Research Article

A Comparative Clinical Study of The Effects Of Oral Melatonin and Gabapentin on Preoperative Anxiety, Sedation, Attenuation of Haemodynamic Response During Laryngoscopy and Intubation, and Postoperative Analgesia in Patients Undergoing Laparoscopic Cholecystectomy Under General Anaesthesia

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Abstract

Background: Preoperative anxiety and the haemodynamic stress response to laryngoscopy and tracheal intubation may contribute to perioperative cardiovascular instability and increased anaesthetic requirements. Melatonin and gabapentin have anxiolytic, sedative and analgesic properties and may attenuate these responses.

Aim: To compare oral melatonin and oral gabapentin as premedication for preoperative anxiety, sedation, haemodynamic responses to laryngoscopy and intubation, postoperative pain, time to first rescue analgesia and adverse events in patients undergoing elective laparoscopic cholecystectomy.

Methods: This prospective, randomized, double-blind comparative study included 60 ASA I–II patients aged 18–60 years. Patients received oral gabapentin 600 mg (Group A, n=30) or melatonin 6 mg (Group B, n=30) 90 minutes before induction. Anxiety was assessed using the Hamilton Anxiety Rating Scale (HAMA), sedation using the Ramsay Sedation Score (RSS), haemodynamic variables at predefined peri-intubation time points, postoperative pain using the Visual Analogue Scale (VAS), and time to first rescue analgesia and adverse events.

Results: Baseline characteristics were comparable. Anxiety and sedation scores did not differ significantly between groups. Heart rate, systolic blood pressure and mean arterial pressure were consistently higher after premedication and intubation in the gabapentin group, with significant intergroup differences at most measured time points. Gabapentin significantly prolonged time to first rescue analgesia (452.60 ±137.06 vs 272.20 ±145.41 min; P<0.001). Postoperative VAS scores were comparable (2.63 ±1.33 vs 2.70 ±1.37; P=0.849). Adverse events were infrequent and not significantly different between groups.

Conclusion: Both agents provided clinically acceptable anxiolysis and sedation. Melatonin showed greater attenuation of the haemodynamic response to laryngoscopy and intubation, whereas gabapentin provided longer postoperative analgesia as reflected by delayed rescue-analgesic requirement. Choice may therefore be individualized according to perioperative priorities.

Keywords: Melatonin; Gabapentin; Premedication; Laryngoscopy; Tracheal Intubation; Haemodynamic Response; Postoperative Analgesia; Laparoscopic Cholecystectomy; General Anaesthesia.

1. INTRODUCTION

Preoperative anxiety is common before elective surgery and may activate the sympathetic nervous system and hypothalamic–pituitary–adrenal axis, producing tachycardia, hypertension and increased anaesthetic requirements. Effective premedication therefore aims not only to reduce anxiety and provide appropriate sedation, but also to attenuate the cardiovascular response to airway manipulation and facilitate postoperative recovery.

Laryngoscopy and tracheal intubation are potent noxious stimuli that cause transient sympathoadrenal activation. The resulting increases in heart rate and arterial pressure are usually tolerated by healthy individuals but may be clinically important in patients with cardiovascular or cerebrovascular vulnerability. Conventional approaches include opioids, β-blockers, lidocaine and α2-adrenergic agonists, but these may cause respiratory depression, excessive sedation, bradycardia or hypotension.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone involved in circadian regulation through MT1 and MT2 receptors. In addition to its chronobiotic effect, it has anxiolytic, sedative, antioxidant, anti-inflammatory and analgesic properties. Its potential sympatholytic effect and lack of clinically important respiratory depression have encouraged its use as an alternative premedicant.

Gabapentin is a structural analogue of γ-aminobutyric acid that binds the α2δ subunit of presynaptic voltage-gated calcium channels and reduces excitatory neurotransmitter release. It has established analgesic activity and has also been studied for perioperative anxiolysis, sedation and opioid-sparing effects. Preoperative administration may delay rescue-analgesic requirement and reduce postoperative analgesic needs.

Laparoscopic cholecystectomy is common and, despite being minimally invasive, involves several perioperative stresses including airway instrumentation, pneumoperitoneum and postoperative visceral pain. An effective oral premedicant may therefore provide benefits at multiple stages of care.

Although both agents have individually demonstrated perioperative benefits, direct comparison across anxiety, sedation, haemodynamic response to laryngoscopy and postoperative analgesia remains limited in this surgical population. The present prospective randomized double-blind study was undertaken to compare oral gabapentin 600 mg with oral melatonin 6 mg administered 90 minutes before induction.

2. AIM AND OBJECTIVES

- To compare preoperative anxiolytic effects using the Hamilton Anxiety Rating Scale.
- To compare premedication-related sedation using the Ramsay Sedation Score.
- To compare attenuation of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure responses to laryngoscopy and tracheal intubation.
- To compare postoperative pain and time to first rescue analgesia.
- To compare the incidence of adverse events.

3. MATERIALS AND METHODS

Study design and setting

This prospective, randomized, double-blind comparative study was conducted in the Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences and Hospital, B.G. Nagara, Karnataka, India, after Institutional Ethics Committee approval. The study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Study population

Sixty adults aged 18–60 years, ASA physical status I or II, scheduled for elective laparoscopic cholecystectomy under general anaesthesia were enrolled.

Eligibility

Inclusion criteria were age 18–60 years, ASA I–II status, elective laparoscopic cholecystectomy under general anaesthesia and ability to provide written informed consent. Exclusion criteria included refusal, ASA III–IV status, hypersensitivity to either study drug, pregnancy or lactation, significant hepatic/renal/cardiovascular/neurological/psychiatric disease, chronic opioid or sedative use, anticipated difficult airway and BMI >35 kg/m².

Sample size, randomization and blinding

Sample size was based on previous studies comparing haemodynamic effects of melatonin and gabapentin, assuming 80% power and 5% alpha error; 30 patients were required per group. Computer-generated randomization allocated patients equally. Allocation concealment used sequentially numbered opaque sealed envelopes. Patients, the attending anaesthesiologist and the investigator recording observations were blinded to allocation.

Intervention and anaesthetic technique

Group A received oral gabapentin 600 mg and Group B received oral melatonin 6 mg with sips of water 90 minutes before induction. Standard fasting and ASA monitoring were followed. Baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded. General anaesthesia was

administered according to the departmental protocol after adequate preoxygenation, intravenous induction and neuromuscular blockade. Direct laryngoscopy and endotracheal intubation were performed by an experienced anaesthesiologist. Anaesthesia was maintained with oxygen, nitrous oxide, volatile anaesthetic and intermittent neuromuscular blockade with controlled ventilation.

Outcome assessment

The primary outcome was attenuation of the haemodynamic response to laryngoscopy and tracheal intubation, assessed using heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure at baseline, 90 minutes after premedication, immediately after intubation and at 1, 3, 5, 10 and 15 minutes after intubation. Secondary outcomes were HAMA anxiety score, RSS, postoperative VAS, time to first rescue analgesia and adverse events.

Pain was assessed at predefined postoperative intervals. Rescue analgesia was administered when VAS was ≥4 or on patient request according to the institutional protocol. Time to first rescue analgesia and cumulative postoperative analgesic requirement were recorded.

Statistical analysis

Continuous variables were expressed as mean ±standard deviation and categorical variables as frequency and percentage. Independent Student's t-test was used for continuous variables and Chi-square/Fisher's exact test for categorical variables. Repeated haemodynamic measurements were analysed using repeated-measures analysis of variance with appropriate post hoc comparisons. $P<0.05$ was considered statistically significant.

4. RESULTS

Sixty patients completed the study, with 30 patients in each group. Baseline demographic, anthropometric, ASA and airway characteristics were comparable between groups.

Table 1. Baseline demographic and clinical characteristics

Variable	Gabapentin (n=30)	Melatonin (n=30)	P value
Age distribution, n	21–30: 5; 31–40: 7; 41–50: 9; 51–60: 9	21–30: 9; 31–40: 8; 41–50: 4; 51–60: 9	0.372
Sex, n	Male 16; Female 14	Male 18; Female 12	0.602
ASA status, n	I: 18; II: 12	I: 24; II: 6	0.091
Weight (kg), mean ± SD	75.57 ± 14.29	75.87 ± 14.31	0.936
Height (cm), mean ± SD	170.50 ± 10.64	171.63 ± 10.80	0.684
BMI (kg/m²), mean ± SD	26.20 ± 5.35	25.95 ± 5.27	0.856
First-attempt intubation, n	29	26	0.161
Airway difficulty, n	1	4	0.161

There were 34 males and 26 females overall. Most patients were ASA I (42/60). First-attempt intubation was achieved in 55 patients; five required a second attempt. None of the baseline differences reached statistical significance.

Table 2. Haemodynamic response: heart rate

Time point	Gabapentin	Melatonin	P value
Baseline	80.53 ± 7.62	76.97 ± 8.05	0.083
T90	81.80 ± 7.13	74.60 ± 7.66	<0.001
T0	88.47 ± 8.50	80.23 ± 7.96	<0.001
T1	91.20 ± 8.66	82.37 ± 8.09	<0.001
T3	86.57 ± 9.13	77.90 ± 8.52	<0.001
T5	83.53 ± 9.43	74.87 ± 8.80	0.026
T10	82.27 ± 9.78	73.27 ± 8.72	<0.001
T15	81.33 ± 9.95	71.93 ± 8.65	<0.001

Heart rate was comparable at baseline but was consistently higher in the gabapentin group after premedication and intubation, with statistically significant differences at T90 and all subsequent measured points.

4. RESULTS : HAEMODYNAMIC OUTCOMES

Table 3. Blood pressure and mean arterial pressure response

Time	SBP: Gabapentin	SBP: Melatonin	P value	DBP: Gabapentin	DBP: Melatonin	P value
Baseline	121.83 ± 11.27	119.40 ± 11.22	0.405	80.63 ± 10.31	79.20 ± 12.58	0.631
T90	121.67 ± 13.20	120.10 ± 10.99	0.619	81.03 ± 10.44	79.73 ± 13.52	0.678
T0	133.37 ± 12.36	124.30 ± 11.62	0.005	87.20 ± 10.71	81.73 ± 12.78	0.078
T1	133.60 ± 13.18	124.97 ± 12.03	0.010	87.50 ± 11.37	81.27 ± 12.78	0.051
T3	129.57 ± 13.84	120.87 ± 12.25	0.012	84.87 ± 11.45	78.10 ± 12.93	0.036
T5	126.20 ± 14.06	117.73 ± 12.03	0.015	82.63 ± 11.41	76.00 ± 12.92	0.039
T10	124.60 ± 14.13	116.03 ± 12.23	0.015	81.77 ± 11.22	75.17 ± 13.39	0.043
T15	123.57 ± 14.29	115.03 ± 12.40	0.016	81.20 ± 11.14	74.60 ± 13.37	0.042

SBP was comparable at baseline and T90. From T0 through T15, SBP was significantly higher in the gabapentin group. DBP was comparable at baseline and T90; differences became statistically significant from T3 onward.

Mean arterial pressure

Time	Gabapentin MAP	Melatonin MAP	P value
Baseline	94.43 ± 10.18	92.60 ± 11.79	0.522
T90	94.53 ± 10.76	93.23 ± 12.29	0.665
T0	102.57 ± 10.87	95.93 ± 12.26	0.031
T1	102.87 ± 11.46	95.77 ± 12.08	0.023
T3	99.70 ± 11.79	92.30 ± 12.25	0.020
T5	97.20 ± 11.63	89.93 ± 12.17	0.021
T10	96.10 ± 11.52	88.77 ± 12.38	0.021
T15	95.33 ± 11.46	88.00 ± 12.54	0.029

MAP was comparable at baseline and T90 but was significantly higher in the gabapentin group at every post-intubation time point. Overall, melatonin demonstrated greater attenuation of the haemodynamic response to airway manipulation.

4. RESULTS : ANXIETY AND SEDATION

Table 4. Anxiety and sedation outcomes

Outcome	Gabapentin (n=30)	Melatonin (n=30)	Test / P value
HAMA before drug, mean ± SD	1.20 ± 0.85	1.23 ± 1.04	P=0.892
HAMA after 90 min, mean ± SD	1.10 ± 0.85	1.17 ± 1.09	P=0.792
RSS 90 min: score 1, n	12	19	χ^2=3.594; P=0.166
RSS 90 min: score 2, n	13	9	
RSS 90 min: score 3, n	5	2	
Postoperative RSS: score 1, n	20	21	χ^2=2.083; P=0.353
Postoperative RSS: score 2, n	8	9	
Postoperative RSS: score 3, n	2	0	

HAMA scores were low and comparable between groups both before drug administration and 90 minutes after premedication. No statistically significant intergroup difference was observed.

At 90 minutes, RSS scores of 1, 2 and 3 were observed in 31, 22 and 7 patients respectively. The distribution did not differ significantly between groups. Postoperatively, most patients had RSS 1 or 2, again without a significant intergroup difference.

Interpretation

Both melatonin 6 mg and gabapentin 600 mg produced clinically acceptable anxiolysis and light sedation in the study population. The absence of a significant difference suggests that neither agent was clearly superior for these endpoints at the doses studied.

4. RESULTS : POSTOPERATIVE OUTCOMES AND SAFETY

Table 5. Postoperative analgesia and adverse events

Outcome	Gabapentin	Melatonin	P value
Postoperative VAS, mean ± SD	2.63 ± 1.33	2.70 ± 1.37	0.849
Time to first rescue analgesia (min)	452.60 ± 137.06	272.20 ± 145.41	<0.001
No adverse event, n	23	24	
Allergic reaction, n	1	1	
Bradycardia, n	0	3	
Excessive sedation, n	4	1	
Hypotension, n	1	0	
Overall adverse events	χ^2=5.821		P=0.324

Postoperative VAS scores were comparable. The mean time to first rescue analgesia was significantly longer with gabapentin (452.60 ±137.06 min) than with melatonin (272.20 ±145.41 min; P<0.001), indicating prolonged analgesic benefit with gabapentin.

Adverse events were uncommon: 47 patients had none, two had allergic reactions, three had bradycardia, five had excessive sedation and one had hypotension. Excessive sedation occurred more often with gabapentin, while bradycardia occurred only in the melatonin group. Overall adverse-event frequency did not differ significantly (χ^2=5.821, P=0.324).

Overall results

The principal between-group differences were haemodynamic and analgesic. Melatonin was associated with lower post-intubation heart rate and arterial pressure, whereas gabapentin significantly delayed the need for rescue analgesia. Anxiety, sedation, postoperative VAS and overall adverse-event rates were comparable.

5. DISCUSSION

This prospective randomized double-blind comparative study evaluated oral gabapentin 600 mg and melatonin 6 mg given 90 minutes before induction in patients undergoing laparoscopic cholecystectomy. The findings demonstrate complementary perioperative effects: both agents provided comparable anxiolysis and sedation, while melatonin more effectively attenuated the haemodynamic response to airway manipulation and gabapentin prolonged the time to first rescue analgesia.

Baseline characteristics and airway variables

The two groups were comparable in age, sex, ASA physical status, weight, height and BMI. Airway-related variables were also similar. First-attempt intubation was achieved in 55 of 60 patients and only five required a second attempt. This standardisation is relevant because repeated or difficult laryngoscopy can independently amplify sympathetic responses. The absence of significant differences in intubation attempts and airway difficulty reduces the likelihood that airway instrumentation imbalance explains the observed haemodynamic differences.

Preoperative anxiety

HAMA scores were low and comparable before and after premedication. The mean score before drug administration was 1.20 ±0.85 in the gabapentin group and 1.23 ±1.04 in the melatonin group (P=0.892); after 90 minutes, values were 1.10 ±0.85 and 1.17 ±1.09, respectively (P=0.792). These findings indicate similar anxiolytic effects at the doses used.

The observed anxiolysis is pharmacologically plausible. Melatonin may modulate central neurochemical and neuroendocrine stress pathways, while gabapentin reduces neuronal excitability through α2δ calcium-channel binding. The present data do not demonstrate superiority of either drug for anxiety reduction.

Sedation

Sedation was comparable both before intubation and postoperatively. Most patients remained lightly sedated and easily arousable. This is clinically relevant because useful premedication should reduce anxiety without excessive central nervous system depression or compromise of perioperative safety.

Although excessive sedation occurred more frequently with gabapentin in the adverse-event data, the overall difference in adverse events was not statistically significant. Thus, both agents demonstrated acceptable sedation profiles in this study population.

Haemodynamic response to laryngoscopy and intubation

The clearest difference between the groups was the cardiovascular response to airway manipulation. Baseline heart rate was comparable (80.53 ±7.62 vs 76.97 ±8.05 beats/min; P=0.083), but after premedication and intubation, heart rate remained consistently higher in the gabapentin group. At one minute after intubation, heart rate was 91.20 ±8.66 beats/min with gabapentin compared with 82.37 ±8.09 beats/min with melatonin (P<0.001). A similar pattern was observed for arterial pressure. At one minute after intubation, SBP was 133.60 ±13.18 mmHg versus 124.97 ±12.03 mmHg (P=0.010), while MAP was 102.87 ±11.46 versus 95.77 ±12.08 mmHg (P=0.023). DBP differences became statistically significant from three minutes onward. These findings support greater attenuation of the pressor response with melatonin.

The haemodynamic effect may reflect melatonin-associated modulation of sympathetic and neurohumoral stress responses. In the present study, melatonin therefore appears preferable when limitation of tachycardia and hypertension during airway manipulation is the principal peri-induction objective.

Postoperative analgesia

Postoperative pain intensity was similar between groups, with VAS 2.63 ±1.33 for gabapentin and 2.70 ±1.37 for melatonin (P=0.849). However, time to first rescue analgesia was significantly prolonged with gabapentin: 452.60 ± 137.06 minutes compared with 272.20 ±145.41 minutes for melatonin (P<0.001).

This finding is consistent with the analgesic pharmacology of gabapentin, which reduces excitatory neurotransmitter release and neuronal hyperexcitability through α2δ calcium-channel modulation. The difference between VAS and time-to-rescue outcomes is clinically relevant: pain intensity at the defined assessment was similar, yet patients receiving gabapentin remained free of rescue-analgesic requirement for longer.

Safety

Overall adverse events were infrequent and did not differ significantly between groups. Excessive sedation was more frequent with gabapentin, while bradycardia occurred only with melatonin. Hypotension and allergic reactions were uncommon. These findings support acceptable tolerability under appropriate perioperative monitoring, while highlighting the need for individualized selection in patients particularly vulnerable to sedation or bradycardia.

6. CLINICAL IMPLICATIONS

The findings suggest that melatonin and gabapentin should not necessarily be viewed as interchangeable agents with identical benefits. Instead, their use may be individualized according to the primary perioperative objective. Melatonin may be particularly useful when cardiovascular stability during laryngoscopy and tracheal intubation is important. Gabapentin may be useful when prolonged postoperative analgesia and delayed rescue-analgesic requirement are priorities.

The comparable anxiolytic and sedative effects provide flexibility in premedication choice. Patient characteristics, cardiovascular risk, surgical factors and anticipated postoperative analgesic needs should be considered when selecting an agent.

7. STRENGTHS

- Prospective randomized comparative design with double blinding.
- Standardized timing of oral premedication (90 minutes before induction).
- Assessment of multiple clinically relevant outcomes, including haemodynamic variables at predefined post-intubation time points.
- Use of HAMA, Ramsay Sedation Score and VAS as structured outcome measures.
- Comparable baseline demographic, anthropometric and airway characteristics between groups.

8. LIMITATIONS

- The sample size was relatively small and may limit generalisability.
- Only ASA I–II patients undergoing elective laparoscopic cholecystectomy were studied; findings may not apply to higher-risk patients or other surgeries.
- Anxiety, sedation and pain were assessed using subjective scoring systems, although validated scales were used.
- Haemodynamic assessment focused on the peri-intubation period and did not evaluate later changes associated with pneumoperitoneum and surgical stimulation.
- Longer-term postoperative analgesic outcomes and cognitive/psychomotor recovery were not assessed.
- Biochemical markers of stress response were not evaluated.

9. CONCLUSION

Oral melatonin 6 mg and gabapentin 600 mg were both effective premedicants in patients undergoing laparoscopic cholecystectomy, providing comparable anxiolysis and sedation. Melatonin produced greater attenuation of heart rate and arterial pressure responses to laryngoscopy and tracheal intubation, whereas gabapentin significantly prolonged the time to first rescue analgesia. Adverse events were infrequent and overall tolerability was comparable. Selection of premedication should therefore be individualized according to cardiovascular and postoperative analgesic priorities.

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