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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 3mg, 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.

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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/m^2, 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 (m^2) (Bray 1992), and obesity grades were defined after the WHO expert consultation (2004) as average (BMI <24.9), overweight (25–<30 kg/m^2), obese (BMI ≥30–<35 kg/m^2), and morbidly obese (BMI ≥35 kg/m^2).

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 IVI). 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% O_2 in air for a tidal volume of 6–8 ml/kg, end-tidal carbon dioxide (ET_{CO2}) of 35–40 mmHg, and inspiration: expiration (I:E) ratio of 1:2. Patients were continuously non-invasively monitored for HR, MAP, SpO_2, and ET_{CO2}. 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, SpO_2, and ET_{CO2} 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

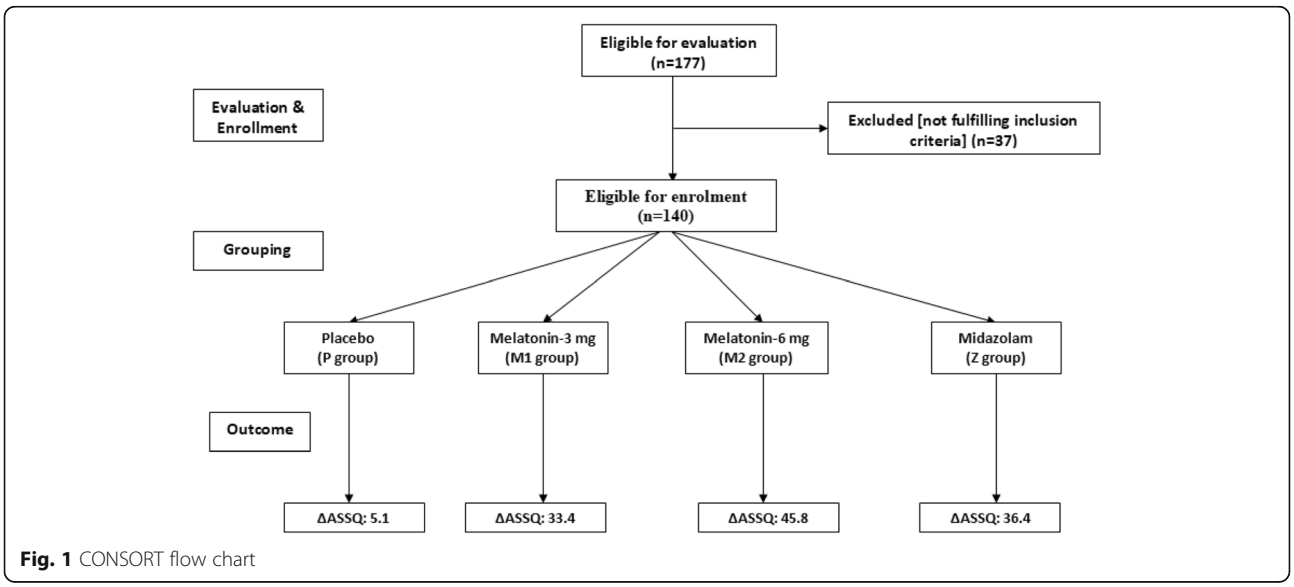

Fig. 1 CONSORT flow chart

rescue analgesia was provided for patients who had NRS score ≥4, as slow intravenous injection of ketorolac tromethamine (Ketolac; amp 30mg/ml; Amryia 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= 1] to very dissatisfied [score=4]

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 α 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,

Table 1 Inclusion data of patients of the four groups

Variables	Groups				*p* value
	P	M1	M2	Z	
Age (years)	46.6±9.3	45±9	47.4±6.6	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%)	
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%)	
High school	11 (31.4%)	8 (22.9%)	13 (37.1%)	8 (22.8%)	
Sec school	4 (11.4%)	5 (14.3%)	2 (5.7%)	7 (20%)	
Illiterate	6 (17.2%)	8 (22.9%)	5 (14.3%)	7 (20%)	
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%)	
Divorced	3 (8.6%)	1 (2.9%)	0	0	
Widow	2 (5.7%)	1 (2.9%)	1 (2.9%)	0	
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	168.8±3.5	168±3.3	0.389
Body mass index (Kg/m^2)	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%)	
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%)	
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%)	
Chest	1 (2.9%)	3 (8.6%)	1 (2.9%)	2 (5.6%)	
Liver	1 (2.9%)	2 (5.6%)	2 (5.7%)	1 (2.9%)	
No	28 (80%)	26 (74.3%)	27 (77.1%)	29 (82.9%)	

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

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, while 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 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	<0.00001	<0.00001	<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	0.646	0.352	0.512	0.32	0.084	0.0017
P3	0.417	0.097	0.0009	0.0117	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

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

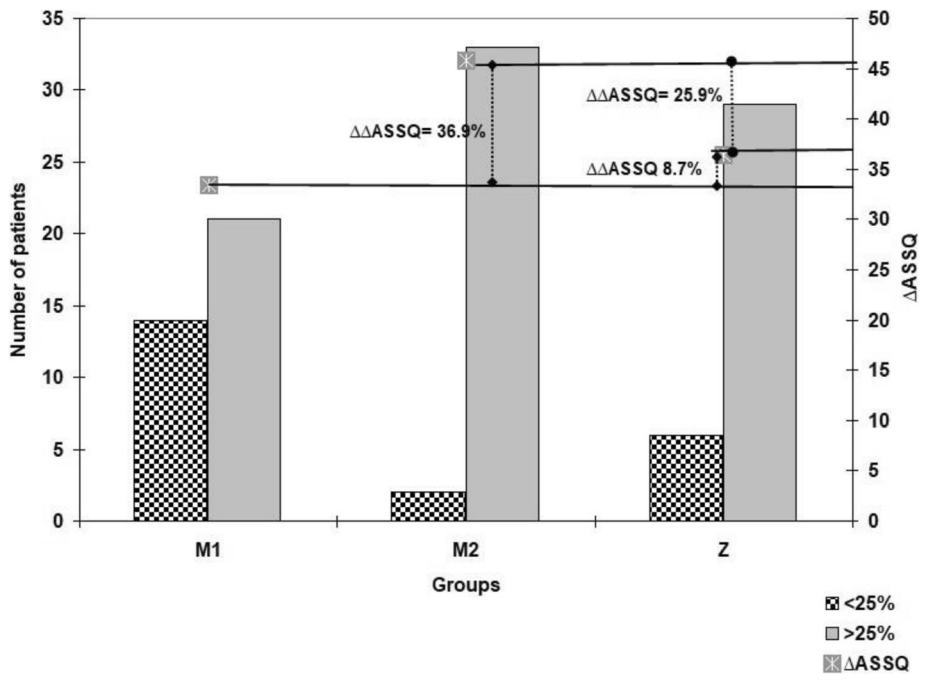

Fig. 2 Percentage of decreased Anxiety Specific to Surgery Questionnaire (ASSQ) score after receiving premedication drugs

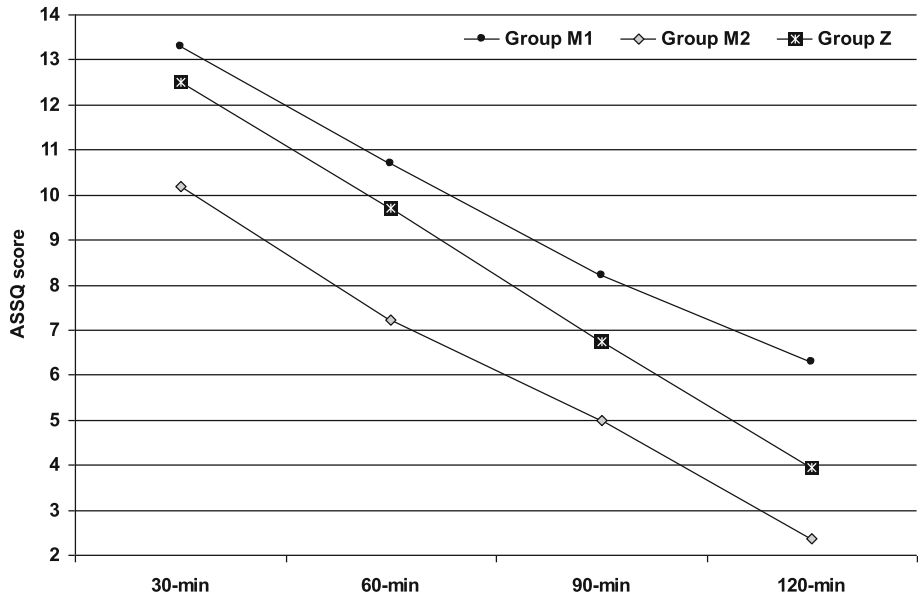

Fig. 3 Mean Anxiety Specific to Surgery Questionnaire (ASSQ) score of patients who received premedication treatment till 120 min

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%)

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

Variables		Group									
		P	M1		M2			Z			
		Score	Score	P1	Score	P1	P2	Score	P1	P2	P3
RSS											
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	P1	Number	P1	P2	Number	P1	P2	P3
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%)			
PO pain data											
No. of requests of analgesia	0	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

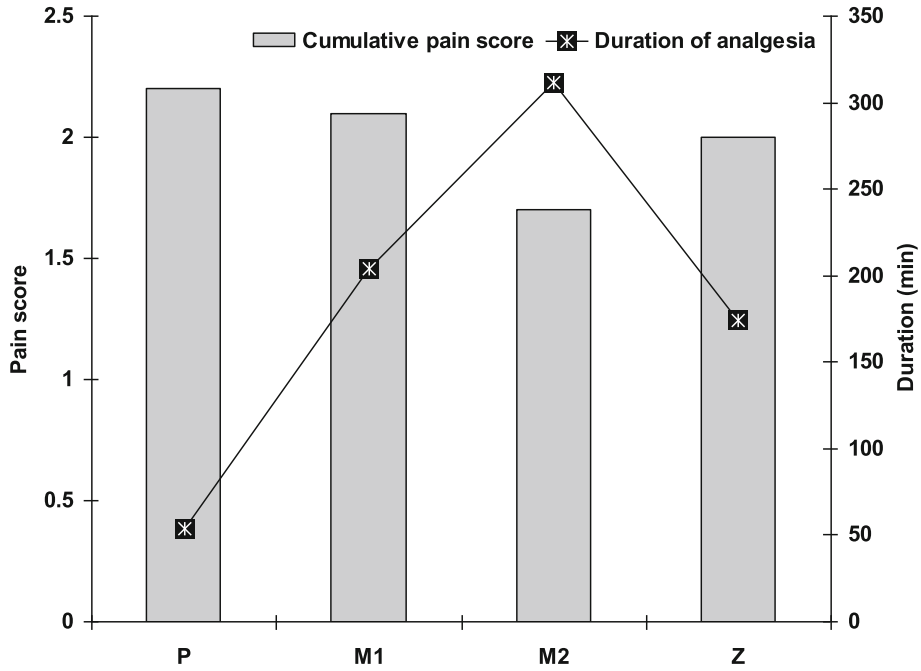

Fig. 4 Postoperative pain data of patients of studied groups

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

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 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, *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 Kunusoth 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 ΔΔASSQ 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 perioperative 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 ΔNRS 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; ET_{CO2}: 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

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Availability of data and materials
The datasets used and analyzed during this study are available from the corresponding author for 6 months after approval for publication.

Declarations

Ethics approval and consent to participate
This study was approved by Tanta University's Institutional Review Board (33858/6/20), and written informed consent was obtained from all subjects participating in the trial.

Consent for publication
Not applicable.

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

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