



# The Effect of Melatonin on Appendectomy Postoperative Pain: A Randomized Clinical Trial

Mahla Khoramvar<sup>1</sup>, Abbas Moallemy<sup>1</sup>, Hashem Jarineshin<sup>1</sup>, Fereydoon Fekrat<sup>1</sup>, Alireza Abdollahzadeh<sup>1\*</sup>

<sup>1</sup>Anesthesiology, Critical Care, and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

\*Corresponding Author: Alireza Abdollahzadeh, Email: [Bagha\\_ar@yahoo.com](mailto:Bagha_ar@yahoo.com)

## Abstract

**Background:** Melatonin is synthesized from the tryptophan amino acid in the pineal gland. Its role in sleep has been confirmed in other studies. Several studies have also shown the effect of melatonin on postoperative pain and sedation. This study aimed to evaluate the effect of melatonin on postoperative pain in patients undergoing appendectomy.

**Methods:** In a double-blind clinical trial, 64 patients aged 18–50 years with ASA I/II anesthesia class who were candidates for appendectomy with general anesthesia were enrolled. The patients were randomly divided into two groups: melatonin and placebo (32 people in each group). The first group received 6 mg of oral melatonin one hour before sleep, while the second group received a placebo. Before surgery and 2, 12, and 24 hours after surgery, patients' pain was measured using the Visual Analogue Scale (VAS). The Ramsay sedation score measured the patients' sedation, and rescue analgesia was measured at the above time points. SPSS software was used to analyze the data, and  $P$ -values  $< 0.05$  were considered significant.

**Results:** Our study showed that pain levels in the melatonin group were lower at the 2nd, 12th, and 24th hours after the appendectomy surgery than in the placebo group. Sedation rates were not significantly different between the two groups. Analgesic consumption was lower in the melatonin group than in the placebo group.

**Conclusion:** Melatonin can reduce the degree of pain (VAS) after appendectomy.

**Keywords:** Melatonin, Postoperative pain, Appendectomy

**Citation:** Khoramvar M, Moallemy A, Jarineshin H, Fekrat F, Abdollahzadeh A. The effect of melatonin on appendectomy postoperative pain: a randomized clinical trial. *Journal of Kerman University of Medical Sciences*. 2024;31(2):93–97. doi: [10.34172/jkmu.2024.16](https://doi.org/10.34172/jkmu.2024.16)

**Received:** August 20, 2023, **Accepted:** January 12, 2024, **ePublished:** April 29, 2024

## Introduction

Pain is an unpleasant sense and emotional experience that could impact a patient's health (1).

Nowadays, millions of people undergo operations as part of their treatment protocol. Postoperative pain control plays an essential role in improving the quality of health care. Many studies have evaluated the untoward effects of inadequate pain control on the physiologic processes of the human body. Despite a large body of literature on this subject, a sufficient and effective method for postoperative pain control is yet to be found (2,3). Although opioids play a significant part in alleviating postoperative pain, their side effects limit their widespread use. In addition to the search for multimodal analgesic pathways, trying to use analgesics other than opioids for postoperative pain control has become the subject of extensive investigation (4-6).

Melatonin (N-acetyl-5-methoxytryptamine) is a potential antioxidant secreted by the pineal gland as a regulator of the circadian rhythm. Its function on the spinal cord indicates that it also plays a role in the pain pathway (7). Melatonin has been evaluated for different

pain conditions, such as neuropathic and inflammatory pain (8). It has even been found to have intracellular modulating effects (9). Melatonin is lipophilic and can be transferred via the cerebrovascular membrane (10).

The effect of melatonin has been evaluated in postoperative pain for some surgeries, such as prostatectomy and hysterectomy, with positive results (11-12). The sedative effect of melatonin has been evaluated in some studies (13,14) for instance, in patients admitted to intensive care units (15). However, its effect on delirium has been studied without any positive results (16).

Considering that a number of surgeries are appendectomies, it is critical to control postoperative pain effectively (17).

## Methods

This study is a double-blind clinical trial and was conducted to evaluate the effect of melatonin on postoperative pain of patients with appendectomy in Iran.

The sample size was calculated rendering to similar preceding study (18) using the formula below for comparing mean data between two groups. Each group



needed 18 patients with a type I error of 0.05 and a type II error of 0.20. To increase the power of the study, we assigned 32 patients to each group.

$$n = \frac{\left( z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 (s_1^2 + s_2^2)}{d^2}$$

After obtaining approval from the Ethics Committee of the university and informed consent from patients to participate in the study, 64 adults aged between 18 and 50 years old with ASA I/II status who were candidates for appendectomy with general anesthesia were enrolled. Random allocation using enveloped cards was done for case assignment (Figure 1).

Patients with uncontrolled concurrent diseases, addiction, allergy to melatonin, neurological or psychiatric disease, sleep disorders, history of taking analgesics for other reasons, and patients needing laparotomy were excluded from the study.

One hour before the operation, the pain score and sedation were measured using the visual analog scale and the Ramsay sedation score, respectively, as baseline data. Then, patients in group M (melatonin) were given 6 mg of melatonin (tablet, Vitane Nature, USA), and those in group P (placebo) were given a placebo. The nurse who presented drugs to patients and the patients were unaware of the groups and drugs.

After entering the operating room and being set on the bed, the patient received anesthesia. In addition to standard electrocardiogram and pulse oximetry

monitoring, blood pressure and baseline hemodynamic parameters were recorded for all patients. Patients in both groups received the same anesthesia. For all patients, a pre-anesthetic dose of 2 mg/kg of midazolam and 2 µg/kg of fentanyl were administered. Induction of anesthesia was performed with propofol at a dose of 2 mg/kg, followed by atracurium at a dose of 0.5 mg/kg. Anesthesia was continued with propofol at 100 µg/kg/min. Analgesia was established by 0.05 mg/kg morphine injection. If necessary, the patients were given other drugs as necessary and were excluded from the study.

The specific outcomes were pain severity measurement using a visual analog scale and the Ramsey sedation score, measured 2, 12, and 24 hours after operation. For the Visual Analogue Scale (VAS) scoring, the patients were trained to announce their pain intensity rating using a visual scale, with 10 as the highest pain score and zero as the lowest. Patients with a VAS score of more than 3 received analgesics, such as Apotel 1 g, and were recorded in the researcher's checklist.

Sedation was evaluated using criteria introduced by Ramsay's sedation scale, which ranged from 1 to 6.

All patients were monitored for presentation of side effects such as hypotension (systolic blood pressure less than 90 mm mercury), bradycardia (heart rate less than 60 beats per minute), and respiratory depression (respiration less than 12 times per minute).

The researcher, who was unaware of the group assignments, recorded the above information in a checklist. Demographic characteristics, including age,

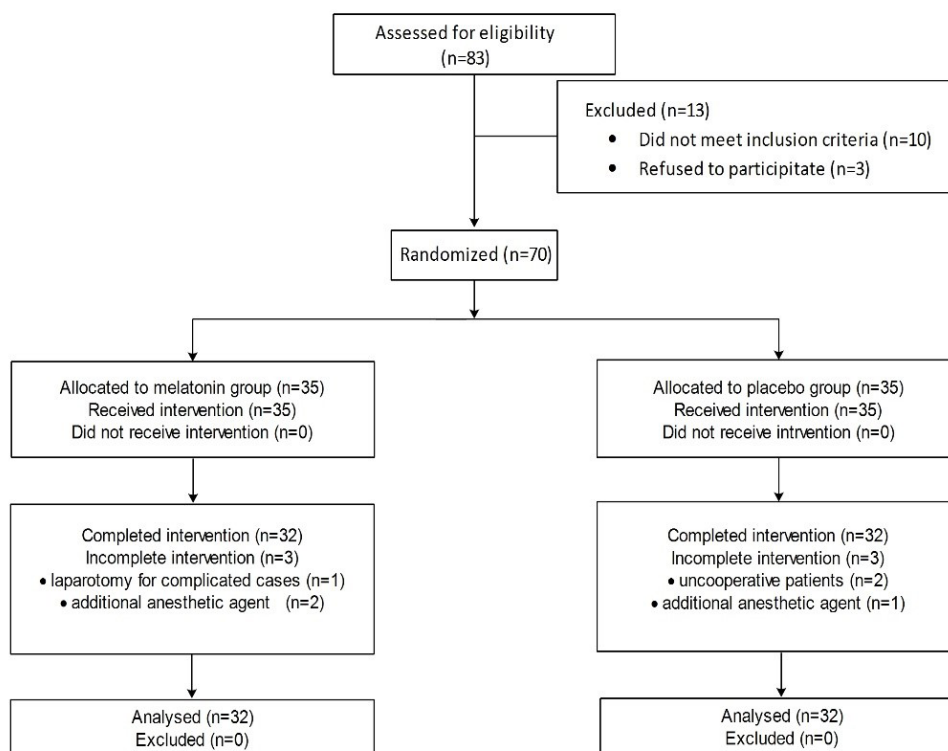


Figure 1. CONSORT flow chart

weight, and gender, were also recorded in this checklist.

### Data analysis

Data were analyzed using SPSS statistical software (IBM, Chicago, Illinois). Descriptive statistics such as mean and standard deviation, frequency, and percentage, as well as independent samples t-test or chi-square, were calculated. In this study, *P* values less than 0.05 were considered statistically significant.

## Results

### Demographic data

In this study, 64 patients participated. Among them, 32 patients (12 female and 20 male) were in the melatonin group (M), and 32 patients (10 female and 22 male) were in the placebo group (P). The average age was  $30.7 \pm 10.2$  and  $27.2 \pm 6.8$  in groups M and P, respectively, without clinical significance. Patient weight was  $66 \pm 7.8$  and  $65.6 \pm 11.2$  in groups M and P, respectively, without clinical significance (Table 1).

### Main findings

The two groups' pain severity, sedation score, and dosage of analgesics used are compared in Table 2.

None of the subjects in our study had complications such as respiratory depression, bradycardia, or hypotension.

### Discussion

Based on the results of this study, pain intensity was lower in the melatonin group than in the placebo group. We used a visual analog scale for pain measurement. Analgesic consumption was lower in the melatonin group, which was significant at 2 and 12 hours after surgery.

Similar studies have shown the effectiveness of melatonin in the control of pain.

In 2021, Hassanzadeh Kiabi et al investigated the effect of preoperative melatonin on cesarean section postoperative pain. Their results showed a reduction of pain and analgesic consumption by 2, 6, 12, and 24 hours after surgery by 10 mg melatonin. Their results were similar but with a higher dose of melatonin in comparison with our study (19).

In another study, Laflı Tunay et al evaluated the effect of 6 mg melatonin on postoperative pain among patients with major abdominal surgery. They reported a significant reduction in pain, which aligns with our findings. Their

measured sedation score was only high in the melatonin group in the first 30 minutes. Considering that the first assessment time was 2 hours after surgery, our study did not show any difference in sedation scores between the two groups. However, the dose of melatonin was lower in our study (20).

In 2018, Haddadi et al evaluated the analgesic effects of melatonin and acetaminophen on patients undergoing cataract surgery under the retrobulbar block. They found that the analgesic effect of melatonin was comparable with acetaminophen, and in addition, the melatonin group had less need for fentanyl (21).

The analgesic effect of melatonin has also been compared with gabapentin in the research of Javaherforooshzadeh et al, among others. They designed a study to evaluate anxiety, patient satisfaction, and pain scores. Even though the analgesic efficacy of melatonin was lower than that of gabapentin, it was significantly higher than that of the placebo. Also, they had the same efficacy in alleviating anxiety and gaining patient satisfaction (18).

The effects of melatonin on pain intensity have been evaluated in three meta-analyses.

Andersen et al, in their systematic review, suggested that preoperative melatonin reduces postoperative pain compared with placebo, but the magnitude of this effect is substantially heterogeneous (22).

Zhu and colleagues' systematic review, which analyzed 19 studies, demonstrated the analgesic effect of melatonin and its ability to reduce analgesic requirements. However, they suggested further study was required to confirm their results (23).

Nao Oh et al conducted a meta-analysis to evaluate the effect of melatonin on chronic pain as well as postoperative pain. The review of 30 trials led to the conclusion that melatonin could be used to treat chronic pain. At the same time, there was insufficient evidence for acute postoperative or procedural pain (24).

Current literature confirms melatonin's analgesic efficacy, but the exact dose and its additional effects, such

**Table 1.** Comparison of demographic variables between the two groups

Variable	Group M	Group P	<i>P</i> value	
Number of patients	32	32	-	
Gender	Female	12	10	-
	Male	20	22	-
Age	$30.7 \pm 10.2$	$27.2 \pm 6.8$	0.11	
Weight	$66 \pm 7.8$	$65.6 \pm 11.2$	0.86	

**Table 2.** Comparison of outcomes between the two groups

Variable	Time	Group M	Group p	<i>P</i> value
Pain severity using VAS	Baseline	$4.19 \pm 1.2$	$4.94 \pm 1.5$	0.849
	After 2 hours	$5.94 \pm 1.9$	$7.09 \pm 1.9$	0.008
	After 12 hours	$4.06 \pm 1.03$	$5.53 \pm 1.4$	0.013
	After 24 hours	$2.97 \pm 0.69$	$3.44 \pm 0.71$	0.032
Ramsey sedation score	Baseline	$1.53 \pm 0.50$	$1.53 \pm 0.50$	>0.05
	After 2 hours	$2.06 \pm 0.75$	$2 \pm 0.95$	>0.05
	After 12 hours	$2.19 \pm 0.59$	$2.16 \pm 0.51$	>0.05
	After 24 hours	$2.22 \pm 0.39$	$2.18 \pm 0.42$	>0.05
Analgesic	After 2 hours	22	29	0.048
	After 12 hours	18	23	0.039
	After 24 hours	7	9	0.562

as its sedative properties, remain a particular concern.

As seen in earlier studies, even in the two meta-analyses, none of the studies was designed to evaluate the analgesic effect of melatonin on appendectomy postoperative pain.

Our study showed the postoperative analgesic effect of melatonin, even at a lower dose than other studies, without any significant rise in sedative effect. It is suggested that future studies evaluate different doses and routes for melatonin administration to treat postoperative pain.

### Conclusion

Preoperative oral administration of 6 mg melatonin could reduce postoperative pain scores and analgesic consumption after appendectomy. There was no significant difference in sedation between the melatonin and placebo groups.

### Acknowledgements

The authors acknowledge the operation room personnel of Shahid Mohammadi Hospital for their cooperation in conducting this research.

### Authors' Contribution

**Conceptualization:** Alireza Abdollahzadeh, Fereydoon Fekrat, Hashem Jarineshin, Abbas Moallemy.

**Data curation:** Alireza Abdollahzadeh, Mahla Khoramvar, Fereydoon Fekrat, Abbas Moallemy.

**Formal Analysis:** Alireza Abdollahzadeh, Mahla Khoramvar, Hashem Jarineshin, Fereydoon Fekrat.

**Investigation:** Alireza Abdollahzadeh, Hashem Jarineshin, Mahla Khoramvar, Fereydoon Fekrat, Abbas Moallemy.

**Methodology:** Alireza Abdollahzadeh, Fereydoon Fekrat, Mahla Khoramvar.

**Project administration:** Alireza Abdollahzadeh, Fereydoon Fekrat, Hashem Jarineshin, Mahla Khoramvar.

**Resources:** Alireza Abdollahzadeh, Fereydoon Fekrat, Hashem Jarineshin, Abbas Moallemy, Mahla Khoramvar.

**Software:** Alireza Abdollahzadeh, Fereydoon Fekrat, Hashem Jarineshin.

**Supervision:** Alireza Abdollahzadeh, Hashem Jarineshin, Abbas Moallemy.

**Validation:** Alireza Abdollahzadeh, Fereydoon Fekrat, Hashem Jarineshin, Abbas Moallemy.

**Visualization:** Alireza Abdollahzadeh, Hashem Jarineshin, Mahla Khoramvar, Fereydoon Fekrat, Abbas Moallemy.

**Writing—original draft:** Alireza Abdollahzadeh, Hashem Jarineshin, Mahla Khoramvar, Fereydoon Fekrat, Abbas Moallemy.

**Writing—review & editing:** Alireza Abdollahzadeh, Mahla Khoramvar, Fereydoon Fekrat.

### Competing Interests

The authors declare that they have no competing interests.

### Ethical Approval

This study was approved by the Ethics Committee of the Hormozgan University of Medical Sciences (Ethical code: IR. HUMS. Rec.1397.203) and registered at the Iranian Registry of Clinical Trials website (identifier: IRCT20220507054763N1) (<https://irct.behdasht.gov.ir/trial/64717>)

### Funding

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

### References

1. Tadayyonfar M, Amadani M, Tajabadi A, Tabaraee Y, Khosrojerdi H. Comparison of effect of promethazine and diclofenac on pain control of appendectomy surgery: a randomized clinical trial. *J Sabzevar Univ Med Sci.* 2016;23(1):14-20. [Persian].
2. Koohestani HR, Baghcheghi N, Rezaei K. Comparison of satisfaction with post-operative pain management and level of functional interference in addicted and non-addicted patients. *J Holist Nurs Midwifery.* 2014;24(3):48-55. [Persian].
3. Momenzadeh S, Mohammadinasab H, Younesi Z, Sayadi M. Evaluation of patients' satisfaction following postoperative acute pain management. *J Iran Med Council.* 2012;29(4):331-7. [Persian].
4. Lee W, Hahn K, Hur J, Kim Y. Effect of topical lidocaine patch on postoperative pain management in laparoscopic appendectomy: a randomized, double-blind, prospective study. *J Laparoendosc Adv Surg Tech A.* 2018;28(9):1061-7. doi: [10.1089/lap.2018.0013](https://doi.org/10.1089/lap.2018.0013).
5. Nesioonpour S, Mokmeli S, Vojdani S, Mohtadi A, Akhondzadeh R, Behaee K, et al. The effect of low-level laser on postoperative pain after tibial fracture surgery: a double-blind controlled randomized clinical trial. *Anesth Pain Med.* 2014;4(3):e17350. doi: [10.5812/aapm.17350](https://doi.org/10.5812/aapm.17350).
6. Imani F, Rokhtabnak F, Radmehr M, Taherifard P. Evaluation of analgesic effect of adding magnesium to lidocaine in patient-controlled regional analgesia (PCRA) after foot surgery. *J Anesth Pain.* 2011;1(3):48-56. [Persian].
7. Jan JE, Reiter RJ, Wong PK, Bax MC, Ribary U, Wasdell MB. Melatonin has membrane receptor-independent hypnotic action on neurons: an hypothesis. *J Pineal Res.* 2011;50(3):233-40. doi: [10.1111/j.1600-079X.2010.00844.x](https://doi.org/10.1111/j.1600-079X.2010.00844.x).
8. Babaei-Balderlou F, Illkhanipour M, Heidari R, Zare S, Bernousi I. Effect of melatonin on peripheral neuropathic pain in diabetic rat. *Iran J Endocrinol Metab.* 2009;11(1):79-87. [Persian].
9. Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. *J Pineal Res.* 2012;52(4):365-75. doi: [10.1111/j.1600-079X.2011.00962.x](https://doi.org/10.1111/j.1600-079X.2011.00962.x).
10. Arendt J, Rajaratnam SM. Melatonin and its agonists: an update. *Br J Psychiatry.* 2008;193(4):267-9. doi: [10.1192/bjp.bp.108.050955](https://doi.org/10.1192/bjp.bp.108.050955).
11. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. *J Anesth.* 2010;24(2):155-60. doi: [10.1007/s00540-010-0891-8](https://doi.org/10.1007/s00540-010-0891-8).
12. Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. *J Pain.* 2009;10(1):100-8. doi: [10.1016/j.jpain.2008.08.007](https://doi.org/10.1016/j.jpain.2008.08.007).
13. Beigom Khezri M, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. *Indian J Ophthalmol.* 2013;61(7):319-24. doi: [10.4103/0301-4738.99637](https://doi.org/10.4103/0301-4738.99637).
14. Küçükakin B, Wilhelmsen M, Lykkesfeldt J, Reiter RJ, Rosenberg J, Gögenur I. No effect of melatonin to modify surgical-stress response after major vascular surgery: a randomised placebo-controlled trial. *Eur J Vasc Endovasc Surg.* 2010;40(4):461-7. doi: [10.1016/j.ejvs.2010.06.014](https://doi.org/10.1016/j.ejvs.2010.06.014).
15. Mistraretti G, Umbrello M, Sabbatini G, Miori S, Taverna M,

- Cerri B, et al. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. *Minerva Anesthesiol.* 2015;81(12):1298-310.
16. de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, et al. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ.* 2014;186(14):E547-56. doi: [10.1503/cmaj.140495](https://doi.org/10.1503/cmaj.140495).
  17. do Carmo de Oliveira Ribeiro M, Simone JC, Ramiro TH, Santos VS, da Silva Nunes M, Barreto-Alves JA JA. Pain in patients undergoing appendectomy. *Rev Dor.* 2014;15(3):198-201. doi: [10.5935/1806-0013.20140043](https://doi.org/10.5935/1806-0013.20140043).
  18. Javaherforooshzadeh F, Amirpour I, Janatmakan F, Soltanzadeh M. Comparison of effects of melatonin and gabapentin on post operative anxiety and pain in lumbar spine surgery: a randomized clinical trial. *Anesth Pain Med.* 2018;8(3):e68763. doi: [10.5812/aapm.68763](https://doi.org/10.5812/aapm.68763).
  19. Hassanzadeh Kiabi H, Emadi SA, Ebadi Jamkhaneh A, Aezzi G, Shahzadeh Ahmadi N. Effects of preoperative melatonin on postoperative pain following cesarean section: a randomized clinical trial. *Ann Med Surg (Lond).* 2021;66:102345. doi: [10.1016/j.amsu.2021.102345](https://doi.org/10.1016/j.amsu.2021.102345).
  20. Laflı Tunay D, Türkeün İlginel M, Ünlügenç H, Tunay M, Karacaer F, Biricik E. Comparison of the effects of preoperative melatonin or vitamin C administration on postoperative analgesia. *Bosn J Basic Med Sci.* 2020;20(1):117-24. doi: [10.17305/bjbms.2019.4379](https://doi.org/10.17305/bjbms.2019.4379).
  21. Haddadi S, Shahrokhirad R, Ansar MM, Marzban S, Akbari M, Parvizi A. Efficacy of preoperative administration of acetaminophen and melatonin on retrobulbar block associated pain in cataract surgery. *Anesth Pain Med.* 2018;8(5):e61041. doi: [10.5812/aapm.61041](https://doi.org/10.5812/aapm.61041).
  22. Andersen LP, Werner MU, Rosenberg J, Gögenur I. A systematic review of peri-operative melatonin. *Anaesthesia.* 2014;69(10):1163-71. doi: [10.1111/anae.12717](https://doi.org/10.1111/anae.12717).
  23. Zhu C, Xu Y, Duan Y, Li W, Zhang L, Huang Y, et al. Exogenous melatonin in the treatment of pain: a systematic review and meta-analysis. *Oncotarget.* 2017;8(59):100582-92. doi: [10.18632/oncotarget.21504](https://doi.org/10.18632/oncotarget.21504).
  24. Oh SN, Myung SK, Jho HJ. Analgesic efficacy of melatonin: a meta-analysis of randomized, double-blind, placebo-controlled trials. *J Clin Med.* 2020;9(5):1553. doi: [10.3390/jcm9051553](https://doi.org/10.3390/jcm9051553).