ORIGINAL CLINICAL RESEARCH

The Role of Preoperative Melatonin in Reducing the Inhaled Isoflurane Requirements in Open Nephrectomy: A Randomized Controlled Study

Amany Saleh [1], Hadir Mamdouh [1*], Hala Goma [1], Karim Mourad [1]

Abstract

Background: Melatonin has recently been used as a premedication to reduce postoperative pain. This study aimed to assess the effect of melatonin on reducing the intraoperative inhaled isoflurane requirements in patients undergoing open nephrectomy.

Methods: This randomized, double-blinded, clinical trial enrolled 30 patients, aged between 20-60 years undergoing open nephrectomy under general anesthesia. They were randomly allocated into two groups. Group melatonin (M) (n=15) received oral melatonin tablet 5 mg and control group C (n=15) received sugar-coated tablets one hour before surgery. Inhaled isoflurane requirements, total intraoperative fentanyl consumption, Numerical Rating Scale (NRS) and Ramsay Sedation Scale at 1, 2, 4, 6, 12, 18, and 24 hours, total postoperative morphine, and first analgesic request were recorded.

Results: Total intraoperative isoflurane consumption was significantly lower in M group than C group (28.75±1.48 vs. 42±1.86 ml, p<0.001). Total intraoperative fentanyl consumption was significantly lower in M group than C group (150.6748.06 vs. 186.67±38.48 µg, p=0.031). Postoperative NRS was significantly lower in M group than C group at 2, 4, 6, and 12 hours. Total postoperative morphine consumption was lower in M group. Time to first analgesic request was significantly delayed in melatonin group.

Conclusion: Using state and response entropy for monitoring the depth of anesthesia and inhalational anesthetic requirements, premedication with 5 mg melatonin orally one hour before surgery seems to be effective in decreasing intraoperative isoflurane consumption. Melatonin also decreased pain scores and postoperative morphine consumption with almost no undesirable effects during open nephrectomy surgery.

Keywords: Isoflurane Consumption; Melatonin; Premedication; Response Entropy; State Entropy.

[1] Department of Anesthesia, Surgical Intensive Care, and Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt

* **Mailing address of the corresponding author**: Hadir M. Mamdouh, Department of Anesthesia, Surgical Intensive Care, and Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; hadir.mamdouh@gmx.com

Introduction

The pineal gland in the brain produces the hormone melatonin. Melatonin performs a variety of bodily tasks, but it is best known for preserving the circadian rhythm, which is managed by the suprachiasmatic nuclei (SCN), a biological clock located in the hypothalamus. The SCN in the hypothalamus contains receptors or nerve terminals to which melatonin can bind. The sites of binding are the melatonin receptors 1 and 2, also known as MT1 and MT2, respectively.[1, 2]

To have a good night's rest, melatonin can be taken as a natural or artificial supplement. In addition to helping those with insomnia, melatonin can help people with jet lag and to avoid disruptions in their sleep and awakening cycles. Moreover, it can be used to treat cancer, headaches and Alzheimer disease.[3] Melatonin is also a sedative, hypnotic, and analgesic drug.[4]

Melatonin has recently been utilized as a premedication to lower postoperative pain scores in patients having radical prostatectomy, although its impact on the need for intraoperative inhalational anesthetics has not yet been studied.[5]

Entropy can be used in adults or children older than two years to monitor the electrical condition of the brain during an operation to determine the depth of anesthesia and the need for inhalational anesthetics. State entropy and response entropy can be used to monitor an anesthetic agent's effects in adults. This will allow the anesthetist to titrate the anesthetic agent to each patient's unique needs. Entropy parameters are also utilized to decrease the amount of anesthetic drug needed, which speeds up anesthesia recovery.[6]

The aim of the current study was to assess the safety and efficacy of premedication with 5 mg oral melatonin on reducing the requirements of intraoperative inhaled isoflurane in adult patients undergoing open nephrectomy under general anesthesia.

Materials And Methods

Ethical considerations

This study was approved by our institutional ethical committee (Cairo University Faculty of Medicine Research Ethics Committee (ID: MD-249-2020) and was registered in the ClinicalTrial.gov (ID: NCT04959825).

Study design and setting

This randomized, double-blinded, parallel-group, controlled clinical trial was

conducted at the Urosurgery operating theatre, Kasr Al Aini Hospital, Egypt.

Eligibility criteria

Thirty patients aged 20-60 years scheduled for open nephrectomy under general anesthesia with American Society of Anesthesiologists (ASA) I and II and body mass index 20 to 25 kg/m^2 were included in the study. Patients with uncontrolled hypertension, patients presenting with (ischemic heart disease, significant arrhythmias, heart failure, renal failure, liver failure), malignancies, history of epileptic seizures, psychoactive medications, neurological disorders, trauma, advanced respiratory disease and pregnancy were excluded from the study.

Randomization

A computer-generated, random list was used to assign patients to research groups, and the group assignments were then sealed in consecutively numbered opaque envelopes. The tablets were given by a person who is not one of the researchers to achieve double-blinded design.

Procedures and interventions

History was taken from all patients (previous medical history, anesthetic history, medications, and dentation). Preoperative laboratory investigations as complete blood picture, coagulation profile, liver enzymes, renal functions, and fasting blood sugar were checked. Other investigations were ordered on demand. Airway assessment was performed. Informed consent also was taken.

Patients were randomized into two groups (15 in each group). Melatonin group (group M) received melatonin as a premedication, one hour before surgery, in a dose 5 mg and Control group (group C) received sugar-coated tablet.

In the operating theatre, a peripheral 18 G cannula was inserted, and volume of crystalloids 10 ml/kg was given over 20 minutes. Standard monitoring (Electrocardiogram, non-invasive blood pressure, pulse oximetry) were attached to each patient. Baseline readings (blood pressure, heart rate, oxygen saturation) were recorded.

Induction of anesthesia was done with fentanyl (2 µg/kg), propofol (1.5-2.5 mg/kg) and atracurium (0.5 mg/kg) and then the patient was intubated and ventilated with tidal volume 6 ml/kg and respiratory rate 12 breaths/min and was readjusted according to end-tidal carbon dioxide (maintained around

35) on 60% oxygen-air and fresh gas flow 2 L. Recordings of blood pressure, heart rate, oxygen saturation were taken immediately after intubation and then every 15 minutes till end of surgery. The entropy sensor was attached on the patient's forehead according to the instructions provided on the sensor pouch.

Anesthesia was maintained with isoflurane according to entropy readings and atracurium 0.1 mg/kg every 20 minutes. Inhaled isoflurane requirement (volume %) was titrated to maintain state entropy and response entropy readings 40-60 measured using GE care station 650-crescent pulse anesthesia machine (GE HealthCare, Chicago, Illinois, USA).[6]

Intraoperative analgesia used was (Fentanyl 2 µg/kg) with top up dose 50 µg was given if blood pressure and heart rate increase more than 30% of baseline. At the end of the surgery, muscle relaxant was reversed with neostigmine (0.05 mg/kg) added to atropine (0.02 mg/kg) and patient was extubated and transferred to the post anesthesia care unit after full recovery. Pain was assessed using Numerical Rating Scale (NRS) at the end of the first hour then at 2, 4, 6, 12, 18, 24 hours postoperative after transferring the patient to the department.[7] Pain was assessed using NRS as follows: 0 no pain,10 severe pain. Postoperative pain was managed as follows: In case of mild pain, paracetamol 1 gm with ketorolac 30 mg were given intravenously; in case of moderate pain, morphine was given in dose 0.02 mg/kg intravenously till NRS < 4; and in case of severe pain, morphine was given in dose 0.02 mg/kg iv and then bolus after 10 minutes till NRS < 4. Sedation also was assessed at the end of first hour then at 2, 4, 6, 12, 18, 24 hours postoperative using Ramsay sedation score.[8]

Study outcomes

Our primary outcome was inhaled isoflurane requirements (ml) to maintain entropy reading between 40-60. Using the equation FGFx % volume x0.05x time interval. Our secondary outcomes were total intraoperative fentanyl consumption (ug), intraoperative hemodynamics, NRS 1, 2, 4, 6, 12, 18, and 24 hours, total postoperative morphine consumption (mg), Ramsay sedation score at 1, 2, 4, 6, 12, 18, and 24 hours, first time of rescue analgesics and complications as nausea and vomiting.

Sample size

Power analysis was performed using G power program on the level of intraoperative isoflurane requirement (ml) for

independent samples using student t test because it is the main outcome variable in the present study. We performed a pilot study on 9 patient which revealed that the mean ± standard deviation isoflurane consumption (ml) in control group (n=4) was 1.1 (0.25) versus 0.85 (0.15) for melatonin group (n=5). For a power of 0.8 and an alpha error of 0.05, a minimum sample size of 12 patients is calculated for each group. A sample size was increased to 15 in each group to compensate for drop out.

Statistical analysis

The SPSS v26 statistical analysis program was used (IBM Inc., Chicago, IL, USA). Unpaired student t-test was used to evaluate quantitative parametric data that we reported as mean and standard deviation. Median and range were used to present and analyze quantitative non-parametric data. When appropriate, the Fisher's exact test or the Chi-square test was used to assess qualitative variables, which were reported as frequency and percentage (%). Statistical significance was defined as $P<0.05$.

Results

In this study, 67 patients were assessed for eligibility, 22 patients did not meet the criteria and 15 patients refused to participate in the study. The remaining 30 patients were randomly allocated into two groups (15 patients in each). All patients (30) were followed up and analyzed statistically (Figure 1). Demographic data were not significantly different between the two groups (Table 1). Intraoperative mean arterial pressure and heart rate were not different between the two groups (Figures 2 and 3). Intraoperative isoflurane requirements were significantly lower in melatonin group compared to control group at all time measurements (Table 2). Total intraoperative fentanyl requirements were significantly lower in melatonin group compared to control group (Table 3). Postoperative NRS was significantly lower in melatonin group compared to control group at 2, 4, 6, and 12 hours postoperatively (Table 4). Time to first analgesic request was significantly delayed in melatonin group compared to control group (Figure 4). Total morphine consumption was significantly lower in melatonin group compared to control group (Table 3). Ramsay sedation scale was not different between both groups (Table 5). The incidence of complications was not different between both groups (Table 6).

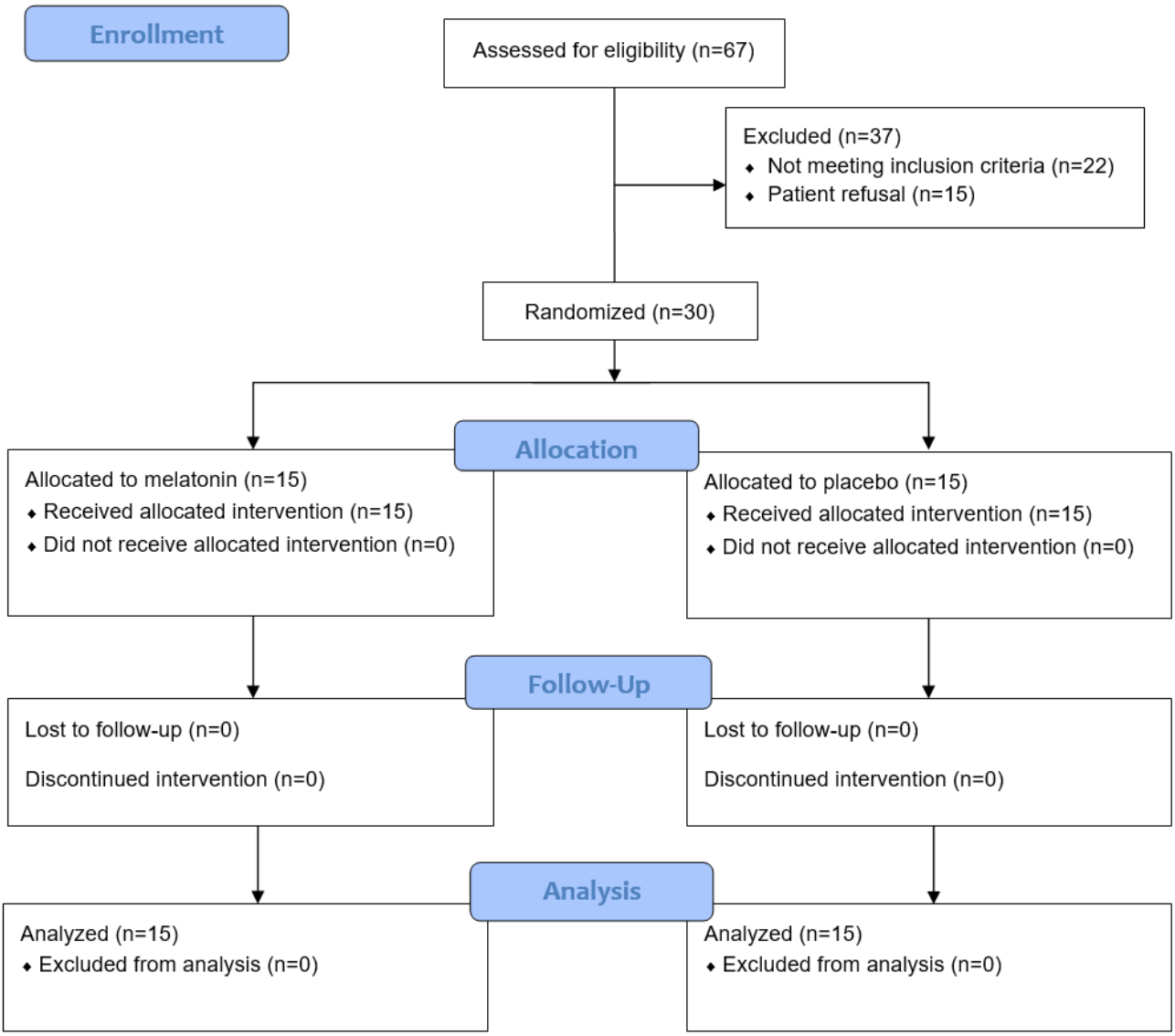

Figure 1. CONSORT flow chart

Table 1. Demographic data of the studied groups

Variable		Control group (n=15)	Melatonin group (n=15)	P-value
Age (years)		40.73 ± 10.33	46.13 ± 8.97	0.138
BMI (kg/m^2)		21.87 ± 0.92	22.2 ± 0.75	0.285
ASA physical status	I	13 (86.67%)	8 (53.33%)	0.109
	II	2 (13.33%)	7 (46.67%)	
Sex	Male	11 (73.33%)	10 (66.67%)	1
	Female	4 (26.67%)	5 (33.33%)	

BMI: Body mass index, ASA: American Society of Anesthesiologists; n: number; SD: standard deviation.

Data was presented as mean ± SD or n (%)

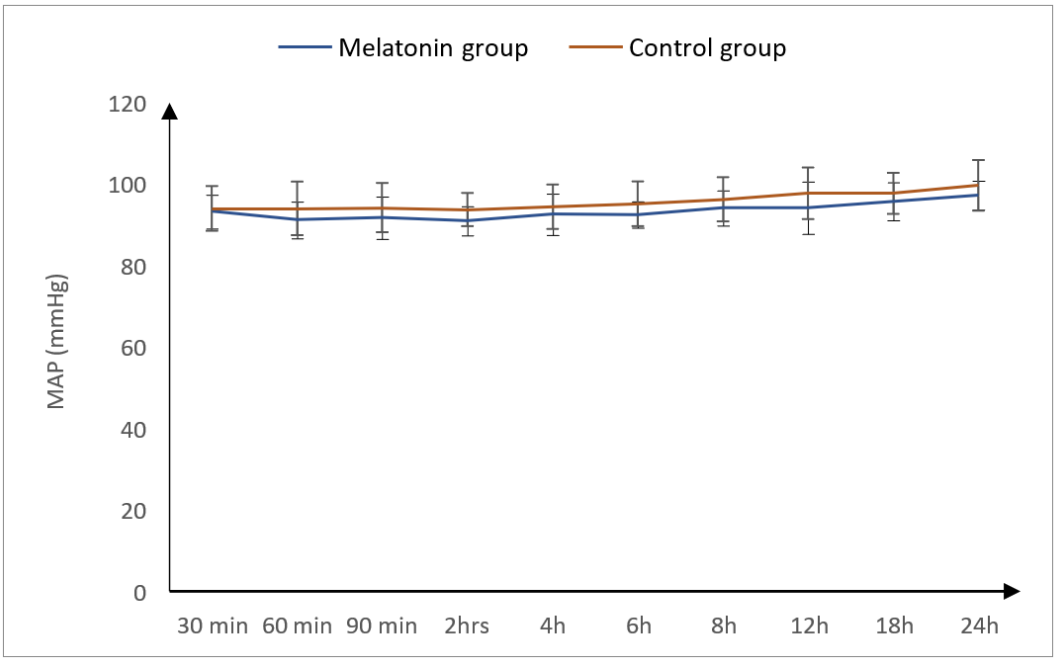

Figure 2. Intraoperative mean arterial pressure (MAP) in both groups

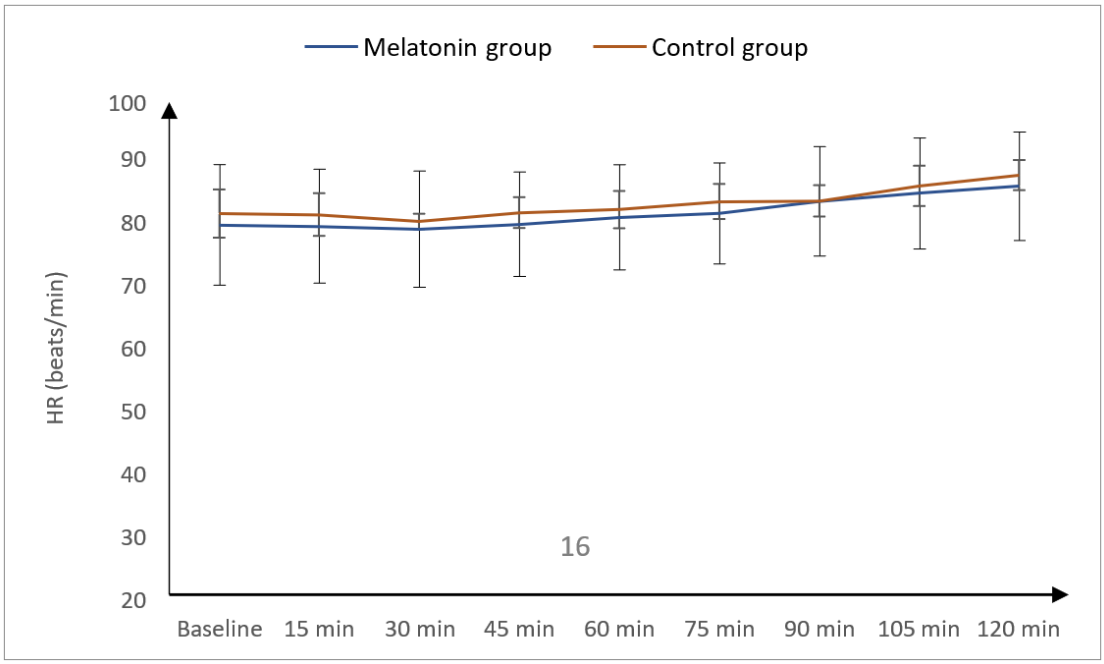

Figure 3. Intraoperative Heart rate (HR) in both groups

Table 2. Intraoperative isoflurane requirements in both groups

Variable	Control group (n=15)	Melatonin group (n=15)	P-value
Baseline	0 ± 0	0 ± 0	---
15 min	1.19 ± 0.04	0.88 ± 0.1	<0.001
30 min	1.53 ± 0.22	0.97 ± 0.16	<0.001
45 min	1.6 ± 0.21	0.94 ± 0.14	<0.001
60 min	1.5 ± 0	0.95 ± 0.17	<0.001
75 min	1.51 ± 0.17	1 ± 0.17	<0.001
90 min	1.45 ± 0.12	0.95 ± 0.2	<0.001
105 min	1.24 ± 0.11	0.95 ± 0.16	<0.001
120 min	1.19 ± 0.04	1.03 ± 0.22	0.009

n: number

Data was presented as mean ± standard deviation

Table 3. Total intraoperative isoflurane and fentanyl requirements and total postoperative morphine consumption in both groups

Variable	Control group (n=15)	Melatonin group (n=15)	P-value
Total intraoperative isoflurane (ml)	42 ± 1.86	28.75 ± 1.48	<0.001
Isoflurane requirements (ml/min)	0.35 ± 0.02	0.24 ± 0.01	<0.001
Total intraoperative fentanyl requirements (µg)	186.67 ± 38.48	150.67 ± 48.06	0.031
Total postoperative morphine consumption (mg)	29.34 ± 1.82	9.82 ± 4.07	<0.001

n: number

Data was presented as mean ± standard deviation

Table 4. Postoperative NRS in both groups

Variable	Control group (n=15)	Melatonin group (n=15)	P-value
1 h	3.2 ± 1.2	2.6 ± 1.3	0.390
2 h	4 ± 1	2.6 ± 0.8	<0.001
4 h	3.7 ± 1.3	1.7 ± 0.6	<0.001
6 h	3.6 ± 1.3	1.5 ± 0.5	<0.001
12 h	3.5 ± 0.8	1.3 ± 0.5	<0.001
18 h	2 ± 0.8	2.7 ± 0.5	0.597
24 h	2.1 ± 1.0	2 ± 1.1	0.394

n: number

Data was presented as mean ± standard deviation

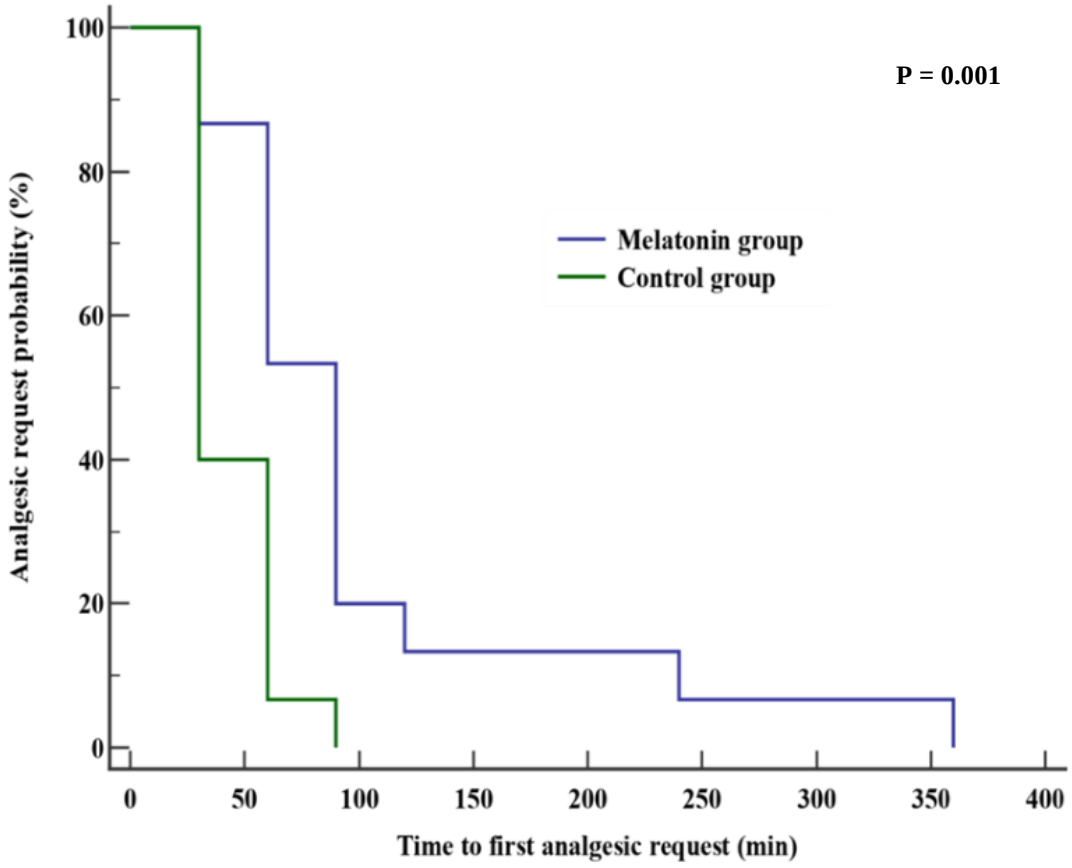

Figure 4. Kaplan Meier curve for first analgesic request in both groups.

Table 5. Ramsay sedation scale in both groups

Variable	Control group (n=15)	Melatonin group (n=15)	P-value
1 h	2 (1.5 - 2)	2 (1 - 2)	0.718
2 h	2 (2 - 2)	2 (1 - 2)	0.317
4 h	2 (2 - 2)	2 (1.5 - 2)	1.00
6 h	2 (2-2)	2 (2-2)	1.00
12 h	2 (2-2)	2 (1-2)	1.00
18 h	2 (2 - 2)	2 (2 - 2)	1.00
24 h	2 (2 - 2)	2 (1 - 2)	1.00

n: number

Data were presented as medians and ranges

Table 6. Complications in both groups

Variable	Melatonin group (n=15)	Control group (n=15)	P-value
Headache, dizziness	1 (6.67%)	3 (20%)	0.598
Nausea, vomiting	1 (6.67%)	4 (26.67%)	0.33
Irritability, abdominal cramps	0 (0%)	4 (26.67%)	0.1

n: number

Data was presented as n (%

Discussion

One of the most upsetting side effects of general anesthesia is awareness for both the patient and the anesthetist. Even with seemingly effective anesthetic care' awareness during anesthesia is possible and typically has nothing to do with pain. However, in a small number of cases, the agony may be unbearable and there may be long term neuropsychiatric effects, such as posttraumatic stress disorder. This unfavorable incident may potentially have significant medical and legal ramifications. The use of premedicants, avoiding the use of muscle relaxants when possible, and using intraoperative monitors to obtain the depth of anesthesia such as BIS or entropy in addition to intraoperative routine monitoring are some strategies that can prevent awareness under anesthesia. It is advised that all adult patients receiving general anesthesia are monitored with entropy.[9]

The pineal gland normally produces and releases the hormone melatonin into the blood. It is also known as sleep hormone as it regulates the circadian rhythm and the sleep wake cycle. Based on its hypnotic, analgesic and anti-inflammatory role melatonin was previously used as an effective alternative premedication.[10, 11]

This study assessed the effect of melatonin as a premedicant on the intraoperative isoflurane requirement. Patients in the melatonin group were given 5mg melatonin one hour before surgery and the control group was given sugar-coated tablet and entropy was used as an intraoperative monitor to assess depth of anesthesia and to titrate accurately the intraoperative isoflurane requirement. The effect of melatonin on intraoperative inhalational anesthetic requirement has not been studied before which makes comparing our results with others somehow difficult.

To the best of our knowledge, this was the first study that assessed the effect of melatonin on the intraoperative inhalational requirements and its role in preventing intraoperative awareness.

Our study revealed that intraoperative isoflurane requirements in patients who received melatonin was significantly lower than the control group at all time measurements.

An important finding was that the postoperative NRS was significantly low in the melatonin group compared to the control group at 2, 4, 6, and 12 hours and 24-hour

postoperative morphine consumption was significantly lower in the melatonin group.

There are many reported studies for the use of melatonin as a premedication and its effect on postoperative pain score as assessed by NRS and visual analogue scale after general or regional anesthesia.[10, 12] The potential analgesic effect of melatonin that we observed is supported by previous studies that have shown that melatonin has an antinociceptive effect and may increase the level of B endorphins and could activate MT2 melatonin receptors in the dorsal horn of the spinal cord; also the analgesic effect may be linked to G(i)- coupled melatonin receptors, to G(i) coupled opioid μ receptors or GABA-B receptors with unknown downstream changes with a sequential reduction in anxiety and pain.[12] Inhibition of the COX-2 and iNOS enzymes, activation of NF-kB, and inhibition of neutrophil infiltration are other potential mechanisms for melatonin's anti-inflammatory actions.[13]

Our results go in line with a study done by Laosuwan et al. which revealed that melatonin reduces postoperative pain in patients undergoing abdominal hysterectomy. Postoperative visual analogue score was lower in melatonin group. Also, morphine requirement was reduced in the melatonin group.[14] These results are in accordance with our study where postoperative NRS was significantly lower in the melatonin group.

Also, similar to our findings, Dubey et.al. showed that melatonin administration resulted in significant reduction in fentanyl consumption in patients undergoing laparoscopic cholecystectomy.[15] Similarly, Borazan et al. and Caumo et al. reported significant reduction in total tramadol and morphine consumption in the postoperative period in patients who received melatonin.[5, 16] Ismail et al. also observed analgesic role of melatonin in cataract surgeries.[17] On the other hand, there have also been some results that were inconclusive and failed to show any impact on pain scores or ability to spare opioids in patients who received melatonin.

Patients in the Naguib and Samarkandi study were given a single dose of oral 5-mg melatonin 100 minutes prior to laparoscopic gynecologic surgery, and the authors reported that melatonin had no effect on the postoperative pain scores at 15, 30, 60, or 90 minutes after surgery or on the amount of postoperative analgesics consumed during the first 90 minutes following surgery. According to that study, the contradictory results could be due to the difference in the types of surgery, short postoperative follow-

up intervals, and the timing of melatonin administration.[18]

In our study, postoperative morphine requirement was significantly lower in the melatonin group compared to the control group. Similar to our findings, Laflı Tunay et al. reported a decrease in analgesia consumption approximately 180–200 min after melatonin administration, which may correspond with the time when they reached their peak plasma levels after giving 6mg preoperative melatonin to adults undergoing abdominal surgery.[19]

In agreement to our study, Yildiz et al. had the similar findings of no significant difference in heart rate after oral administration of melatonin. Mean arterial blood pressure also did not change significantly after oral administration of melatonin.[20] The reason may be that melatonin is a hormone that is secreted by the pineal gland to regulate sleep and its inhibitory action is limited to central nervous system; this may allow the stability of hemodynamics especially during stress response.

Our findings regarding sedation revealed that there was no statistical difference between both groups. In contrast to our finding, melatonin effect on perioperative anxiolysis was studied by Ionescu et al. who compared melatonin intake to midazolam in patients undergoing laparoscopic cholecystectomy. In the melatonin group, 3 mg melatonin was given one night before surgery. Postoperative anxiety score was significantly lower in the melatonin group at every time interval with significant P value < 0.05.[21] Also, Dubey et al. assessed the sedation 30 min and 60 min after administration of morning dose of melatonin and revealed more sedation score in melatonin group than placebo.[15] Other studies also observed the sedative effect of oral melatonin.[5, 18] Those results were inconsistent to our study and may be due to the timing of melatonin administration.

Limitations

Our study has some limitations such as small sample size, the dose of melatonin and time interval for administration and lack of preoperative sedation assessment. Further studies are recommended at higher doses of melatonin given at different time intervals. Also, further studies are needed to evaluate the effect of melatonin on intraoperative isoflurane consumption and the intraoperative awareness.

Conclusion

Using state and response entropies for monitoring the depth of anesthesia and

inhalational anesthetic requirements, premedication with 5 mg melatonin orally one hour before surgery seems to be effective in decreasing intraoperative isoflurane consumption. Melatonin also decreased pain scores and postoperative morphine consumption with almost no undesirable effects during open nephrectomy surgery.

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None.

Conflict of interest

The authors declare no competing interests.

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