Preoperative oral melatonin can reduce preoperative anxiety and postoperative analgesia in a dose-dependent manner

Mohamed Lotfy* and Mohamad Ayaad

Abstract

Background: Preoperative anxiety has deleterious effects on patients’ outcome through its influence on intraoperative requirements of anesthetics and analgesics (Bayrak et al., J Coll Physicians Surg Pak 29:868–873, 2019), postoperative (PO) pain intensity, and analgesia requirement, and may even increase PO morbidity and mortality after certain types of surgery. Melatonin is a methoxyindole synthesized and secreted principally by the pineal gland at night under control of an endogenous rhythm of secretion generated by the suprachiasmatic nuclei. The current study hypothesized that preoperative melatonin could reduce patients’ anxiety and reduce intraoperative (IO) and postoperative (PO) analgesic in a dose-dependent manner.

Results: Preoperative consultation was, to some extent, effective in reducing patients’ anxiety and apprehension. At 1 h after receiving premedication, Anxiety Specific to Surgery Questionnaire (ASSQ) scores were significantly lower in study groups in comparison to baseline scores and at 1 h scores of P group patients (patients who received 3 ml of plain distilled water), and this significant effect extended for 3-h PO. The reported ΔΔASSQ between study groups was 25.9% between M2 (melatonin) and Z (midazolam) groups and 36.9% between groups M1 (received melatonin in a dose of 3 mg) and M2 (received melatonin in a dose of 6 mg). Preoperative anxiolytic therapy allowed reduction of PO pain scores and analgesia consumption with prolongation of duration till 1st request of rescue analgesia, and these effects were more pronounced with melatonin 6 mg in comparison to placebo, melatonin 3 mg, or midazolam.

Conclusion: Preoperative melatonin is an appropriate policy for reduction of preoperative anxiety and provided reduction of PO anxiety, pain scores, and consumption of analgesia thus promoting early recovery and short PO hospital stay. Dose dependency was evident, and preoperative melatonin 6-mg dose provided satisfactory effect.

Keywords: Anxiety, Melatonin, Midazolam, Dose dependency, Postoperative pain

Background
Preoperative anxiety has deleterious effects on patients’ outcome through its influence on intraoperative requirements of anesthetics and analgesics (Bayrak et al. 2019), postoperative (PO) pain intensity, and analgesia requirement, and may even increase PO morbidity and mortality after certain types of surgery (Stamenkovic et al. 2018). Multiple preoperative non-pharmacological modalities as acupressure (Abadi et al. 2018), distraction-based music therapy (Millett and Gooding 2018), aromatherapy skin patch (Jaruzel et al. 2019), or hydration with carbohydrate drinks up until 2 h before surgery (Makaryus et al. 2018) were used to alleviate apprehension and lessen anxiety. Also, pharmacological therapies using midazolam (Impellizzeri et al. 2017), dexmedetomidine (Qiao et al. 2017), and gabapentin (Khan et al. 2019) were found to successfully reduce preoperative anxiety with subsequent minimization of its sequel.

* Correspondence: dr.mohamed_lotfy@hotmail.com
Faculty of Medicine, Tanta University, Tanta, Egypt

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Melatonin is a methoxyindole synthesized and secreted principally by the pineal gland at night under control of an endogenous rhythm of secretion generated by the suprachiasmatic nuclei (Claustrat and Leston 2015) that is synchronized to the light-dark cycle via the retinohypothalamic tract, placing melatonin synthesis as night provided its dark (Amaral and Cipolla-Neto 2018).

Melatonin is a ubiquitous molecule acting as an autocrine and paracrine signal (Cipolla-Neto and Amaral 2018). Melatonin has potent multifunctional effects, both receptor-dependent and receptor-independent effects, and mitigates tissue injury via modification of abnormalities in redox status (Reiter et al. 2017) and downregulation of nuclear factor-κ beta, c-Fos expression, and matrix metalloproteinases-3, which are regulators of pro-inflammatory and pro-fibrotic cytokines (Habtemariam et al. 2017).

The main physiological function of melatonin is to synchronize individual’s biological rhythms, and exogenous melatonin was found to have the same action, even at dose of 0.125 mg (Geoffroy et al. 2019). Moreover, melatonin has sedative, anti-anxiety, and potential analgesic effects when used as pre-surgical medication ( Abbasivash et al. 2019), and experimental studies indicated that melatonin could be used to minimize the level of excitement before general anesthesia and to reduce the required propofol dose for induction (Niggemann et al. 2019).

Hypothesis
The current study hypothesized that preoperative melatonin could reduce patients’ anxiety and reduce intraoperative (IO) and PO analgesia.

Objectives
This study targets to determine the effect of preoperative melatonin on patients’ anxiety and PO pain score and to show if this effect is dose dependent in a placebo-controlled study in comparison to midazolam.

Design
Prospective comparative randomized placebo-controlled study

Methods
This study was approved by our Institutional Review Board (33858/6/20), and written informed consent was obtained from all subjects participating in the trial. All patients assigned for inguinal hernia repair under general anesthesia were eligible to preoperative evaluation. Only adult patients with unilateral inguinal hernia repair, ASA grade I or II, and were free of associated morbidities and exclusion criteria were included in the study. Exclusion criteria included obstructed or complicated hernia; hernia associated with other pathology that needs to be operated upon or during the same setting; and presence of coagulopathy, hormonal disorders, hepatic, cardiac, or renal diseases, diabetes mellitus, hypertension, or history of psychological diseases. Also, patients with body mass index (BMI) ≥35 kg/m², maintained on analgesics, or received any analgesia during the preceding 24 h, and patients who refused to sign the written consent to participate in the study were excluded from the study.

After collection of demographic data including age, gender, education, and marital status, all patients were clinically evaluated, and body mass index (BMI) was calculated according to the equation BMI= weight (kg)/height (m²) (Bray 1992), and obesity grades were defined after the WHO expert consultation (2004) as average (BMI <24.9), overweight (25–<30 kg/m²), obese (BMI ≥30–<35 kg/m²), and morbidly obese (BMI ≥35 kg/m²).

Patient assessment
Patients free of exclusion criteria were included in the study and were asked to attend at the preoperative preparation room at 7 AM for preoperative assessment and to receive the assigned preoperative medication. Patients were assessed before and after receiving the premedication and after recovery using the following instruments:

1. Non-invasive determination of baseline hemodynamic variables including heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), and calculation of mean arterial pressure (MAP).
2. Preoperative anxiety scoring using the Anxiety Specific to Surgery Questionnaire (ASSQ) that was developed to assess the specific patient concerns about what may happen during and after the surgery and is composed of 10 items. Each item was evaluated using a 5-point scale with 1 indicating strongly disagree and 5 indicating strongly agree, except for the 8th item where numbers indicate the reverse, i.e., 1 indicated strongly agree and 5 indicated strongly disagree. Total score was obtained as the sum of the items’ scores, with the higher ASSQ score, the higher the patient’s anxiety (Karanci and Dirik 2003).
3. Level of sedation was evaluated using the Ramsay Sedation Scale (RSS), which is a subjective tool used to precisely evaluate the level of consciousness during titration of sedative medications and included scores 1–2 for behavior observation, score 3 for assessment of response to voice, and scores 4–6 for assessment of response to loud auditory stimulus or light glabellar tap (Ramsay et al. 1974).
Groups and medications
All patients received preoperative anesthetic consultation with the anesthetist in charge for 15 min to explain the anesthetic procedure and how to reduce and manipulate the possible anesthetic complications and how to manage PO pain and the pain for 1-day surgery, in trial to relieve anxiety and apprehension. Then, patients were randomly divided into three equal groups (Fig. 1) using sealed envelopes containing cards carrying the label for each group and were prepared by an assistant not included in the study, and envelopes were chosen by the patient him/herself. Each patient was given a cup containing 3 ml of fluid to drink and stay calm for 1 h after the end of consultation and before transfer to the theater. The three groups were the following:

Group P included patients who received 3 ml of plain distilled water.
Group M included patients who will receive preoperative oral melatonin (Melatonin, Naturals, Canada). Patients of group M were asked to choose another card, also previously prepared by an assistant who was blinded about the significance of the label number, carrying a number label, either one or two. Patients who chose the card labeled as one received melatonin in a dose of 3 mg (M1 group), and patients who chose the card labeled as two received melatonin in a dose of 6 mg (M2 group); melatonin was given dissolved in 3 ml of distilled water.
Group Z included patients who will receive preoperative oral midazolam (Midathetic, Amoun Pharmaceuticals, Cairo, Egypt) in a dose of 0.25 mg/kg for a maximum dose of 20 mg dissolved in 3 ml of distilled water.

Anesthetic procedure
One hour after receiving the premedication, all patients received ondansetron (4 mg IV) and paracetamol (1 g IV). Then, general anesthesia was induced by fentanyl 2 μg/kg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg, and was maintained with sevoflurane 2%, fentanyl 1 μg/kg, and rocuronium 0.1mg/kg as required. After endotracheal intubation, the lungs were ventilated with 50% O₂ in air for a tidal volume of 6–8 ml/kg, end-tidal carbon dioxide (ETCO₂) of 35–40 mmHg, and inspiration: expiration (I:E) ratio of 1:2. Patients were continuously non-invasively monitored for HR, MAP, SpO₂, and ETCO₂. At the end of surgery, residual neuromuscular blockade was reversed using intravenous injection of neostigmine 0.05 mg/kg with atropine 0.02 mg/kg IV; patients were extubated and shifted to the post-anesthesia care unit (PACU).

Postoperative care
In PACU, ASSQ and RSS were determined 30, 60, 90, and 120-min after recovery. Also, HR, MAP, SpO₂, and ETCO₂ were determined every 15 min for 2 h. PACU discharge was dependent on Aldrete recovery score that ranges from 0 (comatose patients) to 10 (complete recovery) (Ghai et al. 2005), and patients were discharged upon achieving a score of ≥8 (Ecoff et al. 2017). PO pain was assessed using the 11-point Pain Numerical Rate Scale (NRS) which included scale from 0 (no pain) to 10 (worst pain). NRS was used, it is more practical than the graphic visual analog scale, easier to perceive for most people, and does not need clear vision, pen, and paper (Williamson and Hoggart 2005). Pain scores were determined half-hourly for 2 h and then every 2 h till 8 h. Duration of PO analgesia was defined as time lapsed since recovery till 1st request of rescue analgesia. PO
rescue analgesia was provided for patients who had NRS score ≥4, as slow intravenous injection of ketorolac tromethamine (Ketolarc; amp 30mg/ml; Amyria Pharmaceuticals, Alex, Egypt) as 1-ml diluted to 10-ml with normal saline (0.9%) and repeated if requested after 8 h for a maximum of 3-doses. All cases were managed as 1-day surgery cases, and duration of PO hospital stay was determined.

Study outcomes

1. Primary outcome was the reduction of preoperative anxiety after administration of premedication therapies.
2. Secondary outcomes are as follows:
   - Differences in ASSQ score between M groups to determine the dose-dependency
   - Patients’ satisfaction scoring as evaluated using a 4-point numerical scale ranging from excellent satisfaction [score= 4] to very dissatisfied [score=1]

Sample size calculation

Previously, Naguib and Samarkandi (1999) and Acil et al. (2004) reported significant reduction of anxiety and sedation scores between preoperative oral melatonin (5 mg) and midazolam (15 mg) compared to placebo with non-significant differences between melatonin and midazolam in studies that included 25 and 22 adult patients per group, respectively. The current study supposed that if the difference between the extents of reduction of ASSQ scores 1 h after administration of study drugs (ΔASSQ) in comparison to before administration showed a difference of 25% between M and Z groups, the difference may be significant. A sample size of 35 patients per group would achieve a power of 80% with a value of 0.05, and β value of 0.2 may fulfill the study target to get significant difference between both of the study groups.

Statistical analysis

Obtained data were presented as mean ± SD, numbers, and percentages. Results were analyzed using paired t-test for intra-group comparisons, one-way ANOVA test for inter-group comparisons, and Chi square test. ΔASSQ was calculated as the percentage of difference between ASSQ determined before and 1 h after receiving premedication therapy in relation to ASSQ determined before administration of therapy, and the difference in ΔASSQ (ΔΔASSQ) of study groups was calculated as the percentage of difference between ΔASSQ of each two of study groups. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

During the study duration since June 2019, 177 patients were eligible for evaluation, and 140 patients were included in the study and divided into 4 study groups (Fig. 1). Inclusion data showed non-significant difference between study groups (Table 1).

Concerning ASSQ scoring, scores determined prior to administration of medications showed non-significant differences between the four groups. In comparison to ASSQ scores determined before preoperative anesthetic consultation, ASSQ scores determined at 1 h after receiving the study medications were non-significantly (p=0.256) lower in patients of P group, while were significantly decreased with medications used and were significantly lower in comparison to that of P group with non-significant differences between M1, M2, and Z groups, despite being lowest in group M2. The calculated ΔASSQ was significantly higher in M2 group in comparison to both M1 (p=0.0003) and Z (p=0.0009) groups with non-significantly (p=0.352) higher ΔASSQ in Z than M1 groups (Table 2). Eighty-three patients had ΔASSQ of ≥25% with significantly higher frequency of patients had ΔASSQ of ≥25% in M2 (p=0.0006) and Z (p=0.034) groups in comparison to M1 group and non-significantly (p=0.133) higher frequency among patients of M2 group in comparison to Z group (Fig. 2). The calculated ΔASSQ for patients of M2 group was higher than that of patients of Z group by 25.9% and then ΔASSQ of patients of M1 group by 36.9%, while ΔASSQ of patients of Z group was higher than that of patients of M1 group by 8.7%.

After recovery of anesthesia, ASSQ scores were still significantly lower in all patients who received preoperative medication in comparison to those who received placebo with significantly lower scores till 120 min after recovery in M2 group in comparison to both M1 and Z groups. Interestingly, the differences in ASSQ between patients of groups M1 and Z were non-significantly lower in Z group till 90 min after recovery, and then, the difference was significant (p=0.0017) at 120 min after recovery (Table 2, Fig. 3).

All patients of M1, M2, and Z groups had significantly higher RSS score at 30 min and significantly lower at 60 min than patients who received placebo with significantly higher RSS scores detected in patients of Z group at both times. Patients of Z group had higher RSS scores at 90 min in comparison to P (p=0.002) and M2 (p=0.0005) groups with non-significant difference between RSS scores of patients of P and M2 groups. At 120 min after recovery, patients of P group had higher RSS scores than patients of M2 (p=0.012) and Z (p=0.098) groups,
with non-significantly ($p=0.344$) lower RSS scores in patients of M2 than Z groups. Sixty-one patients (43.6%) were ready for PACU discharge within 60 min after recovery of anesthesia, 55 patients (39.3%) were ready in time range of 60 to 120 min, and 24 patients were discharged after 120 min with non-significant differences between patients of the four groups (Table 3).

Twenty-two (15.7%) patients, 15 of M2 (42.9%) and 7 of Z (37.1%) groups, did not request rescue analgesia till end of 8-h PO follow-up; 55 patients (39.3%) required rescue analgesia once; 63 patients requested analgesia for two times. The number of requests was significantly lower in patients of M2 group in comparison to patients of groups P, M1, and Z, while was significantly higher in patients of P group in comparison to patients of M1 and Z groups with non-significantly lower number of requests by patients of group Z in comparison to patients of M1 group. Duration of analgesia among patients who requested rescue analgesia was significantly longer in M2 group in comparison to P, M1, and Z groups and in patients of M1 and Z groups in comparison to patients of P group with non-significantly longer duration in M1 in comparison to Z group. Cumulative 8-h NRS pain

| Table 1 Inclusion data of patients of the four groups |
| Variables | Groups | $p$ value |
|-----------|--------|-----------|
| Age (years) | P | 46.6±9.3 | M1 | 45±9 | M2 | 47.4±6.6 | Z | 46.4±5.5 | 0.621 |
| Sex | | | | | | | | | |
| Males | 22 (62.9%) | 27 (77.1%) | 25 (71.4%) | 29 (82.9%) | 0.269 |
| Females | 13 (37.1%) | 8 (22.9%) | 10 (28.6%) | 6 (17.1%) | 0.269 |
| Education level | | | | | | | | | |
| Post-graduate | 5 (14.3%) | 4 (11.4%) | 3 (8.6%) | 2 (40%) | 0.749 |
| College | 9 (25.7%) | 10 (28.6%) | 12 (34.3%) | 11 (31.4%) | 0.121 |
| High school | 11 (31.4%) | 8 (22.9%) | 13 (37.1%) | 8 (22.8%) | 0.121 |
| Sec school | 4 (11.4%) | 5 (14.3%) | 2 (5.7%) | 7 (20%) | 0.121 |
| Illiterate | 6 (17.2%) | 8 (22.9%) | 5 (14.3%) | 7 (20%) | 0.121 |
| Marital status | | | | | | | | | |
| Single | 9 (25.7%) | 11 (31.4%) | 10 (28.6%) | 7 (20%) | 0.861 |
| Married | 21 (60%) | 22 (62.8%) | 24 (68.5%) | 28 (80%) | 0.121 |
| Divorced | 3 (8.6%) | 1 (2.9%) | 0 | 0 | 0.121 |
| Widow | 2 (5.7%) | 1 (2.9%) | 1 (2.9%) | 0 | 0.121 |
| Body weight (kg) | 83.7±8.1 | 86.9±6.1 | 87.5±8 | 85.3±7.2 | 0.136 |
| Body height (cm) | 167.6±3.9 | 168.7±3.1 | 168±3.5 | 168±3.3 | 0.389 |
| Body mass index (Kg/m²) | 29.8±2.6 | 30.5±2.4 | 31±2.9 | 30.2±2.1 | 0.208 |
| ASA | | | | | | | | | |
| Grade I | 32 (91.4%) | 30 (85.7%) | 33 (94.3%) | 31 (88.6%) | 0.662 |
| Grade II | 3 (8.6%) | 5 (14.3%) | 2 (5.7%) | 4 (11.4%) | 0.662 |
| Hernia side | | | | | | | | | |
| Right | 14 (40%) | 12 (34.3%) | 10 (28.6%) | 16 (45.7%) | 0.485 |
| Left | 21 (60%) | 23 (65.7%) | 25 (71.4%) | 19 (54.3%) | 0.485 |
| Associated medical diseases | | | | | | | | | |
| CAD | 2 (5.6%) | 1 (2.9%) | 1 (2.9%) | 0 | 0.838 |
| DM | 3 (8.6%) | 3 (8.6%) | 4 (11.4%) | 3 (8.6%) | 0.838 |
| Chest | 1 (2.9%) | 3 (8.6%) | 1 (2.9%) | 2 (5.6%) | 0.838 |
| Liver | 1 (2.9%) | 2 (5.6%) | 2 (5.7%) | 1 (2.9%) | 0.838 |
| No | 28 (80%) | 26 (74.3%) | 27 (77.1%) | 29 (82.9%) | 0.838 |

Data are presented as mean, standard deviation, numbers, and percentages. $p<0.05$ indicates significant difference; $p>0.05$ indicates non-significant difference. Sec school Secondary school graduate, CAD Coronary artery disease, DM Diabetes mellitus; $p$ value indicates the significance of variance between groups according to one-way ANOVA test for parametric variables and Chi-square test with Yates correction for non-parametric numerical values.
score was significantly lower in M2 group in comparison to P and M1 groups and in Z group in comparison to P group, but non-significantly lower and higher in Z group in comparison to M1 and M2 groups, respectively (Table 3, Fig. 4).

All surgeries were conducted uneventfully within a non-significantly different operative time. PO hospital stay was significantly shorter for patients of M2 group in comparison to patients of P and M1 groups but was non-significantly shorter in comparison to patients of Z.

**Table 2** ASSQ scorings of patients of the four groups till 120-min after recovery of anesthesia

| Group | Time | Medication | ΔASSQ | After recovery |
|-------|------|------------|-------|---------------|
|       | Before | 1 h after | 30 min | 60 min | 90 min | 120 min |
| P     | Value  | 22.5±4.7  | 21.3±4.3 | 5.1±6.6 | 18.3±3.6 | 14.9±3.3 | 11.9±2.7 | 9.5±2.4 |
| M1    | Value  | 23±5.8    | 16±6.8   | 33.4±14.9 | 13.3±6 | 10.7±4.8 | 8.2±4.1 | 6.3±3.6 |
| P1    | 0.685  | 0.0002    | <0.0001 | 0.00008 | 0.00006 | 0.00004 | 0.00004 |
| M2    | Value  | 25±5.5    | 13.6±4.4 | 45.8±12 | 10.2±3.4 | 7.2±2.4 | 5±1.9 | 2.4±1 |
| P1    | 0.055  | <0.0001   | <0.0001 | <0.00001 | <0.00001 | <0.00001 | <0.00001 |
| P2    | 0.144  | 0.088     | 0.0003 | 0.01 | 0.0003 | 0.0001 | <0.0001 |
| Z     | Value  | 24±4.7    | 15.3±4.3 | 36.4±10.7 | 12.5±4.1 | 9.7±3.1 | 6.7±2.7 | 3.9±2.3 |
| P1    | 0.182  | <0.00001 | <0.00001 | <0.00001 | <0.00001 | <0.00001 | <0.00001 |
| P2    | 0.431  | 0.046     | 0.352 | 0.512 | 0.32 | 0.084 | 0.0017 |
| P3    | 0.417  | 0.007    | 0.0009 | 0.0017 | 0.0004 | 0.0025 | 0.0004 |

Data are presented as mean±SD; p value indicates the significance of variance between groups according to one-way ANOVA test for parametric variables. p>0.05 indicates non-significant difference; p<0.05 indicates significant difference. P1 Significance of difference versus group P, P2 Significance of difference versus group M1, P3 Significance of difference versus group M2

**Fig. 2** Percentage of decreased Anxiety Specific to Surgery Questionnaire (ASSQ) score after receiving premedication drugs
group. PO hospital stay for patients of M1 group was non-significantly shorter and longer in comparison to patients of P and Z groups, respectively, while was significantly shorter for patients of Z group in comparison to patients of P group. The frequency of patients among higher satisfaction grades was significantly ($p=0.009$) higher among patients who received premedication in comparison to placebo. Among patients who received premedication prior to anesthesia, 38 patients (36.2%) found the procedure was very satisfying, 35 patients (33.3%) found the procedure satisfying, 24 patients (22.9%) found it good, while 8 patients (7.6%) found the procedure not satisfying.

Table 3: PO sedation and pain data of patients of the four groups

| Variables                             | Group | PO sedation data | PO pain data |
|---------------------------------------|-------|------------------|--------------|
|                                       | P     | M1               | M2           | Z            | M1   | M2   | Z    |
| RSS                                   | Score | Score            | Score        | Score        | P1   | P2   | P3   |
| 30 min                                | 1.7±0.6 | 2±0.6            | 0.018        | 2.1±0.8      | 0.008 | 0.498 | 2.4±0.6 | 0.001 | 0.007 | 0.095 |
| 60 min                                | 2.7±0.5 | 1.8±0.7          | 0.001        | 1.8±0.6      | 0.001 | 0.992 | 2±0.6   | 0.001 | 0.2   | 0.177 |
| 90 min                                | 1.5±0.5 | 2.6±0.5          | 0.001        | 1.66±0.8     | 0.201 | 0.0001| 2±0.8   | 0.002 | 0.0005| 0.078 |
| 120 min                               | 1.8±0.7 | 2.4±0.6          | 0.001        | 1.4±0.5      | 0.012 | 0.0001| 1.5±0.5 | 0.08  | 0.0001| 0.344 |
| Number of patients who achieved Aldrete score permissible for PACU discharge (>8) | | Number | | Number | | Number | | Number | | Number |
| At <60 min                             | 12 (34.3%) | 20 (57.1%) | 0.157     | 16 (45.7%)  | 0.479 | 0.476 | 13 (37.1%) | 0.234 | 0.072 | 0.509 |
| At 60–120 min                          | 18 (51.4%) | 12 (34.3%) | 13 (37.1%) | 12 (34.3%)  |       |       |       |       |       |       |
| At >120 min                            | 5 (14.3%)  | 3 (8.6%)         | 6 (17.2%)   | 10 (28.6%)  |       |       |       |       |       |       |
| No. of requests of analgesia           | 0     | 0                | 0.002       | 15 (42.9%)  | <0.001 | 0.0003| 7 (20%) | 0.0009 | 0.059 | 0.049 |
|                                       | 1     | 10 (28.6%)       | 27 (77.1%)  | 17 (48.5%)  | 19 (54.3%)|       |       |       |       |       |
|                                       | 2     | 25 (71.4%)       | 8 (22.9%)   | 3 (8.6%)    | 9 (25.7%) |       |       |       |       |       |
| Duration of PO analgesia               | 0.9±0.4 | 3.4±1.6          | <0.001      | 5.2±2.2     | <0.001 | 0.0012| 2.9±1.9 | <0.001 | 0.258 | 0.0005|
| Cumulative 8-h NRS pain score          | 2.2±0.4 | 2.1±0.4          | 0.334       | 1.7±0.5     | 0.0002 | 0.019 | 2±0.6  | 0.0004 | 0.12  | 0.078 |

Data are presented as mean±SD, numbers, and percentages. $p<0.05$ indicates significant difference; $p>0.05$ indicates non-significant difference. 
P1 Significance of difference versus group P, P2 Significance of difference versus group M1, P3 Significance of difference versus group M2 according to one-way ANOVA test for parametric variables and Chi-square test with Yates correction for non-parametric numerical values.

Fig. 3: Mean Anxiety Specific to Surgery Questionnaire (ASSQ) score of patients who received premedication treatment till 120 min.
dissatisfying with non-significant (0.687) difference between the three medications used (Table 4).

**Discussion**

The obtained results of this study showed that only 40% of studied patients were highly educated, and this finding supports the inverse relation between educational level and presence and severity of preoperative anxiety. In line with these data, Du et al. (2020) and Mathew et al. (2020) found that preoperative anxiety was associated with decline in the domain of executive function, and low educational attainment is a risk factor of overall neurocognitive disorder and suggested the need for preparatory program. These data assured the value of preoperative anesthetic consultation applied for the study participants of the current study.

In support of this assumption, preoperative anesthetic patients’ consultation was, to some extent, effective in reducing patients’ anxiety and apprehension as evidenced by the reported lower ASSQ scores of P group patients in comparison to their baseline scores. Similarly, Akhlaghi et al. (2020) and Lumb et al. (2020) found that preoperative anesthetic consultation can reduce preoperative sources of anxiety, especially for individuals experiencing high levels of stress.

At 1 h after receiving premedications, ASSQ scores were significantly lower in study groups in comparison to baseline scores and at 1 h scores of P group patients, and this significant effect extended for 3-h PO. These findings indicated the necessity for therapeutic management of preoperative anxiety, despite the benefits

![Fig. 4 Postoperative pain data of patients of studied groups](image)

| Table 4 Operative and PO data of patients of the four groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Variables                      | Groups          | P               | M1              | M2              | Z               |
| Operative time (min)           |                 |                 |                 |                 |
| Mean (±SD)                     |                 | 42.1±9.1        | 43.9±8.1        | 41.1±8.7        | 41.6±9.6        |
| P1                             |                 | 0.409           | 0.639           | 0.799           |                 |
| P2                             |                 | 0.181           | 0.287           |                 |                 |
| P3                             |                 | 0.845           |                 |                 |                 |
| PO Hospital stay (h)           |                 |                 |                 |                 |
| Mean (±SD)                     |                 | 11.4±1.9        | 10.6±2          | 9.6±1.3         | 10±1.8          |
| P1                             |                 | 0.088           | 0.00002         | 0.0024          |                 |
| P2                             |                 | 0.014           | 0.186           |                 |                 |
| P3                             |                 | 0.289           |                 |                 |                 |
| Satisfaction scores            |                 |                 |                 |                 |
| Very satisfying                |                 | 6 (17.1%)       | 11 (31.4%)      | 14 (40%)        | 13 (37.2%)      |
| Satisfying                     |                 | 10 (28.6%)      | 12 (34.2%)      | 12 (34.2%)      | 11 (31.4%)      |
| Good                            |                 | 11 (31.4%)      | 7 (20%)         | 8 (22.9%)       | 9 (25.7%)       |
| Dissatisfying                  |                 | 8 (22.9%)       | 5 (14.4%)       | 1 (2.9%)        | 2 (5.7%)        |
| P1                             |                 | 0.009           |                 |                 |                 |
| P4                             |                 | 0.687           |                 |                 |                 |

Data are presented as means±SD, numbers, and percentages. *p* <0.05 indicates significant difference; *p* >0.05 indicates non-significant difference.

P1 Significance of difference versus group P, P2 Significance of difference versus group M1, P3 Significance of difference versus group M2, P4 Significance of variance between P, M1, and M2 groups according to one-way ANOVA test for parametric variables and Chi-square test with Yates correction for non-parametric numerical values.
of preoperative consultation. In line with these findings, Gupta et al. (2017) found that higher dosage of midazolam improves the quality of anxiolysis and sedation with lesser rates of intraoperative recall and maintains hemodynamic stability, and Kunusoeth et al. (2019) also found that preoperative midazolam is effective in reducing the subjective stress with reliable anxiolysis while preserving protective reflexes.

Moreover, the reported ΔASSQ between study groups was 25.9% between M2 and Z groups and 36.9% between M1 and M2 groups, thus indicating a more pronounced anxiolytic effect of melatonin 6-mg than 3-mg dose and than midazolam premedications. These findings points to the superior anxiolytic effect of melatonin over midazolam and the dose-related effect of melatonin.

In support of these results, Khare et al. (2018) found that premedication using oral melatonin (6 mg) is an effective alternative to alprazolam for providing better anxiolysis, lesser sedation with maintenance of cognitive and psychomotor function. Also, out of systemic literature review, Campbell et al. (2019) reported that peroperative melatonin, given in daily doses of 2–8 mg for 1–9 days starting on the evening before or the day of surgery, reduced the incidence of delirium in older adults assigned for cardiothoracic, orthopedic, or hepatic surgeries. Moreover, Han et al. (2020) in a meta-analysis found that melatonin administered in 5-mg dose before surgery was significantly effective in reducing PO delirium in the entire adult surgical population, and in dose <5 mg, its elimination half-lives can extend postoperatively to significantly reduce the incidence of PO delirium.

In addition to reduction of anxiety, preoperative anxiolytic therapy allowed reduction of PO pain scores and analgesia consumption with prolongation of duration till 1st request of rescue analgesia, and these effects were more pronounced with melatonin 6 mg in comparison to placebo, melatonin 3mg, or midazolam. Similarly, Javaherforooshzadeh et al. (2018) found that, in placebo-controlled study, preoperative melatonin or gabapentin decreases anxiety and pain in lumbar surgery. Also, Lee and Curtin (2020) found that prophylactic melatonin significantly reduced subjective pain and numbness perception by 50% and 30%, respectively in the early PO days, and the effect increased to more than 80% reduction by 3-m PO with significant improvement in objective neurosensory testing and healing profile after orthognathic surgery. Moreover, Palmer et al. (2019) detected significantly higher ANRS during the conditioned pain-modulating task with melatonin than with placebo, and Oh et al. (2020), in a random-effects meta-analysis, found that the use of melatonin reduced chronic pain and significantly reduced acute PO pain. In support of the efficacy of melatonin, Soltani et al. (2020) reported significantly lower morphine consumption and mechanical ventilation time with significant rise of Glasgow Coma Scale in traumatic intracranial hemorrhage patients admitted to surgical ICU and received melatonin, in comparison to other sedatives.

Multiple attributes were provided for the analgesic effect of melatonin; Palmer et al. (2019) reported improved function of the descending pain modulatory system with the use of exogenous melatonin with significant reduction of serum brain-derived neurotrophic factor, tropomyosin kinase receptor B, and S100B-protein, and so concluded that melatonin’s effect on pain is not due to its effect on sleep quality. On the other hand, Lee and Curtin (2020) and Procaccini et al. (2020) attributed melatonin’s favorable effects to its antioxidant and anti-inflammatory actions as evidenced by significant PO reduction in oxidants’ concentrations with significantly higher levels of antioxidant enzymes and strong correlations between antioxidant effects and reduced PO pain and sensory recovery. As another explanation, Hemati et al. (2020) attributed the role of melatonin in pain regulation to reversing the opioid tolerance through regulation of several cellular signaling pathways.

Conclusion
Preoperative preparation of surgical patients using melatonin is appropriate policy for reduction of preoperative anxiety and provided smooth postoperative period with reduction of PO anxiety, pain scores, and consumption of analgesia thus promoting early recovery and short PO hospital stay. Dose dependency was evident, and preoperative melatonin 6-mg dose provided satisfactory effect. However, wider scale studies including more extensive surgical procedures are mandatory to establish the obtained results.

Abbreviations
PO: Postoperative; ASSQ: Anxiety Specific to Surgery Questionnaire; P: Group P included patients who received 3 ml of plain distilled water; M1: Group received melatonin in a dose of 3 mg; M2: Group received melatonin in a dose of 6 mg; Z: Midazolam group; IO: Intraoperative; ICU: Intensive care unit; ASA: American Society of Anesthesiologists; BMI: Body mass index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; RSS: Ramsay Sedation Scale; ETCO2: End tidal carbon dioxide; PACU: Postoperative care unit

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Authors’ contributions
ML and MA designed the study and contributed in writing of the manuscript and implementation of the research. ML was involved in planning and supervised the work. ML and MA processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. MA aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript. All authors have read and approved the final manuscript.
References
Abadi F, Abadi F, Fereidouni Z, Amirkhani M, Karmi S, Najafi Kalyani M (2018) Effect of acupuncture on preoperative cesarean section pain. J Acupunct Meridian Stud 11(6):361–366. https://doi.org/10.1016/j.jams.2018.07.001
Abbasivash R, Salimi S, Ahsan B, Moallemin N, Sane S (2019) The effect of melatonin on anxiety and pain of tourniquet in intravenous regional anesthesia. Adv Biomed Res 8.67. https://doi.org/10.4103/abrar.abrar_16_19
Acil M, Basgil E, Celiker V, Karagöz AH, Demir B, Ayarp U, Acil M, Basgil E, Celiker V, Karagöz AH, Demir B, Ayarp U (2004) Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. Eur J Anaesthesiol 21(7):553–557
Akhalghi F, Azizi S, Malek B, Mahboubi F, Shams S, Karimizadeh M (2020) Effect of preoperative anesthesia consultation on decreasing anxiety in patients undergoing oral and maxillofacial surgery. J Dent (Shiraz) 21(2):102–105. https://doi.org/10.30476/DENTJODS.2019.778830
Amaral FGD, Cipolla-Neto J (2018) A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab 62(4):472–479. https://doi.org/10.20945/2359-3997000000066
Bayrak A, Sagiroglu G, Copuroglu E (2019) Effects of preoperative anxiety on intrathecal hemodynamic and postoperative pain. J Coll Physicians Surg Pak 29(9):868–873. https://doi.org/10.29271/jcppsp.2019.09.868
Bray GA (1992) Pathophysiology of obesity. Am J Clin Nutr 55:488S–494S
Campbell AM, Axon DR, Martin JR, Slack MK, Mollon L, Lee JK (2019) Melatonin for the prevention of postoperative delirium in older adults: a systematic review and meta-analysis. BMC Geriatr 19(1):272. https://doi.org/10.1186/s12877-019-01297-6
Cipolla-Neto J, Amaral FGD (2018) Melatonin as a hormone: new physiological and clinical insights. Endocr Rev 39(6):990–1028. https://doi.org/10.1210/er.2018-00084
Claustreau B, Lenton J (2015) Melatonin: physiological effects in humans. Neurotherapie 61(2-3):77–84. https://doi.org/10.1016/j.neuthi.2015.03.002
Du J, Plas M, Absalom AR, van Leeuwen BL, de Bock GH (2020) The association of preoperative anxiety and depression with neurocognitive disorder following oncological surgery. J Surg Oncol 121(4):676–864. https://doi.org/10.1002/jso.25836
Eccoff L, Palomo J, Stichler JF (2017) Design and testing of a postanesthesia care unit readiness for discharge assessment tool. J Perianesth Nurs 32:389–399
Geoffroy PA, Micoulaud Franchi JA, Lopez R, Schroder CM, membres du consensus Melatonine SFMRM (2019) The use of melatonin in adult psychiatric disorders: expert recommendations by the French Institute of Medical Research on Sleep (SFMRM). Encephale 45(5):413–423. https://doi.org/10.1016/j.encep.2019.04.068
Ghai B, Gandhe RP, Kumar A, Chari P (2005) Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth 15(7):554–559
Gupta R, Santha N, Upadnya M, Manisery JJ (2017) Effect of different dosages of intravenous midazolam premedication on patients undergoing head and neck surgeries- a double blinded randomized controlled study. J Clin Diagn Res 11(8):UC01–UC04. https://doi.org/10.7860/JCDR/2017/26414.10381
Habtemariam S, Daglia M, Sureda A, Selamoglu Z, Gelhan MF, Nabavi SM (2017) Melatonin and respiratory diseases: a review. Curr Top Med Chem 17(4):467–480
Han Y, Wu J, Qin Z, Fu W, Zhao B, Li X, Wang W, Sha T, Sun M, Li J, Zeng Z, Chen Z (2020) Melatonin and its analogues for the prevention of postoperative delirium: a systematic review and meta-analysis. J Pineal Res 68(4):e12644. https://doi.org/10.1111/jpi.12644
Hemmati K, Pourhanifeh MH, Dehshatshian E, Fatemi I, Mehrzadi S, Reiter RJ, Hosseinzadeh A (2020) Melatonin and morphine: potential beneficial effects of co-use. Fundam Clin Pharmacol. https://doi.org/10.1111/fcp.13566
Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Laran R, Russo T, Gravina VR, Arena S, D’Angelo G, Gitti E, Montalto AS, Aliabandi A, Marsiglial, L, Romeo C (2017) Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. Eur J Pediatr 176(7):947–953. https://doi.org/10.1007/s00431-017-2933-9
Jaruzel CB, Gregoski M, Mueller M, Faircloth A, Kelechi T (2019) Aromatherapy for preoperative anxiety: a pilot study. J Perianesth Nurs 34(2):259–264. https://doi.org/10.1016/j.jpen.2018.05.007
Javaherforooshzadeh F, Amirpour I, Jantamrakian F, Soltanazadeh M (2018) Comparison of effects of melatonin and gabapentin on post operative anxiety and pain in lumbar spine surgery: a randomized clinical trial. Anesth Pain Med 8(3):e8673. https://doi.org/10.5812/apam.8673
Karanci AN, Dinik G (2003) Predictors of pre- and postoperative anxiety in emergency surgery patients. J Psychosom Res 55:363–369
Khan MJ, Bamehizry FY, Aqil M, Dammas FA, Fadin A, Khokhar RS (2019) The effect of gabapentin on postoperative pain, morphine sparing effect and preoperative anxiety in patients going for sleeve gastrectomy surgical procedure. J Coll Physicians Surg Pak 29(8):697–701. https://doi.org/10.29271/jcsp.2019.08.697
Khare A, Thada B, Jain N, Singh D, Singh M, Sethi SK (2018) Comparison of effects of oral melatonin with oral alprazolam used as a premedicant in adult patients undergoing various surgical procedures under general anesthesia: a prospective randomized placebo-controlled study. Anesth Essays Res 12(3):657–662. https://doi.org/10.4103/aer.AER_90_18
Kunuroth R, Tej G, Ealla KKR, Kathuroju PK, Ayyagari A, Atlawa AM (2019) Comparative analysis of intravenous midazolam with nasal spray for conscious sedation in minor oral and maxillofacial surgeries. J Pharm Biocl Sci 11(Suppl 1):S42–540. https://doi.org/10.4103/jpbs.JPBS_199_18
Lee TYC, Curtin JP (2020) The effects of melatonin prophylaxis on sensory recovery and postoperative pain following orthognathic surgery: a triple-blind randomized controlled trial and biochemical analysis. Int J Oral Maxillofac Surg 49(4):446–453. https://doi.org/10.1016/j.ijom.2019.07.006
Lumb AB, Latchford GJ, Bekker HL, Hetmanski AR, Thomas CR, Schofield CE (2020) Investigating the causes of postoperative anxiety at induction of anaesthesia: a mixed methods study. J Perioper Pract:1750458920936933. https://doi.org/10.1177/1750458920936933
Makaryus R, Miller TE, Gan TJ (2018) Current concepts of fluid management in enhanced recovery pathways. Br J Anaesth 120(2):376–383. https://doi.org/10.1016/j.bja.2017.10.011
Mathew PJ, Regmi S, Ashok V, Menon P (2020) Current practice of pre-anaesthesia preparation and perioperative parental satisfaction during paediatric ambulatory procedures in a developing country - an observational study. Anesth Crit Care Pain Med52:355–356. https://doi.org/10.1016/j.accpm.2019.10.099
Millet CR, Gooding LF (2018) Comparing active and passive distraction-based music therapy interventions on preoperative anxiety in pediatric patients and their caregivers. J Music Ther 54(4):478. https://doi.org/10.1093/jmt/jmtv014
Nagib M, Samarkandi AH (1999) Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam. Br J Anaesth 82(6):875–880
Niggeman JR, Tichy A, Eberspächer-Schwaed MC, Eberspächer-Schwaed E (2019) Preoperative calming effect of melatonin and its influence on propofol dose for anesthesia induction in healthy dogs. Vet Anaesth Analg 46(5):560–567. https://doi.org/10.1111/vaa.2019.02.009
Oh SN, Myung S-K, Jho HJ (2020) Analgesic efficacy of melatonin: a meta-analysis of randomized, double-blind, placebo-controlled trials. J Clin Med 9(5):1553. https://doi.org/10.3390/jcm9051553
Palmer AC, Souza A, Santos VSD, Cavaleiro JAC, Schuf F, Zuccato AE, Biazus JV, Torres IILDS, Fregni F, Caumo W (2019) The effects of melatonin on the
descending pain inhibitory system and neural plasticity markers in breast cancer patients receiving chemotherapy: randomized, double-blinded, placebo-controlled trial. Front Pharmacol 10:1382. https://doi.org/10.3389/fphar.2019.01382

Procaccini DE, Lobner K, Anton B, Kudchadkar SR (2020) Melatonin use in hospitalized children for non-anesthetic indications: a systematic review. Pharmacotherapy 40(7):692–703. https://doi.org/10.1002/phar.2408

Qiao H, Xie Z, Jia J (2017) Pediatric premedication: a double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine. BMC Anesthesiol 17(1):158. https://doi.org/10.1186/s12871-017-0454-8

Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone-alphadolone. BMJ 2:656–659

Reiter RJ, Rosales-Corral S, Tan DX, Jou MJ, Galano A, Xu B (2017) Melatonin as a mitochondria-targeted antioxidant: one of evolution’s best ideas. Cell Mol Life Sci 74(21):3863–3881. https://doi.org/10.1007/s00018-017-2699-7

Soltani F, Salari A, Javaherforooshzadeh F, Nasajjani N, Kalantari F (2020) The effect of melatonin on reduction in the need for sedative agents and duration of mechanical ventilation in traumatic intracranial hemorrhage patients: a randomized controlled trial. Eur J Trauma Emerg Surg 1–7. https://doi.org/10.1007/s00068-020-01449-3

Stamenkovic DM, Rancic NK, Latas MB, Neskovic V, Rondovic GM, Wu JD, Cattano D (2018) Preoperative anxiety and implications on postoperative recovery: what can we do to change our history. Minerva Anestesiol 84(11):1307–1317. https://doi.org/10.23736/S0375-9393.18.12520-X

WHO expert consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363(9403):157–163

Williamson A, Hoggart B (2005) Pain: a review of three commonly used pain rating scales. J Clin Nurs 14(7):798–804

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