

## The Effect of Melatonin on Anxiety and Pain of Tourniquet in Intravenous Regional Anesthesia

### Abstract

**Background:** Melatonin has anxiolytic and potential analgesic effects. Several studies have indicated the sedative and anti-anxiety effects of melatonin when used as premedication before surgery. Hence, we assessed the efficacy of melatonin premedication in tourniquet-related pain and analgesia in patients receiving intravenous regional anesthesia (IVRA). **Materials and Methods:** Fifty patients undergoing elective hand surgery under IVRA were randomly divided into two groups (25 patients each) to receive either melatonin 6 mg (melatonin group) or placebo (control group) as oral premedication. IVRA was achieved with lidocaine, 3 mg/kg, diluted with saline to a total volume of 40 mL. Anxiety scores, sensory and motor block onset and recovery times, tourniquet pain, and 24-h analgesic requirements were recorded. **Results:** The onset of motor and sensory block was statistically significantly shorter in Group M ( $P < 0.001$ ), and recovery of motor and sensory block was statistically significantly longer in Group M ( $P < 0.001$ ). The time of starting tourniquet pain was longer in Group M ( $P < 0.001$ ). The mean anxiety score in the study group was  $3 \pm 0.81$  and in the control group was  $4.20 \pm 1.04$  ( $P = 0.001$ ). There was a statistically significant difference in the need for opioids between the two groups ( $P < 0.05$ ). **Conclusions:** Melatonin is an effective premedication before IVRA because it reduces patient anxiety, decreases tourniquet-related pain, and improves perioperative analgesia.

**Keywords:** Anxiety, intravenous regional anesthesia, melatonin, pain

### Introduction

The technique of intravenous regional anesthesia (IVRA), or “Bier block,” was first introduced by the German surgeon August Bier in 1908. The Bier block has advantages, including the ease of conducting, fast recovery, rapid onset, muscle relaxation, and controllable block range; it is also a great way to perform short-term open surgeries (<60–90 min) and closed reduction of a fractured bone. In this method, the anesthetic solution is injected into the venous circulation in the upper or lower extremities, which is isolated from central blood circulation by a tourniquet. Anesthesia occurs as a result of direct release of topical anesthetics from the vein to the surrounding nerves. In fact, this block is an easy and cost-effective approach, and its benefits have been proven even in emergency cases and outpatients.<sup>[1-3]</sup> However, IVRA is also accompanied by complications. Early or accidental deflation of the tourniquet or

the excessive use of topical anesthetic may lead to toxic reactions. The disadvantages of this block include pain caused by tourniquet during surgery, limited operation time, and inadequate postoperative analgesia. The aim of this study was to evaluate the effect of oral melatonin before surgery to reduce these disadvantages. Other complications of this method include the possibility of neurological damage, phlebitis, compartment syndrome, and amputation.<sup>[1]</sup> Melatonin or N-Acetyl-5-methoxytryptamine is essentially a nervous system hormone produced from the pineal gland. The pineal gland is the main source of melatonin production.<sup>[4]</sup> One of the functions of this hormone is the reduction of blood pressure and the level of catecholamines in the blood.<sup>[5]</sup> Melatonin has been reported to have an analgesic effect in patients with extensive tissue damage.<sup>[6]</sup> Several studies have indicated the sedative and anti-anxiety effects of melatonin when used as premedication before surgery.<sup>[7,8]</sup> Therefore, due to its appropriate effects,

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it may be possible to use this drug as premedication for surgery. The absorption rate of oral melatonin is high, and peak plasma occurs 20–60 min after ingestion of the tablet.<sup>[9,10]</sup> Considering that few studies have been conducted in this regard inside and outside Iran, it seems that further analysis of the effect of melatonin on patients' comfort and analgesia during surgery could be useful. One of the issues that patients undergoing RA for surgery are confronted with is anxiety and worry in surgery, either caused by the operating room environment or because of the nature of surgery. Therefore, considering the results of previous studies and the effect of melatonin on anxiety and analgesia, we decided to conduct this study in the orthopedic operating room of Imam Khomeini Hospital.

## Materials and Methods

This randomized, double-blind, prospective clinical trial was conducted on fifty American Society of Anesthesiologists Class I and II patients of 20–60 years' old who underwent hand surgery such as carpal tunnel syndrome, trigger finger, release surgery, or tendon repair with IVRA in the orthopedic operating room of Imam Khomeini Hospital after being approved by the Research and Ethics Committee of Urmia University of Medical Sciences. People with a history of Raynaud's disease, sickle cell anemia, chronic pain syndrome, depression or schizophrenia, seizure, leukemia, autoimmune disease and diabetes; people who received analgesics and sedatives within the past 24 h; those who were allergic to any of the drugs in this study; and pregnant or lactating women were excluded from the study. The sample size was determined as 25 patients in each group rendering to a similar preceding study<sup>[11]</sup> to detect the differences with a confidence interval of 95% and 80% power. To compensate shifting from normality in data distribution, 25 cases were used in each group and using random allocation software, they were randomly divided into two groups of 25 [Figure 1] receiving 6-mg melatonin (Nature, LCC, USA) and placebo. The drugs were placed in similar boxes with A and B labels, and the researcher was unaware of the group of each patient and became aware at the end of the study after collecting the data; also, the patients were not aware about the assigned groups. The drug was administered orally 90 min before surgery. No analgesic or sedative drugs were administered as premedication.

On preoperative visit, the level of pain based on verbal pain score (VPS) (0: painless and 10: the worst pain ever experienced) and the level of anxiety based on verbal anxiety score (VAS) (0: quite calm and 10: the worst anxiety ever experienced) were explained to the patients by an anesthetist. Heart rate, mean blood pressure, and arterial oxygen saturation were measured and recorded for each patient before premedication. After admission of the patient to the operating room, the patient's anxiety was assessed based on VAS 90 min

after receiving premedication. Patients were monitored by electrocardiogram, noninvasive blood pressure and pulse oximetry. Two venous ways were embedded: one in the third and final parts of the operated hand and the other in the opposite hand for using the necessary drugs and injecting fluids during surgery. After double tourniquet was placed in the upper arm, the arm was raised and after the venous discharge, the Esmarch bandage was used. Proximal cuff was measured up to 250 mmHg (100 mmHg above systolic blood pressure), and poor blood circulation was measured and compared by checking radial pulse and pulse oximetry with the opposite hand. Then, IVRA was injected within 90 s with lidocaine 3 mg/kg body weight diluted with saline in a total volume of 40 ml. Sensory block was evaluated 30 s after injection with needle size 22 based on pin-prick method. Patient response was examined in dermatomes associated with antebrachial cutaneous, ulnar, median, and radial nerves. The motor function of the limb was recorded, and for this purpose, the patient was asked for the flexion of the wrists and fingers every 30 s and the complete motor block when he/she was unable to move. The starting time of the sensory and motor block was recorded from the moment of injection until the completion of anesthesia of all the dermatomes and immobility of the limbs. When complete block was achieved for surgery, the surgical cuff (distal cuff) was filled up to 250 mmHg, and the proximal cuff was emptied. The mean blood pressure, heart rate, and arterial oxygen saturation were measured and recorded before and immediately after filling the tourniquet at 10, 20, 30, 40, and 50 min and after opening the tourniquet. The tourniquet-induced pain was immediately measured by VPS after filling the tourniquet and at 10, 20, 30, 40, and 50 min. The initial time of the tourniquet-induced pain was recorded since the filling of the distal cuff until the first complaint of pain. When the patient's pain exceeded number 4, 0.5 µg/kg body weight of fentanyl was injected and was repeated every 5 min until the pain was relieved. The distal tourniquet was not emptied until 30 min after the injection of lidocaine. At the end of the surgery, the tourniquet was emptied within 1–2 min. The sensory block duration after emptying the tourniquet was checked through pin-prick test every 30 s until the restoration of sense in all dermatomes. The motor block duration was evaluated since the emptying of tourniquet until the beginning of the movement of the fingers. The patient's request for analgesia was measured from the moment the tourniquet was emptied after surgery. The data were analyzed statistically after total collection. All the statistical analyses were performed using SPSS software version 20 (Chicago, Illinois: SPSS Inc.), and all the main outcomes were presented as mean ( $\pm$ standard deviation) and frequency (%). Univariate analysis was done by the independent *t*-test, Mann–Whitney test, and Chi-square test, and Fisher's exact test was used to evaluate the differences between the groups.

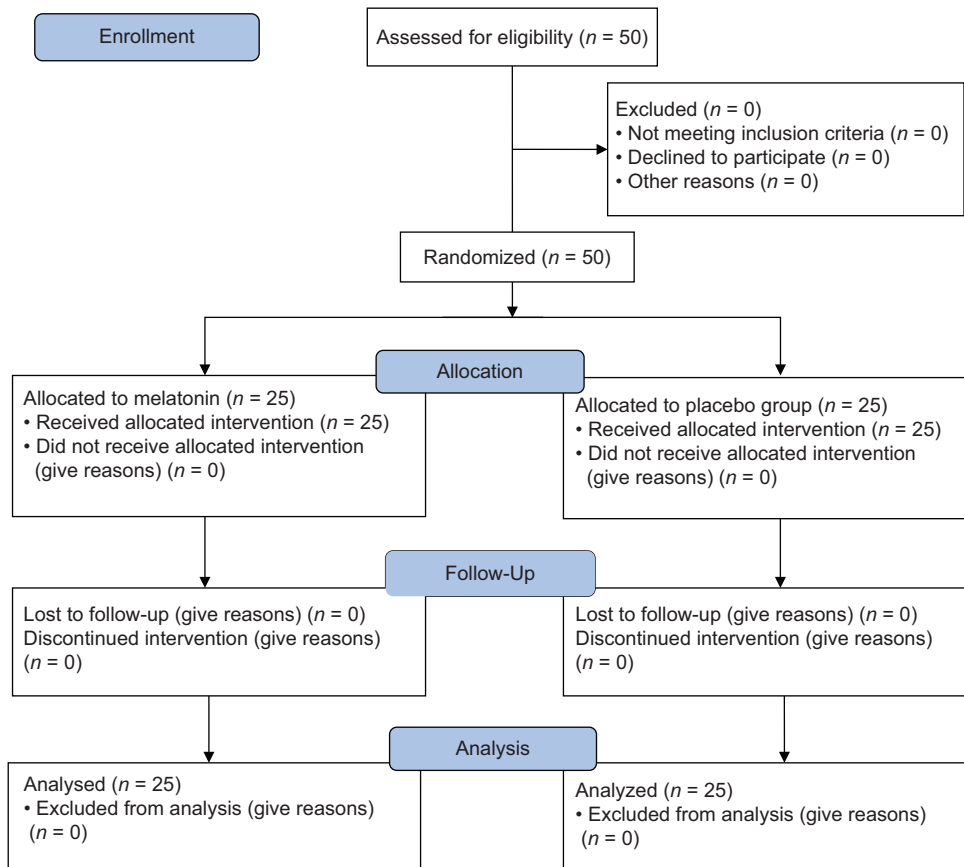


Figure 1: CONSORT Flow Diagram

## Results

In this randomized, double-blind prospective study, fifty Class I and II patients were divided into two groups of 25: 25 patients in the melatonin group and 25 patients in the placebo group. The demographic data of patients in each group are summarized in Table 1, and there was no significant difference between the two groups in terms of age and gender.

The mean sensory block creation time in the study group was  $3.04 \pm 1.33$  min and  $4.54 \pm 0.55$  min in the control group. There was a significant difference in the sensory block creation time between the two groups. The mean motor block creation time was  $34.4 \pm 7.94$  in the study group and  $43.52 \pm 6.27$  in the control group. The mean starting time of tourniquet pain in the study group was  $17.05 \pm 3.14$  and  $7.08 \pm 3.78$  min in the control group. The mean sensory block duration in recovery was  $7 \pm 0.54$  min in the study group and  $4.08 \pm 0.34$  in the control group. The mean motor block duration in recovery was  $7.44 \pm 0.58$  min in the study group and  $4.68 \pm 0.40$  min in the control group [Table 2].

The need for opioids in the study group was found among three patients (12%) and among 25 (100%) patients in the control group. According to the Fisher’s exact test, there was a statistically significant

Table 1: Demographic data of the study patients

Variables	Control group	Study group	P
Male (%)	11 (44)	12 (48)	0.77
Female (%)	14 (56)	13 (52)	
Age (years)	31.68±8.80	34.23±9.05	0.06
Weight (kg)	62.58±8.49	63.04±8.75	0.28
BMI (kg/m <sup>2</sup> )	25.70±3.74	25.80±3.57	0.87

BMI: Body mass index

difference in the need for opioids between the two groups ( $P < 0.05$ ) [Table 3].

The mean anxiety score in the study group was  $3 \pm 0.81$  and  $4.20 \pm 1.04$  in the control group. There was a significant difference in the anxiety scores between the two groups [Table 4].

## Discussion

This study showed that the use of melatonin as a premedication drug reduced anxiety, tourniquet pain, and the time to reach the sensory and motor block and provided adequate analgesia during and after the surgery without creating signs and symptoms of certain complications.

Melatonin is not only an important hormone, but also an antioxidant and anti-inflammatory agent. In addition, its protective role against obesity, diabetes, and sepsis has been

**Table 2: The mean sensory and motor block creation and duration time (min)**

Variable	Study group	Control group	P
Sensory block creation time	3±0.81	4.20±1.04	0.001
Motor block creation time	34.40±7.94	43.52±6.27	0.001
Sensory block duration in recovery	7±0.54	4.08±0.34	0.001
Motor block duration in recovery	7.44±0.58	4.68±0.40	0.001
Starting time of tourniquet pain	17.05±3.14	7.08±3.78	0.001

**Table 3: Need for opioids in the study groups**

Group	The need for opioid		Total (%)
	Yes (%)	No (%)	
Study group	3 (12)	22 (88)	25 (100)
Control group	25 (100)	0 (0)	25 (100)
Total	28 (56)	22 (44)	50 (100)

**Table 4: The mean anxiety score in the study groups**

Variables	Study group	Control group	P
Mean anxiety score	3±0.81	4.20±1.04	0.001

observed. This hormone significantly improves the quality of sleep, anxiety, and depression. In addition, melatonin receptors have been identified in the spinal cord tissue. Therefore, melatonin may have antinociceptive effects on pain stimuli. Interestingly, the perception of pain, especially the pain caused by heat and cold, changes throughout the day, which may be due to changes in the level of melatonin in the body. Reduction in internal melatonin increases neuropathic pain caused by nerve damage. Nerve damage induced pain after use of tourniquet was the point that has been considered in this study. Recent empirical evidence has also shown that melatonin may significantly reduce pain behaviors under certain circumstances.<sup>[12]</sup>

In this study, we used 6-mg melatonin for patients undergoing upper limb surgery 90 min before the surgery. This study showed that the mean tourniquet-induced pain and anxiety of patients was lower in melatonin-treated group during surgery, and this was statistically significant. In addition, the mean sensory and motor block creation time was lower in the study group, and the sensory and motor block duration was higher in the melatonin group, and this difference was statistically significant (0.001). The mean starting time of pain in the melatonin group was longer than that of the control group, and the results showed a statistically significant difference (0.001).

Mowafi and Ismail evaluated the effect of melatonin administration on relief from tourniquet pain and improvement of pain in patients undergoing IVRA. The results of their study are consistent with our results. The sensory and motor block creation time, the score of

tourniquet-induced pain, and the level of anxiety during surgery were lower in the study group and were statistically significant. In the present study, we also evaluated the sensory and motor block duration.<sup>[13]</sup>

Borazan *et al.* evaluated the efficacy of preoperative oral melatonin administration on the relief, sleep quality, and severity of postoperative pain in patients undergoing selective prostatectomy. The results showed that there was no statistically significant difference between the two groups in terms of the measured parameters, which was not consistent with the present study. The type of surgery, the type of anesthesia, the type of drugs used, and the gender of the patients in the two studies may justify this difference.<sup>[11]</sup>

Caumo *et al.* evaluated the effect of oral melatonin on postoperative anxiety and analgesia. Their findings showed that preoperative melatonin had clinical anxiolytic and analgesic effects, especially during the first 24 h after surgery, and also improved rest-activity circadian rhythm. Caumo *et al.* also carried out a study to investigate the anxiolytic and analgesic effects of melatonin and clonidine on improving postoperative pain management. They found that melatonin or clonidine reduced preoperative anxiety, pain intensity, and postoperative morphine use in patients with abdominal hysterectomy. In our study, the mean score of anxiety and tourniquet-induced pain was lower in the melatonin group.<sup>[14,15]</sup>

Khezri and Merate evaluated the effect of preoperative melatonin on patients' pain and anxiety, surgical conditions, and intraocular pressure during cataract surgery under topical anesthesia in Iran and concluded that administration of melatonin sublingual before the surgery reduced the level of anxiety and provided excellent surgical conditions but could not affect postoperative pain compared with the control group. The type of surgery may affect the results of our study or theirs in terms of pain during and after the surgery. The results of these two studies were consistent in terms of anxiety scores.<sup>[16]</sup>

Considering that pain intensity after dental surgery can be moderated and preoperative anxiety is also combined with this pain in young people, Seet *et al.* conducted a study to evaluate the effect of preoperative melatonin administration on postoperative pain and preoperative anxiety in patients undergoing surgical removal of wisdom teeth and concluded that the use of melatonin cannot definitely improve pain or anxiety recovery in all patients. In this study, male and female patients were examined separately; the results were different in pain score in female patients, and the pain score was lower. This difference was statistically significant. Perhaps, if we have evaluated patients according to their gender in our study, we would have achieved results similar to their study.<sup>[17]</sup>

Melatonin is an important hormone for regulating circadian rhythms and cellular homeostasis in mammals. Recent

evidence has shown that melatonin has antinociceptive effects on pain stimuli of the nervous system in animals and humans.

## Conclusions

However, the effect of melatonin is still controversial according to clinical studies. The main aim of this study was to evaluate the mean score of pain caused by tourniquet, and melatonin proved to be effective on pain in this study and patients who received this drug suffered from less pain compared with the control group, and the difference was statistically significant.

Considering the above studies and comparing them with the results of our research, it seems that the use of this drug at different doses and in different surgeries can reduce the pain and anxiety of patients during and after surgery.

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## Conflicts of interest

There are no conflicts of interest.

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