

The effect of melatonin on delirium incidence in orthopedic patients: a clinical trial study

Fatemeh Rahavi^{1*}, Fatemeh Hosseini², Mohammad Reza Sobhan³, Mahmoud Vakili⁴, Abbas Meidany⁵

ABSTRACT

Introduction: Delirium is an acute psychiatric condition that can lead to very unpleasant consequences in post-operative orthopedics patients. Therefore, extensive studies have been done on the diagnosis, prevention and treatment of cognitive impairment especially delirium in patients admitted to the intensive care unit, orthopedic surgeries, organ transplantation and heart surgery departments. The aim of this study was to determine the efficacy of melatonin on prevention of delirium in orthopedics patients. **Materials and methods:** The present study was a double-blind randomized clinical trial which was performed on 100 patients admitted to orthopedics department. Patients were randomly divided into two groups to achieve optimal matching, using random numbers table. The first group received sublingual melatonin from the day before the surgery and on days 1, 2 and 3 after the operation, and second group received placebo. All of the two groups were evaluated for delirium on a daily basis (from day before surgery to 3 days later) at a specific and identical hour by a fixed and definite person by using the CAM test. **Result:** In this study, 100 patients were examined. The results showed that the mean age in the case group was 42.88 years with a standard deviation of 12.53, while the control group was 46.94 years with a standard deviation of 15.42 and there was no significant difference between the two groups according to $p = 0.152$. Also, there was no significant difference in gender and educational level of patients in the two groups. The results of the CAM test showed no significant difference between the two groups on the day before and the first, second and third days after the operation. **Conclusion:** According to the results of this study, the administration of melatonin did not have an effect on the incidence of delirium in the orthopedics department, but extensive multi-center studies and the use of different doses of the drug could be useful in determining the optimal dose of melatonin.

Keywords: Melatonin, Delirium, Orthopedic ward, prevention

¹Department of Psychology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

²Department of Psychology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

³Department of Orthopedics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

⁴Department of Community Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

⁵Medical Doctor, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

*Responding Author

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According to the fourth edition of the Diagnostic and Statistical Manual of Psychiatric Disorders, delirium is an acute and wobbly disorder of consciousness with cognitive changes (memory defects, orientation, concentration, attention and perceptual disturbance) (Mahanna et al., 1996), which is associated with an intensification in disability and mortality, Especially during the first year after surgery, increased hospitalization duration, increased re-hospitalization after discharge and delayed cognitive impairment (Newman et al., 2001; Selnes & McKhann, 2001; Stygall et al., 2003). Delirium is also associated with increased risk of problems such as myocardial infections, lung edema, pneumonia, and respiratory interruption (Moller et al., 1998).

The most important risk factors for delirium include older age, male gender, previous cognitive impairment, sensory defects, dehydration and inappropriate nutrition, alcohol abuse, treatment with psychoactive and anticholinergic drugs and related physical diseases (Yoshitaka et al., 2013). Among the above factors, older age, previous cognitive impairments and associated medical disorders are more specific factors in the development of postoperative delirium (Al-Aama et al., 2011; Andersen, Werner, Rosenberg, & Gögenur, 2014; de Jonghe et al., 2014).

Delirium as the most common cognitive impairment in orthopedic patients has always been a concern for physicians and researchers (Al-Aama et al., 2011; Shigeta et al., 2001), so that the lack of attention to treatment and its chronicity can lead to increased shelf-life in the hospital and delayed rehabilitation programs, increased costs Related to patient care and increased risk of long-term cerebrovascular accidents and even mortality. Therefore, extensive studies have been done on the diagnosis, prevention and treatment of cognitive impairment especially delirium in patients admitted to the intensive care unit, orthopedic surgeries, organ transplantation and heart surgery departments. Although many of these studies have been conducted on the treatment of this cognitive disorder, but limited studies have been published on the prevention of Delirium, which have reported the effectiveness of various antipsychotics and other drug groups in the form of clinical trials (Hanania & Kitain, 2002). this study, designed to determine the efficacy of melatonin in preventing delirium occurrence in orthopedics patients, the prevention approach is considered within the framework of a clinical trial.

MATERIALS AND METHODS

This double-blind randomized clinical trial study was designed with the aim of determining the efficacy of melatonin. 100 patients who were admitted to the orthopedic department were selected and after the initial assessment of the inclusion criteria, the informed consent was obtained from the patient accompaniment and they entered the study. The inclusion criteria were over 30 years of age, referral for elective orthopedic surgery, without reducing consciousness with or without mechanical ventilation with informed consent. Also, patients with acute I-axis psychiatric disorders, trauma and cerebral hemorrhage, and poor mental coordination, drug dependence, and cognitive impairment as dementia and delirium were excluded from study. Patients were randomly divided into two groups to achieve optimal matching, using random numbers table. The first group, from the night before surgery, up to 3 days, received 3 mg sublingual melatonin daily (made in Canada, packed in Atra, Tehran). The second group received placebo at the same time. In the examined trials, the nurse who prescribes drugs and the relevant assistant who examined the delirium status with CAM test were completely unaware of the prescribing status of the drug and the placebo, and the only drug counselor was aware of this. Drugs numbered by the pharmaceutical advisor were

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administered randomly to the patients who were enrolled in the study by nurse. All specimens of the two groups were evaluated for delirium on the day before the surgery and days 1, 2 and 3 after the operation at a specific and identical hour and by one definite person using the CAM test. Then the collected data were analyzed by SPSS software version 17 using Chi-square, T-test and Anova tests. Significance was reported at the conventional $p < 0.05$ level.

RESULTS

The present study was conducted as a randomized, double-blind randomized clinical trial with a preventive approach and aimed at determining the efficacy of melatonin on 100 patients hospitalized in the orthopedic ward.

The results showed that the mean age in the case group was 42.88 ± 12.5 years, while the control group was 46.94 ± 15.4 years and there was no significant difference between the two groups ($p=0.152$). also, the results showed that in case group, 32 (64%) and 24 (48%) were male and in case group 18 (36%) and control group, 26 (52%) were female ($p=0.2$). The level of education did not differ significantly between the two groups (table 1).

The results of the CAM-ICU test showed that on the day before the operation 7 patients (14%) were positive in the case group and 3 patients (6%) in the control group. there was no significant difference in prevalence of delirium in the two groups before surgery ($p=0.18$). We evaluated each group with CAM-ICU test for 3 days after surgery but there was no statistical difference between group in prevalence of delirium after surgery (table 2).

Only one patient in the case group suffered from headache and one patient had dizziness and the other patients were uncomplicated. Side effects were not significantly different between the two groups ($p=84$).

Table 1. preoperative clinical patient's characteristics: comparison of the control and melatonin group

	Control group Total (n=50)	Melatonin Group Total (n=50)	p-value
Age (years), Mean \pm SD	46.9 \pm 12.5	42.8 \pm 15.4	0.15
Men	24 (48%)	32 (64%)	0.98
Women	26 (52%)	18 (36%)	
Diabetes Mellitus	2 (4%)	2 (4%)	0.61
Hypertension	2 (4%)	1 (2%)	
Hyperlipidemia	2 (4%)	1 (2%)	
Thyroid dysfunction	1 (2%)	-	
Gastrointestinal Disorder	-	1 (2%)	

DISCUSSION

Delirium, as one of the most common psychiatric disorders, has always been a concern for researchers in behavioral and therapeutic sciences, and although extensive research has been done on symptoms, risk factors and therapies, less studies have been done to prevent it.

Table 2. incidence of delirium in orthopedic patients with CAM_ICU

CAM Renaults	Control group Total (n=50)	Melatonin Group Total (n=50)	p-value
Before surgery	3 (6%)	7 (14%)	0.18
One day after surgery	8 (16%)	9 (18%)	0.79
Two day after surgery	6 (12%)	6 (12%)	-
Three day after surgery	1 (2%)	2 (4%)	0.5

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In fact, delirium after a surgery is a common disorder that is associated with an increase in mortality, the length of hospitalization and treatment costs. It seems that this disorder has a higher risk of developing complications in people of higher age. The prevalence of delirium after hip surgery is reported to be 16 to 41% by spinal anesthesia or general anesthesia.

The results of this study showed that there was no significant difference in age, sex, and degree of education in the two groups. The results of the CAM test showed no significant difference between the two groups on the day before and the first, second and third days after the operation.

In a Cochrane review study, Siddiqi et al. Examined various interventions to prevent delirium in patients who were admitted to non-ICU wards. In their study 39 clinical trials with 16082 participants and 22 different interventions were evaluated. 32 studies were performed on patients undergoing surgery and most of these studies were performed in orthopedic wards. Their findings showed that cholinesterase inhibitors, antipsychotics, or melatonin did not reduce the incidence of delirium, and there was no difference between the case and control groups that were consistent with the findings of the present study (Najma Siddiqi et al., 2016).

Bourne et al. Showed that melatonin administration improves sleep and delirium in patients admitted to ICU, while Ibrahim et al. showed no improvement in sleep and delirium in patients with melatonin administration (Bourne, Mills, & Minelli, 2008; Egi et al., 2006). Of course, this difference may be due to the dose of melatonin that used in studies, the delirium examination test, the ward of hospitalization of patients, and also the underlying diseases in patients and, of course, the small number of samples. In the present study, 3 mg of melatonin was prescribed for orthopedic patients, while in the Bourne et al. study, 10 mg for 4 days, and in the Ibrahim et al. study 3 mg for at least 2 days until discharge was administered to patients admitted to ICU.

In another study, Artemiou et al. examined 250 patients after heart surgery, which unlike the present study, the prevalence of delirium was lower in the group receiving melatonin (8% vs. 20.8%). In this study, age was introduced as a predictor of delirium (Artemiou et al., 2015). In the study of Jonghe et al, 378 patients who were candidates for hip surgery received 3 mg melatonin for 5 consecutive days. In consistent with present study, the results of Jonghe et al. Showed that there was no significant difference in the incidence of delirium in the two groups. Of course, in this study, the mean age of patients was 84 years and 55.6% of them had cognitive impairment before admission, which probably contrasted with other studies (de Jonghe et al., 2014).

However, in a study by Sherif et al. Who investigated the effect of melatonin on the prevention and treatment of delirium after hip arthroplasty, the results showed that the incidence of delirium in the melatonin group (5 mg a day before surgery and an additional dose of 90 minutes before of the action) was less. Also, administration of 5 mg melatonin in 58.06% of patients with delirium was associated with successful treatment, although this difference was not significant (Sultan, 2010). Similar to the study by Sherif, Kenneth et al. Found the effect of olanzapine on delirium after knee and hip surgery. In the study, patients were treated with 5 mg olanzapine before and after operation in the case group. The prevalence of delirium in the case group was significantly lower than the control group (Larsen et al., 2010).

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In another study by the Fan et al. who examined the effect of melatonin on postoperative cognitive decline after surgery, the results showed that administration of 1 mg oral melatonin for 5 days, one hour before bed time from a day before surgery, compared to placebo, it can improve postoperative cognitive status, as well as improve circadian rhythms and patients' sleep quality (Fan, Yuan, Ji, Yang, & Gao, 2017). Findings of the study by Scholtens et al., 2016 showed that the level of melatonin in CSF fluid in elderly patients did not show a significant difference in hip surgery before and after surgery. In their study, 21% of patients had delirium after surgery. They suggested that if there is a disturbance in the secretion of melatonin after surgery, it is probably due to post-operative inflammation (Scholtens, de Rooij, Vellekoop, Vrouenraets, & van Munster, 2016).

In another study by Abbasi et al in 2018, the results showed that administration of melatonin in the first 24 hours of admission for 5 consecutive days in the case group did not have a significant difference in the incidence of delirium with the control group, which was consistent with the present study. The dosage of the drug and the evaluation of delirium were similar with our study (Abbasi, Farsaei, Ghasemi, & Mansourian, 2018).

According to different results of the studies, it seems that the optimal dose and duration of administration of melatonin to improve sleep and reduce delirium in patients is still a good topic for further investigation. Further studies are recommended to evaluate the different doses of melatonin, the severity and duration of delirium, and sleep disorders in patients. In addition, the precautionary effect of melatonin in the long-term outcome of patients, the degree of morbidity and mortality, hospitalization time and delayed cognitive function require more extensive studies.

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Conflict of Interest

The author declared no conflict of interests.

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