

Original Article: Comparison of Effects of Oral Melatonin and Gabapentin on Pain and Hemodynamic Symptoms in Patients Undergoing Upper Limb Orthopedic Surgery



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ABSTRACT

Introduction: Pain and anxiety after surgery is an unpleasant experience that occurs following various stimuli and humans react to it. This process causes physiological disorders in all body systems. Therefore, the purpose of this study is to compare the effect of oral melatonin and gabapentin on pain and anxiety in patients undergoing upper extremity orthopedic surgery under general anesthesia.

Methods: In this double-blind randomized clinical trial study, 90 patients with anesthesia class 1 and 2 underwent upper limb orthopedic surgery with general anesthesia. Patients were divided into 3 groups, gabapentin, melatonin, and placebo. VAS scale was used to measure patients' pain. Patients' hemodynamic symptoms were further investigated. Data analysis was done using descriptive and inferential statistical tests at a significance level of $P < 0.05$.

Results: 90 patients underwent upper limb orthopedic surgery under general anesthesia. There was no significant difference between the three groups of gabapentin, melatonin, and placebo in the incidence of pain at different times ($P < 0.05$). Trends in mean diastolic blood pressure was not significant ($P = 0.612$). Trends in the average heart rate from the time before entering the operating room to recovery and its exit was not significant ($P < 0.05$).

Conclusion: The results of the present study showed that both gabapentin and melatonin drugs have no effect on postoperative pain in patients undergoing upper limb orthopedic surgery, and it may be better to use other drugs or in combination with other sedative drugs.

Introduction

Surgery is an intentional change in the anatomical structures of the body to make comfort, relieve, or eliminate pathological processes, and repair traumatic injuries, which may be elective or emergency, small or large, diagnostic or therapeutic, invasive or non-invasive, and to include a part or an organ of the body [1]. It is always a great experience for the patient and his or her family [2], accompanied by many psychological complications for patients [3]. Anxiety is an uncomfortable mental state or a feeling of helplessness related to a threatening situation or anticipation of an unknown threat to oneself or others [4]. In this case, the person is not in comfort and balance, and thereby feels under pressure [5]. The chronic and long-term anxiety in a person can cause major destructive physiological changes in the body, and these destructive effects include weakening the body's immune system, increasing blood serum cholesterol, increasing the likelihood of cardiovascular diseases, increasing blood pressure, headaches, migraines and tension, digestive disorders, and many psychosomatic diseases [6]. Post-operative pain is also a source of suffering for patients and can cause anxiety, insomnia, fear, stimulation of the patient's autonomic nervous system, sensitization, excessive perception of pain, and acute post-operative pain to become painful [7-8]. In addition, post-operative pain causes a fundamental change in the body's metabolism in susceptible people by causing adverse consequences and affecting various mechanisms, and can also cause increased blood pressure, cardiac ischemia, respiratory, digestive and kidney problems, and even increased mortality in patients. Likewise, post-operative pain increases hospitalization time and treatment costs by delaying the patient's movement and walking time. Usually, race, age, gender, level of ability to express pain, underlying disease, doctor's level of awareness, and fear of causing complications are among the factors preventing the proper pain control in patients [9]. The American Pain Association announced that every year about 50 million Americans suffer from chronic pain and 25

million people suffer from acute pain caused by injury or surgery, so that absenteeism and leaving work due to pain is equivalent to 3 billion dollars in financial losses and 50 million days of absence. It causes unemployment in the country [10]. Some studies have reported that gabapentin has an effective role in chronic pain control, postoperative pain control, reducing the hemodynamic response to endotracheal intubation, reducing postoperative nausea and vomiting, reducing preoperative anxiety, and postoperative delirium [11-12]. Indeed, it is one of the anticonvulsant drugs exerting its effects through voltage-dependent calcium channels. This drug leads to the release of amino acids in the posterior horn of the spinal cord and causes a decrease in the response to nerve inputs and the blockade of misplaced charges from nerves will be damaged [13-14]. In addition to bergabapentin, melatonin has neuroprotective properties against cell damage and malfunction. In people with bitter experiences in life and as a result of anxiety, melatonin action causes fluctuations in the expression of opioid receptors and beta-endorphin levels, and in this way, melatonin leads to the reduction of anxiety and depression. It has been observed that in depressed patients, plasma level of stress-related beta-endorphin is extremely high. On the other hand, it stimulates several activating or expressing antioxidant enzymes such as superoxide dismutase and glutathione peroxidase [15]. Melatonin is the main product of the pineal gland. Melatonin is a derivative of tryptophan. It is synthesized in the cells of the pineal gland and is released without being stored [16]. Therefore, according to the mentioned cases, this study was conducted with the aim of comparing two oral prodrugs, melatonin and gabapentin, on the pain and anxiety level of patients in orthopedic surgery of the upper limb.

Methodology

In this double-blind randomized clinical trial study, 90 patients undergoing upper extremity orthopedic surgery under general anesthesia in the orthopedic operating room of Peymaniyeh Hospital were studied. Before conducting the study, the consent of the samples to participate

in the study was obtained and permission was obtained from the Ethics Committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1397.148). All patients were anesthetized with the same method. Anesthetic drugs in this study include sodium thiopental (4 mg/kg), atracurium (1 mg/kg), fentanyl (100 µg/kg), midazolam (2 mg/kg), xylocaine (40 mg/kg), and morphine (15 mg/kg). Inclusion criteria include upper limb orthopedic surgeries. Like clavicle, there is no chronic and cancer pain, no hearing or speech defects, hemodynamic stability, no anxiety and mental diseases, and no chronic pain. Likewise, the exclusion criteria include unstable hemodynamic status is a statement of non-satisfaction to continue the research and people who need medication or another measures other than routine care during the surgery to eliminate complications and reduce pain. Sampling was straightforward and the patients were divided into three groups of 30 people by a simple random method. The person performing the steps of work and collecting the data and the patients were unaware of the type of used drug. The patients of the melatonin group received 6 mg of melatonin in tablet form and the patients of the gabapentin group received 600 mg of gabapentin capsules 90 minutes before entering the operating room. Capsules were given orally to patients in the placebo group. The pain level (at 1, 6, 12, and 24

hours after the operation) was evaluated and recorded. The anxiety level was further measured before giving the drug and when entering the operating room. Hemodynamic symptoms, chills, nausea, and vomiting were measured at times (before entering the operating room, when entering the operating room, 15, 30, 45, 60, 75, 90, and 120 minutes during recovery and exiting from recovery). The data collection tool in this research includes two questionnaires. The first part of the questionnaire is the visual pain scale. The amount of pain was measured based on the verbal pain scale; zero is assigned to have no pain and 10 is the sign of the maximum pain (17). Data analysis was done using SPSS (version 21) Software and through the descriptive and inferential statistical tests at a significance level ($P < 0.05$).

Results

90 patients undergoing the upper limb orthopedic surgery under general anesthesia were evaluated in the age range of 11 to 75 years old (in three groups of 30 people). The majority of gabapentin group patients (60%), melatonin group patients (66.7%), and placebo group patients (50%) were male. It showed that the study groups are similar in terms of age and gender variables ($P < 0.05$) (Table 1).

Table 1. The frequency of qualitative variables of patients according to the two groups of gabapentin, melatonin, and placebo

		Gabapentin		Melatonin		Placebo		P-value
		Frequency	%	Frequency	%	Frequency	%	
Gender	Male	18	60.0%	20	66.7%	15	50.0%	0.873
	Female	12	40.0%	10	33.3%	15	50.0%	
Age	<20	2	6.7%	3	10.0%	5	16.7%	0.418
	20-30	5	16.7%	6	20.0%	7	23.3%	
	31-40	8	26.7%	10	33.3%	7	23.3%	
	41-50	8	26.7%	5	16.7%	7	23.3%	
	>40	7	23.3%	6	20.0%	4	13.3%	

At 60 minutes, after surgery, there was a significant difference between the gabapentin, melatonin, and placebo groups in terms of mean systolic and diastolic blood pressure ($P=0.010$). however, in the times before entering the operating room, entering the operating room,

15, 30, 45, 75, 90, and 120 minutes after the operation, in recovery and its outside, there was a significant difference between the groups of gabapentin and melatonin, and also there was no placebo in terms of mean systolic and diastolic blood pressure ($P < 0.05$) (Figure 1). In

the gabapentin group, trends in the average systolic and diastolic blood pressure from the time before entering the operating room to recovery and its exit was not significant ($P < 0.05$). In the melatonin group, trends in

average systolic blood pressure from the time before entering the operating room to recovery and its exit was significant ($P = 0.026$). However, trends in mean diastolic blood pressure was not significant ($P = 0.612$) (Figure 2).

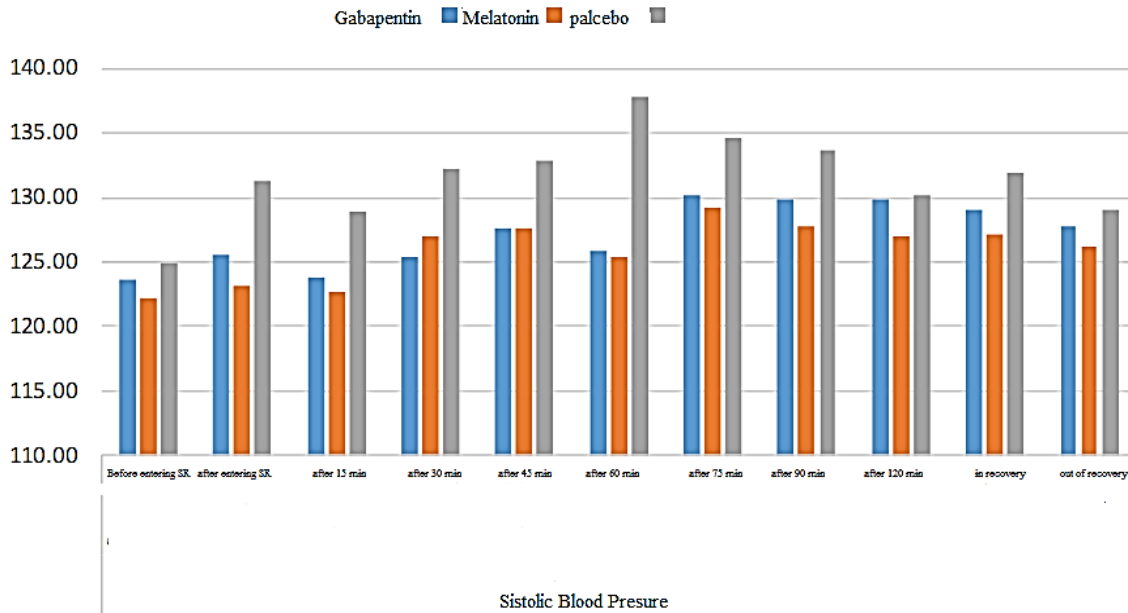


Figure 1. Changes in systolic blood pressure between three groups of gabapentin, melatonin, and placebo at different times.

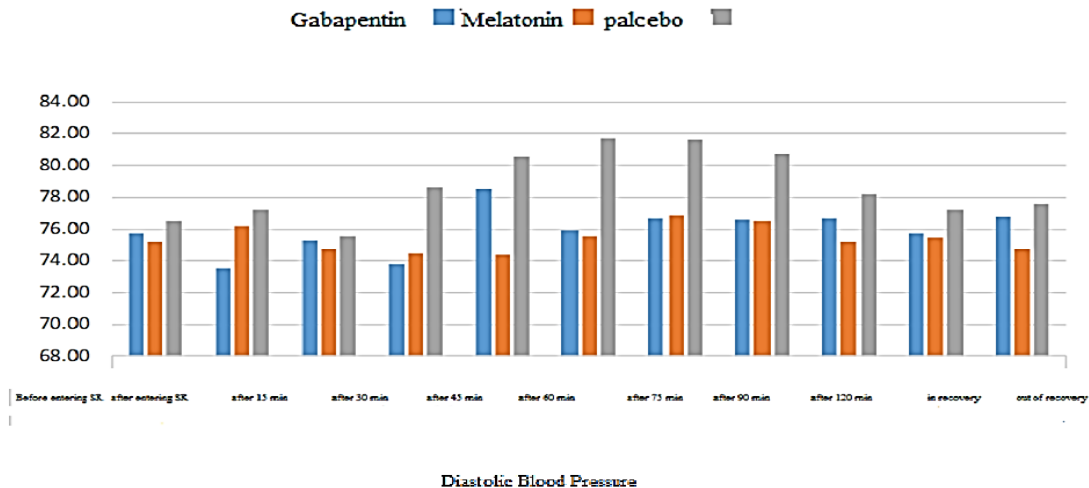


Figure 2. Changes in diastolic blood pressure between three groups of gabapentin, melatonin, and placebo at different times.

In the times before entering the operating room, entering the operating room, 15, 30, 45, 60, 75, 90, and 120 minutes after the operation, in recovery and its outside, there is a significant difference between three groups. Gabapentin, melatonin, and placebo were not present in

terms of mean heart rate ($P < 0.05$). Separately in gabapentin, melatonin, and placebo groups, trends in average heart rate from the time before entering the operating room to recovery and its outside was not significant ($P < 0.05$) (Figure 3).

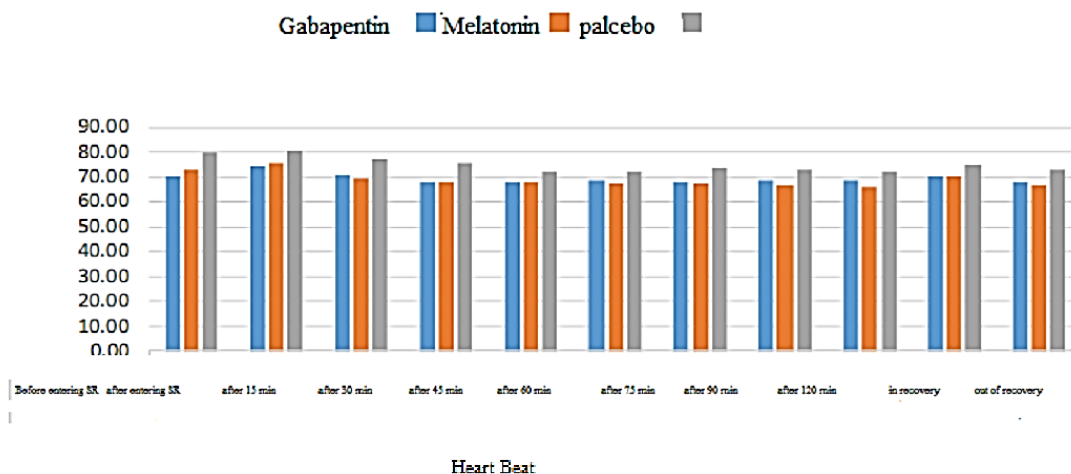


Figure 3. Changes in heart rate between three groups of gabapentin, melatonin, and placebo at different times

At 60 minutes, after the operation, there was a significant difference between the gabapentin, melatonin, and placebo groups in terms of mean MAP ($P = 0.002$). The mean MAP was higher in the melatonin group than in the gabapentin and control groups. In the times before entering the operating room, entering the operating room, 15, 30, 45, 60, 75, 90, and 120 minutes after the operation, in recovery and its outside, there is a significant difference between the three groups. Gabapentin, melatonin, and placebo did not have any effect on mean MAP ($P < 0.05$). Separately in gabapentin, melatonin, and placebo groups, the trend of mean MAP changes from the time before entering the operating

room to recovery and recovery was not significant ($P < 0.05$).

In the first hour, the majority of patients in the gabapentin group with moderate, mild, and severe pain were negative. However, in the melatonin group, 10% of patients had severe pain at 6 hours and 12 hours after the surgery. The frequency of moderate and severe pain was increased in the study groups. The results of statistical analysis showed that there was no significant difference between three groups of gabapentin, melatonin, and placebo in the pain occurrence at different times ($P < 0.05$) (Table 2).

Table 2. Frequency and percentage of pain between three groups of gabapentin, melatonin, and placebo at different times

Time		Gabapentin		Melatonin		Placebo		P-value
		N	%	N	%	N	%	
The 1st hour	No pain	17	56.7%	15	50.0%	12	41.4%	0.178
	Mild pain	10	33.3%	5	16.7%	7	24.1%	
	Moderate pain	3	10.0%	7	23.3%	6	20.7%	
	Severe pain	0	0.0%	3	10.0%	4	13.8%	
	No pain	1	3.3%	0	0.0%	0	0.0%	0.124

The 6th hour	Mild pain	5	16.7%	6	20.0%	3	10.3%	
	Moderate pain	14	46.7%	16	53.3%	11	37.9%	
	Severe pain	10	33.3%	8	26.7%	15	51.7%	
The 12th hour	No pain	1	3.3%	2	6.7%	0	0.0%	0.476
	Mild pain	6	20.0%	3	10.0%	6	20.7%	
	Moderate pain	17	56.7%	17	56.7%	12	41.4%	
The 24th hour	Severe pain	6	20.0%	8	26.7%	11	37.9%	0.397
	No pain	4	13.8%	3	10.3%	2	6.9%	
	Mild pain	13	44.8%	11	37.9%	10	34.5%	
	Moderate pain	10	34.5%	11	37.9%	14	48.3%	
	Severe pain	2	6.9%	4	13.8%	3	10.3%	

Discussion

90 patients undergoing upper limb orthopedic surgery under general anesthesia were evaluated in three groups (each included 30 people). The results of the present study showed that the study groups are similar in terms of age and gender variables. The results of the current study are consistent with the studies of Cumo *et al.* [18], Imani *et al.* [19], Mirkheshti *et al.* [20], and Khazari *et al.* [21].

At 60 minutes, after the operation, there was a significant difference between the gabapentin, melatonin, and placebo groups in terms of mean systolic and diastolic blood pressure. However, in the times before entering the operating room, entering the operating room, 15, 30, 45, 75, 90, and 120 minutes after the operation, in recovery and outside recovery, there was a significant difference between the groups of gabapentin and melatonin, and also there was no placebo in terms of mean systolic and diastolic blood pressure. In the gabapentin group, trends in the average systolic and diastolic blood pressure from the time before entering the operating room to recovery and recovery were not significant. In the melatonin group, trends in mean systolic blood pressure from the time before entering the operating room to recovery and recovery were significant. However, trends in mean diastolic blood pressure were not significant.

In a study, Khazari *et al.* investigated systolic and diastolic blood pressure and did not observe any significant difference in all surgical stages between the melatonin, gabapentin, and control groups [22]. The results of the present

study are consistent with the study of Khazri *et al.* In the present study, there was no significant difference between the three groups, while it is not consistent with the studies of Turan *et al.* and Shoaibi *et al.* In Turan *et al.*'s study, the results indicated that gabapentin significantly reduced systolic blood pressure compared with the placebo group [23]. Furthermore, Shoaibi compared the effect of tizanidine and gabapentin on intraoperative hemodynamic parameters and postoperative analgesia in patients undergoing tibial fracture surgery. The results of this study showed that there is a significant difference in systolic and diastolic blood pressure between the two groups. The gabapentin group had lower systolic and diastolic blood pressure than tizanidine group [20].

In the times before entering the operating room, entering the operating room, 15, 30, 45, 60, 75, 90, and 120 minutes after the operation, in recovery and its outside, there is a significant difference between three groups of gabapentin, melatonin, and placebo in terms of mean heart rate. Separately in gabapentin, melatonin, and placebo groups, trends in average heart rate from the time before entering the operating room to recovery and its exit was not significant.

The results of Shoaibi's study revealed that there is no significant difference in terms of heart rate between the two groups [20]. The results of the study by Begum Khazri *et al.*, which was conducted on the effect of melatonin on cesarean section women under spinal anesthesia, showed that there is no statistically significant difference between two groups of melatonin and placebo in terms of heart rate

[21]. Haddadi *et al.* showed that there is no significant difference between melatonin group and control group in all stages of surgery [24]. Moreover, Khazari *et al.* examined the heart rate and did not find any significant difference in all surgical stages between melatonin, gammapentin, and control groups [26]. The results of the above studies are consistent with the present study. In the current study, there was no statistically significant difference in three groups.

In the first hour, the majority of patients in the gabapentin group had moderate and mild pain, and severe pain was negative, while in melatonin group, 10% of patients had severe pain at 6 and 12 hours after the surgery. The frequency of moderate and severe pain was increased in the study groups. The results of statistical analysis showed that there was no significant difference between three groups of gabapentin, melatonin, and placebo in the pain incidence at different times.

Acute pain after surgery is a complex physiological reaction that occurs due to the tissue damage, visceral stretching, or disease. This pain causes several physiological effects such as reduction of pulmonary ventilation, and thereby atelectasis [27]. Pain may restrict the patient and increase the chance of deep vein thrombosis due to immobility [28], or increase the blood pressure and heart rate [29]. One of the most common methods is to use painkillers before the onset of pain, thus protecting the central nervous system from becoming sensitive to pain nerve stimulation that leads to an increase in pain [30].

In his study, Shoaibi compared the effects of tizanidine and gabapentin on intraoperative hemodynamic parameters and postoperative analgesia in patients undergoing tibial fracture surgery. The results of this study showed that there is no significant difference in terms of pain between both groups [20]. In a study conducted by Begum Khazari *et al.* with the aim of investigating the effect of pretreatment of melatonin in women undergoing caesarean section with spinal anesthesia, the results showed that 6 mg of melatonin had no significant difference with placebo group in

reducing the amount of postoperative pain [21]. Haddadi *et al.*, in their study which was conducted with the aim of investigating the administration of melatonin and acetaminophen on the pain and hemodynamic changes of patients in retrobulbar block cataract surgery, showed that there was a difference between both groups of melatonin and acetaminophen as well as the placebo group in terms of postoperative pain. There is no significant difference [24]. The results of the above studies are consistent with the current research. In the present study, there was no statistically significant difference between three groups in terms of pain after surgery.

In their study, Imani *et al.* investigated the effect of oral prodrug gabapentin on pain after thoracotomy. The results of this study showed that compared with the control group, gabapentin reduced the amount of pain in the first hour after the operation [19]. In their study, Kilderi *et al.* investigated the pethidine consumption in gabapentin recipients after surgery. The results of this study showed that taking gabapentin in the form of oral capsules for a short period before surgery has reduced the pain of patients in the 10th, 18th, and 26th hours after the operation [31]. Forozan Fard *et al.* conducted a study with the aim of investigating the effect of gabapentin on pain and the consumed narcotics amount after abdominal hysterectomy surgery. The results of this study showed that gabapentin reduces pain during and after abdominal hysterectomy surgery [32]. In their study, Cumo *et al.* investigated the analgesic effect of melatonin and clonidine as well as the reduction of morphine consumption after abdominal hysterectomy surgery. The results showed that melatonin reduced the amount of postoperative pain compared with the placebo group [18]. In their study, Hossein Alizadeh *et al.* investigated the effect of melatonin in reducing pelvic pain in women with endometriosis referred to hospitals affiliated to Tehran Islamic Azad University of Medical Sciences. The results of this study showed that compared with placebo, melatonin reduces chronic pelvic pain and dysmenorrhea [33]. In a systematic analysis of the analgesic effects of melatonin in different

stages of the surgical procedure, Youssef *et al.* suggested that these effects are limited and there are contradictory results, and this contradiction can be caused by factors such as dosage, gender, anxiety level, and also factors such as bias caused by small sample size used in different studies. However, evidence from clinical trials suggests that melatonin as an analgesic drug can be a suitable alternative candidate for drugs prescribed before surgery [34].

However, these apparently controversial findings may be due to differences in melatonin doses, the use of single doses rather than multiple doses of gabapentin, or the dissimilarity of populations, and types of surgeries as well as types of anesthesia. However, it has been shown that the analgesic properties of melatonin depend on the inhibition of inflammatory pathway and tissue damage by influencing the activity of COX-2 and nitric oxide [35-36]. In addition, there is evidence that melatonin affects glutamatergic systems through the NMDA receptor. Recent studies illustrate that melatonin can exert its analgesic effects through indirect interaction with a number of neurotransmitter systems, including benzodiazepine receptors, opiate, and sigma receptors [37-38].

Conclusion

The results of the present study showed that both gabapentin and melatonin drugs have no effect on postoperative pain in patients undergoing the upper limb orthopedic surgery, and it may be better to use the other drugs or in combination with other sedative drugs.

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Authors' contributions

All authors contributed toward data analysis, drafting, and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of interest

There are no conflicts of interest in this study.

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