

# Assessing the Effects of Premedication Using Oral Melatonin on Quality of Sedation and Pain Control During and After Cataract Surgery under Sedation and Local Anesthesia

Mojtaba Rahimi Varposhti, Behzad Nazemroaya\*, Shahrzad Andalib

Department of Anesthesiology and Critical Care, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

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## ABSTRACT

**Background:** Providing adequate sedation in patients undergoing cataract surgery, can create analgesia and sedation during injection and retrobulbar surgery in order to prevent eye movement during open eye surgery. This study was aimed to assess the effects of melatonin premedication on the quality of sedation and pain control during cataract surgery.

**Methods:** The study was a triple-blind randomized clinical trial which was performed in Isfahan on 40 patients. The patients were allocated randomly into two groups of 20 subjects; one group receiving 3 mgs of sublingual melatonin pill and another group 3mgs of placebo. 60 minutes prior to surgery.

Hemodynamic parameters, level of pain and sedation were measured at specific intervals. In order to measure the level of pain and sedation, the VAS score and Richmond scales were used respectively.

**Results:** Surgery duration (P value=0.059), duration of anesthesia (P value=0.14), duration of recovery (P value=0.34), ASA (P value 0.27), Richmond scale (P value=0.45), Oxygen saturation level (P value=0.12), PR (P value=0.87) did not show a significant difference between the two groups. The changes in mean arterial pressure (P value=0.02) and pain intensity (P value=0.04) were significantly higher in the placebo group compared to the melatonin group.

**Conclusion:** Premedication with oral melatonin was beneficial in providing better pain control and hemodynamic stability in patients undergoing cataract surgery under sedation and local anesthesia.

## Introduction

The darkening of the lens of the eye, cataract, is usually due to aging and is a painless and progressive condition that affects contrast and color perception and changes refraction and leads to partial or complete loss of vision. [1]. In cataract surgery, the opaque lens is replaced with an artificial lens by various methods such as phacoemulsification [1-2] and since elderly people with underlying diseases such as heart disease, high blood pressure and diabetes are candidates for it. The method of sedation and local

anesthesia is more common for cataract surgery because it is safe and painless [3-4].

The purpose of sedation in patients undergoing cataract surgery is to keep the patient pain-free and calm during injection and retrobulbar surgery in order to prevent eye movements during open eye surgery and to minimize complications [5]. In recent years, most cataract surgeries are performed in the form of phacoemulsification under local anesthesia. Local anesthesia protects the patient from damage to the optic nerve, respiratory arrest and perforation of the globe and causes no interference with vision, faster recovery of vision, absence of injection pain

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\*Corresponding author.

E-mail address: behzad\_nazem@med.mui.ac.ir

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and unrestricted movement of the eyeball without increasing the volume of the globe [5-7].

Various drugs such as propofol, benzodiazepine, opioid and dexmedetomidine have been used for sedation and drugs such as tetracaine and oxy-buprocaine for local anesthesia [7-8]. These drugs have different indications and are used to reduce the patient's physiological and psychological pain and suffering and increase the patient's tolerance, and have different side effects such as excessive sedation, disorientation and respiratory suppression, confusion, decrease in blood oxygen saturation, bradycardia [9-10]. Therefore, finding a drug that, in addition to providing sufficient analgesia and sedation, also has fewer side effects, is of particular importance to the Melatonin, as a common hypnotic drug, is effective in starting and continuing sleep and is known as an antioxidant and anti-inflammatory that regulates the circadian rhythm [7,11].

Likewise, its role against obesity, diabetes, sepsis and fibrosis has also been proven [12]. Melatonin is produced in the pineal gland and retina, and the receptors of this drug have been identified in the spinal cord [13-14]. This drug produces important effects as a prodrug in reducing restlessness during surgery without cognitive impairment such as memory impairment and can be used as a harmless drug to reduce pain and restlessness during cataract surgery [12-15]. Therefore, in the present study, the effect of premedication with oral melatonin on the quality of sedation and pain control during and after surgery in cataract surgery under sedation and local anesthesia in Feyz Hospital, Isfahan has been investigated.

## Methods

### Study Design

This study is a triple-blind, randomized, controlled clinical trial designed to investigate the effect of oral melatonin premedication on the quality of sedation and pain scale in cataract surgery. The trial was approved by the Ethics Committee in Biomedical Research of Isfahan University of Medical Sciences (approval number: IR.MUI.MED.REC.1399.768).

### Setting and Participants

The trial was conducted at Feyz Hospital in Isfahan, Iran. Participants included cataract surgery candidates who met the inclusion criteria: adults aged over 18 years, classified as ASA I, II, or III, and who provided informed consent to participate in the study. Exclusion criteria included a history of obstructive sleep apnea, use of psychiatric drugs, autoimmune diseases, diabetes, nystagmus, leukemia, deafness, allergies to the drugs used, use of painkillers in the past week, and a BMI over 35.

### Randomization and Blinding

Participants were randomly allocated into two groups using random allocation software. Each participant was assigned a code using a random number table, with even and odd numbers determining group allocation. This process continued until the required sample size of 40 patients was reached. The trial was triple-blinded; the patients, outcome assessors, and data analysts were unaware of the group assignments. The blinding was maintained by ensuring that the clinical caregiver evaluating the symptoms was different from the person performing the intervention. Furthermore, patients were unaware of the type of intervention they received, and data analysts did not have access to the group allocations during the analysis phase.

### Interventions

#### Intervention Group (Group A)

In this group, patients received a sublingual tablet containing 3 mg of melatonin manufactured by Norm Life one hour before surgery. After being placed on the surgical bed, patients were subjected to cardiac and respiratory monitoring. An intravenous line was established for drug injection, and the measurement criteria were explained to the patient. The patient was then put under anesthesia, and the operation began. The patient's symptoms were measured and recorded until the end of the operation and during the recovery period. This intervention falls under the category of prevention.

#### Control Group (Group B)

In this group, patients received a placebo sublingual tablet one hour before surgery. The placebo was similar to the melatonin tablet in terms of color, smell, and appearance. After being placed on the surgical bed, patients were subjected to cardiac and respiratory monitoring. An intravenous line was established for drug injection, and the measurement criteria were explained to the patient. The patient was then put under anesthesia, and the operation began. The patient's symptoms were measured and recorded until the end of the operation and during the recovery period. This intervention falls under the category of placebo.

### Data Collection and Outcome Measures

Patients underwent continuous monitoring of heart rate, respiratory rate, oxygen saturation, and blood pressure. Measurements were taken at the following time points: before administration of melatonin or placebo (baseline), before the injection of anesthetic (pre-anesthesia), one minute, five minutes, and every ten minutes after the anesthetic injection until the end of the surgery, and every ten minutes during the recovery period until discharge from the recovery room.

The primary outcome variable was pain intensity, measured using the Visual Analog Scale (VAS), where patients rated their pain from 0 (no pain) to 10 (worst pain imaginable). Secondary outcomes included sedation quality, assessed using the Richmond Agitation-Sedation Scale (RASS) [16], which scores from -5 (unarousable) to +4 (combative), and hemodynamic parameters such as blood pressure, heart rate, and oxygen saturation levels measured at specific intervals.

### Statistical Analysis

All statistical analyses were conducted using SPSS software version 22.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean  $\pm$  standard deviation (SD), while categorical variables were presented as frequencies and percentages. The independent t-test was employed to compare the mean differences between the melatonin and placebo groups for continuous variables such as age, weight, surgery time, anesthesia time, recovery time, and various hemodynamic parameters. Chi-square tests were used to assess the differences in categorical variables such as gender and ASA status. Pain intensity measured by the Visual Analog Scale (VAS) and sedation levels assessed by the Richmond Agitation-Sedation Scale (RASS) were analyzed using repeated measures ANOVA to evaluate

the effect of time, group, and their interaction. The significance level was set at  $P$  value  $< 0.05$  for all statistical tests.

The sample size was calculated to ensure sufficient power to detect a significant difference in pain intensity with 80% power and a 5% significance level, resulting in a target sample size of 40 participants (20 in each group).

### Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethics committee reference number: IR.MUI.MED.REC.1399.768). Written informed consent was obtained from all participants before enrollment. The trial was registered with the Iranian Registry of Clinical Trials (IRCT20160307026950N45) on 2022-09-10.

### Results

#### Demographic and Baseline Characteristics

The study included 40 patients, all of whom completed the trial without any exclusions (Figure 1).

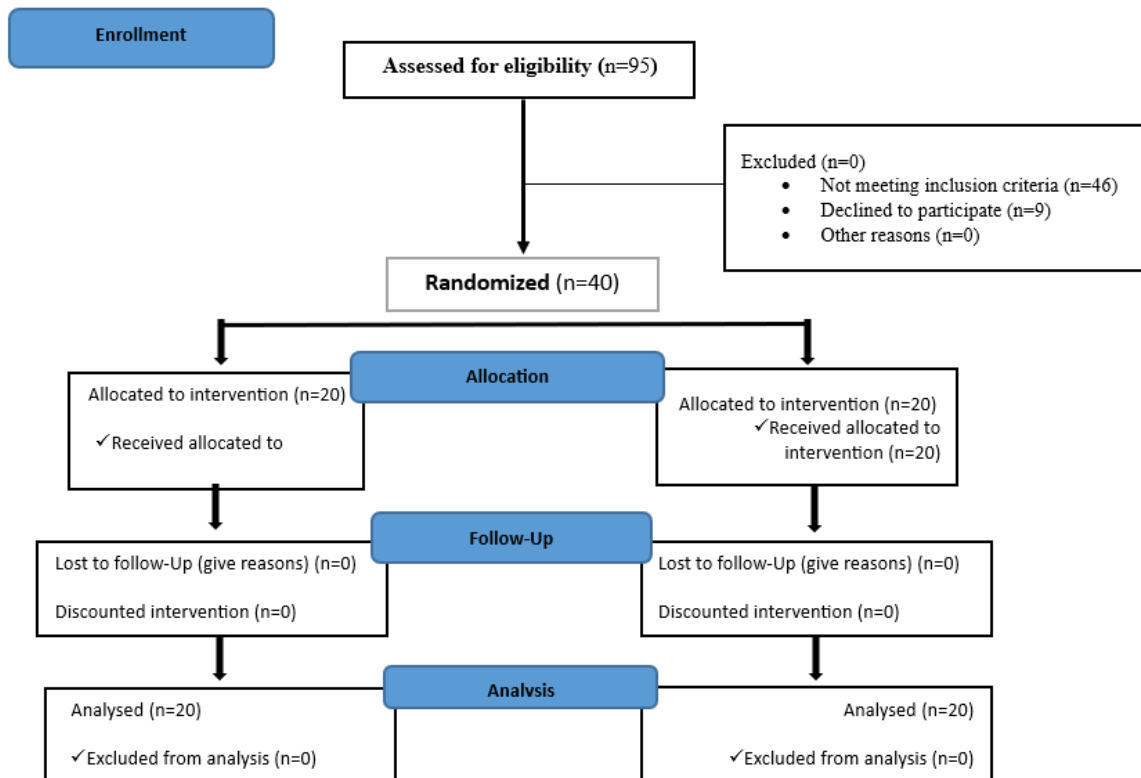


Figure 1- Study flow diagram

There were no significant differences between the melatonin and placebo groups in terms of age ( $P$

value=0.11), weight ( $P$  value=0.76), surgery duration ( $P$  value=0.059), anesthesia duration ( $P$  value=0.14),

recovery duration (P value=0.34), gender (P value=0.74), or ASA status (P value=0.27). The detailed comparison of these parameters is presented in (Table 1).

#### Pain Intensity.

Pain intensity was significantly lower in the melatonin group compared to the placebo group (P value=0.04). The

detailed data regarding pain intensity at various time points is presented in (Table 2).

#### Sedation Levels

The Richmond Agitation-Sedation Scale (RASS) scores did not show a significant difference between the two groups (P value=0.45). Detailed sedation data is shown in (Table 3).

**Table 1- Demographic and Baseline Characteristics of the Study Groups**

Parameter	Melatonin (N = 20)	Placebo (N = 20)	P value
Age (years)	57.25 ± 14.10	64.25 ± 13.51	0.11*
Weight (kg)	69.05 ± 12.83	68.00 ± 9.21	0.76*
Surgery Time (min)	48.00 ± 19.22	37.75 ± 12.30	0.059*
Anesthesia Time (min)	54.75 ± 21.12	46.50 ± 12.15	0.14*
Recovery Time (min)	41.00 ± 12.42	37.00 ± 13.58	0.34*
Gender (Female)	12 (60%)	11 (55%)	0.74**
Gender (Male)	8 (40%)	9 (45%)	
ASA 1	9 (45%)	5 (25%)	0.27**
ASA 2	9 (45%)	14 (70%)	
ASA 3	2 (10%)	1 (5%)	

\*Independent t-test \*\*Chi-square test

**Table 2- Pain Intensity Comparison at Different Time Points**

Time Point	Melatonin (Mean ± SD)	Placebo (Mean ± SD)	P value
VAS.pre	0.05 ± 0.22	0.10 ± 0.31	0.56
VAS.preAnesthesia	0.10 ± 0.31	0.15 ± 0.37	0.64
VAS (1 min)	0.40 ± 0.60	0.65 ± 0.93	0.32
VAS (5 min)	0.80 ± 0.70	1.00 ± 0.92	0.44
VAS (10 min)	1.00 ± 0.56	1.65 ± 1.09	0.02
VAS (20 min)	0.85 ± 0.67	1.55 ± 1.23	0.03
VAS (30 min)	0.75 ± 0.72	1.30 ± 1.26	0.09
VAS End of surgery	0.95 ± 0.94	1.65 ± 1.76	0.12
VAS recovery (10 min)	0.40 ± 0.60	1.25 ± 1.74	0.05
VAS recovery (20 min)	0.50 ± 0.61	1.05 ± 1.50	0.13
VAS recovery (end)	0.50 ± 0.69	1.10 ± 1.25	0.05

\*Repeated measures ANOVA: P1 (Time effect), P2 (Interaction effect), P3 (Intervention effect) \*\*Independent t-test

**Table 3- Richmond Agitation-Sedation Scale (RASS) Scores**

Time Point	Melatonin (Mean ± SD)	Placebo (Mean ± SD)	P value
RASS.pre	0.10 ± 0.31	0.26 ± 0.45	0.19
RASS.preAnesthesia	0.30 ± 0.98	0.20 ± 0.52	0.68
RASS (1 min)	-0.20 ± 1.20	-0.25 ± 1.25	0.89
RASS (5 min)	-0.55 ± 1.32	-0.80 ± 1.24	0.54
RASS (10 min)	-0.95 ± 1.19	-0.90 ± 1.37	0.90
RASS (20 min)	-0.90 ± 1.45	-0.95 ± 1.39	0.91
RASS (30 min)	-1.00 ± 1.15	-1.05 ± 1.28	0.90
RASS End of surgery	-0.45 ± 1.47	-0.85 ± 0.99	0.31
RASS recovery (10 min)	-0.40 ± 1.14	-0.10 ± 1.25	0.43
RASS recovery (20 min)	-0.10 ± 1.25	0.05 ± 1.23	0.76
RASS recovery (end)	0.05 ± 1.22	0.16 ± 0.90	0.70

\*Repeated measures ANOVA: P1 (Time effect), P2 (Interaction effect), P3 (Intervention effect) \*\*Independent t-test.

#### Hemodynamic Parameters

There were no significant differences in oxygen saturation levels (P value=0.12) or heart rate (P value=0.87) between the groups. However, mean arterial

pressure changes were significantly higher in the placebo group compared to the melatonin group (P value=0.02). Detailed hemodynamic parameters are shown in (Table 4).

**Table 4- Hemodynamic Parameters**

Parameter	Time Point	Melatonin (Mean ± SD)	Placebo (Mean ± SD)	P value
Heart Rate	Preoperative	76.55 ± 11.46	68.95 ± 17.97	0.11
	Pre-Anesthesia	75.20 ± 10.89	71.95 ± 7.82	0.25
	1 Minute Post-Op	73.15 ± 11.34	73.65 ± 11.11	0.88
	5 Minutes Post-Op	71.50 ± 11.75	72.25 ± 10.98	0.83
	10 Minutes Post-Op	70.95 ± 13.14	72.20 ± 11.45	0.75
	20 Minutes Post-Op	70.65 ± 14.67	71.15 ± 10.21	0.90
	30 Minutes Post-Op	67.17 ± 14.58	70.90 ± 9.94	0.47
	End of Surgery	71.55 ± 13.59	71.10 ± 7.23	0.89
	Recovery 10 Min	70.65 ± 11.87	70.85 ± 6.18	0.94
	Recovery 20 Min	70.25 ± 12.19	70.40 ± 7.13	0.96
	Recovery End	70.55 ± 11.30	71.05 ± 7.29	0.86
SpO <sub>2</sub>	Preoperative	97.15 ± 1.76	97.05 ± 2.67	0.88
	Pre-Anesthesia	97.20 ± 1.79	96.45 ± 2.28	0.25
	1 Minute Post-Op	98.30 ± 1.49	98.05 ± 1.43	0.59
	5 Minutes Post-Op	98.55 ± 1.61	98.45 ± 1.39	0.83
	10 Minutes Post-Op	99.10 ± 1.02	98.55 ± 1.43	0.17
	20 Minutes Post-Op	98.90 ± 1.07	98.40 ± 1.27	0.18
	30 Minutes Post-Op	98.86 ± 1.41	98.65 ± 1.04	0.62
	End of Surgery	98.85 ± 1.18	97.90 ± 1.68	0.04
	Recovery 10 Min	98.55 ± 1.50	97.80 ± 1.67	0.14
	Recovery 20 Min	98.45 ± 1.10	97.30 ± 2.23	0.04
	Recovery End	98.45 ± 1.43	97.95 ± 1.32	0.25
MAP	Preoperative	99.85 ± 14.06	104.60 ± 15.76	0.32
	Pre-Anesthesia	99.70 ± 13.95	104.05 ± 26.86	0.52
	1 Minute Post-Op	101.05 ± 16.30	108.15 ± 13.40	0.14
	5 Minutes Post-Op	97.70 ± 13.35	107.25 ± 14.60	0.03
	10 Minutes Post-Op	97.65 ± 11.89	104.95 ± 12.63	0.06
	20 Minutes Post-Op	96.80 ± 11.75	106.60 ± 12.04	0.01
	30 Minutes Post-Op	96.50 ± 12.21	105.85 ± 13.23	0.03
	End of Surgery	100.60 ± 12.91	105.70 ± 13.22	0.22
	Recovery 10 Min	101.85 ± 11.67	113.15 ± 12.21	0.005
	Recovery 20 Min	102.65 ± 11.95	110.35 ± 11.96	0.04
	Recovery End	100.20 ± 11.85	107.70 ± 11.59	0.05

\*Repeated measures ANOVA: P1 (Time effect), P2 (Interaction effect), P3 (Intervention effect) \*\*Independent t-test

## Discussion

Cataract surgery, as a frequently repeated surgery for refractive errors of the eye, has undergone a huge revolution in recent years, and an operation that in the past required hospitalization and long-term vision

rehabilitation, is now a fast daily and urgent procedure [17]. On the other hand, the use of new technologies and effective drugs made cataract surgery the safest and most predictable eye surgery [18] and even today, there is the potential to be able to perform cataract surgery in the early stages and saved the patients from a period of severe vision impairment by maintaining good conditions in terms of surgical quality and quality of life [17-18].

One of the conditions that increase satisfaction in eye surgery is creating appropriate pain relief and relaxation, such as using a suitable prodrug like melatonin. Melatonin is found naturally in the body, and its main function is to regulate sleep. Excess consumption of

melatonin increases the natural amount of this hormone in the body and helps to improve the quality of sleep [13-15]. On the other hand, melatonin and its analogs reduce the intraocular pressure in eyes with normal blood pressure and high blood pressure, making it a suitable option in cataract surgery [19].

In the present study, the results showed that surgery, anesthesia and recovery times, ASA and Rich criteria did not show significant differences between the melatonin and placebo groups. The level of oxygen saturation and pulse rate (PR) also had no significant difference between the two groups. However, changes in mean arterial pressure were higher in the placebo group. Importantly, the intensity of pain was significantly lower in the melatonin group compared to the placebo group.

These findings are consistent with previous studies. Khazaei et al. found that both melatonin and gabapentin reduced pain during cataract surgery, with the gabapentin group showing a reduction in retrobulbar pain compared to placebo [20]. Ismail et al. reported that melatonin premedication in patients undergoing cataract surgery



under local anesthesia had the effects of reducing restlessness, improving anesthesia, and reducing intraocular pressure, which improved the surgical conditions [15]. Haddadi et al. also showed that both acetaminophen and melatonin were effective in reducing pain during retrobulbar injection in cataract surgery [4]. A recent meta-analysis by Oh et al. further confirmed the analgesic effects of melatonin in various surgeries, emphasizing the need for more studies [21].

The evidence suggests that the circadian rhythm and associated molecules, such as melanopsin and melatonin, play an important role in regulating homeostasis and even treating some eye diseases. Many eye pathologies, including dry eye, corneal wound healing, cataracts, myopia, retinal diseases, and glaucoma, are affected by this cycle, and melatonin or its analogues can not only be used as a primary treatment, but can also improve the circadian pattern or provide antioxidant and anti-angiogenic properties as an adjuvant [22]. This is because melatonin activates its cognate membrane receptors, MT1 and MT2, which are present in many eye tissues, leading to different signaling pathways depending on the tissue [23].

In the present study, the results of better analgesia and hemodynamic stability, as evidenced by the average arterial pressure, were confirmed. However, the use of a larger sample size may provide stronger results regarding the sedation level, and it is suggested that a larger sample size be examined in the presence of other prodrugs.

## Conclusion

In cataract surgery, creating sedation and proper local anesthesia is necessary to perform the surgery, as pain can cause agitation and then unwanted complications. The use of melatonin pretreatment in cataract surgery confirmed the results of pain relief and hemodynamic stability (MAP) in the present sample.

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