clinically significant respiratory depression or major perioperative haemodynamic adverse effect was documented in any group. Considering the immediate post-intubation values across all four variables, Group B showed the greatest attenuation, Group C displayed an intermediate response, and Group A showed the largest early haemodynamic increase.

Discussion

This study compared three oral premedication strategies used before elective general anaesthesia. The principal finding was that melatonin produced the most favourable early haemodynamic pattern around laryngoscopy and intubation. Immediately after intubation, Group B had lower mean heart rate, systolic pressure, diastolic pressure, and mean arterial pressure than Groups A and C. Pregabalin showed an intermediate response, whereas the clonidine group demonstrated the largest immediate increase. Intergroup differences remained significant for heart rate, diastolic pressure, and mean arterial pressure throughout the recorded post-intubation period; systolic pressure differed significantly through 3 minutes. These observations support the concept that orally administered premedicants can modify the sympathoadrenal response, although they do not produce identical effects.

The melatonin findings agree with Gupta et al., who reported that 6 mg administered 120 minutes preoperatively attenuated cardiovascular responses to laryngoscopy and intubation.[8] Choudhary et al. also found oral melatonin superior to oral clonidine, particularly for early heart-rate and rate-pressure-product control.[9] More recent randomized evidence showed smaller post-intubation increases in heart rate and arterial pressures, together with reduced propofol and fentanyl requirements, after 6 mg oral melatonin.[10] The present pattern is biologically plausible because melatonin combines anxiolysis and mild sedation with sympathomodulatory and antinociceptive actions. Its timing in this study was also compatible with the variable absorption profile described for immediate-release oral preparations.[5]

Pregabalin was less effective than melatonin but provided better immediate control than clonidine in the available data. Rastogi et al. demonstrated dose-related attenuation of the pressor response with oral pregabalin and identified 150 mg as the more effective tested dose.[11] Sundar et al. similarly observed attenuation of the intubation response after 150 mg in patients undergoing off-pump coronary artery bypass surgery.[12] Pregabalin reduces excitatory neurotransmitter release through alpha-2-delta calcium-channel binding, which can dampen nociceptive transmission and perioperative anxiety.[6]

Comparisons between clonidine and pregabalin have produced inconsistent rankings. Parveen et al. reported stronger haemodynamic attenuation with clonidine 0.3 mg than pregabalin 150 mg, while Gupta et al. also favoured clonidine for laryngoscopy and laparoscopy but noted more bradycardia.[13,14] Conversely, other comparative work has shown distinct parameter-specific effects, with clonidine controlling heart rate and gabapentinoids controlling arterial pressure.[3] Dose differences are important: the 100 µg clonidine dose used here was lower than the 200-300 µg doses used in several comparative trials. The non-random exposure assignment and marked descriptive differences in baseline haemodynamic values also limit causal interpretation. Nevertheless, the consistent early separation of the melatonin group suggests a clinically relevant signal that warrants confirmation in an adequately powered randomized trial with standardized sedation scoring and adverse-event surveillance.

Limitations

This single-centre study had a modest sample and non-random exposure assignment, creating susceptibility to selection bias and baseline imbalance. Exact F statistics and post hoc comparisons were unavailable in the source output. Sedation, anxiety, anaesthetic consumption, catecholamine concentrations, extubation responses, and detailed adverse-event frequencies were not measured. Participants were young, low-risk adults; therefore, generalisability to elderly or cardiovascularly compromised patients is limited.

Conclusion

Oral clonidine, melatonin, and pregabalin were associated with different haemodynamic patterns during laryngoscopy and tracheal intubation in adults undergoing elective general anaesthesia. Melatonin 6 mg, administered 120 minutes preoperatively, provided the greatest early stability in heart rate and arterial pressures. Pregabalin 150 mg produced intermediate attenuation, whereas clonidine 100 µg showed the largest immediate pressor response in this cohort. The findings favour melatonin as an oral premedicant when early haemodynamic control is desired. Interpretation should remain cautious because treatment allocation was observational and baseline haemodynamic values were not uniform. Larger randomized trials should compare equivalent clinically accepted doses, quantify sedation and anxiety, and systematically assess adverse effects and anaesthetic-sparing outcomes.

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