BENHA MEDICAL JOURNAL bmj
Print ISSN 1110-208X.
Online ISSN 2357-0016

Original article

Comparison between Two Different Doses of Sublingual Melatonin to Alleviate Anxiety and Pain Associated with Elective Gynecological Surgeries under General Anesthesia; a Randomized Controlled Trial

Mariam A. Ahmed, Ehab A. El-Sahat, Ahmed H. Abd El-Rahman, Samar R. Amin

Anesthesia and Intensive Care Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Mariam A. Ahmed.
Anesthesia and Intensive Care Department, Faculty of Medicine Benha University, Egypt.
Email: Mariamabdallh410@gmail.com

Received:
Accepted:

Abstract:

Background: Perioperative anxiety and postoperative pain are common challenges in women undergoing elective gynecological surgeries. Traditional anxiolytics carry risks such as sedation, respiratory depression, or cardiovascular effects, highlighting the need for safer alternatives. This study aimed to determine the anxiolytic effect of preoperative sublingual melatonin and its associated impact on postoperative pain scores when two different doses used in females undergoing elective gynecological surgeries. **Methods:** This a randomized controlled study included 96 females underwent elective gynecological surgeries. The cases were divided into three equal groups: Group M1: received 3 mg of sublingual melatonin the night and 1 hour before the surgery. Group M2 received 6 mg at the same time points; Group C received no premedication. Beck anxiety inventory (BAI) and Numerical rating Scale (NRS) were recorded as primary outcomes. Side effects related to the drug and Time of 1st rescue analgesia request were also assessed. **Results:** Both melatonin groups showed significantly diminished BAI scores at 2 and 12 h postoperatively in contrast with baseline and intraoperative scores ($p<0.001$). Postoperative NRS scores were significantly reduced in group M2 at 6 and 12 h, and in both M1 and M2 at 24 h ($p<0.05$). Morphine consumption and time to first rescue analgesia were significantly improved in both melatonin groups versus control. Adverse effects were minimal and dose-related. **Conclusion:** Sublingual melatonin is a safe and effective premedication for reducing perioperative anxiety and postoperative pain in elective gynecological surgery, with the 3 mg dose offering optimal efficacy and tolerability.

Keywords: Sublingual Melatonin; Alleviate Anxiety; Elective Gynecological Surgeries; General Anesthesia.

Introduction

Elective gynecological surgery is a critical component of women's healthcare, aimed at addressing various medical conditions, ranging from benign gynecological disorders to oncological procedures. While these surgeries are essential for managing women's health, they often generate considerable anxiety and pain, creating a substantial burden on both cases and healthcare providers [(1)].

The perioperative period is particularly critical for patients. It is a time of heightened vulnerability, as women not only endure the physical stress of the surgical procedure but also the psychological distress associated with anticipating it. This increased anxiety can trigger a cascade of both physiological and psychological reactions that can negatively influence surgical outcomes, pain management, and overall patient satisfaction. Studies consistently show that the female population tends to exhibit higher levels of perioperative anxiety compared to other groups [(2)].

Perioperative anxiety is a widespread and distressing phenomenon experienced by surgical patients, particularly in the context of concerns regarding anesthesia, surgical outcomes, postoperative pain, and a perceived loss of control. This anxiety can adversely affect hemodynamic stability, alter anesthetic requirements, hinder postoperative recovery, and diminish overall patient satisfaction [(3)]. Several pharmacological options for managing preoperative anxiety are available, including benzodiazepines, gabapentinoids, and beta-blockers; however, each of these drugs comes with notable disadvantages such as sedation, inconsistent effectiveness, and increased cardiovascular risk [(4)]. These limitations highlight the urgent need for safer, more effective alternatives to manage preoperative anxiety without compromising patient safety or the quality of recovery.

Among the potential premedication options, melatonin, a naturally occurring hormone that regulates the sleep-wake cycle, has gained attention for its possible anxiolytic and analgesic effects. Known as the "hormone of darkness," melatonin is primarily synthesized by the pineal gland in response to decreasing light levels, signaling the body to prepare for sleep. In addition to its role in regulating circadian rhythms, melatonin has demonstrated potential benefits in managing a variety of health conditions, such as insomnia, jet lag, pain, and anxiety[(5)]. Although melatonin is available in a variety of different formulations, sublingual administration has emerged as a particularly attractive method due to its rapid onset of action, favorable bioavailability, and ease of use. This method allows for a quick absorption of the hormone, which can result in more immediate therapeutic effects, making it a compelling option for preoperative management. Despite the increasing interest in melatonin as a potential preoperative medication, there remains a substantial gap in comprehensive research specifically investigating its efficacy, especially in the context of elective gynecological surgeries. As such, this remains a critical and necessary area of exploration, as further evidence is required to determine whether melatonin can be consistently beneficial in this particular surgical population [(6)].

This research aimed to assess the effectiveness of two different doses of sublingual melatonin administered preoperatively in decreasing anxiety and postoperative pain in elective gynecological surgeries under general anesthesia (GA). Additionally, it sought to compare the clinical outcomes and safety of both doses to determine the most appropriate and well-tolerated dose for perioperative use.

Patients and methods:

This randomized, controlled clinical trial was carried out on 96 female cases who underwent elective gynecological surgical procedures at Benha University Hospitals over a defined period of 12 consecutive months, extending from January 2024 to January 2025. All participants provided written informed consent after being thoroughly briefed about the nature, aims, and potential implications of the study. Ethical approval for the research was obtained from the Research Ethics Committee of the Faculty of Medicine, Benha University, and was assigned the identification number (ms14-12-2023). Furthermore, the study protocol was prospectively registered on ClinicalTrials.gov and was issued the unique registration number (NCT06997263).

Inclusion criteria were Female case scheduled for open elective gynecological surgeries (hysterectomy, ovarian cystectomy, myomectomy) under general anaesthesia, age 18-65 y and American Society of Anesthesiologists (ASA) physical status (ASA I –II).

Exclusion criteria were cases with a history of uncontrolled hypertension, ischemic heart disease, uncontrolled diabetes, bronchial asthma, psychiatric illness, sleep disorders, obesity (patients with BMI >30kg/m² were excluded to minimize pharmacokinetic variability, as obesity can influence melatonin metabolism, anesthetic requirements, and perioperative respiratory risks), cases taking antipsychotic, antidepressants, sedatives, anxiolytics, and anti-epileptic drugs, pregnant and lactating females.

Following an initial eligibility screening, participants were randomly assigned to one of three intervention groups, each consisting of 32 cases. The first group, designated as Group M1, received a sublingual dose of 3 mg melatonin both on the night prior to the surgical procedure and one hour before its commencement. Group M2, on the other hand, was administered a higher dose of 6 mg melatonin sublingually at the same time intervals. The third group, which acted as the control arm (Group C), was given a placebo sublingually identical in both shape and color to the melatonin tablets, ensuring the maintenance of the double-blind nature of the study. These placebo tablets contained no active pharmacological agents, and formulated to match the melatonin tablets in shape, color, size, and sublingual dissolution characteristics to preserve blinding integrity.

Randomization and Blinding

The process of randomization was rigorously carried out using computer-generated random numbers. These numbers were securely enclosed in opaque, sealed envelopes to guarantee the concealment of allocation. The envelopes were opened by the chief nursing officer the evening before surgery, and this individual was not involved in any aspect of the study design, patient care, or data collection. This process ensured that neither the participants, anesthesia providers, nor those assessing the outcomes were aware of the group allocations, thereby maintaining the integrity of the double-blind design throughout the trial.

Preoperative Evaluation and Clinical Assessment

All enrolled cases underwent a comprehensive and thorough preoperative evaluation. This included an extensive collection of personal history, covering demographic factors such as age, residence, occupation, socioeconomic status, and lifestyle habits, including smoking and alcohol consumption. Additionally, pertinent information about medical comorbidities, previous surgical interventions, and relevant family medical history was gathered to better understand each patient's clinical profile.

A detailed physical examination was conducted, including an overall clinical assessment of the patient’s general condition. Vital signs, such as body

temperature, blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation (SpO_2), were carefully monitored. Routine laboratory tests were performed, encompassing a complete blood count, hepatic and renal function tests, and a coagulation profile, all of which are essential for evaluating baseline health status and guiding anesthesia management.

Anesthetic Protocol

Approximately one hour following the administration of premedication, general anesthesia (GA) was induced according to a standardized and widely recognized protocol. This included the intravenous administration of fentanyl (1–2 μg/kg), propofol (2 mg/kg), and atracurium (0.5 mg/kg). Anesthesia maintenance was sustained with inhalational isoflurane at a concentration of 1.8%, complemented by intermittent doses of atracurium (0.1 mg/kg) as necessary. Following successful endotracheal intubation, mechanical ventilation was initiated using a mixture of 50% oxygen in air, targeting a tidal volume of 6–8 ml/kg. The end-tidal carbon dioxide ($ETCO_2$) concentration was meticulously maintained between 35 and 40 mmHg, with the inspiration-to-expiration (I: E) ratio adjusted to 1:2 to optimize ventilation.

Continuous, non-invasive monitoring of critical parameters, including heart rate (HR), mean arterial pressure (MAP), arterial oxygen saturation (SpO_2), and $ETCO_2$, was implemented throughout the surgical procedure. Upon completion of surgery, the residual neuromuscular blockade was reversed using intravenous neostigmine (0.05 mg/kg) combined with atropine (0.02 mg/kg). The endotracheal tube was subsequently removed, and the patients were transferred to the post-anesthesia care unit (PACU) for ongoing observation and monitoring.

Postoperative Care and Analgesic Protocol

Following the conclusion of the surgical procedure, patients were carefully observed and monitored in the PACU until they demonstrated a satisfactory Aldrete recovery score of 8 or higher. This score serves as a critical indicator of sufficient recovery from the effects of anesthesia, ensuring that the patient has regained adequate physiological stability and responsiveness. In order to manage postoperative pain, a structured and standardized approach was followed. All patients received intravenous paracetamol at a dose of 1 g every 6 h and ketorolac at a dose of 30 mg every 8 h, which are commonly used for routine pain management following surgery. These medications were intended to provide baseline pain relief and help maintain comfort during the early recovery period.

If additional pain relief was required beyond the routine medication, rescue analgesia was provided through intravenous morphine. The morphine was administered in boluses of 0.05 mg/kg, with the option for subsequent doses every 5 to 10 minutes, depending on the patient's individual pain level and needs. This rescue approach was employed until the patient achieved adequate pain relief, with a maximum total dose of 15 mg. This strategy was particularly important in cases where the patient’s pain exceeded a certain threshold, especially when the NRS pain score rose above 3, indicating a moderate level of discomfort. Through this comprehensive and flexible approach to pain management, the goal was to ensure that the patient’s recovery process was as comfortable and pain-free as possible while minimizing the risk of complications.

Measurements:

Outcome Measures

Primary Outcomes

1. Beck Anxiety Inventory (BAI):

The level of perioperative anxiety was assessed using the Beck Anxiety Inventory (BAI), a well-established and validated psychometric tool consisting of 21 descriptive items related to anxiety symptoms. Patients were asked to rate

each item on a four-point Likert scale, where 0 indicated no symptoms and 3 denoted the highest level of severity. The assessments were carried out at three key time points: preoperatively, two hours after emergence from anesthesia, and 12 hours postoperatively. The total BAI score ranged from 0 to 63, with categories classified as minimal (0–10), mild (11–19), moderate (20–30), and severe (31–63) levels of anxiety [(7)].

2. **Numerical Rating Scale (NRS) for Pain:**

Postoperative pain intensity was assessed using the Numerical Rating Scale (NRS), which ranges from 0 (no pain) to 10 (worst possible pain). Pain scores were recorded at multiple time intervals: immediately upon recovery, and at 1, 6, 12, and 24 hours after surgery. Opioid analgesia, in the form of intravenous morphine, was provided to patients whose NRS score reached 4 or above. The NRS was selected for its practicality, ease of use, and minimal reliance on visual or motor skills, making it a convenient tool for a wide range of patient populations [(8)].

Secondary Outcomes

Secondary outcomes included case demographics (age, BMI, ASA classification), pre-existing medical and surgical histories, duration of anesthesia (from induction to extubation), surgical time (from skin incision to closure), incidence of postoperative nausea and vomiting (PONV), drug-related side effects, PACU discharge timing, total hospital stay length, total opioid consumption within 24 h post-surgery, and time to 1st request for rescue analgesia.

The sample size was calculated utilizing G*Power statistical software, incorporating a significance level (α) of 0.05, a statistical power (1−β) of 80%, and a clinically relevant effect size based on a projected 20% reduction in perioperative anxiety, consistent with previous observations [(9)]. A dropout rate of 10% was anticipated, leading to a final allocation of 32 participants per group.

Approval code: MS 14-12-2023

Statistical analysis

All collected data were statistically analyzed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Parametric quantitative variables were presented as means and standard deviations (SD) and analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Non-parametric variables were reported as medians with interquartile ranges (IQR) and analyzed using the Kruskal-Wallis test, with pairwise comparisons performed using the Mann-Whitney U test. Repeated measures ANOVA was applied for evaluating changes over time within subjects. Categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test. A p-value less than 0.05 was considered statistically significant in all tests.

Results:

Initially, 107 cases were screened for eligibility, of which 9 were excluded for not meeting the inclusion criteria, and 2 declined to participate. As a result, 96 cases satisfied the eligibility requirements and were randomly assigned to one of three groups, each comprising 32 participants. All cases who were enrolled successfully completed the study protocol, and their data were included in the final analysis **(Figure 1).**

Baseline demographic characteristics, including age, body mass index (BMI), ASA classification, marital status, history of previous surgical procedures, and operative data were comparable among the three groups, indicating effective randomization and balanced distribution of key confounding factors **(Table 1).**

In Group M1, the BAI scores measured at 2 and 12 h postoperatively showed significant reductions when in contrast with both baseline and intraoperative values (p<0.001 and p=0.001, respectively). In Group M2, BAI scores exhibited a statistically significant decline

during the intraoperative period and continued to decrease at 2 and 12 h postoperatively in comparison to the baseline values (p=0.005, <0.001, and <0.001, respectively). Additionally, BAI scores at both postoperative intervals were significantly diminished than the intraoperative scores (p=0.005 and <0.001). In contrast, Group C showed a decrease in BAI scores at 2 and 12 h following surgery in contrast with baseline (p=0.021 and <0.001), though intraoperative scores were elevated relative to baseline (p=0.005). A progressive reduction in anxiety was also noticed from 2 to 12 h postoperatively (p<0.001) **(Table 2)**.

The NRS pain scores recorded at recovery and at 1 hour postoperatively were comparable across all study groups. However, at 6 and 12 h postoperatively, Group M2 reported significantly diminished NRS values than Group C (p=0.009 and p=0.039, respectively), while no significant differences were found between Groups M1 and M2, or between M1 and C. At the 24-hour postoperative mark, both M1 and M2 groups demonstrated significantly reduced pain scores in comparison to the control group (p=0.001 for both), with no significant difference noted between the two melatonin groups **(Figure 2).**

Baseline mean arterial pressure (MAP) at T0 was comparable among all three groups. At T1, MAP was significantly reduced in Group M2 in contrast with Group C (p=0.024), while Group M1 did not differ significantly from the other groups. At T2, Group M2 exhibited diminished MAP in contrast with both Group M1 (p=0.011) and Group C (p=0.002), with no significant difference noticed between Groups M1 and C. Regarding heart rate (HR), values were comparable at baseline and at T2 across the three groups. However, at T1, both Group M1 and M2 recorded significantly diminished HR values in contrast with the control group (p=0.001), with no statistical difference noticed between the two melatonin groups **(Figure 3)**.

Total morphine consumption over the 1st 24 postoperative h was significantly diminished in Groups M1 and M2 in contrast with Group C (p=0.016 and <0.001, respectively), while no statistically significant difference was noticed between the two melatonin groups. The time to 1st request for rescue analgesia was significantly prolonged in both melatonin-treated groups in comparison to the control group (p<0.001), with no meaningful difference between M1 and M2. Discharge time from the PACU was significantly extended in Group M2 in contrast with Group C (p<0.001), whereas discharge times were comparable between Group M1 and the other two groups. Additionally, the total duration of hospital stay was comparable across all groups, indicating that melatonin administration did not significantly influence incase length of stay **(Table 3)**.

The incidence of PONV was comparable among the three study groups. In terms of drug-related side effects, one case in Group M1 reported experiencing a headache. In Group M2, two cases experienced drowsiness, while three others complained of mild headaches. No adverse events (AEs) were reported in the controls. Although the overall incidence of side effects differed significantly among the groups (p=0.023), pairwise analysis showed that AEs were significantly more frequent in Group M2 in contrast with Group C (p=0.019), Group M1 and the other two groups were comparable **(Table 4)**.

Table 1: Case's demographic data, history of previous operations and operative data among the three groups

		Group M1 (N=32)	Group M2 (N=32)	Group C (N=32)	P value
Age (years)		47.9 ± 11.53	45.1 ± 12.78	46.7 ± 12.04	0.655
BMI (Kg/m^2)		24.7 ± 3.32	26.4 ± 3.76	25.3 ± 3.7	0.148
ASA	**ASA I**	18 (56.25%)	16 (50%)	18 (56.25%)	0.621
	ASA II	14 (43.75%)	16 (50%)	14 (43.75%)	
Marital status	**Single**	1 (3.13%)	1 (3.13%)	3 (9.38%)	0.795
	Married	30 (93.75%)	30 (93.75%)	28 (87.5%)	
	Widow	1 (3.13%)	1 (3.13%)	1 (3.13%)	
History of previous operations		13 (40.63%)	17 (53.13%)	18 (56.25%)	0.417
Operative data					
Surgery type	**TAH**	21 (65.63%)	16 (50%)	20 (62.5%)	0.585
	Diagnostic laparoscope	1 (3.13%)	0 (0%)	0 (0%)	
	Adnexal mass	7 (21.88%)	11 (34.38%)	8 (25%)	
	Myomectomy	3 (9.38%)	7 (21.88%)	5 (15.63%)	
Surgery time (minutes)		130.3 ± 40.04	127.8 ± 41.48	131.6 ± 39.85	0.148

Data presented as mean ± SD or frequency (%), TAH: Total Abdominal hysterectomy, BMI: body mass index, ASA: American Society of Anesthesiologists physical status.

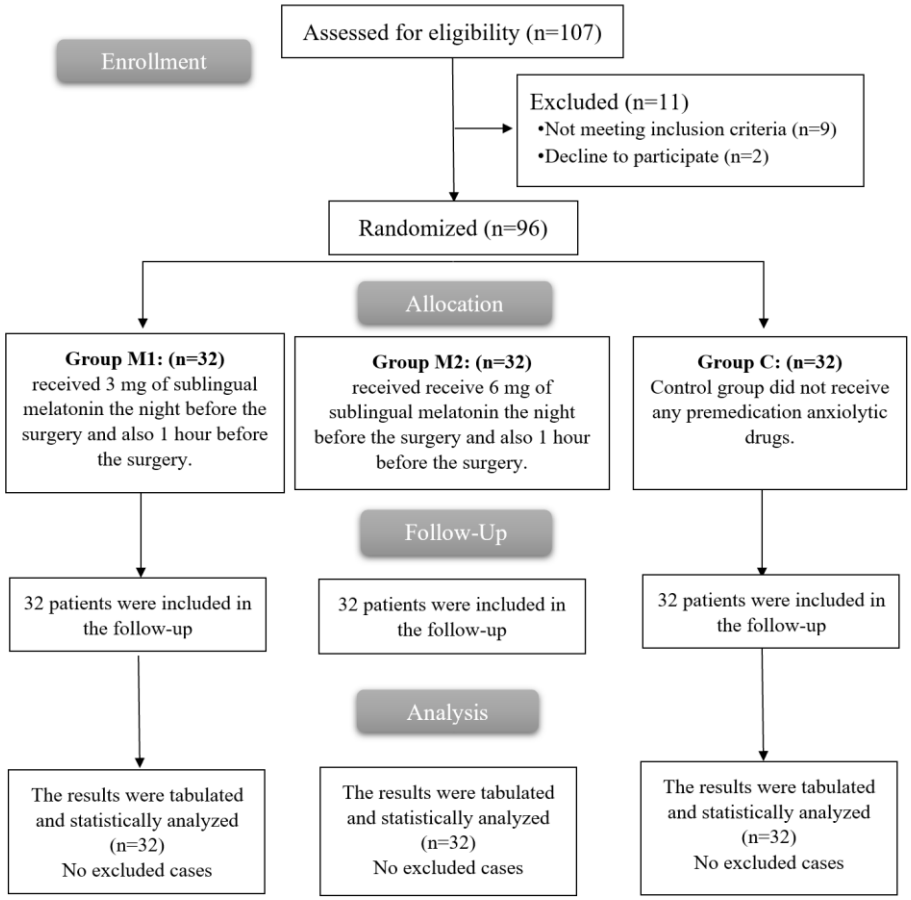


Figure 1: CONSORT flow chart of the enrolled cases.

Table 2: Comparison of baseline, in operating room, 2hr post-operative, and 12 hrs. post-operative BAI score among the studied groups

	Group M1 (N=32)	Group M2 (N=32)	Group C (N=32)	P-value	Post hoc
Baseline	14.84 ± 7.17	16.53 ± 10.36	15.94 ± 5.91	0.697	
In operating room	12.22 ± 4.61	10.72 ± 4.64	20.84 ± 7.59	**<0.001***	P1=0.199 **P2<0.001*** **P3<0.001***
2hr post-operative	8.75 ± 3.59	7.75 ± 3.29	12.81 ± 4.54	**<0.001***	P1=0.25 **P2<0.001*** **P3<0.001***
12 hrs. post-operative	7.25 ± 3.89	6.31 ± 4.35	8.66 ± 3.31	0.056	

*: significant as p value <0.05. P1: P value between groups M1 and M2, P2: P value between groups M1 and C, P3: P value between groups M2 and C.

Table 3: Amount of morphine consumption, first rescue analgesia request, time of PACU discharge and length of hospital stay among the studied groups

	Group M1 (N=32)	Group M2 (N=32)	Group C (N=32)	P value	
Total Morphine Consumption (mg)	13.3 ± 7.68	11.6 ± 6.89	18 ± 7.5	0.002*	P1=0.349 P2=0.016* P3<0.001*
First rescue analgesia request (H)	8.9 ± 6.03	10.1 ± 5.82	3.9 ± 2.28	<0.001*	P1=0.414 P2<0.001* P3<0.001*
Time of PACU discharge (minutes)	22.4 ± 6.79	25 ± 6.01	19.7 ± 5.74	0.004*	P1=0.111 P2=0.096 P3<0.001*
Length of hospital stay (days)	2.3 ± 1.06	2.3 ± 1.11	2.5 ± 1.02	0.540	

*: significant as p value <0.05. PACU: Post-anesthesia care unit, P1: P value between groups M1 and M2, P2: P value between groups M1 and C, P3: P value between groups M2 and C.

Table 4: Post-operative complications among the studied groups

	Group M1 (N=32)	Group M2 (N=32)	Group C (N=32)	P value	
Incidence of PONV	11 (34.38%)	12 (37.5%)	15 (46.88%)	0.567	
Side effects related to the drug	١ (٣.١٣%)	٥ (١٥.٦٣%)	0 (0%)	0.023*	P1=٠.٠٨٦ P2 =0.313 P3=0.019*

Data presented as frequency (%), *: significant as p value <0.05. P1: P value between groups M1 and M2, P2: P value between groups M1 and C, P3: P value between groups M2 and C. PONV: Postoperative nausea and vomiting

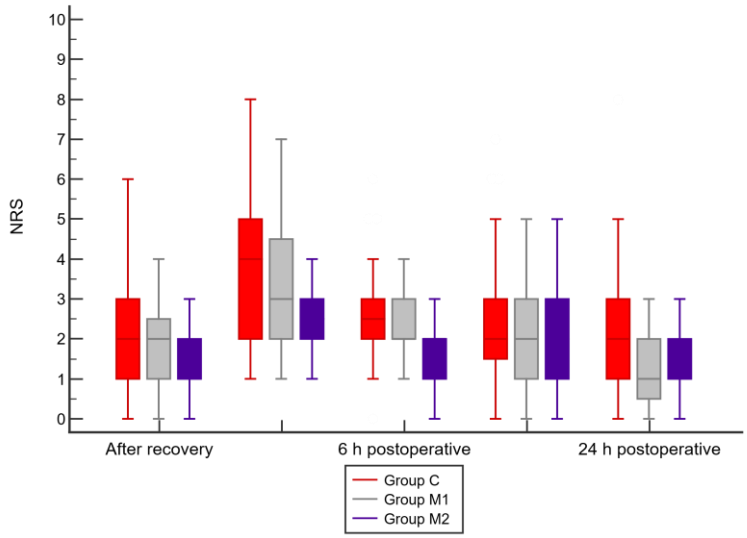
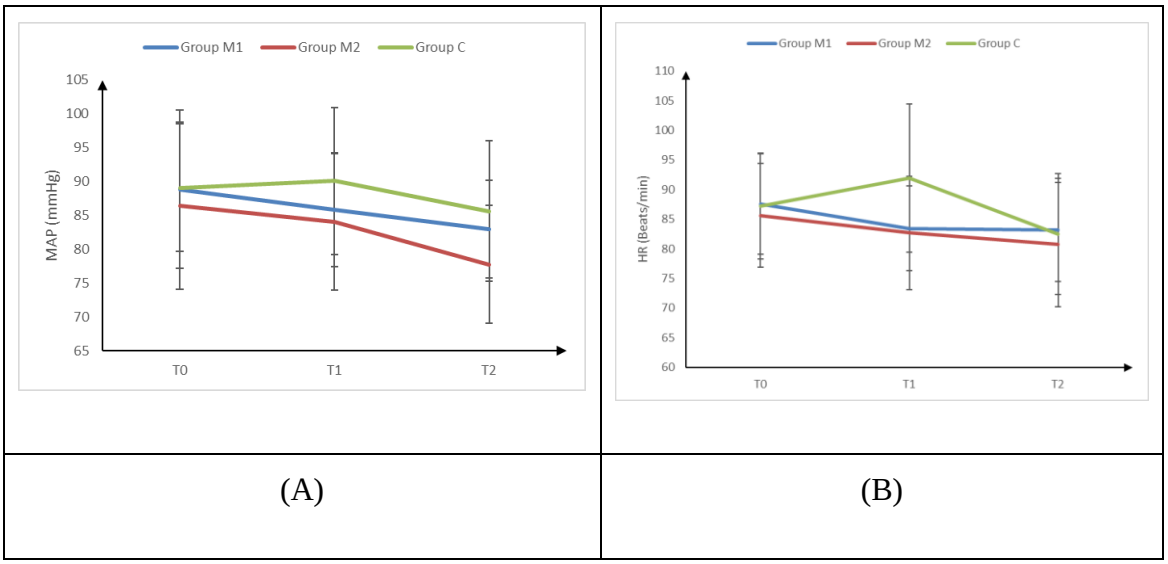


Figure 2: Comparison of NRS score after recovery, 1 h postoperative, 6 h postoperative, 12 h postoperative and 24 h postoperative among the studied groups



(A) (B)

Figure 3: (A) Comparison of MAP at different readings among the studied groups and (B) Comparison of HR at different readings among the studied groups

Discussion:

This randomized controlled trial demonstrated that preoperative sublingual melatonin, at both 3 mg and 6 mg doses, effectively reduced perioperative anxiety and postoperative pain in elective gynecological surgeries. Both melatonin groups showed significantly diminished BAI scores at 2 and 12 h postoperatively in contrast with baseline and intraoperative values. Additionally, pain scores (NRS) were significantly reduced in the higher-dose group at 6 and 12 h, and in both melatonin groups at 24 h postoperatively. Total opioid consumption was diminished,

and the time to 1st rescue analgesia was longer in both melatonin groups in contrast with the control. Importantly, the 3 mg dose achieved comparable anxiolytic and analgesic effects to the 6 mg dose, with fewer reported side effects, suggesting its optimal balance of efficacy and safety. Due to its efficacy with fewer side effects, the 3 mg dose of sublingual melatonin may be considered the preferred premedication in routine elective gynecological procedures. Its favorable tolerability profile enhances its feasibility for outpatient and ambulatory settings, especially where rapid recovery and early discharge are priorities.

Our study detected that BAI in the operating room and at 2 h postoperatively was significantly diminished in Group M1 and Group M2 in contrast with Group C ($P<0.05$), with no significant difference between Group M1 and M2. This outcome may be attributed to melatonin's multifaceted molecular mechanisms, which involve its interaction with specific receptors located both on the cell membrane and within the nucleus. Melatonin primarily exerts its effects through activation of two high-affinity receptors, MT1 and MT2, which are members of the G-protein-coupled receptor family and are expressed on cellular membranes. In addition, a third receptor, MT3, identified as quinone reductase, contributes to melatonin's broader physiological actions through intracellular signaling pathways [(10)].

This observation corresponds with observations reported by Daneshvar and co-authors [(11)], who conducted a randomized trial involving 60 individuals diagnosed with Parkinson's disease. The participants were allocated into two equal groups and instructed to consume either 10 mg of melatonin (administered as two 5 mg capsules) or a placebo once daily, approximately one hour prior to bedtime, over a 12-week period. The results demonstrated that melatonin supplementation led to a statistically significant reduction in BAI scores in contrast with the placebo group, highlighting its anxiolytic efficacy [(11)].

In a similar context, Samarkandi and co-authors [(12)] examined the effects of melatonin in a pediatric population, enrolling 80 children who received either 0.5 mg/kg of melatonin or midazolam as a premedication before anesthesia induction. Their observations indicated that melatonin achieved anxiety reduction on par with midazolam, with no statistically significant differences in preoperative anxiety scores between the groups. Notably, melatonin conferred these benefits without inducing adverse respiratory events, underscoring both its efficacy and safety in pediatric surgical candidates [(12)].

In our present investigation, postoperative pain scores measured by the NRS at 6 and 12 h were significantly diminished in Group M2 in contrast with Group C. Furthermore, by 24 h postoperatively, both Groups M1 and M2 exhibited significantly reduced pain scores relative to the control. The two melatonin-treated groups at this later time point were comparable. These results may be explained by the anxiolytic effects of melatonin, which likely contribute to reduced perioperative stress responses, and by its analgesic properties that lessen the requirement for intraoperative anesthetic agents such as propofol. Moreover, melatonin's analgesic efficacy appears to enhance postoperative pain control without delaying recovery [(13)].

This pattern of observations is further supported by the work of Lotfy and Ayaad [(13)], who aimed to explore the impact of preoperative melatonin on anxiety and postoperative pain, while also assessing whether the outcomes were dose-dependent. In their placebo-controlled investigation, participants were stratified into distinct groups: Group M received oral melatonin as premedication, with Group M1 being administered 3 mg and Group M2 receiving 6 mg. A third cohort, Group Z, was treated with preoperative

oral midazolam at a dose of 0.25 mg/kg, with a maximum of 20 mg dissolved in 3 ml of distilled water. Their analysis revealed that Group M2 demonstrated a marked reduction in the cumulative 8-hour NRS pain scores, significantly outperforming both the placebo group and Group M1 in terms of pain relief.

Similarly, Group Z demonstrated significantly diminished scores than placebo. Although Group Z had pain scores that were numerically diminished than those of Group M1 and higher than those of Group M2, these differences did not reach statistical significance [13].

Additionally, our study documented that the total amount of morphine administered postoperatively was significantly reduced in both Groups M1 and M2 in contrast with Group C, with no meaningful difference in opioid consumption between the two melatonin groups. The time to the 1st request for rescue analgesia was also significantly extended in both melatonin-treated groups relative to the control.

These results are in line with those of Hemati and co-authors [14], who confirmed the analgesic properties of melatonin both as a standalone agent and in combination with other antinociceptive medications. Their observations emphasized melatonin's potential to decrease opioid requirements across a variety of clinical conditions, further validating its role in multimodal analgesia strategies [14].

From a hemodynamic perspective, our study identified that MAP in Group M1 decreased significantly at T2 in contrast with baseline (T0). Group M2 demonstrated reductions in MAP at both T1 and T2 relative to T0, while no significant changes were noticed in Group C.

These hemodynamic effects are consistent with previous literature highlighting melatonin's modulatory influence on vascular tone. Ismail and Mowafi documented significant reductions in MAP following administration of 10 mg of melatonin as premedication in cases undergoing intravenous regional anesthesia. Similarly, Ismail and Mowafi [15] noticed comparable MAP attenuation during cataract surgeries conducted under topical anesthesia [12, 15].

Notably, our study also revealed that Group M2 had significantly diminished MAP values at T2 when in contrast with both Group M1 (P=0.011) and Group C (P=0.002). These observations align with those of Rajan and co-authors [16], who demonstrated that a 6 mg dose of melatonin administered prior to anesthesia induction resulted in attenuated MAP values and reduced propofol requirements. Mohamed and co-authors [17] reported similar dose-dependent reductions in MAP when comparing 6 mg and 9 mg melatonin doses to placebo during the intubation phase of surgery [16,17].

In terms of heart rate responses, our data indicated that HR at T1 was significantly diminished in Groups M1 and M2 in contrast with Group C. This observation is consistent with the results of Kumar and co-authors [18], who conducted a randomized trial involving 64 cases undergoing laparoscopic cholecystectomy. Participants received either two tablets of melatonin (3 mg each) or two tablets of vitamin D3 as placebo, administered 120 minutes prior to anesthesia. The authors found that the post-intubation increase in HR was markedly attenuated in the melatonin group (10.59%) in contrast with the placebo group (37.08%) at the 1-minute mark [18].

The noticed reduction in heart rate is likely stemming from the synergistic interaction between melatonergic and GABAergic neurotransmitter systems, enhancing melatonin's anxiolytic effect. Additionally, melatonin appears to reduce mean blood pressure in healthy individuals via a multifactorial mechanism, including binding to specific vascular melatonin receptors, blunting the vascular response to catecholamines, and promoting smooth muscle relaxation through increased nitric oxide bioavailability [18, 19].

In terms of AEs, no side effects were reported in Group C. In contrast, Group M2 exhibited a notably higher incidence of mild AEs in contrast with Group C (P=0.019). Group M1 showed no substantial variation in adverse event occurrences relative to the other two groups. While higher doses of melatonin are generally well tolerated, there is limited literature on its potential adverse outcomes. Schrire and co-authors [(20)]investigated the safety profile of high-dose melatonin (≥10 mg) in adults aged 30 years and older, analyzing the occurrence of AEs, serious AEs (SAEs), and treatment discontinuations. Remarkably, 29 of the studies included in the review (37%) did not report any data on AEs. Among those that did report, an increased incidence of drowsiness, headache, and dizziness was noticed in patients receiving melatonin in contrast with those on placebo [(20)].

Our study demonstrated that the time to discharge from the PACU was significantly longer in Group M2 relative to Group C (P<0.001). This is in agreement with observations reported by Rajan and co-authors[(16)], who evaluated the impact of 6 mg oral melatonin premedication on perioperative hemodynamics and postoperative recovery parameters. Their randomized trial revealed that melatonin premedication was associated with increased postoperative sedation and prolonged recovery, as evidenced by delayed PACU discharge. The authors attributed these effects to melatonin's sedative properties, which, although beneficial in modulating stress responses, may extend the duration of recovery. This mirrors our observations, further supporting the hypothesis that melatonin exerts a dose-dependent influence on postoperative recovery dynamics, particularly with respect to sedation and discharge readiness [(16)].

This study, despite its methodological rigor and clinical relevance, presents certain limitations that should be considered. The sample size of 96 cases, while adequate for preliminary comparisons, may not be sufficient to capture the full spectrum of variability among surgical populations or detect smaller effect sizes. Expanding the sample in future research would enhance the statistical power and the precision of estimated effects. Conducting the trial within a single academic medical center may also limit the generalizability of the observations to other healthcare institutions, there protocols, surgical practices, and case demographics may differ. Institutional-specific factors, including clinician expertise and resource availability, could have influenced outcomes. In addition, the relatively short duration of postoperative follow-up (24 hours) limited the assessment to early-phase outcomes such as anxiety, pain, opioid use, and hemodynamic parameters, thereby precluding evaluation of prolonged analgesic or anxiolytic benefits and restricting conclusions regarding sustained efficacy or delayed adverse effects. This design precluded evaluation of longer-term effects, including the persistence of analgesia, delayed complications, or overall case satisfaction. Addressing these limitations in future multicenter investigations with larger populations and extended follow-up will be essential for validating the reproducibility and durability of the noticed benefits.

Conclusion:

This trial demonstrates that sublingual melatonin is an effective and safe premedication for diminishing perioperative anxiety and postoperative pain in elective gynecological surgeries under GA. Both 3 mg and 6 mg doses significantly diminished anxiety and pain scores, reduced opioid consumption, and prolonged the time to 1st rescue analgesia in contrast with control. Notably, the 3 mg dose provided comparable benefits to the 6 mg dose with fewer side effects, suggesting that the diminished dose may

offer an optimal balance between efficacy and safety. These observations support the use of low-dose sublingual melatonin as a valuable adjunct in perioperative care.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

The authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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To cite this article: Mariam A. Ahmed, Ehab A. El-Sahat, Ahmed H. Abd El-Rahman, Samar R. Amin. Comparison between Two Different Doses of Sublingual Melatonin to Alleviate Anxiety and Pain Associated with Elective Gynecological Surgeries under General Anesthesia; a Randomized Controlled Trial. BMFJ XXX, DOI: 10.21608/bmfj.2025.396654.2487.