Original Article

Investigating The Effect Of Sublingual Melatonin On The Rate Of Using Opioids In Laparotomy Patients Admitted To ICU

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Abstract

Introduction: Melatonin has sleep-inducing, analgesic, anti-inflammatory, and antioxidant properties, making it an appropriate supplement for managing pain in patients admitted to the intensive care unit (ICU). The present study aims to investigate the effect of sublingual melatonin on the rate of using opioids in laparotomy patients admitted to the ICU.
Methods: This double-blinded randomized clinical trial was conducted on midline laparotomy patients hospitalized in the ICU of Imam Khomeini Hospital, Ahvaz in 2022. Fifty-five patients were randomly assigned to two groups, including one test group that received 5 mg of melatonin (n=27) for 3 consecutive nights and one placebo group (n=28). The rate of used opioids, pain intensity by visual analog scale (VAS), hemodynamic parameters, side effects, and duration of hospitalization in ICU were compared in two groups.
Results: The rate of using opioids on the second day (81.5% vs. 100%; P=0.017) and the third day of hospitalization (55.6% vs. 82.1%; P=0.033) in the melatonin group was significantly lower than the control group. On the third day of hospitalization, the rate of using opioids (P=0.047) and the mean pain score (P=0.030) were significantly lower in the melatonin group compared to the control group. The mean duration of hospitalization in the ICU was not significant between the melatonin and placebo groups (P=0.428). Patients of the melatonin group experienced insignificantly less nausea and vomiting (18.5% vs. 35.7%) and hypotension (55.6% vs. 64.3%) compared to the placebo group.
Conclusion: The present study revealed that the rate of using opioids and pain intensity was significantly lower in the melatonin group compared to the control group. Nocturnal melatonin supplementation can be recommended for managing pain in ICU patients and reducing the need for opioids and their side effects.

Keywords: Melatonin, Pain, Analgesia, Intensive Care Unit, Laparotomy, and Surgery.

INTRODUCTION

Effective control or management of postoperative pain significantly improves patient satisfaction and reduces postoperative complications and length of hospital stay (1, 2). Opioids are analgesics used extensively for managing and controlling postoperative pain. However, they are associated with many complications, such as nausea, vomiting, itching, urinary retention, dizziness, drowsiness, hypotension, and respiratory depression (3, 4). Hence, reducing the need for opioids is crucial for controlling pain and reducing its side effects (2, 5). Thus, it is crucial to use compounds or drugs that can intensify the analgesic effects of opioids and create better analgesic effects by reducing the rate of using opioids (6). Melatonin (N-acetyl-5-methoxytryptamine) is primarily produced by the pineal gland in the brain. It plays a role in regulating circadian rhythms (7). It is also a neuroprotective agent and has chronobiotic, antioxidant, anti-anxiety, sedative, and analgesic properties (8-11). Experimental and clinical studies have proven its analgesic property in patients undergoing surgery (11-13).

Studies have revealed that the combined administration of melatonin and morphine increases the analgesic effect of morphine and reduces the need for opioids for relieving pain and its side effects (5, 14). Studies have also proven that melatonin affects opioid receptors, gamma-aminobutyric acid (GABA), and glutamate in the central nervous system. These receptors are involved in transmitting pain or modulating pathways (15). It has been also reported that melatonin mitigates pain indirectly by reducing oxidative stress in nerve cells (16). Based on the available evidence, melatonin can be effective in mitigating and controlling surgery-caused pain, regardless of its exact mechanism in mitigating pain. Thus, the present study aims to investigate the effect of sublingual melatonin on analgesia and the rate of using opioids in laparotomy patients admitted to the ICU.

Methods

The present double-blinded randomized controlled clinical trial was conducted on patients admitted to the ICU of Imam Khomeini Hospital, Jundishapur University of Medical Sciences of Ahvaz in 2022. It was conducted after obtaining permission from the research council and approval from the ethics committee of Ahvaz University of Medical Sciences (code of ethics: IR.AJUMS.HGOLESTAN.REC.1401.043) and registration in Iran's clinical trial system with approval code of IRCT20220807055631N1. Informed consent was obtained from all patients before treatment. Also, the provisions of the ethics statement in Helsinki's research and the patient's information confidentiality principles were observed in all stages of this study.

The sample size was calculated at 25 people in each group considering the confidence level of 90%, power of 90%, and the results of similar studies (15, 17), and using the formula comparing two means. Due to the possibility of dropout in the sample, the final sample size was determined to be 30 people in each group (60 patients in total).o

n=Z1-α2+Z1-β2S12+S22X1-X22

In this formula: $\alpha=0.01$, $\beta=0.1$, $S_1=1.53$, $S_2=1.19$, $X_1=3.81$, and $X_2=5.87$

Patients over 18 years of age who needed hospitalization in the intensive care unit for more than 48 hours owing to laparotomy surgery were selected for the study. Patients with liver failure (liver enzyme more than three times the normal limit), kidney failure (GFR<60), brain tumor, and patients with a history of allergy to melatonin were excluded from the study. Figure 1 shows the study process and participants' exclusion.

Grouping and Intervention

The patients were randomly assigned to two groups, including the melatonin or intervention group and the placebo or control group. The patients were randomly divided into two groups based on the first random permutation of 4 by a person who was not involved in the study. The patients received a 5 mg sublingual melatonin tablet (Amin Pharmaceutical Company) or a placebo tablet containing starch (5 mg, Amin Pharmaceutical Company) when admitted to the ICU at 9:00 PM. Medicines were administered for 3 consecutive nights. The appearance of the placebo was similar to the melatonin tablet. All patients were anesthetized with the same drug and the same procedure. All patients were anesthetized by midazolam, fentanyl, sodium thiopental, and atracurium. Before the study, the drugs were packed and coded in similar and indistinguishable packages. Then, they were submitted to the person in charge of the study. Thus, the patient, the person evaluating the results, and the statistical analyzer of the results did not have any information about the patient's grouping. Hence, the study was conducted in a double-blinded manner.

Evaluation of outcomes

Demographic information of the patients was checked and recorded at the beginning of hospitalization. Hemodynamic parameters, including blood pressure and heart rate, were evaluated regularly in the study groups after admitting to the ICU and during hospitalization in this unit. The rate of using opioids prescribed for the patient and the pain intensity of the patients were evaluated based on a visual analog scale (VAS) three days after surgery and hospitalization in ICU. The VAS scale assesses the patient's pain intensity using scores from 0 (no pain) to 10 (the most intense pain). The duration of hospitalization in the intensive care unit and the mortality rate in the intensive care unit were compared in two groups.

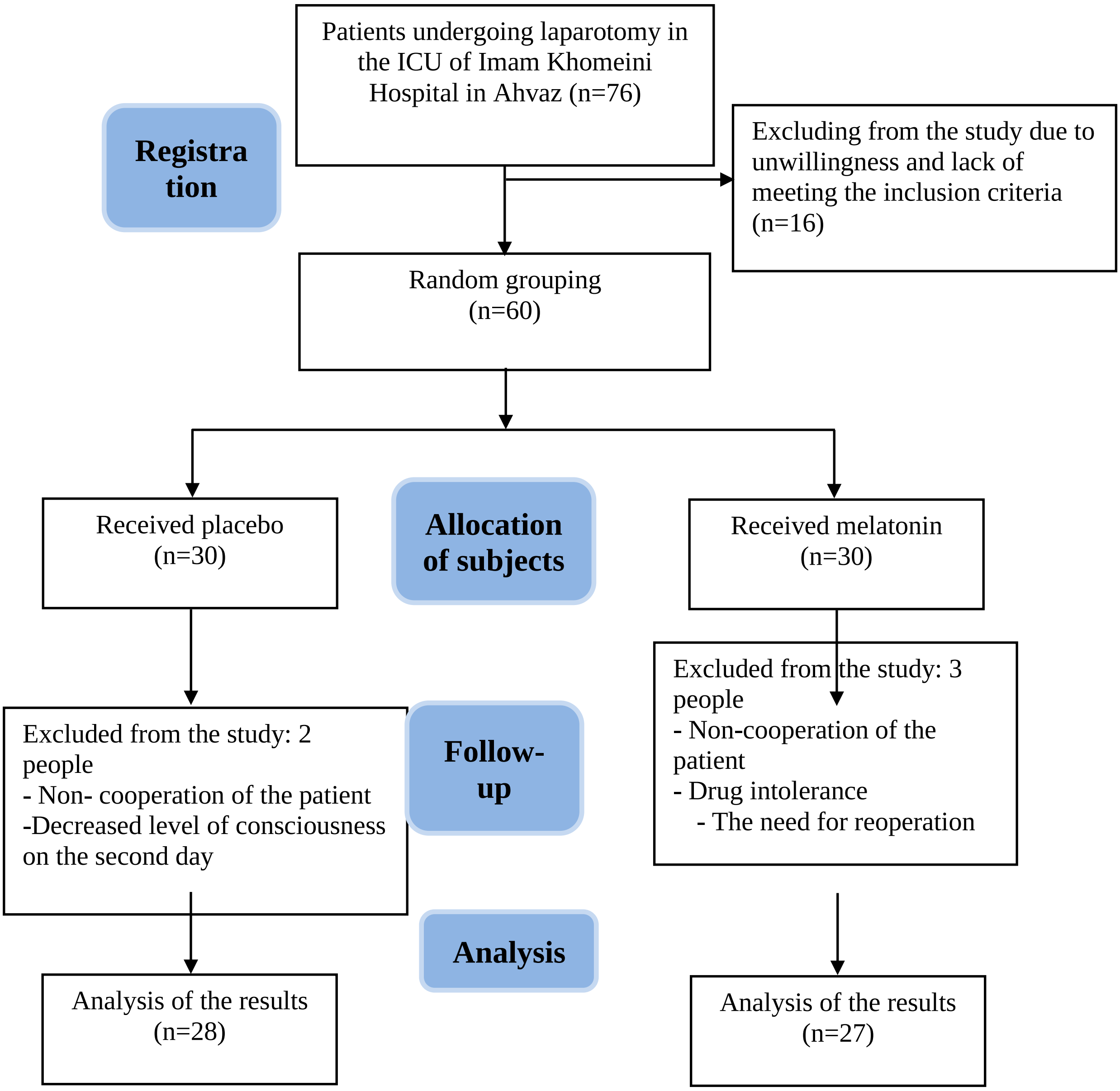

Figure 1- Research flowchart

Statistical Analysis

SPSS-22 Software (SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analysis. Mean, standard deviation, frequency, and percentage were used to describe the data. The normality of data was examined by the Kolmogorov-Smirnov test. The homogeneity of variances was examined by Levene's test. An Independent t-test was used to compare the mean variables between the two groups. The Chi-square test was used to compare qualitative variables between the two groups. Paired t-test was used to compare the results before and after the intervention. The significant level in the tests was considered at 0.05.

Results

Sixty patients who underwent elective surgery with midline laparotomy participated in this study. All patients were hospitalized in ICU and non-intubated. During the study, 5 people were excluded from the study due to several reasons, such as patient non-cooperation, decreased level of consciousness, and drug intolerance. Finally, 55 people were analyzed. Table 1 presents the basic characteristics of the studied patients of two groups. No significant differences were observed between the two groups regarding age, gender, weight, and BMI (P<0.05). The duration of hospitalization in the intensive care unit was not significantly different between the two groups (P=0.428)

Table 2 presents the results of using opioids and pain intensity scores in two groups of patients during hospitalization are presented in Table 2. On the first day of hospitalization, all patients in both melatonin and placebo groups needed to receive opioids. The frequency of needing opioids on the second and third days of hospitalization in the melatonin group was lower than placebo (P=0.017 and P=0.033, respectively). The rate of using opioids and the pain intensity of the patients decreased significantly in both groups (P<0.0001). The rate of using opioids and pain score did not differ significantly between the two groups on the first and second days of hospitalization. However, the rate of using opioids (P=0.047) and pain score (P=0.030) were significantly lower in the melatonin group compared to the control group on the third day of hospitalization.

Table 3 presents the changes in vital signs after admitting to the ICU and during 3 days of hospitalization in the ICU in the melatonin and placebo groups. The mean pulse and the systolic and diastolic blood pressures were significantly different between the two groups at any of the studied times (P<0.05). Table 4 presents the results of opioid-related side effects in the two melatonin and control groups. No significant difference was found between the two groups regarding the incidence of side effects of nausea and vomiting (P=0.152), itching (P=0.670), and hypotension (P=0.674). Also, no mortality was observed in the ICU in the studied patients.

Table 1- The basic characteristics of the studied patients of two groups

Variable	Group	Placebo (N=28)	Melatonin (n=27)	P-value
Age (year), (Mean ± SD)		10.68 ± 47.5	11.15 ± 48.48	*0.390
Gender, n (%)	Female	13) 46.4(	11) 40.7(	**0.671
	Male	15) 53.6(	16) 53.9(	
Weight (kg), Mean ± SD		15.53 ± 73.74	14.67 ± 73.18	*0.658
BMI(kg/m^2), (Mean ± SD)		6.16 ± 26.9	4.41 ± 25.24	*0.263
Hospitalization in ICU (days), Mean ± SD		4.17 ± 6.55	3.72 ± 7.31	*0.428

* Independent t-test

** Chi-square test

BMI: Body mass index; ICU: intensive care unit

Table 2- Comparing two groups regarding the need for opioids need and pain intensity during hospitalization

Variable	Time	Placebo (n=28)	Melatonin (n=27)	P-value
Need for opioid, n (%)	The first day of hospitalization	28 (100%)	27 (100%)	-
	The second day of hospitalization	28 (100%)	22 (81.5%)	*0.017
	The third day of hospitalization	23 (82.1%)	15 (55.6%)	*0.033
Rate of using opioid mg, (Mean ± SD)	The first day of hospitalization	4.40 ± 10.29	3.12 ± 10.53	**0.962
	The second day of hospitalization	3.01 ± 7.89	3.62 ± 6.70	**0.191
	The third day of hospitalization	3.37 ± 5.21	3.50 ± 3.41	**0.047
	***P-value - days 1&2	0.0001<	0.0001<	-
	*** P-value - days 2&3	0.001	0.0001<	-
	*** P-value - days 1&3	0.0001<	0.0001<	-

Pain score (VAS) Mean ± SD	The first day of hospitalization	1.82 ± 7.93	1.38 ± 8.19	**0.995
	The second day of hospitalization	1.57 ± 6.46	1.51 ± 6.07	**0.361
	The third day of hospitalization	2.18 ± 5.04	1.72 ± 3.85	**0.030
	***P-value - days 1&2	0.0001<	0.0001<	-
	*** P-value - days 2&3	0.0001<	0.0001<	-
	*** P-value - days 1&3	0.0001<	0.0001<	-

* Chi-square test
** Independent t-test
*** Paired t-test

Table 3- Comparing two groups regarding the hemodynamic parameters at different times

Variable	Time	Placebo (n=28)	Melatonin (n=27)	P-value*
PR) rate/min(	Admission to intensive care	10.08 ± 93.28	11.99 ± 95.40	0.866
	The first day of hospitalization	10.71 ± 94.08	9.59 ± 94.91	0.949
	The second day of hospitalization	9.05 ± 93.65	9.68 ± 96.28	0.444
	The third day of hospitalization	8.99 ± 94.43	9.48 ± 95.87	0.773
SBP) mmHg(	Admission to intensive care	9.42 ± 116.53	10.30 ± 119.93	0.265
	The first day of hospitalization	9.27 ± 117.85	8.45 ± 121.10	0.157
	The second day of hospitalization	7.12 ± 120.95	7.52 ± 122.83	0.513
	The third day of hospitalization	7.72 ±124.88	7.63 ± 126.93	0.501
DBP) mmHg(	Admission to intensive care	5.89 ± 69.00	5.86 ± 72.60	0.104
	The first day of hospitalization	5.38 ± 70.13	5.64 ± 73.05	0.849
	The second day of hospitalization	4.12 ± 71.87	4.87 ± 72.08	0.366
	The third day of hospitalization	3.71 ± 71.53	3.76 ± 74.68	0.207

*Chi-square test

Discussion

This double-blinded randomized controlled clinical trial showed that melatonin can help in pain management, including reducing the pain intensity and rate of using opioids in patients undergoing laparotomy in the ICU. In the present study, the need for opioids on the second (81.5% vs. 100%) and the third days of hospitalization (55.6% vs. 82.1%) were significantly lower in the melatonin group patients compared to the control group patients. The rate of using opioids and pain intensity (based on VAS score) decreased significantly in both groups receiving melatonin and placebo during hospitalization. However, the rate of using opioids and pain intensity was significantly lower in the melatonin group compared to the control group on the third day of hospitalization. No significant difference was found between the two groups regarding the duration of hospitalization in the ICU.
Opioids and benzodiazepines are the most common drugs used as sedatives and analgesics in the ICU. They have

respiratory depression effects (9, 18, and 19). They are also associated with some side effects such as nausea, vomiting, dizziness, drowsiness, hypotension, and itching (3-5). Some studies have shown that a combination of an adjuvant and an opioid reduces the need for opioids for relieving pain and the rate of drug-related side effects (5, 20). Melatonin is a neuroprotective agent with hypnotic, anti-inflammatory, and antioxidant nature, anticonvulsant, anti-anxiety, sedative, and analgesic effects without respiratory depression effects (9-11). These properties make it an appropriate adjunctive sedative drug for managing pain in ICU patients. Melatonin increases the levels of beta-endorphins in the central nervous system. It interacts with opioids, GABA, or the N-methyl-D-aspartate receptor system (21). Melatonin activates opioid receptors and reduces the creation of cAMP in neurons. Also, it opens potassium channels through opioid receptors. It also activates the spinal cord analgesia system by hyper-polarization and accordingly it inhibits pain transmission. Melatonin can reduce the expression of lipoxygenase and cyclooxygenase enzymes and prevent the formation of inflammatory precursors (9).

Soltani et al. examined trauma patients with intracranial hemorrhage under mechanical ventilation in ICU. They showed that melatonin significantly reduces the rate of using morphine and reduces mechanical ventilation duration. However, the mean duration of hospitalization in the ICU was not significantly different between the two groups (14). Mistraletti et al. showed that the administration of melatonin as an adjunctive treatment in the ICU reduced the need for sedative agents, and improved neurological indicators (the rate of neuroactive drugs, pain, agitation, anxiety, sleep, and the need for additional sedation). The mortality and the duration of hospitalization in mproICU were not significantly different in the two groups (22). In the study conducted by Dianatkhah, receiving enteric nocturnal melatonin in hemorrhagic stroke patients was associated with a significant reduction in the duration of hospitalization in the ICU, the need for mechanical ventilation, and a non-significant reduction in mortality (10). In a meta-analysis, 11 randomized clinical trials were reviewed. Its results showed that melatonin significantly reduces the rate of using analgesic drugs compared to a placebo. In the analysis of subgroups according to pain type, using melatonin decreased the rate of using analgesics in acute pain after surgery under general anesthesia (23).

Melatonin supplementation has been recommended for postoperative pain management (24). However, few studies have been conducted to investigate the analgesic effectiveness of adding melatonin to opioids after surgery in non-intubated patients hospitalized in the ICU. Also, most studies have examined the preoperative effectiveness of prophylactic melatonin analgesia. Tunay et al. showed that oral melatonin (6 mg) administration one hour before major elective abdominal surgery reduced pain scores, the rate of using morphine, the need for additional analgesia, and the incidence of postoperative side effects of nausea and vomiting (5). Javaherforooshzadeh et al. showed that 6 mg of melatonin 100 minutes before the surgery compared to the placebo significantly reduced pain intensity and anxiety levels in patients undergoing lumbar spine surgery with general anesthesia. Also, the melatonin and gabapentin effectiveness was the same in reducing pain and anxiety (9). The study conducted by Javaherforoosh Zadeh et al. also showed that melatonin can reduce delirium incidence and severity in the ICU after cardiac surgery (25). Saber Moghaddam showed that subcutaneous melatonin one hour before surgery compared to placebo significantly reduced the pain intensity score 12 and 24 hours after colorectal surgery (26). In the study conducted by Kiabi et al., using 5 and 10 mg of oral melatonin before the cesarean section with spinal anesthesia was safe and reduced the pain intensity of patients, increased the postoperative analgesia duration, and reduced the need for postoperative analgesia. However, the effect of a higher dose of melatonin was greater (27). The studies conducted by Borazan et al. (17) and Caumo et al. (15) also reported that receiving melatonin one night and one hour before surgery reduces postoperative pain and the need for opioids (tramadol and morphine) 24 and 48 hours after surgery. Also, Sadat Hosseini et al. showed that using melatonin reduced the pain intensity significantly after laparoscopic cholecystectomy compared to the control group. It is consistent with the results of our study (28). Also, some conflicting results have not shown any reduction in the need for opioids or pain scores. For example, the study conducted by Naguib and Samarkandi showed that receiving an oral dose of melatonin (5 mg) compared to placebo 100 minutes before gynecological laparoscopic surgery did not reduce the need for an intraoperative opioid, pain scores, and using analgesic 90 minutes after the surgery (29). Acil et al. reported that a 5 mg dose of oral melatonin before laparoscopic surgery did not reduce pain scores compared to a placebo (30). These contradictory results are due to differences in the intervention methods (time and dose of melatonin received and different sedation protocol), short follow-up periods after the surgery, and different surgeries.

Different studies have examined the effectiveness of different doses of melatonin (3 to 10 mg), different ways of

administration (enteral or oral and sublingual tablets), and administration at different times (before or after surgery) in different patients hospitalized in ICU, and different anesthesia protocols. Hence, it is impossible to comprehensively and accurately compare the results of this study with the results of other studies. However, the general results and available evidence suggest that using melatonin can reduce and control pain and the need for opioids and sedative agents after surgery. Therefore, it can reduce their side effects (including respiratory depression and delirium) and improve the outcomes in ICU. More multicenter studies with different sedation protocols are necessary to confirm the results of the present study. No serious side effects were observed in any of the groups in the present study. The side effects of using opioids such as nausea, vomiting, and hypotension were lower in the melatonin group compared to the placebo group. However, no significant difference was observed between the two groups. Also, changes in blood pressure and pulse during the study did not show any significant difference between the two groups. The study conducted by Javaherforooshzadeh et al. (9) showed no significant changes in blood pressure in melatonin and placebo groups at different times after the surgery, which is consistent with the present study.
Tunay et al. showed that administration of oral melatonin before surgery compared to placebo reduced preoperative nausea and vomiting after surgery. Other side effects such as itching, hypotension, and bradycardia were very mild and did not differ significantly between the two groups (5). Other clinical trials have not reported any serious side effects for melatonin (31-33). These results indicate that melatonin administration in patients hospitalized in ICU does not cause any dangerous side effects and can be used as a cheap and safe drug in preventing opioid-induced complications. The present study suffered some limitations. It was conducted in a single center. Also, the used sedative drugs were based on one hospital ICU's guidelines, which may be different from other hospital ICUs' guidelines. Also, all the patients in the present study were non-intubated and the results were not compared with patients under mechanical ventilation. The small sample size was another limitation of the study. The small sample size and the single-center nature of the study limit the generalizability of the results. Also, only the short-term effects of melatonin were investigated in this study. Therefore, conducting more studies with a larger sample size and at multiple centers can provide better results.

Conclusion

The present study showed that using melatonin after the surgery decreased the pain intensity and the need for opioids in the patients who underwent Midline laparotomy and were admitted to the ICU compared to the placebo group patients. Therefore, nocturnal melatonin supplementation can be recommended as an effective, safe, cheap, and available drug for managing pain in ICU patients and reducing the need for using opioids and their side effects.

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