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Preventive Dose of Melatonin on Postoperative Pain in Total Abdominal Hysterectomy: A Clinical Trial Study

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ABSTRACT

Background & Objective: Studies have shown contradictory results regarding the use of pregabalin and melatonin as analgesic agents. Because the analgesic effects of these drugs as preemptive have not been compared in abdominal hysterectomy, one of the most common surgical procedures in women with moderate to severe pain, under general anesthesia. The aim of this study was to compare the pretreatment effects of melatonin and pregabalin on postoperative pain intensity in total abdominal hysterectomy (TAH).

Materials & Methods: Ninety Patients were randomly divided into three groups (N=30): the first group received oral melatonin (6 mg), the second group received pregabalin (50 mg), and the third one who took no drug. Serum melatonin and beta-endorphin levels were measured before and after the surgery. Pain intensity was assessed by the Numerical Rating Scale at 1,6,12, and 24 hours after the surgeries.

Results: At 12 hrs after the surgery, mean pain intensity in the melatonin group was significantly lower than the pregabalin group, and in the pregabalin group was significantly lower than the third group ($P<0.05$). At 24 hrs after the TAH, the mean pain intensity in the melatonin group was significantly lower than the third group ($P<0.05$).

Conclusion: injection preventive melatonin is more effective than pregabalin to reduce pain throughout the first 24 hrs after the TAH.

Keywords: Hysterectomy, Melatonin, Pain, Pregabalin

Introduction

Nowadays, postoperative pain control is one of the most important concerns of the medical team. They are looking for the best and the most affordable ways for postoperative pain management. In addition to the best kind of pain control, reduction of the side effects of drugs also minimizes the costs imposed on hospitals and patients **(1, 2)**. Currently, the most common methods of pain management are the use of opioid analgesics, non-drug analgesics, and local anesthetics used in regional anesthesia. Although opioids have serious side effects, they are still commonly prescribed for pain management **(3)**. Recent studies have been presented, the commencement of pain control before the surgery is one of the most important factors to reduce postoperative pain and stress. According to this hypothesis, analgesia will be more effective when begins before the initial surgical stimulation. Prescribing analgesic agents before the onset of pain gives the drug enough time to reach the proper serum level before patients complain of pain. In this case, pain control can be better, faster, and more effective **(4, 5)**.

Melatonin (N-acetyl-5-methoxytryptamine), a hormone secreted by the pineal gland, is a good option for use as a preemptive due to its sedative, analgesic, and its anti stress effects. Melatonin is made from the amino acid tryptophan in the pineal gland and presents

as a hormone and antioxidant in all tissues of the body **(6, 7)**. Although the results of several studies have shown; preoperative melatonin administration reduces opioid consumption and postoperative pain, its analgesic effects have not yet been fully elucidated. Therefore, it is necessary to compare the antinociceptive effects of melatonin alone with other drugs prescribed as pain medication **(8)**.

Anticonvulsant drugs are prescribed to control chronic neuropathic pain. These drugs, such as pregabalin, appear to be effective to control and manage postoperative pain **(9)**. Pregabalin is a gamma aminobutyric acid (GABA) analogue. Past studies have shown that this drug has a high affinity for binding to the α2-δ protein. This protein is found in calcium voltage channels in the central nervous system **(10, 11)**. This drug inhibits the release of many neurotransmitters, including glutamate, noradrenaline, and substance p. It is used to control neuropathic pain, generalized and partial seizures, and post-operative pain **(12)**. Studies have shown contradictory results regarding the use of pregabalin and melatonin as analgesic agents. Also, the analgesic effects of these drugs as preemptive have not been compared in abdominal hysterectomy, one of the most common surgical procedures in women with moderate to severe pain, under general anesthesia. We designed this study to compare the effects of melatonin and pregabalin as a preventive drug to postoperative pain control in patients undergoing Total abdominal hysterectomy (TAH).

Methods

After approval by the University Ethics Committee (ethical code: IR.GUMS.REC.1394.230 & IRCT registration number: IRCT2015090816325N3), 90 patients candidates for elective TAH THA with physical status I, II according to American Society of Anesthesiologists criteria were enrolled in a double-blind clinical trial study with informed consent. During 2017-2018, these patients were referred to Al-Zahra Obstetrics and Gynecology Center (Rasht, Iran) for treatment of uterine fibroids, uterine prolapse, endometriosis, persistent prolonged bleeding. Patients with cardiac, pulmonary, hepatic, renal, autoimmune, psychiatric disorders, diabetes, gastrointestinal, seizure, leukemia, allergy, sleep disorders, and chronic history of analgesic and psychotropic medication usage during one week before the surgery were not included in the study **(13-15)**.

The night before the surgery, patients were randomly divided into three groups: melatonin, pregabalin, and no drug. In the melatonin group, patients received 6 mg of melatonin (two pills each one with the dosage of 3 mg) **(16, 17)**, 2 hrs before the surgery, and in the pregabalin group, patients received 50 mg of pregabalin and the third group did not receive any drug **(18, 19)**. The volunteers in the study were unaware of the groups, and the medication was administered by a member of the treatment staff who was not aware of the grouping. To prevent dehydration, Ringer intravenous injection was started before induction of anesthesia for all three groups.

Anesthesia was induced with fentanyl (as opioid) "2 µg / kg", thiopental (as hypnotic) "5 mg / kg" and atracurium (as relaxant) "0.6 mg / kg". Maintenance was followed with Isoflurane with a MAC dose of 1-1.5, 50% / 50% N2O / O2, and fentanyl maintenance doses of "1 µg / kg" (if heart rate increases by more than 20% above baseline before anesthesia), and atracurium (0.2 mg/kg). Neuromuscular block was reversed at the end of surgery with Neostigmine 0.02 mg / kg + Atropine 0.04 mg / kg.

During anesthesia and surgery, monitoring was performed by ECG, SaO2, and capnography to determine CO2 **(35-34)** and non-invasive blood pressure monitoring every five minutes. The amount of neuromuscular block was assessed by a nerve stimulator. The duration of surgery, the time of anesthesia, and the amount of fentanyl dosage were carefully recorded. Postoperative pain was controlled using 1 µg / kg fentanyl injections in consideration of NRS ≥ 4. In the early hours after the surgery, heart rate, mean arterial pressure, respiratory rate, SpO2, and fentanyl levels were recorded. Any side effects including nausea, vomiting, respiratory depression, dizziness, diplopia, itching, and tremor were recorded and reported to the anesthesiologist. Ondansetron with a dosage of 4 mg IV injection is used to control nausea.

Pain severity was measured with the numeric rating Scale (NSR) at 1, 6, 12, and 24 hours after the surgery. The NSR contains 10 points that patients report using their pain level. The number 0 is considered as painless, 1-3 mild pain, 4-6 moderate pain, and 7-10 severe pain.

Serum melatonin and beta-endorphin levels were measured immediately before and after the surgery with 5 cc blood samples in all three groups. The samples were then centrifuged at 3500 rpm for 15 minutes. Isolated serum was stored at -20 ° C. ELISA technique was used to measure serum melatonin (EASTBIOPHARM melatonin (H) _96Test) and beta-endorphin (EASTBIOPHARM Beta-Endorphin (H) _96Test) levels.

Statistical analysis

The results of this study were evaluated using SPSS (Statistic Package for Social Science) software, version 16.0 (IBM, USA). ANOVA test was used to compare the severity of pain in the postoperative hours after the surgery and to compare the beta-endorphin and melatonin levels before and after the surgery. The results were expressed as mean and standard deviation and the significance level was considered as less than 5 percent in all tests.

Results

Postoperative Pain intensity

The mean pain intensity at 1, 6, 12, and 24 hrs after the surgery was compared between three groups and data analysis showed a significant difference in pain intensity. The results presented; the pain intensity at one hour after the surgery in the melatonin group was lower than the third group significantly (P = 0.01). At 12 hours after the surgery, the mean pain intensity in the melatonin group was lower than the pregabalin group significantly (P = 0.001) and in the pregabalin group was lower than the third group significantly (P = 0.004). At 24 hrs after the surgery, the mean pain intensity in the melatonin group was significantly lower than the third group (P = 0.003) (Table 1).

Table 1. Comparison of pain intensity in the first 24 hours after surgery between the three groups (Mean ± SD)

Pain Intensity	Study Groups			P value
	Melatonin	Pregabalin	Placebo	
1 hour after surgery	4.8 ± 2.41	5.8 ± 2.48	8.2 ± 1.39	0.009
6 hour after surgery	5.85 ± 1.95	7 ± 1.41	7.1 ± 1.59	0.3
12 hour after surgery	4.14 ± 1.95	8 ± 1	5 ± 1.15	0.001
24 hour after surgery	1.28 ± 0.48	2.2 ± 0.83	3.9 ± 1.79	0.002

Serum Beta-Endorphin levels before and after the surgery

Comparing the mean beta-endorphins of the three groups before surgery did not show a significant difference (Table 2). Comparison of postoperative beta-endorphin levels showed a significant difference between melatonin and the third group (P = 0.04).

Table 2. Serum beta-endorphin level before and after surgery (Mean ± SD)

Groups	before surgery	after surgery
Melatonin	37.52 ± 27.43	42.33 ± 30.31
Pregabalin	57.74 ± 40.13	63.1 ± 33.87
Placebo	77.85 ± 59.4	94.19 ± 67.94
P value	0.09	0.04

Serum melatonin levels before and after the surgery

Comparison of mean melatonin levels in three groups showed no significant difference before and after the surgery (Table 3).

Table 3. Serum melatonin levels before and after surgery (Mean ± SD)

Group	before surgery	after surgery
Melatonin	32.52 ± 20.07	33 ± 13.79
Pregabalin	37.46 ± 18.02	36.77 ± 13.47
Placebo	36.46 ± 24.94	48.39 ± 26.19
P value	0.8	0.1

Discussion

In the present study, we assessed mean postoperative pain intensity, and compared serum melatonin and beta-endorphin levels throughout the preoperative and postoperative periods in patients undergoing total abdominal hysterectomy. The results illustrated; patients receiving melatonin before the surgery have less pain intensity than other groups during the first 24 hours after the surgery, which could reduce opioid consumption during this period.

We have shown in previous studies that the use of anesthetic supplements such as magnesium sulfate reduces the severity of postoperative pain and opiate consumption **(13)**. In this study, we evaluated the severity of postoperative pain following melatonin and pregabalin administration. Some studies show that melatonin reduces the intensity of pain induced by electrical, mechanical, chemical, and surgical stimuli **(20)**. Caumo et al. investigated the antinociceptive

effects of preoperative administration of melatonin. The results showed that melatonin reduces the severity of pain and drug usage in the first two hrs after the surgery, which is in line with the results of the present study **(21)**. Hosseini, Yekta **(22)** studied the analgesic effects of preoperative melatonin administration at a dose of 5 mg on patients undergoing laparoscopic cholecystectomy. They observed that melatonin reduces pain intensity and opioid consumption after the surgery **(22)**. Nethra and coworkers concluded; preemptive melatonin with a dosage of 3 mg produced analgesia within six hrs after the surgery, so the need for analgesics decreased throughout the 24 hours. The results were the same as ours **(23)**. A study by Khezri et al. showed sublingual usage of melatonin with a dosage of 30 mg could not make analgesia after Cesarean Section, which was contrary to our findings and may be due to differences in the type of surgery and anesthesia **(24)**.

In animal studies, the antinociceptive effects of melatonin have been shown to be dose-dependent. The mechanism of the analgesic effects of melatonin is not well understood **(25)**. Melatonin exerts analgesic effects through GABA-B receptors, opiate receptors, and activation of melatonin receptors. Melatonin also reduces the pain intensity by suppressing the expression of TNF-alpha and other inflammatory factors **(26)**.

In our study, the mean pain intensity in patients receiving pregabalin was lower than the third group, but there was no significant difference between the two groups. The results of the study of Imam et al. showed that administration of 150 mg of pregabalin before the surgery reduces the severity of pain in the first 24 hrs after abdominal hysterectomy, which was the same as ours **(27)**. The results of the Ghai et al. study showed prescribing 300 mg of pregabalin one hour before the abdominal hysterectomy, reduces preoperative anxiety and pain without unpleasant sedative effects in the first hours of recovery **(28)**. In the study of Jokela et al., preoperative administration of 300 mg pregabalin in patients undergoing laparoscopic abdominal hysterectomy reduced postoperative pain and opioid consumption, which is consistent with the results of the present study **(29)**.

Pregabalin seems to have analgesic effects by binding to the α1,2-δ subunit of the voltage-gated calcium channel. Chronic administration of pregabalin also reduces the level of expression of this subunit in the dorsal horn of the spinal cord and presynaptic nerve terminals and controls pain, especially chronic pain **(30, 31)**. In this study, we measured and compared serum levels of melatonin and beta-endorphin before and after the surgery to evaluate the antinociceptive effect of melatonin and pregabalin. There was no significant difference between preoperative and postoperative melatonin levels, but beta-endorphin levels were significantly different in the three groups. Also, the beta-endorphin level after the surgery was higher than the pre-surgical level. Studies show that beta-endorphin levels increase following abdominal surgery **(32)**. The beta-endorphin antinociceptive mechanism in the central nervous system is well-defined, but the plasma analgesic effects of beta-endorphin are not fully understood **(33)**.

It seems in this study, preoperative administration of melatonin and pregabalin increases the endogenous opioid, which reduces postoperative pain intensity and opioid consumption. Previous studies have also illustrated beta-endorphin levels increases after melatonin administration **(34)**. In this regard, maybe measurement of plasma level of beta-endorphin could be used to assess acute and chronic postoperative pain. In a study by Popovic et al., measurement of serum beta-endorphin levels before and after abdominal surgery showed; the level of this endogenous opioid increased within the first 24 hrs after the surgery, which is consistent with the results of our study **(35)**. Beta-endorphin levels increase following general anesthesia, and opioid consumption inhibits this increase severely, but nonopioid supplement agents did not decrease serum beta-endorphin levels in this study **(36)**.

Our results showed; there was no significant difference between serum melatonin levels before and after the surgery. Although opiate drugs increase serum melatonin levels, in this study, its serum level did not change significantly following the administration of melatonin and pregabalin. Factors such as anesthesia and surgery affect serum melatonin levels **(37)**. It has been proved that following general anesthesia, serum melatonin levels decrease on the first night after the surgery, causing sleep disturbances in patients. In a study on patients undergoing orthopedic surgery, urine sulfatoxymelatonin (the main metabolite of melatonin) decreased in the early hours after the surgery following general anesthesia with thiopental and isoflurane **(38)**. However, some studies reported conflicting results. For example, during anesthesia with fentanyl and thiopental, serum melatonin levels increased, which is in agreement with our study. Anesthetic drugs are effective at the serum melatonin levels. For example, isoflurane increases melatonin level during the surgery and sevoflurane decreases its level **(39)**.

In conclusion, preoperative administration of melatonin and pregabalin reduces the pain intensity throughout the first 24 hrs after the abdominal hysterectomy under general anesthesia. But further clinical studies on the beneficial effects of melatonin in different surgical procedures are recommended.

Conclusion

Preoperative administration of both melatonin and pregabalin reduces the pain intensity throughout the first day after the TAH under GA, but preventive melatonin is more effective than pregabalin to reduce pain in the patients.

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Conflict of Interest

The authors report no conflict of interest regarding publication of this paper.

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