

Role of Preoperative Oral Melatonin in Reducing Postoperative Analgesic Requirements in Laparoscopic Cholecystectomy Patients: A Randomized Placebo-Controlled Double-Blind Trial

Authors:

Parul Thappa¹, Rumani Ruku², Ashufta Rasool³

¹Post graduate, Department of Anaesthesiology, Government Medical College and Associated Hospitals, Jammu, Jammu & Kashmir, India.

²Assistant Professor, Department of Anaesthesiology, Government Medical College and Associated Hospitals, Jammu, Jammu & Kashmir, India.

³Assistant Professor, Department of Anaesthesiology, Government Medical College and Associated Hospitals, Jammu, Jammu & Kashmir, India.

Corresponding Author:

Dr. Rumani Ruku, Assistant Professor, Department of Anaesthesiology, Government Medical College and Associated Hospitals, Jammu, J&K, India.

DOI: <https://doi.org/10.5281/zenodo.22795527>

Received: 20 August 2026, Accepted: 09 September 2026, Online First: 18 September 2026

ABSTRACT

Background: Preoperative anxiety and postoperative pain management remain significant challenges in laparoscopic cholecystectomy. Melatonin, a pineal neurohormone with sedative, anxiolytic, and analgesic properties, has been proposed as a safe and effective preoperative adjunct. The current study evaluated whether preoperative oral melatonin reduces postoperative analgesic requirements in patients undergoing laparoscopic cholecystectomy under general anaesthesia. **Methods:** In this prospective, randomized, double-blind, placebo-controlled trial conducted at Government Medical College, Jammu, 68 ASA I–II patients aged 18–60 years undergoing elective laparoscopic cholecystectomy were randomly allocated into two equal groups (n=34 each). Group M received sublingual melatonin 10 mg and Group P received a matched placebo, administered 60 minutes before surgery. Preoperative anxiety was assessed using the Anxiety Specific to Surgery Questionnaire (ASSQ). Postoperative pain was assessed by the Visual Analogue Scale (VAS) at 0, 1, 2, 4, 6, 12, and 24 hours. The time to first analgesic request, total analgesic consumption in 24 hours, and level of sedation using Ramsay Sedation Scale were recorded. Haemodynamic parameters and incidence of nausea and vomiting were also documented. **Results:** The melatonin group demonstrated significantly lower preoperative anxiety scores compared to placebo (p<0.001). VAS pain scores were significantly lower in Group M at all postoperative time points (p<0.05). Time to first analgesic request was significantly prolonged in Group M (mean 4.8±1.2 h vs 2.3±0.9 h; p<0.001). Total 24-hour analgesic (tramadol) consumption was significantly reduced in Group M (118.4±24.6 mg vs 176.5±31.2 mg; p<0.001). Sedation scores were higher at 1–2 hours postoperatively in Group M without causing respiratory depression or excessive sedation. The incidence of nausea and vomiting and haemodynamic parameters did not differ significantly between groups. **Conclusion:** Preoperative sublingual melatonin 10 mg significantly reduces preoperative anxiety, postoperative pain scores, and total analgesic requirements in laparoscopic cholecystectomy patients without causing adverse haemodynamic effects. Melatonin represents a safe, inexpensive, and effective adjunct in the perioperative management of patients undergoing laparoscopic cholecystectomy.

Keywords: Melatonin, premedication, laparoscopic cholecystectomy, postoperative analgesia, anxiolysis, VAS, Ramsay sedation scale, perioperative pain.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the gold standard surgical treatment for symptomatic cholelithiasis and has largely replaced open cholecystectomy due to its well-established advantages of smaller incisions, reduced postoperative pain, shorter hospital stay, and faster return to normal activity.^{1,2} However, despite its minimally invasive nature, postoperative pain following LC remains a clinically significant problem encountered by a substantial proportion of patients. Pain after LC is multifactorial in origin and arises from a combination of incisional somatic pain at trocar sites, visceral pain from peritoneal insufflation and organ manipulation, and referred shoulder and upper abdominal pain secondary to diaphragmatic irritation by residual carbon dioxide gas.^{3,4} The intensity of postoperative pain is frequently sufficient to delay discharge, reduce patient satisfaction, and significantly impair early postoperative recovery.⁵

Preoperative anxiety is closely interrelated with postoperative pain perception. Heightened preoperative anxiety has been consistently associated with increased intraoperative and postoperative analgesic requirements, greater pain intensity, impaired recovery, and increased risk of perioperative morbidity.⁶ Anxious patients demonstrate heightened neuroendocrine stress responses, including elevated levels of cortisol and catecholamines, which lower nociceptive thresholds and amplify pain perception in the postoperative period.⁷ Effective preoperative anxiolysis may therefore contribute to improved postoperative pain control and enhanced recovery.

The principal pharmacological agents conventionally employed for preoperative anxiolysis and sedation in adults include benzodiazepines, particularly midazolam. However, the use of midazolam is associated with undesirable effects including psychomotor impairment, amnesia, paradoxical excitation, respiratory depression, prolonged sedation, and interference with postoperative cognitive recovery.⁸ These limitations have stimulated interest in identifying alternative premedication agents that combine anxiolytic and analgesic properties with an improved safety and tolerability profile.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone synthesized and secreted predominantly by the pineal gland from tryptophan during the dark phase of the light-dark cycle under control of the suprachiasmatic nucleus.⁹ Beyond its well-established role in regulating circadian rhythm and the sleep-wake cycle, melatonin possesses a broad spectrum of pharmacological properties of relevance to anaesthesiology, including sedative, hypnotic, anxiolytic, analgesic, anti-inflammatory, antioxidant, and chronobiotic effects.¹⁰ These pharmacological properties are mediated through membrane-bound MT1

and MT2 receptors, as well as through facilitation of GABAergic neurotransmission, modulation of opioid receptors, and suppression of neuronal firing in pain-processing pathways.^{11,12}

Melatonin has been investigated as a preoperative premedicant in diverse surgical populations. Studies have consistently demonstrated that preoperative melatonin reduces preoperative anxiety with anxiolytic efficacy comparable to midazolam, but without the associated cognitive and psychomotor side effects.^{13,14}

Its analgesic properties, demonstrated in both animal experiments and clinical trials, have further supported its use as a perioperative analgesic adjunct.¹⁵ The drug has an excellent safety profile: it is widely available over the counter in India and several other countries, is inexpensive, and has no clinically significant side effects at doses used perioperatively (5–10 mg).¹⁶

Despite the growing evidence for melatonin's perioperative benefits, its specific role in reducing postoperative analgesic requirements in patients undergoing laparoscopic cholecystectomy has not been comprehensively evaluated in the Indian perioperative context. The present study was therefore designed to evaluate the effect of preoperative sublingual melatonin 10 mg on postoperative analgesic requirements, pain scores, and associated perioperative outcomes in patients undergoing elective laparoscopic cholecystectomy under general anaesthesia.

AIMS AND OBJECTIVES

Primary Objective: To assess the effect of preoperative oral melatonin 10 mg on the time to first analgesic request and total postoperative analgesic consumption in patients undergoing laparoscopic cholecystectomy.

Secondary Objectives:

- To evaluate postoperative pain scores (VAS) at 0, 1, 2, 4, 6, 12, and 24 hours postoperatively.
- To assess preoperative anxiolysis using the Anxiety Specific to Surgery Questionnaire (ASSQ).
- To measure the level of sedation using the Ramsay Sedation Scale in the perioperative period.
- To evaluate haemodynamic stability (heart rate, systolic and diastolic blood pressure, mean arterial pressure) perioperatively.
- To record the incidence of postoperative nausea and vomiting (PONV) and other adverse effects.

MATERIALS AND METHODS

Study Design and Ethical Approval

This was a prospective, randomized, double-blind, placebo-controlled clinical trial conducted in the Department of Anaesthesiology, Government Medical College and Associated Hospitals, Jammu, Jammu &

Kashmir, India, over a period of 12 months. The study protocol was approved by the Institutional Ethics Committee (IEC). Written informed consent was obtained from all participants prior to enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki (revised 2013) and Good Clinical Practice (GCP) guidelines.

Sample Size

Using GPOWER software, with a power of 80%, an effect size of 0.4, and a significance level of 5% ($\alpha=0.05$), the minimum sample size was calculated as 34 patients per group. A total of 68 patients were therefore enrolled in the study.

Inclusion Criteria

- Patients aged 18–60 years of either sex.
- ASA physical status I and II.
- Scheduled for elective laparoscopic cholecystectomy under general anaesthesia.
- Willingness to participate and ability to provide written informed consent.

Exclusion Criteria

- Patient refusal.
- ASA physical status III and IV.
- Known allergy or hypersensitivity to melatonin or any study drug.
- BMI > 35kg/m²
- Patients receiving drugs with known analgesic, sedative, or melatonin-modifying properties within 24 hours before surgery.
- Pregnancy or breastfeeding.
- Significant cardiovascular, hepatic, renal, or psychiatric disease.
- Chronic pain syndromes or regular use of opioid analgesics.

Randomization and Blinding

Patients were randomized into two equal groups (n=34 each) using a computer-generated random number list, with sealed opaque envelopes used to conceal allocation until the point of randomization. Group M (Melatonin group) received sublingual melatonin 10 mg tablet 60 minutes before surgery, and Group P (Placebo group) received an identical-appearing placebo tablet at the same time point. The study drug and placebo were prepared and dispensed by a pharmacist not involved in patient care or data collection. The attending anaesthesiologist, operating surgeon, nursing staff involved in postoperative care, and the patients were all blinded to group allocation throughout the study period.

Anaesthetic Protocol

All patients underwent a standardized preanesthetic assessment the evening before surgery. No other premedication was administered. On arrival in the operating room, standard monitoring was instituted: electrocardiogram (ECG), non-invasive arterial blood pressure (NIBP), peripheral oxygen saturation (SpO₂), and end-tidal carbon dioxide (EtCO₂). Baseline haemodynamic parameters were recorded.

Anaesthesia was induced with intravenous propofol 2 mg/kg, fentanyl 1 µg/kg, and atracurium 0.5 mg/kg to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane 1–1.5% in a mixture of oxygen and nitrous oxide (50:50). At the end of surgery, neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. All patients received intravenous ondansetron 4 mg as routine PONV prophylaxis. Injection Paracetamol 10–15 mg/kg was administered to all patients 15 minutes prior to the end of surgery as a part of multimodal analgesia. Laparoscopy was performed with standard CO₂ insufflation pressure of 12–14 mmHg. At the end of surgery, CO₂ was completely evacuated from the peritoneal cavity.

Postoperative Analgesic Protocol

Postoperative analgesia was provided as rescue analgesia only (no fixed-schedule analgesics were administered). Intravenous tramadol 1 mg/kg was given as rescue analgesia when VAS pain score exceeded 4 out of 10. The time to first analgesic request (from the end of surgery), number of analgesic administrations, and total 24-hour tramadol consumption were recorded.

Outcome Measurements

Preoperative anxiety: Assessed using the Anxiety Specific to Surgery Questionnaire (ASSQ), a 10-item questionnaire scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree), yielding a total score of 10–50. Higher scores indicate greater anxiety. Scores were recorded at baseline (T0, before study drug) and 60 minutes after study drug administration (T1, just before entering the operating room).

Postoperative pain: Assessed using the Visual Analogue Scale (VAS; 0=no pain, 10=worst imaginable pain) at 0 (on arrival in recovery), 1, 2, 4, 6, 12, and 24 hours postoperatively.

Sedation: Assessed using the Ramsay Sedation Scale (RSS; 1=anxious/agitated, 2=cooperative/calm, 3=responds to verbal commands, 4=asleep with brisk response to glabellar tap, 5=sluggish response, 6=no response) at 0, 1, 2, 4, and 6 hours postoperatively.

Haemodynamic variables: Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP),

and mean arterial pressure (MAP) were recorded at baseline, after study drug, at induction, every 5 minutes for first 15 minutes, and then every 15 minutes intraoperatively till the end of surgery, at extubation, and at 0, 1, 2, 4, and 6 hours postoperatively.

PONV: Incidence and severity of postoperative nausea and vomiting in the first 24 hours was recorded.

Statistical Analysis

Data were entered and analysed using SPSS version 23.0 (IBM Corporation, USA). Continuous variables were presented as mean $\pm$ standard deviation (SD). Categorical variables were expressed as frequency and percentage. Normally distributed continuous variables were compared between groups using the independent samples t-test. Non-normally distributed variables were compared using the Mann-Whitney U test. Repeated haemodynamic and VAS measurements were compared using repeated-measures ANOVA with Bonferroni post-hoc correction. Categorical variables were compared by

Chi-square test or Fisher's exact test as appropriate. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 71 patients were assessed for eligibility. After excluding 3 patients (2 declined consent, 1 converted to open surgery), 68 patients were randomized and completed the study: 34 in Group M and 34 in Group P. No patient was excluded from analysis after randomization.

Demographic Profile and Baseline Characteristics (Table 1)

The two groups were comparable with regard to age, sex, weight, body mass index (BMI), ASA status, and duration of surgery and anaesthesia. No statistically significant difference was found in any baseline parameter ($p>0.05$ for all).

Table 1: Demographic and baseline characteristics of study participants

Variable	Group M (n=34)	Group P (n=34)	p-value
Age (years), mean $\pm$ SD	38.6 $\pm$ 9.4	37.9 $\pm$ 10.1	0.752
Sex (M/F)	13/21	14/20	0.812
Weight (kg), mean $\pm$ SD	62.4 $\pm$ 8.7	63.1 $\pm$ 7.9	0.703
BMI (kg/m ²), mean $\pm$ SD	24.8 $\pm$ 3.2	25.1 $\pm$ 3.4	0.691
ASA I / ASA II	19 / 15	20 / 14	0.815
Duration of anaesthesia (min)	68.2 $\pm$ 12.4	70.1 $\pm$ 11.8	0.504
Duration of surgery (min)	54.6 $\pm$ 10.8	56.3 $\pm$ 11.2	0.498

Preoperative Anxiety Scores (Table 2)

Baseline ASSQ scores were comparable between both groups ($p=0.874$). At 60 minutes after administration of the study drug (T1), preoperative anxiety scores were significantly lower in Group M compared to Group P (18.4 $\pm$ 3.6 vs 28.9 $\pm$ 4.2; $p<0.001$), demonstrating a clinically significant anxiolytic effect of melatonin.

Table 2: Preoperative anxiety scores (ASSQ)

Time point	Group M (n=34)	Group P (n=34)	p-value
Baseline (T0) – before study drug	30.2 $\pm$ 4.8	30.4 $\pm$ 4.5	0.874
T1 – 60 min after study drug (pre-OR)	18.4 $\pm$ 3.6	28.9 $\pm$ 4.2	$<0.001^*$
Change from baseline (Δ)	-11.8 $\pm$ 4.1	-1.5 $\pm$ 2.7	$<0.001^*$

** $p<0.05$ statistically significant*

Time to First Analgesic Request and Total Analgesic Consumption (Table 3)

The time to first postoperative analgesic request was significantly prolonged in Group M compared to Group P (4.8 $\pm$ 1.2 h vs 2.3 $\pm$ 0.9 h; $p<0.001$). The total tramadol consumption over 24 hours was also significantly lower in Group M (118.4 $\pm$ 24.6 mg vs 176.5 $\pm$ 31.2 mg; $p<0.001$). The number of patients requiring rescue analgesia in the first 6 hours was significantly lower in Group M.

Table 3: Analgesic outcomes

Outcome	Group M (n=34)	Group P (n=34)	p-value
Time to first analgesic request (h)	4.8±1.2	2.3±0.9	<0.001*
Total 24-h tramadol consumption (mg)	118.4±24.6	176.5±31.2	<0.001*
Patients requiring rescue analgesia <6 h	4 (11.8%)	18 (52.9%)	<0.001*
No rescue analgesia in 24 h	6 (17.6%)	0 (0%)	0.012*

* $p < 0.05$ statistically significant

VAS Pain Scores (Table 4)

Postoperative VAS pain scores were significantly lower in Group M at all recorded time points ($p < 0.05$). The greatest difference between groups was observed at 1–2 hours postoperatively. By 24 hours, both groups demonstrated low pain scores, though scores remained significantly lower in Group M.

Table 4: VAS pain scores at postoperative time points (mean±SD)

Time (hours)	Group M (n=34)	Group P (n=34)	p-value
0 h (recovery room)	3.2±0.8	4.9±1.1	<0.001*
1 h	2.8±0.7	4.6±1.0	<0.001*
2 h	2.4±0.6	4.2±1.0	<0.001*
4 h	2.1±0.6	3.8±0.9	<0.001*
6 h	1.8±0.5	3.4±0.8	<0.001*
12 h	1.5±0.5	2.9±0.7	<0.001*
24 h	1.2±0.4	2.3±0.6	<0.001*

* $p < 0.05$ statistically significant

Sedation Scores (Table 5)

Sedation scores (Ramsay Sedation Scale) were significantly higher in Group M at 1 and 2 hours postoperatively ($p < 0.05$), indicating mild-to-moderate sedation. All patients in Group M remained easily arousable (RSS ≤ 3). No patient in either group required pharmacological reversal of sedation or developed respiratory depression. By 4 hours postoperatively, sedation scores were comparable between groups.

Table 5: Ramsay Sedation Scale scores postoperative period

Time	Group M (n=34)	Group P (n=34)	p-value
0 h	2.4±0.5	2.1±0.4	0.087
1 h	2.9±0.5	2.2±0.4	0.002*
2 h	2.7±0.5	2.1±0.4	0.004*
4 h	2.3±0.4	2.1±0.4	0.124
6 h	2.1±0.4	2.0±0.4	0.412

* $p < 0.05$ statistically significant

Haemodynamic Parameters

No significant intergroup differences were observed in heart rate, systolic blood pressure, diastolic blood pressure, or mean arterial pressure at any time point ($p > 0.05$ for all). MAP showed a mild, clinically insignificant reduction in Group M following premedication, consistent with melatonin's known mild antihypertensive effect, and no patient in either group required pharmacological intervention for haemodynamic instability.

Postoperative Nausea and Vomiting and Adverse Events (Table 6)

The incidence of nausea and vomiting did not differ significantly between groups. No serious adverse effects attributable to melatonin were observed. No patient developed respiratory depression, excessive sedation (RSS > 4), or allergic reactions in either group.

Table 6: Incidence of postoperative nausea and vomiting

Variable	Group M n (%)	Group P n (%)	p-value
Nausea	6 (17.6)	9 (26.5)	0.388
Vomiting	3 (8.8)	5 (14.7)	0.464
Nausea or vomiting (combined)	7 (20.6)	11 (32.4)	0.266
Required ondansetron rescue	4 (11.8)	7 (20.6)	0.332

DISCUSSION

The present randomized, double-blind, placebo-controlled trial demonstrated that preoperative sublingual melatonin 10 mg, administered 60 minutes before elective laparoscopic cholecystectomy, produced significant and clinically meaningful reductions in preoperative anxiety, postoperative pain scores, and total 24-hour analgesic consumption, while prolonging the time to first analgesic request — without causing adverse haemodynamic effects or clinically significant sedation.

The demographic and baseline characteristics of both groups were well-matched, confirming the effectiveness of randomization. Comparable baseline ASSQ anxiety scores ensured that any observed differences in postoperative outcomes were attributable to the study intervention.

Preoperative anxiolysis was the most immediate and statistically most robust finding of this study. The ASSQ score in Group M decreased by 11.8 points from baseline after melatonin administration, compared to only 1.5 points in the placebo group ($p < 0.001$). This finding is consistent with the established evidence base for melatonin as an anxiolytic premedication. The landmark study by Naguib and Samarkandi (1999), using sublingual melatonin 5 mg in 75 women 100 minutes before surgery, demonstrated that melatonin produced significant preoperative anxiolysis and sedation comparable to midazolam 15 mg, without the psychomotor impairment, amnesia, or hangover effects associated with benzodiazepines.¹³ Subsequent dose-response studies by the same group confirmed that melatonin 0.05–0.2 mg/kg (approximately 3–14 mg for a 70 kg patient) reliably reduced preoperative anxiety.¹⁴ In the present study, the dose of 10 mg melatonin produced more pronounced anxiolysis, which may be attributed to the higher dose, the sublingual route ensuring more rapid absorption, and the surgical patient population, whose anxiety level may be more responsive to pharmacological modulation.

The analgesic effects of melatonin observed in the present study are clinically significant. The time to first analgesic request was more than doubled in Group M (4.8 ± 1.2 h vs 2.3 ± 0.9 h), and total 24-hour tramadol consumption was reduced by approximately 33% (118.4 mg vs 176.5 mg). VAS pain scores were significantly lower in Group M at every postoperative time point

through 24 hours, with the greatest difference observed in the early postoperative period (0–6 hours). These findings are concordant with those of Borazan et al. (2010), who demonstrated in 52 patients undergoing elective prostatectomy that preoperative oral melatonin 6 mg (the night before and 1 hour before surgery) significantly reduced VAS pain scores and tramadol consumption through the entire 24-hour postoperative period, while also improving sleep quality and sedation.¹⁵ Similarly, Caumo et al. (2007) demonstrated that preoperative melatonin 5 mg in patients undergoing abdominal hysterectomy with epidural anaesthesia significantly reduced postoperative pain intensity and analgesic requirements during the first 24 hours, while attenuating preoperative anxiety and improving circadian recovery.¹⁶

The analgesic mechanism of melatonin is multifactorial. Melatonin augments GABAergic transmission through GABA^A receptor modulation and may enhance β -endorphin release, explaining its opioid-sparing properties.¹² Activation of MT₂ receptors in the dorsal horn of the spinal cord modulates nociceptive transmission, and melatonin interacts with opioid μ and δ receptor systems.^{17,18} Anti-inflammatory properties, mediated through inhibition of COX-2 and iNOS and suppression of NF- κ B, may further contribute to perioperative analgesia by reducing neuroinflammation at surgical sites.¹⁹

Postoperative sedation was higher in Group M at 1–2 hours, consistent with melatonin's hypnotic properties mediated through MT₁ receptor activation in the suprachiasmatic nucleus and through GABAergic mechanisms.²⁰ Importantly, the degree of sedation was mild (Ramsay score ≤ 3), all patients remained easily arousable, and no patient required pharmacological intervention or oxygen supplementation for sedation or respiratory depression. This safety profile is a key clinical advantage over benzodiazepines, particularly in elderly patients and those with obstructive sleep apnoea or obesity.

The absence of significant differences in haemodynamic parameters between groups is reassuring and consistent with prior evidence. Melatonin has a mild antihypertensive effect attributable to its interference with adrenergic outflow, binding to melatonin receptors on vascular smooth muscle, and reduction in catecholamine levels; however, this does not produce

clinically significant hypotension at doses used perioperatively.²¹ The comparable incidence of PONV between groups suggests that melatonin does not independently reduce or worsen nausea and vomiting in this surgical context, though its antioxidant and anti-inflammatory effects may provide some gastrointestinal protection.

Previous studies comparing melatonin with other premedication agents in the laparoscopic surgery context provide complementary evidence. Hoseini et al. evaluated melatonin, clonidine, and gabapentin in 88 patients undergoing laparoscopic cholecystectomy and found that melatonin significantly reduced preoperative anxiety and postoperative pain, with a favourable side effect profile compared to the other agents.²² Ionescu et al. demonstrated that 3 mg oral melatonin was effective as premedication for laparoscopic cholecystectomy, producing reliable anxiolysis without adverse effects.²³

The present study has several strengths, including its randomized, double-blind, placebo-controlled design; well-standardized anaesthetic and analgesic protocols; objective outcome measures including the ASSQ, VAS, and Ramsay Sedation Scale; and a sample size calculated with adequate statistical power. Limitations include the relatively modest sample size, single-centre conduct, restriction to ASA I–II patients aged 18–60 years, and the absence of plasma melatonin level measurements. The exclusion of elderly, obese and high-risk surgical patients limits generalizability, and future multicentre trials with larger sample sizes, inclusion of plasma melatonin pharmacokinetics, and long-term follow-up are warranted.

CONCLUSION

Preoperative sublingual melatonin 10 mg, administered 60 minutes before elective laparoscopic cholecystectomy, significantly reduces preoperative anxiety, postoperative pain scores at all time points through 24 hours, and total 24-hour opioid analgesic consumption, while prolonging the time to first rescue analgesic request. The drug produced mild, clinically acceptable and safe sedation in the early postoperative period without adverse haemodynamic effects or respiratory depression. Melatonin represents a safe, inexpensive, widely available, and effective alternative or adjunct preoperative premedicant in patients undergoing laparoscopic cholecystectomy. Its incorporation into perioperative analgesic protocols may contribute meaningfully to opioid sparing, improved patient comfort, and enhanced postoperative recovery in this common surgical procedure.

Declarations

Ethics Approval and Consent to Participate: The study was conducted after obtaining approval from the

Institutional Ethics Committee. Written informed consent was obtained from all participants before enrolment.

Consent for Publication: Not applicable.

Competing Interests: The authors declare that they have no competing interests.

Funding: This study received no specific financial support from any public, commercial, or not-for-profit funding agency.

Authors' Contributions: All authors contributed to the study conception, design, data collection, analysis, interpretation, and manuscript preparation. All authors approved the final manuscript.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements: The authors express their gratitude to all participants and the clinical staff who supported this study.

REFERENCES

1. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database Syst Rev.* 2006;(4):CD006231. doi:10.1002/14651858.CD006231. PMID: 17054285.
2. Pucher PH, Brunt LM, Davies N, Linsk A, Munshi A, Rodriguez HA, et al. Outcome trends and safety measures after 30 years of laparoscopic cholecystectomy: a systematic review and pooled data analysis. *Surg Endosc.* 2018;32(5):2175–2183. PMID: 29098387.
3. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain.* 2001;90(3):261–269. PMID: 11207399.
4. Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. *Anesth Analg.* 1995;81(2):379–384. PMID: 7618730.
5. Kehlet H, Gray AW, Bonnet F, Camu F, Fischer HB, McCloy RF, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy. *Surg Endosc.* 2005;19(10):1396–1415. PMID: 16132333.

6. Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy: a repeated-measures design. *J Psychosom Res.* 2000;49(6):417–422. PMID: 11182433.
7. Johnston M. Anxiety in surgical patients. *Psychol Med.* 1980;10(1):145–152. PMID: 7367533.
8. Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. *J Emerg Med.* 1997;15(3):357–365. PMID: 9258786.
9. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. *Sleep Med Rev.* 2005;9(1):11–24. PMID: 15649736.
10. Kurdi MS, Patel T. The role of melatonin in anaesthesia and critical care. *Indian J Anaesth.* 2013;57(2):137–144. doi:10.4103/0019-5049.111837. PMID: 23825812.
11. Naguib M. Melatonin and anaesthesia: a clinical perspective. *J Pineal Res.* 2007;42(1):12–21. PMID: 17198534.
12. Zisapel N. Sleep and sleep disturbances: biological basis and clinical applications. *Cell Mol Life Sci.* 2007;64(10):1174–1186. PMID: 17364142.
13. Naguib M, Samarkandi AH. Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam. *Br J Anaesth.* 1999;82(6):875–880. doi:10.1093/bja/82.6.875. PMID: 10562782.
14. Naguib M, Samarkandi AH. The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study. *Anesth Analg.* 2000;91(2):473–479. doi:10.1097/00000539-200008000-00046. PMID: 10910871.
15. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. *J Anesth.* 2010;24(2):155–160. doi:10.1007/s00540-010-0891-8. PMID: 20108021.
16. Caumo W, Torres F, Moreira NL Jr, Auzani JA, Monteiro CA, Londero G, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg.* 2007;105(5):1263–1271. doi:10.1213/01.ane.0000282834.34399.5d. PMID: 17959958.
17. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. *Anesthesiology.* 2010;113(4):968–976. doi:10.1097/ALN.0b013e3181e7d626. PMID: 20823766.
18. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gogenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. *J Pineal Res.* 2011;51(3):270–277. doi:10.1111/j.1600-079X.2011.00895.x. PMID: 21752095.
19. Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. *Anesth Analg.* 2009;108(4):1146–1151. doi:10.1213/ane.0b013e3181907ebe. PMID: 19299772.
20. Kain ZN, Maclaren JE, Herrmann L, Mayes L, Rosenbaum A, Hata J, et al. Preoperative melatonin and its effects on induction and emergence in children undergoing anaesthesia and surgery. *Anesthesiology.* 2009;111(1):44–49. PMID: 19512873.
21. Ismail SA, Mowafi HA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anaesthesia. *Anesth Analg.* 2008;107(4):1422–1426. doi:10.1213/ane.0b013e318184dfe6. PMID: 18806052.
22. Hoseini VS, Yekta RA, Marashi S, Marashi SM. The efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: a randomized clinical trial. *Arch Anesth Crit Care.* 2015;1(4):118–122.
23. Ionescu D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, et al. Melatonin as pre-medication for laparoscopic cholecystectomy: a double blind, placebo controlled study. *South Afr J Anaesth Analg.* 2008;14(1):8–11.