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Effect of Melatonin on Postoperative Pain after Simple Nephrectomy: A Randomized Double-Blinded Controlled Study

Karim Hussein Mourad Ghaleb *, Kiroulus Ghaly Nady, Sahar Ali Mohamed Marzouk, Amany Hassan Saleh
Anesthesia and Critical Care Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt
*** Corresponding Author:** Karim Hussein Mourad, **E-mail:** karim.ghaleb87@gmail.com, **Phone:** 01007451161

ABSTRACT

Introduction: Simple nephrectomy (SN) refers to resecting the kidney enveloped by Gerota's fascia. However, SN is associated with moderate to severe postoperative pain. This pain is not always adequately controlled with opioids and they are associated with side effects such as sedation, nausea, pruritus, vomiting and constipation. Melatonin is a hormone produced by pineal gland within brain. Recent research has highlighted multiple advantages of its perioperative administration, such as enhanced postoperative recovery quality, alleviation of depressive symptoms, and decreased pain scores.

Aim: To assess the effectiveness of melatonin in controlling postoperative pain after SN.

Patients and Methods: This randomized, double-blind, controlled study enrolled 45patients scheduled for SN. Participants were randomly allocated into two groups: Group **M** (n=20) which received 4 mg of prolonged-release oral melatonin at 8 PM the evening prior to surgery and again two hours before procedure, and group **C**(n=20) which received placebo tablets. Postoperative pain was evaluated using VAS score at different time points. Additionally, first analgesic request time, anxiety scores, total analgesic consumption during first 24 hours, case satisfaction and incidence of adverse effects were documented.

Results: VAS scores at 2 and 4 hours postoperatively were lower in Group M, with statistical significance noted at both intervals (P=0.004 and P=0.03 respectively). The duration for first rescue analgesia was markedly prolonged in Group M (P< 0.001), and total morphine consumption within first 24 hours was substantially reduced in this group (P< 0.001).

Conclusion: Melatonin administration in cases undergoing SN was associated with a longer time to first rescue analgesia request, reduction in total morphine consumption, and lower anxiety levels.

Keywords: Melatonin, Simple Nephrectomy, Postoperative Analgesia.

INTRODUCTION

Simple nephrectomy (SN) entails excision of the kidney enclosed within Gerota's fascia. This procedure is indicated for benign renal conditions leading to a poorly functioning or nonfunctioning kidney, including obstruction, chronic infection, or calculus-related disease [1]. Nonetheless, SN frequently results in moderate to severe pain during early postoperative period. Standard strategies for postoperative analgesia encompass systemic opioid use, administered either through intravenous patient-controlled analgesia (IV PCA) or by means of an epidural catheter [2].

Pain is not always adequately controlled with opioids, even when moderate to large doses of morphine are used. Furthermore, opioids use is frequently accompanied by side effects, including postoperative nausea and vomiting (PONV), sedation, constipation, and pruritus [3]. Consequently, there is growing interest in investigating alternative analgesic strategies that offer effective pain control while reducing incidence of adverse effects [4].

Melatonin, or N-acetyl-5-methoxytryptamine, is a hormone secreted by pineal gland in brain [5]. Light serves as the principal regulator of melatonin synthesis. Melatonin exerts significant biological effects and is pivotal in modulating sleep–wake cycle. [6] Beyond its role in stabilizing circadian rhythms, exogenous melatonin has been examined for its potential impacts on blood pressure regulation, thermoregulation, modulation of cortisol levels, enhancement of immune responses, and reinforcement of antioxidant defense [7].

Recent investigations have revealed multiple benefits of administering short-acting melatonin perioperatively across diverse case populations, including enhanced postoperative recovery quality, mitigation of depressive symptoms, and reduced pain scores [8]. The precise mechanisms underlying melatonin's analgesic properties remain incompletely elucidated. Nonetheless, β-endorphins, opioid receptors, gamma-aminobutyric acid (GABA) receptors, and nitric oxide–arginine pathway within brain are thought to contribute to its analgesic effects [9,10].

A previous study demonstrated that melatonin reduced postoperative pain following abdominal hysterectomy while avoiding side effects associated with opioid use [11]. However, the melatonin analgesic effect in perioperative period remains controversial and warrants further investigation [12]. There is a paucity of literature evaluating role of melatonin in managing postoperative pain in cases undergoing SN. Therefore, this investigation assesses melatonin effectiveness in managing postoperative pain in cases undergoing SN.

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PATIENTS AND METHODS

Between March and June 2025, this randomized, double-blind, controlled investigation enrolled 40 cases scheduled for SN at Cairo University Hospitals.

Eligibility criteria:

Cases undergoing SN, aged 18 to 65 years, of either sex, and classified as American Society of Anesthesiologists (ASA) physical status I or II were enrolled. Cases were excluded if they declined participation; had a documented melatonin allergy; were on medications possessing analgesic or sedative effects; exhibited a body mass index (BMI) exceeding 40 kg/m²; or had a history of alcohol or substance abuse, cardiovascular disease, renal failure, or cognitive impairment.

Randomization and blindness:

Through an online randomization tool (http://www.randomizer.org), a randomization sequence was created, with each case's assignment concealed in a sealed opaque, envelope. Participants were randomly allocated in a 1:1 ratio to two parallel groups: **Group M (n = 20):** Cases received 4 mg of prolonged-release oral melatonin at 8 PM, night before procedure and another dose two hours before surgery. **Group C (n = 20):** Cases were administered sugar-coated placebo tablets at 8 PM on the evening preceding the procedure and an additional dose two hours prior to surgery.

Cases and assessors were blinded. Medications were prepared by an independent pharmacist.

METHODS

a) Preoperative:

The medical and surgical histories of cases were recorded, followed by clinical examinations. Routine laboratory investigations, including complete blood count (CBC), coagulation studies, renal function tests, and liver function tests, were performed.

One day prior to surgery, all cases were assessed by same anesthesia resident, who explained procedure, obtained informed consent, and instructed cases on using visual analog scale (VAS) [13] (0 = no pain; 10 = worst pain) to rate postoperative pain and report anxiety levels.

b) Intraoperative:

Cases were connected to standard monitors—electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximetry, temperature probe, and capnography (initiated post-induction). General anesthesia was initiated through a 20G intravenous (IV) cannula using IV fentanyl (2 µg/kg) and IV propofol (2–2.5 mg/kg). Subsequently, IV atracurium (0.5 mg/kg) was administered to enable endotracheal intubation.

Anesthesia was maintained with isoflurane (1–1.5%) in 50–100% oxygen. Incremental doses of IV atracurium at 0.1 mg/kg were administered every 20 minutes. Cases were mechanically ventilated, with end-tidal carbon dioxide (CO_2) maintained between 35–45 mmHg. If heart rate (HR) or mean arterial pressure (MAP) rose more than 20% above baseline, and other potential causes were excluded, additional IV fentanyl boluses (1 µg/kg) were administered. At the end of surgery, inhalational anesthetics were discontinued, and cases were observed until they regained motor power and consciousness. Reversal of neuromuscular blockade was then achieved with IV neostigmine at 0.03–0.07 mg/kg and atropine at 0.02 mg/kg.

c) Postoperative:

A standardized postoperative analgesic protocol was implemented, with all cases receiving paracetamol 1 g every six hours as routine analgesia. Rescue analgesia with IV morphine was administered as a 3 mg bolus if VAS score exceeded 3, and repeated every 30 minutes if pain persisted until VAS score was reduced to below 3. VAS scores were assessed at 0, 2, 4, 6, 8, 12, 18, and 24 hours postoperatively.

Adverse effects were monitored: hypotension (>20% drop in mean arterial pressure) was managed with IV fluids; bradycardia (HR <60 bpm) with IV atropine (0.02 mg/kg); respiratory depression (SpO_2 <92% requiring oxygen) was documented; and PONV was treated with 4 mg ondansetron every 6 hours as needed.

Level of anxiety was assessed using the Amsterdam Preoperative Anxiety and Information Scale (APAIS) Thai version.[14] Anxiety score ranged from 4- 20 (anxiety score >13 is possible to high level of anxiety).

Study outcomes

The primary outcome was VAS score at 2 hours postoperatively. Secondary outcomes comprised total morphine consumption within first 24 hours, time to initial rescue analgesia, intraoperative and postoperative hemodynamic measurements, anxiety scores, case satisfaction, and incidence of adverse events.

Sample size

Sample size determination was conducted utilizing G*Power 3.1.9.2 (Universität Kiel, Germany). A preliminary pilot study comprising 5 cases per group revealed mean VAS scores of 2.2 ± 1.30 in Group M and 3.8 ± 1.92 in controls. Using these results, an effect size of 0.976 was determined. With a confidence level of 95%, statistical power of 80%, and a 1:1 allocation ratio, plus an additional two cases per group to account for potential dropouts, 20 participants were recruited into each group.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Cairo University (Approval ID: MS-31-2025). The study was registered

at ClinicalTrials.gov (ID: NCT06872944). All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analysis was executed using SPSS version 27 (IBM, Armonk, NY, USA). Through Shapiro-Wilk test normality of distribution was evaluated in conjunction with histogram visualization. Non-parametric quantitative data were expressed as median and interquartile range (IQR) and analyzed using Mann-Whitney test, whereas parametric quantitative variables were presented as mean ± standard deviation (SD) and assessed with unpaired Student's t-test. Qualitative variables were expressed as frequencies and percentages, with intergroup comparisons carried out using either Fisher's exact test or Chi-square test, depending on applicability. Significance was defined as P value less than 0.05.

RESULTS

A total of 51 cases were evaluated for eligibility in this investigation; 7 did not fulfill inclusion criteria, and 4 declined their participation. The remaining individuals were randomized into two equal groups. All enrolled participants completed follow-up period and were incorporated into statistical analysis.

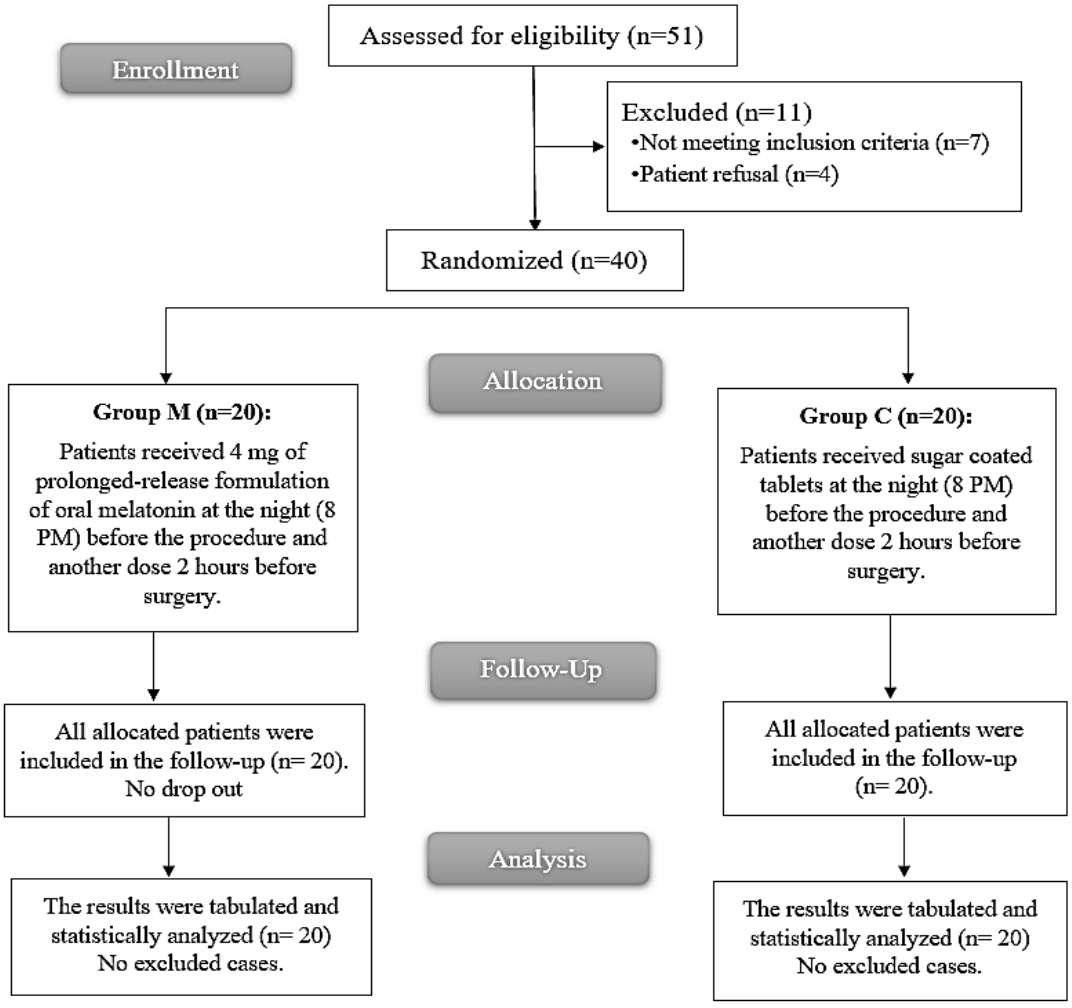

Fig 1: CONSORT flowchart of enrolled cases.

BMI, ASA physical status, height, weight, age, sex, and surgery duration showed no substantial variations between groups (**Table 1)**.

Table 1: Demographic characteristics and operative duration of studied groups

		Group M (n=20)	Group C (n=20)	P value
Age (years)	**Mean ± SD**	44.15 ± 9.14	46.2 ± 12.44	0.4009
	Range	27 - 63	24 - 65	
Sex	**Male**	11 (55%)	8 (40%)	0.342
	Female	9 (45%)	12 (60%)	
Weight (kg)	**Mean ± SD**	72.25 ± 9.34	75.9 ± 7.15	0.173
	Range	59 - 91	65 - 89	
Height (cm)	**Mean ± SD**	172.6 ± 4.56	173.7 ± 5.68	0.503
	Range	161 - 179	161 - 180	
BMI (kg/m^2)	**Mean ± SD**	24.3 ± 3.22	25.16 ± 1.83	0.308
	Range	19.3 - 29.4	22.1 - 29.1	
ASA physical status	**I**	11 (55%)	13 (65%)	0.519
	II	9 (45%)	7 (35%)	
Duration of surgery (min)	**Mean ± SD**	106.25 ± 19.46	110.25 ± 13.42	0.454
	Range	70 - 135	85 - 130	

ASA: American society of anaesthesiologists, BMI: Body mass index.

Intraoperative HR did not differ substantially between both groups at baseline, 15, 30, 45, 60, 75, 90, 105, 120 minutes, or at end of surgery **(Figure 2)**.

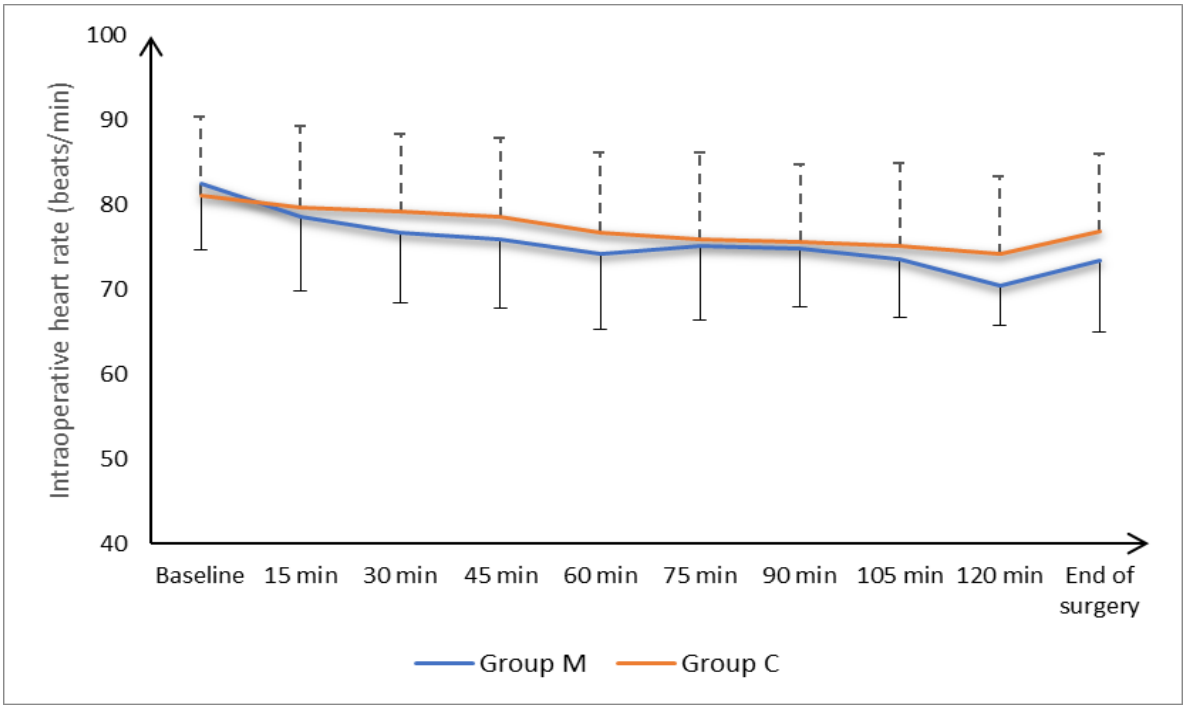

Fig 2: Intraoperative heart rate of studied groups.

Intraoperative MAP did not differ significantly between both groups at baseline, 15, 30, 45, 60, 75, 90, 105, and 120 minutes, or at end of surgery **(Figure 3)**.

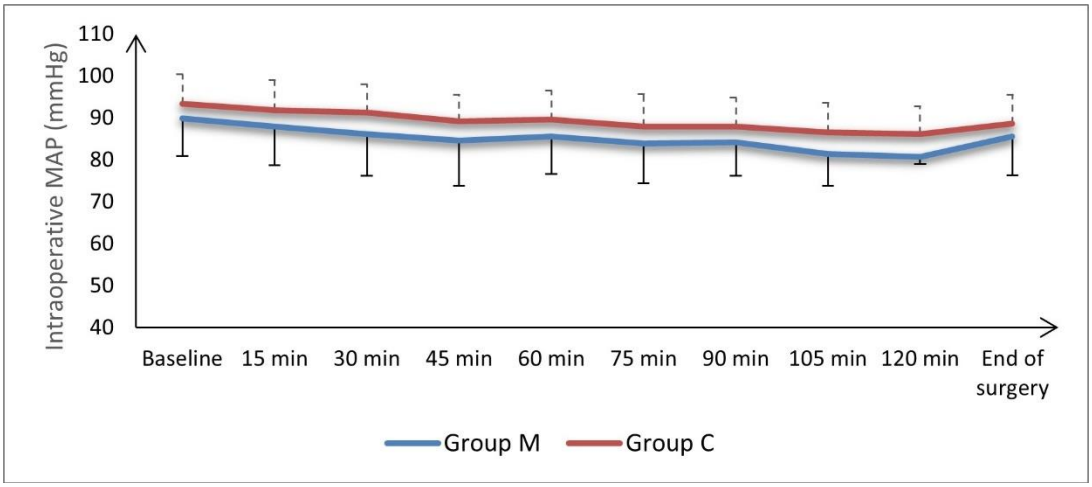

Fig 3: Intraoperative mean arterial pressure (MAP) of studied groups.

The interval until the initial request for rescue analgesia was substantially extended in Group M relative to controls. Additionally, total morphine consumption was markedly reduced in Group M relative to controls (**Table 2)**.

Table 2: Time to first rescue analgesic request and total morphine consumption in studied groups

		Group M (n=20)	Group C (n=20)	P value
Time to first request of rescue analgesia (hr)	**Mean ± SD**	5.1 ± 0.85	1.9 ± 0.79	**<0.001***
	Range	4 - 6	1 - 3	
Total morphine consumption (mg)	**Mean ± SD**	7.5 ± 1.54	10.65 ± 1.81	**<0.001***
	Range	6 - 9	6 - 12	

*: Significant

VAS scores did not differ substantially between groups at 0, 6, 8, 12, 18, and 24 hours postoperatively, however, at 2 and 4 hours, Group M exhibited markedly lower scores than controls (**Table 3)**.

Table 3: VAS of studied groups

	Group M (n=20)	Group C (n=20)	P value
0 h	1(1 - 2)	1(1 - 2)	0.799
2 h	1(1 - 2)	2(2 - 4.25)	**0.004***
4 h	2(1 - 4)	3(2 - 5)	**0.03***
6 h	2(1 - 4)	2(2 - 4)	0.512
8 h	3(2 - 4)	4(2 - 5)	0.221
12 h	3(2 - 4)	3(2 - 4)	0.883
18 h	4(2.75 - 4)	4(3 - 5)	0.327
24 h	3(2 - 3.25)	3(2.75 - 4)	0.565

Data presented as median (Interquartile range), *: Significant.

Postoperative HR did not differ substantially between groups at 0, 6, 8, 12, 18, and 24 hours, but was substantially lower at 2 and 4 hours in Group M when compared to controls (**Table 4)**.

Table 4: Postoperative heart rate of studied groups

	Group M (n=20)	Group C (n=20)	P value
0 h	74.8±8.39	79.6±8.96	0.088
2 h	79.1±8.3	92.95±17.9	**0.003***
4 h	85.3±15.44	96.1±13.27	**0.023***
6 h	87.3±13.32	91.2±18.14	0.443
8 h	87.25±14.15	94.3±12.72	0.106
12 h	88.2±14.46	92.55±15.89	0.371
18 h	91.05±13.74	97.45±15.43	0.174
24 h	84.45±14.38	90.85±13.22	0.151

Data presented as Mean (± SD), *: Significant.

Postoperative MAP did not differ substantially between groups at 0, 6, 8, 12, 18, and 24 hours, but was markedly lower at 2 and 4 hours in Group M when compared to controls (**Table 5)**.

Table 5: Postoperative MAP of studied groups

	Group M (n=20)	Group C (n=20)	P value
0 h	86.9±9.37	90.35±7.28	0.201
2 h	90.85±9.56	104.05±15.4	**0.002***
4 h	96.3±14.06	105.65±13.77	**0.04***
6 h	99.8±13.24	102.4±14.15	0.552
8 h	98.85±14.53	106.95±14.31	0.084
12 h	99.3±17.36	102.3±13.94	0.550
18 h	103.3±11.24	109.1±15.7	0.187
24 h	96.05±14.98	101.8±14.05	0.218

Data presented as Mean (± SD), MAP: Mean arterial pressure, *: Significanct.

The level of anxiety, as measured by APAIS, was markedly lower in Group M relative to controls (**Table 6)**.

Table 6: Level of anxiety using APAIS of studied groups

		Group M (n=20)	Group C (n=20)	P value
Anxiety level	**Mean ± SD**	7.9 ± 1.83	9.8 ± 2.12	**0.004***
	Range	5 - 11	7 - 14	

Data presented as Mean (± SD), APAIS: Amsterdam preoperative anxiety and information scale.

Hypotension, bradycardia, and PONV did not differ substantially between both groups. Respiratory depression did not occur in any cases in either group **(Figure 4)**.

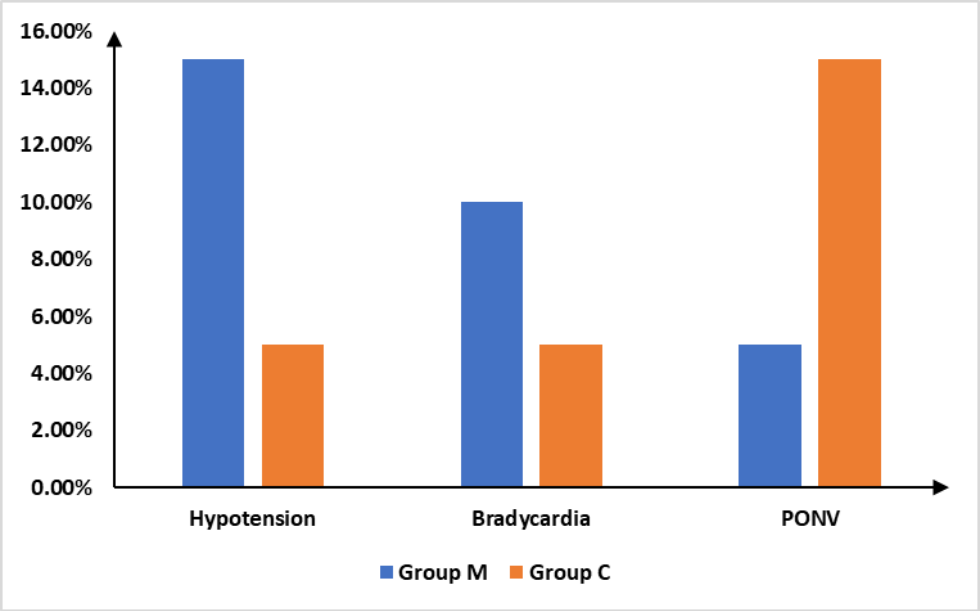

Figure 4: Complications of studied groups.

Cases satisfaction did not differ substantially between both groups **(Figure 5)**.

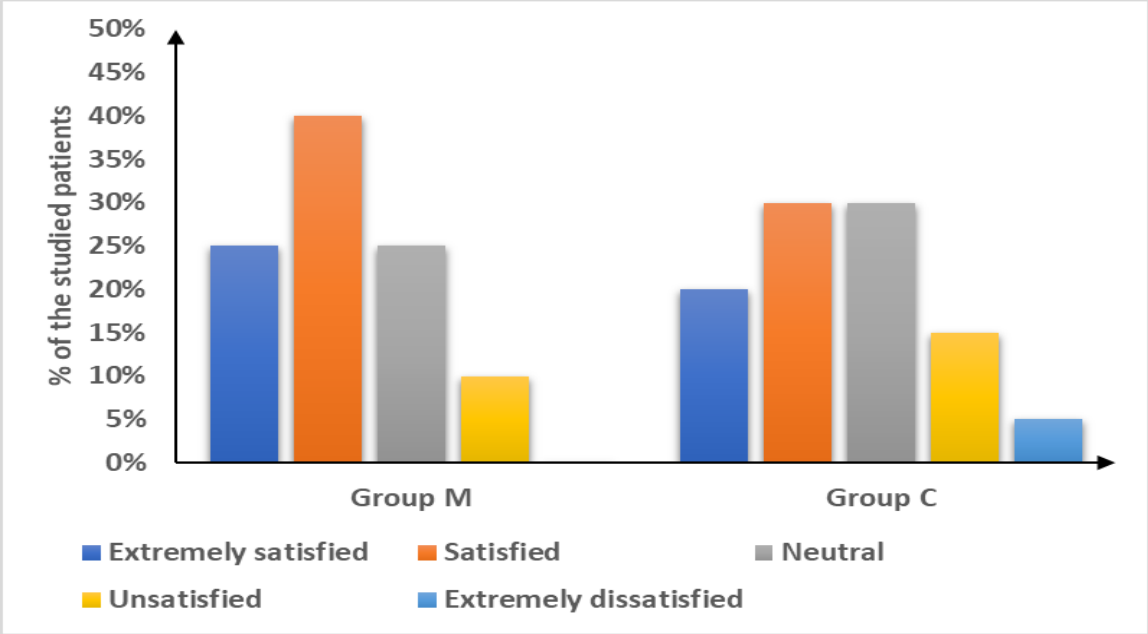

Figure 5: Patient satisfaction of studied groups.

DISCUSSION

SN is a common but potentially high-risk surgical procedure performed for benign kidney diseases. It involves removal of a nonfunctional kidney [15]. However, SN carries an elevated risk of heightened postoperative pain, surgical site infections, extended hospitalizations, and prolonged recovery periods. [16]

Postoperative pain substantially influences both recovery trajectory and case satisfaction in postoperative period. It can lead to adverse physiological effects such as shallow breathing and impaired clearance of respiratory secretions, increasing the risk of atelectasis and pulmonary complications. Moreover, postoperative pain can lead to increased HR and BP, development of ileus, and extended periods of bed rest. Immobility resulting from pain may also increase risk of deep vein thrombosis. [17,18]

Therefore, implementing pain mitigation strategies with minimal complication rates is a critical objective in postoperative care. The efficacy of multimodal analgesic approaches for postoperative pain management has been well established. Moreover, narcotics are linked to dose-dependent adverse effects, such as urinary retention, nausea, drowsiness, respiratory depression, vomiting, pruritus, and postoperative ileus. [19]

Melatonin is among the most frequently utilized agents for alleviating acute postoperative pain and augmenting analgesic efficacy. Melatonin, or N-acetyl-5-methoxytryptamine, is a hormone synthesized by pineal gland within brain. [6] Melatonin exerts profound biological effects within body and is essential for regulation of sleep–wake cycle. [20]

Research involving surgical cases has demonstrated that both surgery and anesthesia contribute to decreased plasma melatonin concentrations. Therefore, supplemental melatonin administration is recommended for cases undergoing surgery [10,21]. Moreover, multiple investigations have demonstrated the advantageous effects of administering melatonin in perioperative period, such as alleviation of preoperative anxiety, a reduced incidence of postoperative delirium, decreased anesthetic needs, and attenuation of pain intensity [21,22].

According to our current knowledge, there are limited studies investigating melatonin use for reducing postoperative pain in cases undergoing SN. Therefore, this trial assesses melatonin efficacy in managing postoperative pain in these cases.

This randomized, double-blind, controlled study included 40 cases (18–65 years) undergoing SN. Group M (n=20) received 4 mg prolonged-release oral melatonin at 8 PM preoperatively and two hours before surgery; controls (n=20) received placebo tablets at the same times.

In present study, intraoperative MAP and HR did not differ notably between both groups at all times of the measurement. Postoperative HR and MAP were also not significantly different at 0, 6, 8, 12, 18, and 24 hours; however, both were substantially lower at 2 and 4 hours in Group M when compared to controls.

This aligns with **Saleh *et al.*** [23] who carried out a study on 30 cases undergoing open nephrectomy, allocated cases to receive either 5 mg oral melatonin or placebo one hour preoperatively. They observed no

substantial variations in intraoperative MAP or HR between groups.

Similarly, **Ismail *et al*.** [24] studied 40 cataract surgery cases under topical anesthesia, randomized to receive either 10 mg oral melatonin or placebo 90 minutes before surgery. They found significantly lower postoperative MAP in melatonin group, with comparable HR between groups.

In present study, the interval until initial request for rescue analgesia was substantially extended in Group M relative to controls. Additionally, total morphine consumption was markedly reduced in Group M relative to controls. This concurs with **Saleh *et al*.** [23], who demonstrated a substantially extended interval to initial analgesic request and a reduction in total morphine consumption among patients receiving melatonin relative to controls.

Likewise, **Baradari *et al*.** [21] carried out a clinical trial with 80 cases undergoing elective mini-open microdiscectomy procedures. Cases in Groups A, B, and C received 3 mg, 5 mg, and 10 mg melatonin tablets, respectively, while Group D received a placebo tablet one hour before surgery. They observed that postoperative opioid consumption was reduced across all three melatonin groups compared to placebo group.

This is corroborated by **Kiabi *et al*.** [6], who in a trial of 204 elective cesarean section patients randomized into three groups (5 mg melatonin, 10 mg melatonin, and placebo), found that the interval to first analgesic request was substantially longer and mean opioid consumption markedly lower in melatonin groups compared to placebo.

Similarly, **Laosuwan *et al*.** [11] in a study involving 54 hysterectomy cases, reported substantially lower morphine consumption among those administered 4 mg of prolonged-release melatonin compared to placebo group.

Additionally, **Khezri *et al***. [25] studied 120 cesarean cases under spinal anesthesia, randomized to 3 mg melatonin (M3), 6 mg melatonin (M6), or placebo (P) given sublingually 20 minutes pre-anesthesia. Analgesic requests within 24 hours were substantially fewer in M3 than in P and M6, while time to first analgesic request was similar across groups. These variations may relate to surgery type and melatonin dosage.

The present study revealed that VAS scores did not differ substantially between both groups at 0, 6, 8, 12, 18, and 24 hours, but were markedly lower at 2 and 4 hours in Group M compared to controls.

Similarly, **Ashokkumar *et al*.** [26] conducted a randomized controlled trial involving 64 cases undergoing zygomaticomaxillary fracture fixation, who were prophylactically administered either oral melatonin or an identical placebo for 15 consecutive days. They reported that melatonin notably reduced VAS scores compared to controls.

These observations concur with **Saleh *et al*.** [23] who reported that postoperative pain scores were substantially lower in melatonin group relative to controls.

Additionally, **Haryalchi *et al*.** [27] studied 90 abdominal hysterectomy cases randomized to 6 mg oral melatonin, 50 mg pregabalin, or no medication (n=30 each). At 24 hours post-surgery, mean pain intensity was substantially lower in melatonin group relative to no-medication group.

In addition, **Baradari *et al*.** [21] reported that postoperative pain was significantly lower in all three groups receiving melatonin at different doses compared to placebo group.

This perspective is supported by evidence presented by **Laosuwan *et al*.** [11] who reported that postoperative VAS pain scores were substantially lower in melatonin group relative to controls. Similarly, **Kiabi *et al*.** [6] demonstrated that pain intensity was substantially lower in melatonin groups relative to placebo group. The greatest pain reduction was observed in the 10 mg melatonin group, followed by 5 mg melatonin group, and then placebo group.

According to our findings, anxiety levels assessed using APAIS were markedly decreased in Group M compared to controls.

Consistent with our findings, **Grima *et al*.** [28] conducted a study involving 33 cases to evaluate efficacy of melatonin supplementation for sleep disturbances in cases with traumatic brain injury (TBI). They demonstrated that melatonin reduced anxiety compared to placebo. Supporting our findings, **Khezri *et al*.** [25] demonstrated that anxiety scores were significantly lower in the 6 mg melatonin group compared to placebo group.

In same manner, **Khezri *et al*.** [29] in a study involving 60 cataract surgery cases, found that administering 3 mg of sublingual melatonin 60 minutes before surgery substantially reduced anxiety scores from 5 to 3 after premedication, maintained at 3 during procedure, and decreasing further to 0 prior to discharge from recovery room.

Additionally, **Ionescu *et al*.** [30] performed a study on 53 laparoscopic cholecystectomy cases under GA. Cases were assigned to 3 mg melatonin, 3.75 mg midazolam, or placebo, administered the night before and as premedication. They found that postoperative anxiety scores were consistently lowest in melatonin group compared to controls at all time intervals.

In contrast, **Laosuwan *et al*.** [11] found no substantial variation in preoperative or postoperative anxiety levels between melatonin and placebo groups. This discrepancy may be attributed to differences in type of surgery.

In the current study, hypotension, bradycardia, and PONV did not differ substantially between both groups, and respiratory depression did not occur in any cases. Case satisfaction was also similar between groups. These outcomes are reinforced by findings of **Saleh *et al*. [23]** who reported no substantial variations in the incidence of complications between melatonin group and controls.

Similarly, **Baradari *et al*. [21]** reported that incidence of postoperative vomiting did not differ significantly between the melatonin groups and placebo group.

Additionally, **Khezri *et al*. [25]** reported no substantial variations between the 3 mg melatonin, 6 mg melatonin, and placebo groups regarding intraoperative and postoperative adverse effects, such as nausea, vertigo, pruritus, vomiting, and respiratory depression. Nevertheless, the 6 mg melatonin group exhibited a markedly higher incidence of headache relative to other groups.

Regarding case satisfaction, **Laosuwan *et al*. [11]** reported that satisfaction scores were elevated in melatonin group relative to placebo group.

LIMITATIONS

This study has several limitations. First, the sample size was relatively small, which may limit the generalizability of the findings and reduce statistical power for detecting less prominent effects. Second, the follow-up period was limited to the first 24 hours postoperatively; thus, longer-term outcomes such as chronic pain or sleep quality were not assessed. Third, the study focused solely on a single melatonin dose and administration schedule, without evaluating the effects of varying doses or timings. Additionally, subjective tools such as the VAS and APAIS were used, which may introduce response bias. Lastly, this study was conducted at a single center, potentially limiting external validity across diverse surgical settings and patient populations.

CONCLUSION

The administration of melatonin in cases undergoing SN was correlated with a substantial delay in the time to first request for rescue analgesia, a reduction in total morphine consumption, and lower anxiety levels.

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Conflict of Interest: Nil.

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