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The Effect of Preoperative Sublingual Melatonin on Postoperative Pain Severity in Patients Undergoing Colorectal Surgery: A Triple-Blinded Randomized Trial

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Abstract

Background: Postoperative pain has detrimental physiologic and psychologic effects on patients' outcomes, such as increased postoperative morbidity, delayed recovery, and reduced patient satisfaction. This study aimed to determine the effect of preoperative sublingual melatonin on pain severity after colorectal surgery.

Methods: We performed a randomized, placebo-controlled, triple-blinded study to test the efficacy of 6 mg of sublingual melatonin or placebo 1 hour preoperative on pain severity and sedation of 60 patients after colorectal surgeries. Pain and sedation were assessed by numerical verbal response (NVR) and the Ramsey sedation score, respectively, at the baseline, 1, 2, 6, 12, and 24 hours after surgery. The repeated measures analysis of variance was used to assess group × time interaction, and the Bonferroni adjustment was used for between-group comparisons.

Results: A total of 60 patients with a mean ± SD age of 49.35 years were equally randomized to the study groups. There was no significant difference between groups with respect to the baseline characteristics. The mean score of pain severity of patients in the melatonin group was significantly lower compared with the placebo group at 2, 6, 12, and 24 hours after surgery. The total mean pain score for the first 12 hours (mean difference [MD] [SE], 0.41 [0.12]; 95% CI, 0.17-0.65; [P = 0.012]) and the mean score of pain in 24 hours after surgery were significantly lower in the melatonin group in comparison with the placebo group (MD [SE], 0.44 [0.13]; 95% CI, 0.19-0.69; [P = 0.001]). Compared with the placebo group, the percent of patients who were cooperative, aware, and calm was significantly higher in the melatonin group at the baseline (43.3% vs 53.3%) and at 1 (36.7% vs 60%) and 2 hours (33.3% vs 80%).

Conclusion: The use of 6 mg preoperative melatonin sublingual tablet in patients with colorectal surgeries could reduce the severity of postoperative pain, patients' restlessness and anxiety, and increase patients' cooperation and calmness. Therefore, it seems that sublingual melatonin is an effective drug in controlling postoperative pain.

Keywords: Pain, Postoperative Pain, Melatonin, Colorectal Surgery

Conflicts of Interest: None declared
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Introduction

Postoperative pain remains a substantial problem in colorectal surgery (1, 2). Postoperative pain may cause negative physiological effects, including respiratory depression and airway secretion retention, atelectasis, increased heart

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↑What is "already known" in this topic:
Postoperative pain remains a substantial problem in colorectal surgery, which may cause negative physiological effects on patients, the surgery's outcomes, and patients' satisfaction with care. Previous studies have shown that melatonin can improve the pain-relieving effects of opioids after surgery.

→What this article adds:
The use of 6 mg preoperative melatonin sublingual tablet in patients with colorectal surgery could reduce the severity of postoperative pain, patient's restlessness, and anxiety, and increase patients' cooperation and calmness.

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rate, hypertension, ileus, nausea, and vomiting (3). In patients undergoing colorectal surgery, postoperative pain can lead to delayed ambulation, increase in the length of hospital stay; hence, high cost of care.

In addition, postoperative pain may affect the outcome of the surgery and patients' satisfaction with care. Moreover, postoperative pain along with other major complications in patients undergoing colorectal surgery can increase the risk of morbidity and mortality (4).

Postoperative pain relief remains a medical challenge. To relieve the postoperative pain in surgical patients, various therapeutic modalities have been applied, including the use of opioid and nonopioid analgesics by various routes (oral/systemic/ intrathecal/epidural) (5). Typically, narcotics, especially in injectable forms, are widely used as the first choice for pain relief in colorectal surgery. However, the narcotics usually are accompanied by a long list of adverse effects (6).

Increasing the conception of the pathophysiological mechanisms of pain has shown that strategies that prevent or reduce excessive irritability of the central nervous system can play a critical role in reducing postoperative pain. One of the advanced treatment strategies of postoperative pain is preemptive analgesia, in which analgesics are recommended before, during, or immediately after surgery (7, 8). In this regard, previous studies have shown that melatonin can directly reduce acute pain and improve the pain-relieving effects of opioids after surgery (9, 10). Melatonin or N-acetyl methoxytryptamine is a hormone already secreted by the pineal gland in the brain that has crucial biological effects on multiple body organs, such as regulating the sleep-wake cycle (11, 12). In addition, increasing the number of evidence demonstrates the protective function of melatonin in various diseases, such as cancer, cardiovascular disease, Alzheimer, diabetes, mood disorders, gastrointestinal diseases, fibromyalgia, and mental disorders (13, 14).

Although the mechanism of the analgesic effects of melatonin is not well understood, the stimulation of beta-endorphin secretion, as well as its effects on various receptors including opioid, benzodiazepine, muscarinic, and serotonergic receptors in the spinal cord has been proposed (15).

Considering the importance of postoperative pain and its effect on the outcomes related to the patient and the health system, this study was designed to evaluate the effect of preoperative sublingual melatonin (6 mg) on postoperative pain severity and patients' sedation after colorectal surgery.

Methods

Design

The study was a randomized, triple-blinded, placebo-controlled clinical trial (trial ID: IRCT20190811044506N1). The study was approved by the Regional Ethics Committee of Mashhad University of Medical Sciences. Written informed consent was received from all patients participated in the study.

Participants and Settings

The candidate patients of colorectal surgery referred to Ghaem hospital affiliated to Mashhad University of Medical Sciences during 2020. The inclusion criteria were patients' willingness to participate in the study, the age range of 18 to 65 years, the ASA physical status I or II, no history of diabetes mellitus, confirmed psychological disease, seizures, alcohol or other drug abuse, and not taking any analgesic or sedative during the past 24 hours before the surgery. The reluctance to continue participating in the study, occurrence of any unusual complication (eg, severe bleeding), cardiopulmonary resuscitation, and melatonin-related side effects (eg, hypothermia, severe headache, or severe weakness) during or postsurgery were considered as the exclusion criteria.

Interventions

Patients in the melatonin group received 1 melatonin sublingual tablet 6 mg, approximately 1 hour before the induction of general anesthesia and patients in the placebo group received 1 identical-looking placebo in the same time. The placebo was made by pharmacists in a similar way to melatonin pills.

Randomization

A coded list of the patients who were candidates for colorectal surgery was prepared. The patients were randomly assigned into 2 equal groups of melatonin and placebo using a random number table.

Blindness

To maintain blindness, all drugs were prepared in identical tablets and were put in numbered boxes. The study drugs were administered by the operating room nurse who was not involved in any other part of the study. Pain severity levels and sedation scores were assessed by a blinded and well-educated observer who was unaware of other steps of the study. Patients were unaware of their group.

Procedures

The surgeon and the anesthesiologist were identical for all patients. Patients were fasted for at least 8 hours. For all patients in both groups, midazolam (0.15 mg/kg) and fentanyl (2 to 3 µg/kg) were given as premedication. Then, propofol 2.0 to 2.5 mg/kg was applied as the induction and atracurium 0.5 mg/kg as the muscle relaxant. After 3 minutes, endotracheal intubation was performed. In patients of both groups, intraoperative monitoring was implemented, including the noninvasive measurement of blood pressure, heart rate, respiratory rate, arterial oxygen saturation, and electrocardiogram. Neostigmine (0.03 to 0.07 mg/kg) and atropine (0.02 mg/kg) were administered for reversal of neuromuscular blockade.

Outcomes and Measurements

The primary outcome was postoperative pain severity. For evaluating the pain severity, patients in both groups were examined at different time points, including baseline (on return to the ward from the operating room), 1, 2, 6, 12, and 24 hours postoperative by the numerical verbal

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Table 1. Ramsay sedation scale

Levels	Description	Score
Awake levels	The patient is anxious or restless, or both	1
	The patient cooperates, is aware and calm	2
	The patient responds to the command	3
Asleep levels	Only the patient responds quickly to a light tap on the eye or a loud auditory stimulus	4
	The patient responds slowly to light stroking of the eye or auditory stimulus with a loud voice	5
	The patient is unresponsive	6

response (NVR). This scale has 4 degrees (painless = 0, mild = 1, moderate = 2, and severe =3). We considered the time when patients arrived to the surgical ward as baseline information.

The secondary outcome was sedation status. The patients' sedation was evaluated using the Ramsay Sedation Score (RSS). The RSS is a 6-level and 2-category scale (Table 1).

Sample Size

The sample size in this study was calculated based on the mean score of postoperative pain in the study of Borazan et al (10) and using G-Power software by 2-sample t-test (V 3). Our sample size estimation indicated that 18 patients per group would give a power of 0.9, with a significance level of 5%. However, we increased the sample size per group to 30 patients (60 in sum), considering the attrition rate (or dropout) of 20%.

Statistical Analysis

The results were presented as mean ± SD for quantitative variables and were summarized by frequency (percentage) for categorical variables. The Kolmogorov-Smirnov test was used to check the distribution of the data. For statistical analysis, the t test or the Mann-Whitney U test were used to compare quantitative variables based on the normality of the data. Likewise, the chi-square test or the Fisher exact test were employed to compare the categorical variables and the repeated analysis of variance test was performed for the change in the quantitative variable. Statistically, $P \leq 0.05$ was considered as a significant difference. The study data were analyzed by SPSS Statistics for Windows, Version 24.0 (NY, USA).

Results

Study Characteristics

A total of 60 patients, 30 per group, were enrolled in the study and none was excluded (Fig. 1). Both melatonin and placebo groups were matched in baseline characteristics, including demographics, anthropometric parameters, surgery, anesthesia duration, and the mean dose of analgesics used. There was no significant difference between groups with respect to the baseline characteristics (Table 2). The total mean age of all patients was 49.35 ± 10.84 years (min, 25; max, 75).

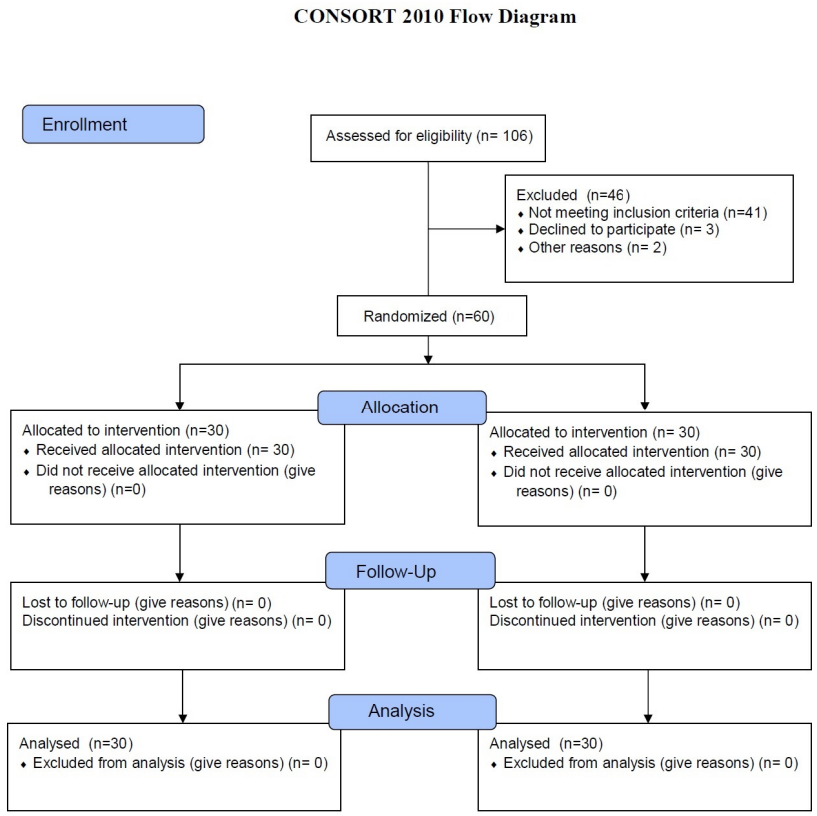

Fig. 1. Flow chart of study

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Table 2. Baseline characteristics in melatonin and placebo groups

Characteristics	Placebo (n=30)	Melatonin (n=30)	*P*-value
Mean age, year	50.58 ± 11.00	48.40 ± 11.91	0.431*
Mean weight, kg	69.16 ± 12.42	67.20 ± 13.22	0.550*
Mean height, cm	167.83 ± 10.61	170.26 ± 8.46	0.332*
Mean operation time, hour	3.84 ± 0.80	3.53 ± 0.78	0.140*
Mean anesthesia time, hour	4.29 ± 0.80	3.99 ± 0.78	0.151*
Mean number of analgesics	1.33 ± 1.24	2.43 ± 1.22	0.002*
Receiving analgesics, n (%)	27 (90.0)	19 (63.3)	0.010*
Male gender, n (%)	17 (56.7)	14 (46.70)	0.431*
Type of surgery, n (%)			0.898**
Colon	11 (36.70)	10 (33.30)	
Stoma	8 (26.70)	9 (30.0)	
Rectum	5 (16.70)	6 (20.0)	
Others	4 (13.30)	2 (6.70)	
Sigmoid	2 (6.70)	3 (10.0)	

* T-test; ** Chi-Square= 1.064; df=4

Primary Outcome

The distribution of patients in both groups based on postoperative pain severity is shown in Table 3. The mean scores of postoperative pains during 24 hours are shown in Table 4. The patients in the melatonin group experienced lower pain severity scores during 24 hours post-surgery. However, the mean score of pain severity of patients in the melatonin group was significantly lower compared with those of the placebo group at 2, 6, 12, and 24 hours after surgery. In addition, the total mean pain score for the first 12 hours and the mean score of pain in 24 hours after surgery were significantly lower in the melatonin group compared with the placebo group.

As depicted in Figure 2, the total mean scores of postoperative pain severity in both groups decreased over time (from 2.72 to 1.12). A repeated measure analysis of variance, with a Greenhouse-Geisser correction, determined that the mean value of postoperative pain has been statistically significant between different time points, including base, 6, 12, and 24 hours ($p = 0.001$). There was no interaction between groups and time points. The post hoc test using the Bonferroni correction revealed a significant decrease in the mean of pain scores between the baseline and 6, 12, and 24 hours after surgery ($p = 0.001$).

Secondary Outcome

Table 5 shows the distribution of sedation levels of patients in both groups. During postoperative time points, none of the patients in the 2 groups was placed in the fifth and sixth levels of the Ramsey sedation scale. To find whether the second level of sedation is different between the 2 groups, we divided the levels of sedation into 2 classes: the second level and the other levels. At time points of the baseline, 1, and 2 hours, the number of patients who were cooperative, aware, and calm (level 2) was significantly higher in the melatonin group (Table 6; $p = 0.025$).

Table 3. Distribution of patients in both groups based on postoperative pain severity

Time points		Groups			
		Placebo (n=30)		Melatonin (n=30)	
		n	Column %	n	Column %
Pain score at base	No Pain	0	0.0	0	0.0
	Mild Pain	0	0.0	1	3.30
	Moderate Pain	5	16.70	10	33.30
	Severe Pain	25	83.30	19	63.30
Pain score at 1h	No Pain	0	0.0	0	0.0
	Mild Pain	0	0.0	1	3.30
	Moderate Pain	6	20.0	10	33.30
	Severe Pain	24	80.0	19	63.30
Pain score at 2h	No Pain	0	0.0	1	3.30
	Mild Pain	0	0.0	2	6.70
	Moderate Pain	6	20.0	11	36.70
	Severe Pain	24	80.0	16	53.30
Pain score at 6h	No Pain	1	3.30	5	16.70
	Mild Pain	5	16.70	7	23.30
	Moderate Pain	10	33.30	13	43.30
	Severe Pain	14	46.70	5	16.70
Pain score at 12h	No Pain	4	13.30	8	26.70
	Mild Pain	5	16.70	9	30.0
	Moderate Pain	11	36.70	9	30.0
	Severe Pain	10	33.30	4	13.30
*Pain score at 24h	No Pain	5	16.70	12	40.0
	Mild Pain	12	40.0	12	40.0
	Moderate Pain	9	30.0	5	16.70
	Severe Pain	4	13.30	1	3.30

*Example of table interpretation: 13.3% (n=4) of patients in the placebo group had severe pain, while only 3.3% (n=1) of patients in the melatonin group had severe pain.

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Table 4. The mean scores of postoperative pains for 24 hours

Time points after surgery (hour)	Groups (Mean ± SD)			95% CI		*P*-Value (T-test)
	Placebo (n=30)	Melatonin (n=30)	MD (SE)	Lower	Upper	
Pain score at base	2.83 ± 0.37	2.60 ± 0.56	0.23 (0.12)	-0.01	0.48	0.070
Pain score at 1	2.80 ± 0.40	2.60 ± 0.56	0.20 (0.13)	-0.05	0.45	0.140
Pain score at 2	2.80 ± 0.40	2.40 ± 0.77	0.40 (0.16)	0.08	0.72	0.020
Pain score at 6	2.23 ± 0.85	1.60 ± 0.96	0.63 (0.24)	0.16	1.11	0.010
Pain score at 12	1.90 ± 1.02	1.30 ± 1.02	0.60 (0.26)	0.07	1.13	0.020
Pain score at 24	1.40 ± 0.93	0.83 ± 0.83	0.57 (0.23)	0.11	1.02	0.010
*Pain score of the first 12 hours	2.51 ± 0.38	2.10 ± 0.54	0.41 (0.12)	0.17	0.65	0.010
**Total pain score	2.33 ± 0.42	1.88 ± 0.54	0.44 (0.13)	0.19	0.69	0.001

Note: *Total means score of pain for the first 12 hours after surgery. ** Mean pain score for a total of 24 hours after surgery.
T-test was used to determine if there is a significant difference between the mean scores of two groups at each time point. MD: Mean Difference

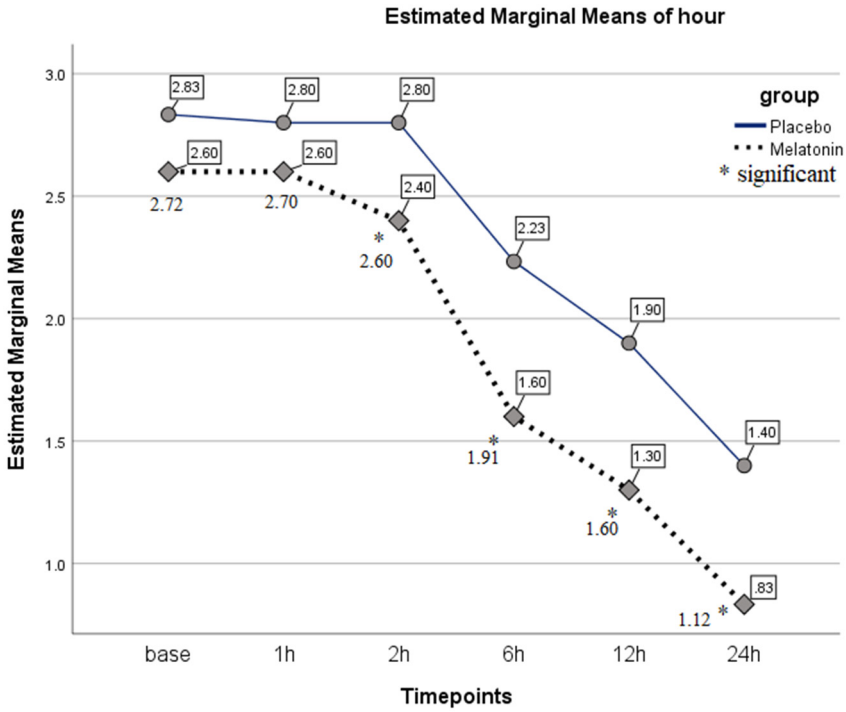

Fig. 2. The total mean scores of postoperative pain over time

As shown in Table 7, the mean score of sedation of patients in the melatonin group was significantly lower compared with those of the placebo group at the baseline, 2, and 6 hours after surgery.

Discussion

The main purpose of the present triple-blind, randomized clinical trial was to evaluate the effect of preoperative sublingual melatonin on postoperative pain in patients undergoing colorectal surgery. The result of our study revealed that the use of 6 mg preoperative melatonin sublingual tablet could reduce the severity of postoperative pain. We found that after the administration of sublingual melatonin in the induction phase, its analgesic effects begin about 2 hours after surgery. This is because the pain severity scores of patients at the time of admission to the ward and 1 hour later were not significantly different between the 2 groups. Patients receiving melatonin had less pain severity for both the first 12 hours and the total 24 hours. We also found that although the severity of postoperative pain in both groups decreased about 50% over time, patients in the melatonin groups experienced less intense pain at 6, 12, and 24 hours after surgery. This finding suggests that the analgesic effects of melatonin increase over time.

In terms of sedation levels, many patients experience anxiety and restlessness in the early hours of leaving the recovery room. Our findings showed that the use of melatonin sublingual tablets could reduce the patient's restlessness and anxiety and increase patients' cooperation during the 2 hours after surgery. In this regard, the number of patients who were cooperative, aware, and calm (level II of Ramsay sedation scale) was higher in the melatonin group. Based on our findings, the sedative effects of melatonin were predominant in the melatonin group in the first 6 hours after surgery, but over time, the sedative effects

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Table 5. Distribution of sedation levels of patients in both groups

		*Groups					
		Placebo		Melatonin		Total	
Time points	State	n	%	n	%	n	%
[a] Sedation score at base	1	12	40.0	1	3.30	13	21.70
	2	13	43.30	16	53.30	29	48.30
	3	5	16.70	10	33.30	15	25.0
	4	0	0.0	3	10.0	3	5.0
	5	0	0.0	0	0.0	0	0.0
	6	0	0.0	0	0.0	0	0.0
[a] Sedation score at 1h	1	11	36.70	2	6.70	13	21.70
	2	11	36.70	18	60.0	29	48.30
	3	8	26.70	9	30.0	17	28.30
	4	0	0.0	1	3.30	1	1.7
	5	0	0.0	0	0.0	0	0.0
	6	0	0.0	0	0.0	0	0.0
[a] Sedation score at 2h	1	7	23.30	2	6.70	9	15.0
	2	10	33.30	24	80.0	34	56.70
	3	13	43.30	4	13.30	17	28.30
	4	0	0.0	0	0.0	0	0.0
	5	0	0.0	0	0.0	0	0.0
	6	0	0.0	0	0.0	0	0.0
Sedation score at 6h	1	14	46.70	2	6.70	16	26.70
	2	16	53.30	22	73.30	38	63.30
	3	0	0.0	6	20.0	6	10.0
	4	0	0.0	0	0.0	0	0.0
	5	0	0.0	0	0.0	0	0.0
	6	0	0.0	0	0.0	0	0.0
Sedation score at 12h	1	16	53.3	0	0.0	16	26.7
	2	14	46.7	21	70.0	35	58.3
	3	0	0.0	9	30.0	9	15.0
	4	0	0.0	0	0.0	0	0.0
	5	0	0.0	0	0.0	0	0.0
	6	0	0.0	0	0.0	0	0.0
Sedation score at 24h	1	3	10.0	3	10.0	6	10.0
	2	25	83.3	25	83.3	50	83.3
	3	1	3.3	2	6.7	3	5.0
	4	0	0.0	0	0.0	0	0.0
	5	1	3.3	0	0.0	1	1.7
	6	0	0.0	0	0.0	0	0.0

[a] The chi-square (Fisher exact test) is significant at the .05 level.
Interpretation note: percent is related to column for each time point.
*Reading example: A state of sedation of 21.7% of all patients was 1 at baseline.
Sedation state: 1) anxious or restless; 2) cooperative, aware and calm; 3) responds to command; 4) responds quickly to stimulus; 5) responds slowly to strong stimulus; 6) unresponsive

Table 6. Distribution of patients based on level 2 of sedation

		Groups					
		Placebo		Melatonin		Total	
		n	%	n	%	n	%
[a] Sedation levels at base	Other	17	56.7	14	46.7	31	51.7
	Level two	13	43.3	16	53.3	29	48.3
[a] Sedation levels at 1h	Other	19	63.3	12	40.0	31	51.7
	Level two	11	36.7	18	60.0	29	48.3
[a] Sedation levels at 2h	Other	20	66.7	6	20.0	26	43.3
	Level two	10	33.3	24	80.0	34	56.7
Sedation levels at 6h	Other	14	46.7	8	26.7	22	36.7
	Level two	16	53.3	22	73.3	38	63.3
Sedation levels at 12h	Other	16	53.3	9	30.0	25	41.7
	Level two	14	46.7	21	70.0	35	58.3
Sedation levels at 24h	Other	5	16.7	5	16.7	10	16.7
	Level two	25	83.3	25	83.3	50	83.3

Interpretation: [a] Two-sided tests with significance level of 0.05 (Mann-Whitney U test). Tests are adjusted for using the Bonferroni correction

decreased so that in the following hours there was no significant difference between the 2 groups.

Regarding the postoperative analgesic effects of melatonin, some studies have shown contradictory results on its efficacy in various surgeries. Consistent with the findings of the present study, Maitra et al stated that melatonin could increase postoperative analgesia and reduce the need for postoperative analgesics (16). Gitto et al noted that melatonin, like midazolam, may be effective on analgesia in patients undergoing surgery (17). Nickkholgh et al documented that melatonin could reduce the use of analgesics in patients undergoing liver surgery (18). Lee et al found that there was higher pain relief in patients receiving melatonin (19). In contrast to our findings,

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Table 7. Mean and standard deviation of sedation scores between control and intervention groups at each time point

Sedation score at:	Group		*P*-value
	Control	Melatonin	
	M ± SD	M ± SD	
base	1.77 ± 0.728	2.50 ± 0.731	0.016
1 hour	1.90 ± 0.803	2.30 ± 0.651	0.031
2 hour	1.80 ± 0.80	2.07 ± 0.45	0.001
6 hour	1.53 ± 0.50	2.13 ± 0.50	0.014
12 hour	2.47 ± 0.50	2.30 ± 0.46	0.110
24 hour	2.03 ± 0.66	1.97 ± 0.41	0.980

Interpretation: a Two-sided tests with significance level of 0.05 (Independent Samples T-test)

Laosuwan et al observed no significant difference between the score of pain at 1, 6, and 24 hours after hysterectomy in the patients undergoing receiving melatonin compared with the placebo group (20).

Marzban compared the effect of melatonin and gabapentin on pain and anxiety in patients undergoing cataract surgery and found significant reduction in the severity of pain after surgery (21). In addition, Anderson et al (2014) found that 3 mg intravenous melatonin could not reduce pain after laparoscopic cholecystectomy (15).

Although the exact mechanism of melatonin is unclear, it assumed that the analgesic effects of melatonin are mediated by central and peripheral effects. Centrally, specific receptors of melatonin (MT1 and MT2) interact with opioid receptors and the peripheral effects of melatonin are attributed to anti-inflammatory properties (15). In addition, it is assumed that melatonin affects pain perception; therefore, melatonin plays a crucial role in regulating pain under normal physiological conditions due to its pain perception (22). In other words, melatonin could weaken the response to various painful stimuli (23).

Several proinflammatory mediators as well as activation of neurotransmitter receptor sites can induce pain in the central nervous system (24). In contrast, several animal and human studies have shown that melatonin can control the release of proinflammatory mediators, such as cytokines, and inactivates the sites of receptors involved in pain perception in the central nervous system. In addition, by improving sleep quality, melatonin can moderate pain perception (25). According to these mechanisms, the use of melatonin has been recommended in controlling pain in several conditions, such as postoperative pain, chronic headaches, cancer pain, neuropathic pain, and fibromyalgia (26, 27).

Limitations

This study had limitations that may limit the generalizability of the results. First, the time of the patient leaving the recovery room was not in our control. Hence, baseline data may not be collected at the same time in different patients. Second, patient reporting of pain can be influenced by individual, cultural, and environmental characteristics as well as previous experience of pain perception. This issue was not under our control, but by randomly assigning patients to 2 groups and evaluating postoperative pain by external evaluator, we reduced the impact of this issue on the results of the study. Third, although we accurately recorded the dose of analgesics received by patients in both groups, accurate control of the effects of these analgesics and differentiation of these effects from the studied drugs was not under our control. This issue was also negligible by the random allocation of patients.

Conclusion

The use of 6 mg preoperative melatonin sublingual tablet in patients with colorectal surgery could reduce the severity of postoperative pain, patients' restlessness and anxiety and increase patients' cooperation and calmness. Therefore, it seems that sublingual melatonin is an effective, low-cost drug with a low rate of side effects in controlling postoperative pain.

Acknowledgment

The authors thank the all participants in this study.

Ethical Approval

This randomized controlled trial was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethical No. IR.MUMS.MEDICAL.REC.1398.149).

Conflict of Interests

The authors declare that they have no competing interests.

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