Effect of Melatonin on Incidence Rate of Delirium in Elderly Patients Undergoing Open-Heart Surgery without a Pump: A Clinical Trial

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A B S T R A C T

Introduction: Delirium has been considered as the most common cognitive disorder after major surgery. Melatonin therapy is effective in reducing the incidence of delirium after open heart surgery with pain relief mechanism and adjustment of the sleep cycle and the absence of specific side effects. This study was conducted to determine the effectiveness of melatonin on prevention of delirium after coronary artery bypass surgery.

Methods: The double blind randomized controlled clinical trial recruited 140 patients, equally decided, who underwent coronary artery bypass surgery in Afshar Hospital, Yazd city, 2016. All participants of the two groups were evaluated for the presence of delirium on the day of surgery and three days after by the Confusion Assessment Method for ICU (CUM-ICU). Respectively, The intervention and control group received 3 mg melatonin and 3 mg placebo orally before and after the operation. Data were analyzed by Chi-square, T-test, paired t-test and Cochran tests.

Results: The incidence of delirium in the melatonin and the control group was 35.7% and 5.7% on the day of operation, 68.6% and 31.4% three days after the operation, respectively. The results showed that there was a significant difference in the frequency of cognitive test of CAM-ICU on day of surgery and three days after surgery between the two groups (p <0.001).

Conclusion: Despite the efficacy of melatonin therapy in reducing delirium, further studies on the effects of other effective drugs on the treatment of delirium, such as antipsychotics and receptor blockers, should be considered.

Keywords: Melatonin, Delirium, Surgery, Older Adults, Clinical Trial

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to occur more frequently within the first few days of operation than other cognitive impairments (4); however, the risk of developing delirium after CABG conducted by Off-pump and other surgical procedures is similar (5). Delirium refers to a disturbance of consciousness with a reduced ability to focus or sustain attention that usually begins suddenly and is characterized by disorientation, short-term memory loss, change in sensory perception (illusion), the process of abnormal thinking and disturbing behavior (6, 7). In fact, delirium refers to a disturbance of consciousness and a change in the cognitive status, and is not associated with previous cognitive impairments or consciousness, including dementia (8). The prevalence of delirium at admission to hospital is 14-24% that reaches 56% during hospitalization. Its incidence increases with increasing age and due to medications and comorbidities (9, 10). The incidence rate of delirium has been reported to be 47% after heart surgery and 40% after orthopedic surgeries (11, 12).

Several studies have shown that melatonin imbalance in the pituitary gland can be considered one of the causes of delirium due to disturbed circadian rhythm (13, 14). In addition, neglecting these disorders can cause them to persist and become chronic and, after surgery, also to bring about long-term suffering for the patient. The use of various drugs for the prevention and treatment of early postoperative cognitive dysfunction has attracted the attention of many researchers in recent years, and haloperidol, chlorpromazine and other second generation antipsychotics have undergone clinical trials more than other drugs. It seems that medications that can regulate sleep and circadian rhythm can be effective to prevent postoperative cognitive dysfunction. One of these drugs is melatonin, which is used to treat shift work disorder, delayed sleep phase and sleep disorders in the elderly, and its regulatory effects are characterized by a reduction in the decomposition of tryptophan and serotonin with negative feedback effects in the prevention of delirium (15).

The results of a systematic review showed melatonin reduces postoperative delirium by regulating the circadian rhythm and sleep-wake cycle (16). Some studies have shown the effect of melatonin in decreasing the incidence of delirium (17-19) and some others have suggested no efficacy on delirium for this drug (20). Delirium's effects and consequences are more important due to lack of early diagnosis and quick treatment. Although delirium is one of the most common and dangerous complications in patients admitted to the postoperative care unit after heart surgery, unfortunately a high proportion of patients suffering from delirium after surgery are not diagnosed and therefore received no treatment for it, which can in turn lead to certain consequences such as increased mortality, length of hospital stay, need for nursing care and debilitating mental complications in patients. Since delirium occurs in over 80% of ICU patients, declines individual functioning, lengthens hospital stay, increases the rate of pathogenicity and mortality, unpleasant prognosis and costs (10, 21, 22).

Therefore, early diagnosis of the syndrome, identification of risk factors and the methods to prevent it will be effective in reducing morbidity and mortality, as well as health care costs. Given that the effectiveness of various antipsychotics has been investigated for the prevention of delirium in few clinical trials, this study was conducted to investigate the effectiveness of melatonin pill to prevent the incidence of delirium following CABG.

Methods

Study design and participants

The present double-blind randomized, clinical trial was conducted to investigate the preventive effect of melatonin on delirium in the Afshar hospital, Yazd, Iran in 2016. In this study, 140 patients undergoing CABG were selected and then enrolled in the study after an initial evaluation if they fulfilled inclusion criteria. Then, they were randomly assigned to two groups of 70 each by using a random number table in order to achieve the desired matching. In group 1, 3 mg/day oral melatonin was administered from three days before beginning of the intervention until three days after its completion. Group 2 received placebo for seven days. The participants, the prescribing nurse and the resident who examined the participants for delirium by the Confusion Assessment Method for the ICU (CAM-ICU), were completely blind to the treatment assigned for the two groups, and only pharmaceutical consultant was informed about the treatment for each participant.

Drugs labeled with numbers by the pharmaceutical consultant, were administered by the nurse of the department according to the numbers (box 1 drugs to patient number 1, box 2 to patient number 2, etc.). All participants in the two groups were evaluated for delirium using the CAM-ICU test at baseline the study (the day of surgery) and at completion of the intervention (three days after surgery).

Inclusion criteria was age of 40-70 years and providing informed written consent to participate in the study, and exclusion criteria was undergoing emergency surgery, having taken dopamine since the past until the beginning of the study, drinking alcohol and drug use, comorbidity of psychiatric disorders, based on the revised version of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, cerebral lesions, renal failure (creatinine level higher than 1.4), liver failure and epilepsy.

According to a similar study in which the incidence of postoperative delirium was estimated at approximately 30% (23), with 95% confidence interval, and test power of 80%, with the assumption that in the melatonin group, the incidence of delirium was lower by 10%, the required sample size for each group was estimated at 70. Eligible individuals were enrolled in the study and randomly assigned to either treatment group or placebo group. The sampling process continued until the sample size of interest was achieved.

Instruments

The instruments used in this study were Richmond Agitation Sedation Scale (RASS) and CAM-ICU.

RASS that is a standard scale to assess the level of agitation and sedation in ICU patients (24). This tool consists of 10 items each of which represents one of the levels of consciousness (aggressiveness to severe drowsiness and lack of alertness). In order to determine the RASS score, first, without any interactions, only the patient was visited and, if he/she is conscious, the appropriate score (0 - +4) was assigned to him/her. But, if the patient was not
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Results

The mean age of melatonin group was 64.03 and that of placebo group 64.5 years, with no statistically significant difference (p = 0.8). There was no significant difference in the frequency of gender, education level and sleep disorders between the two groups (p > 0.05). (Table 1 and 2)

With respect to the drugs taken for sleep disorders, there was no significant difference in the frequency of sleep disorders and the drugs taken between the two groups (p > 0.05) (Table 3).

There were no significant differences in mean potassium, sodium, AST and creatinine levels between the melatonin and placebo groups (p > 0.05) (Table 4).

Based on the results, there was a significant difference in the frequency of the CAM-ICU result on the day of surgery between the two groups, so that the delirium was lower in melatonin group (p < 0.001). There was also a significant difference in the frequency of CAM-ICU result three days after surgery between the two groups, so that in melatonin group, the incidence rate of delirium was still lower (p < 0.001). (Table 5)

A total of 32 patients complained of headache, of which 20 were in melatonin group and the rest in placebo group. Vertigo was reported in 43 patients, of whom 16 were in melatonin group the rest in placebo group. Dizziness was reported in 20 people, of whom 5 were in melatonin group and 15 in placebo group. Clear dream was reported in only one case in placebo group and gastrointestinal discomfort including abdominal pain and cramp in 16 cases, of which 11 were in melatonin group and only 5 in placebo group. A total of 25 patients developed no complications, of which 15 were in melatonin group and 10 in control group, with a significant difference in the frequency of drug side effects between the two groups. Headache and digestive disorders were higher in control group than in control group (p = 0.009). (Table 6)
Table 1. The frequency distribution of the demographic variables in terms of the two groups

| Variables               | Group 1 (Melatonin) N(%) | Group 2 (Placebo) N(%) | p  |
|-------------------------|--------------------------|------------------------|----|
| Gender                  |                          |                        |    |
| Male                    | 57 (87.1)                | 61 (81.7)              | 0.35|
| Female                  | 13 (18.6)                | 9 (12.9)               |    |
| Age                     |                          |                        |    |
| 45-49                   | 8 (11.4)                 | 3 (4.3)                |    |
| 50-54                   | 14 (20)                  | 16 (22.9)              | 0.18|
| 55-59                   | 18 (25.7)                | 15 (21.4)              |    |
| 60-64                   | 19 (27.1)                | 15 (21.4)              |    |
| Education level         |                          |                        |    |
| Illiterate              | 9 (12.9)                 | 14 (20)                |    |
| ≤ Diploma               | 35 (50)                  | 41 (58.6)              | 0.28|
| Academic                | 26 (37.1)                | 15 (21.4)              |    |
| Sleep disorder          |                          |                        |    |
| Yes                     | 45 (64.3)                | 53 (75.7)              | 0.14|
| No                      | 25 (35.6)                | 17 (24.3)              |    |

Table 2. Determine and compare the distribution of abnormalities of sleep disorders in the two groups

| Variables               | Initial N(%) | Terminal N(%) | Intermittent N(%) | Hypersomnia N(%) | Non N(%) | p  |
|-------------------------|--------------|---------------|-------------------|------------------|----------|----|
| Group 1 (Melatonin)     | 8 (11.4)     | 8 (21.4)      | 4 (5.7)           | 25 (35.7)        | 25 (35.7)| 0.28|
| Group 2 (Placebo)       | 13 (18.6)    | 9 (12.9)      | 1 (1.4)           | 30 (42.9)        | 17 (24.3)| 0.28|
| Total                   | 21 (15)      | 17 (12.1)     | 5 (3.6)           | 55 (39.3)        | 42 (30)  |    |

Table 3. The distribution of the type of drug used in sleep disorders in the two groups

| Variables               | Lorazepam N(%) | Alprazolam N(%) | Clonazepam N(%) | Perphenazine N(%) | Eskasoni* N(%) | Nortriptyline N(%) | Librium** N(%) | p  |
|-------------------------|----------------|-----------------|-----------------|-------------------|---------------|-------------------|---------------|----|
| Group 1 (Melatonin)     | 7 (10)         | 4 (5.7)         | 3 (4)           | 2 (2.9)           | 2 (2.9)       | 0 (0)             | 3 (4)         | 0.7|
| Group 2 (Placebo)       | 2 (2.9)        | 7 (10)          | 7 (10)          | 6 (8.6)           | 7 (10)        | 2 (1.9)           | 1 (1.4)       |    |
| Total                   | 9 (6.4)        | 10 (7.1)        | 11 (7.9)        | 8 (5.7)           | 9 (6.4)       | 2 (1.4)           | 4 (2.9)       |    |

*Trifluoperazine Hcl
**Chlordiazepoxide

Table 4. Determine and compare CR, AST, NA, K, and ALT according to the two groups

| Variables | K          | Na         | Ast        | Alt        | Cr         | p  |
|-----------|------------|------------|------------|------------|------------|----|
| Group 1 (Melatonin) | 4.09 ± 0.31 | 138.38 ± 3.12 | 23.51 ± 4.11 | 22.74 ± 4.21 | 0.99 ± 0.13 | 0.03|
| Group 2 (Placebo)    | 4.13 ± 0.32 | 138.35 ± 3.70 | 22.62 ± 3.80 | 22.07 ± 3.97 | 1.04 ± 0.14 |    |
| p        | 0.46       | 0.96       | 0.18       | 0.33       | 0.03       |    |

Table 5. The frequency distribution of the CAM-ICU test result day and 3 day after surgery

| Variables | MCI on the day after surgery N(%) | MCI on the 3 day after surgery N(%) | p  |
|-----------|----------------------------------|------------------------------------|----|
| Positive  | Negative                         | Positive                           | Negative |    |
| Group 1 (Melatonin) | 25 (35.7) | 45 (64.3) | 4 (5.7) | 66 (99.4) | < 0.001 |    |
| Group 2 (Placebo)    | 48 (68.6) | 22 (31.4) | 22 (31.4) | 48 (68.6) | < 0.001 |    |
| p        | < 0.001                           | < 0.001                             |    |

*Cochrane
Postoperative delirium is one of the most severe and costly complications. Due to the severity of the associated disability, mortality, and costs imposed on the patient and the health care system, it is much more important to prevent rather than treat delirium. The aim of this study was to determine the effect of melatonin on prevention of delirium development after CABG. The results showed on the day of surgery and three days later, the incidence rates of delirium were lower in melatonin group.

The mean age of the melatonin and placebo groups was over 60 years, which indicates that age is one of the risk factors for postoperative delirium; no significant difference was observed in the mean age of the two groups, which is not consistent with the results of other studies. In the study of Cheraghi et al. (27), the incidence rate of delirium was significantly different in terms of age, so that it was higher in older people. In the study of Rajabpour et al. (23), the incidence of delirium was significant in terms of age. There was a significant relationship between the trend of increasing age and the delirium occurrence (28-30).

In our study, the incidence rate of delirium on the day of surgery and three days after the surgery were 35.7% and 5.7% in melatonin group and 68.6% and 31.4% in control group, respectively. Delirium has been reported in 10%-60% of cases (37). The incidence rate of delirium after elective and emergency surgery in elderly patients was obtained 20.8% in the study of Sabol et al. (38). In other studies, this rate has been reported between 3% and 50% (39-41).

In our study, the incidence rate of delirium on the day of surgery and three days after the surgery were 35.7% and 5.7% in melatonin group and 68.6% and 31.4% in control group, respectively. Delirium has been reported in 10%-60% of mechanically ventilated patients, with a reported estimate of over 73% in older patients. In ICU, 81% of patients have been reported to develop delirium (31, 32). The incidence rate of delirium in patient after cardiac surgery was obtained 20.8% in the study of Sabol et al. (38). In other studies, this rate has been reported between 3% and 50% (39-41).

Inconsistent findings can be due to the type of patient admission and the number of men and women participating in the study. In the study of Zolfaghari et al. the incidence of delirium was not significantly correlated with sleep disorders (26). In the study of Cheraghi et al. (27), there was a significant difference in sleep disorders and incidence of delirium between the patients. The reason for the inconsistency in the results of our study with other studies may be that in our study, the Pittsburgh Sleep Quality Index was not used and a self-report instrument was administered to assess sleep status and quality. Low sleep quality can independently lead to delirium. After open heart surgery, patients with poor quality sleep are at comparatively higher risk of developing delirium (35).

Based on the findings, complications such as headache, dizziness, confusion and dullness, clear dream and abdominal pain and cramp were observed after surgery. There was a significant difference in the frequency of drug side effects between the melatonin and placebo groups in our study. The incidence of headache and digestive disorders was higher in patients receiving melatonin and stomach and dizziness in the control group. A study by Mistrletti et al. (36) found that melatonin improved issues such as pain, ejaculation, and sleep, which confirmed the study done by Andersen et al. (37). The most common side effects of this drug include dizziness-headache-live dreams, and nightmare, which are mild and transient and do not cause drop-outs after drug discontinuation in most cases (37).

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There was no significant difference between the frequency of gender, education level and sleep disturbance between the intervention and control groups. There was also no significant difference in the frequency of sleep disorders and the type of drug used between the two groups. In the study of Cheraghi et al. (27), the incidence of delirium was higher in men than in women, but no significant association with respect to education level and marital status was found. In the study of Rajabpour et al. (23), the incidence of delirium was not significant in terms of gender. Inconsistent findings can be due to the type of patient admission and the number of men and women participating in the study. In the study of Zolfaghari et al. the incidence of delirium was not significantly correlated with sleep disorders (26). In the study of Cheraghi et al. (27), there was a significant difference in sleep disorders and incidence of delirium between the patients. The reason for the inconsistency in the results of our study with other studies may be that in our study, the Pittsburgh Sleep Quality Index was not used and a self-report instrument was administered to assess sleep status and quality. Low sleep quality can independently lead to delirium. After open heart surgery, patients with poor quality sleep are at comparatively higher risk of developing delirium (35).

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The incidence rate of delirium after elective and emergency surgery in elderly patients was obtained 13.2% in the study of Ansaloni et al. (42). A systematic review reported 11%-51% of patients develop delirium after surgery (33). The prevalence of delirium in hospitalized patients that have undergone open heart surgery is estimated to range between 23% and 25%. Patients undergoing open heart surgery are at risk of sleep disorders and postoperative sleep deprivation (43, 44).

The results showed there was a significant difference in the frequency of the CAM-ICU result.
on the day and three days after surgery between the two groups, so that in melatonin group, the incidence rate of delirium was lower. As one of the typical features of delirium is disruption of sleep-wake cycle and circadian rhythm (45), therefore Melatonin plays an essential role in the regulation of sleep-wake cycle (46). The results of trials suggest a potential role for melatonin in preventing and treating delirium in older adults (47-48, 25).

The results of the study by Martinez et al. (18), on 850 ICU patients treated with 3 mg melatonin for 14 days were consistent with the present study. In the study of Vijayakumar et al. the prevalence of delirium in the intervention group decreased significantly after 3 days when compared to the control group (49). In the study of Nishikimi et al. the incidence and duration of delirium significantly decreased in the group administered with ramelteon (melatonin agonist) (17). In recent years, melatonin has been used to reduce and treat delirium due to its role in regulating sleep-wake cycle (50). In the study of Artemiou et al. the prevalence of delirium in the intervention (melatonin-administered) group was significantly lower than in the control group (19). A systematic review has reported melatonin reduces delirium after surgery by regulating the circadian rhythm and sleep-wake cycle (16).

In the study of Jongh et al. there was no difference in the incidence of delirium between the patients administered with melatonin and placebo, but the group receiving melatonin experienced a relatively shorter period of delirium. In other words, administration of melatonin had no effect on development of delirium in the case group compared to the control group (20). The results of a review by Siddiqi et al. (51) showed there is strong evidence on the effectiveness of multi-stage interventions to prevent delirium in hospitalized patients.

Conclusion
Consider that circadian rhythm disorders are one of the factors affecting the development of delirium, it seems that due to the lower significance of the level of delirium in the melatonin group on the one hand and the need for less amount of morphine, with analgesic and sedative effects, in this group, on the prevention of delirium, this drug has a beneficial effect on the prevention and treatment of delirium by improving sleep. The application of the results of this study, along with non-pharmacological interventions, can reduce the incidence of delirium and the complications of this neuropsychiatric syndrome. Therefore, administration of melatonin is associated with a significant reduction in the incidence of delirium after heart surgery, and therefore should be considered in patients who are candidate for heart surgery.

Study limitations
Our study was not performed in patients with high risk of developing delirium such as those aged over 70 years old or previous cognitive impairments, which is a risk factor for delirium after surgery, especially heart surgery. The other major limitation was related to the delirium measure used that was the CAM-ICU alone. One of the other limitations of our study was inclusion of only one center, as well as the lack of examination of other drugs used by the patient and their effect on the efficacy of melatonin.

Conflict of interest
The authors declare that there is no conflict of interests.

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Authors’ contributions
All authors contributed to the design of study, implementation and analysis of data. Also, they contributed to draft and modify the article. All authors have read and approved the final version of the article.

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