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Investigating the Effectiveness of Melatonin in the Treatment of Critically Ill Patients with COVID-19 Hospitalized in the Intensive Care Unit: A Double-Blind Randomized Clinical Trial

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Abstract

Background: Melatonin, a tryptophan product, has anti-inflammatory and virucidal effects. A study evaluated whether melatonin is more effective than placebo in critically ill COVID-19 patients.

Methods: The present study used a double-blind, randomized clinical trial in patients with COVID-19 hospitalized in the intensive care unit of Rasool Akram Hospital, Tehran. Iran. Melatonin 10 mg and placebo were given to the patients at night before bed. Patients were randomly divided into 2 groups. The first group was given melatonin with a therapeutic dose of 10 mg daily, and the second group was given a placebo with the same dose of 10 mg daily. Patients received melatonin or placebo for 7 days.
The chi-square or Fisher exact test was used to compare qualitative variables. The study analyzed the mean of the variables under investigation by conducting a 2-factor repeated measures analysis of variance at 3 different time intervals in those administered medication or placebo.

Results: The study analyzed 44 melatonin patients and 42 placebo groups. The mean intensive care unit (ICU) hospitalization days were 11.23 ± 4.73 days in the melatonin group and 11.90 ± 6.52 days in the placebo group (P = 0.582). The mean days of hospitalization in the melatonin group were 19.70 ± 8.77 days and 21.48 ± 10.85 days in the placebo group (P = 0.407). The mean oxygen saturation before and after discharge from ICU in the melatonin group was 81 ± 6.73%, 91.02 ± 1.17%, and in the placebo group, 83.36 ± 8.27%, 91.21 ± 1.26, respectively (P = 0.467 and P = 0.150)

Conclusion: Melatonin can significantly reduce inflammation and oxidative stress markers in patients, making it a promising therapeutic option for COVID-19 patients. Further research is needed to determine the optimal treatment dosage and duration. Nonetheless, these results offer a promising avenue for future research and clinical practice.

Keywords: Melatonin, COVID-19, Intensive Care Unit

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Introduction

Coronaviruses are a group of ribonucleic acid viruses that cause disease in mammals and birds. These viruses

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↑What is "already known" in this topic:
Melatonin is essential to maintaining good health because of its anti-inflammatory and antiviral properties. The pineal gland and other organs synthesize it, which has been shown to possess antiaging properties while effectively combating infectious diseases. Studies have confirmed the positive impact of melatonin on human health, highlighting it as a critical component in maintaining overall well-being.

→What this article adds:
To reduce inflammation and oxidative stress markers in COVID-19 patients, it is recommended that oral melatonin supplements be administered at a daily dosage of 10 mg. This intervention is effective and may have important implications for managing COVID-19 patients. As such, it is advisable that health care professionals be made aware of this treatment option and that further research be conducted to understand its potential benefits better.

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cause respiratory tract infections that can be mild to fatal. Their mild disease can cause symptoms similar to a cold, and in advanced cases, they can cause generalized body involvement. In the past 20 years, 2 coronavirus epidemics, both of which originated from China, have caused human disease. The scale of the conflict in both epidemics was pervasive, causing disease in >20 countries and infecting 8000 people (1).

Melatonin is one of the products of tryptophan, which is made in the body by the pineal gland and almost all body organs because melatonin production depends on mitochondria. Various studies report the importance of melatonin in feeling healthy and reducing the aging process in the body. The critical point is the anti-inflammatory and virucidal effects of melatonin, which has attracted the attention of researchers in its use in infectious diseases (2). It is estimated that 30 mg per day of melatonin is secreted from the pineal gland of humans at night, which plays a role in sleep, creating circadian rhythm and reducing inflammation and the aging process. This substance has been used to treat sleep disorders, atherosclerosis, respiratory diseases, and viral infections (3). Previous studies have shown that the symptoms caused by COVID-19 occur after an inflammatory storm caused by the increase of interleukin 1 and 6, TNF, and other inflammatory cytokines. Whereas in a study conducted by Nordlund et al in 1997, the use of melatonin in high doses (25 mg per day) for 6 months caused a significant decrease in the number of interleukins 1 and 6 in the body of patients. Also, using melatonin has decreased the production of NF-κB in patients with acute respiratory distress syndrome (4).

NF-κB is an essential factor in the production of inflammatory cytokines, and by reducing it, melatonin has been able to preserve lung tissue in patients with severe lung involvement (5). With the help of its 2 G-mediated receptors (MT 1 and MT 2), melatonin reduces the concentration of cAMP in the cell. It reduces the aggressive activity of both the humoral and cellular arms of the immune system (6, 7).

The present study aimed to determine the effectiveness of melatonin compared with placebo in critically ill patients with COVID-19 who were admitted to the ICU.

Methods

A double-blind, randomized clinical trial study was conducted on patients with COVID-19 hospitalized in the ICU of Rasool Akram Hospital from 2022 to 2023. The criteria for entering the study include age of >20 years, definite diagnosis of COVID-19 disease, ability to sign a consent form and sufficient literacy for the study, no use of melatonin during the study, no other systemic diseases (such as uncontrollable hypertension, uncontrolled diabetes, depression, an increase of liver enzymes more than 3 times than normal, cirrhosis, chronic kidney disease with glomerular filtration rate <30 cc/min), history of no allergy to melatonin, no use of anticoagulant drugs such as warfarin or heparin with a therapeutic dose. Patients were excluded from the study if they did not tolerate the treatment regimen, if the patient did not agree to continue the treatment, if severe drug complications occurred, or if the patient died before the end of the treatment period.

Patient information—including demographic information (age, sex, education, occupation, medical history, and medications)—was collected by a predesigned checklist from the patient's clinical record or by interview. Clinical symptoms, received treatments, and clinical progress of the patients were recorded in clinical records, history, and laboratory results.

The study's primary outcomes were measuring inflammatory factor levels, total hospitalization and ICU residency duration, and oxygenation level. Secondary outcomes included monitoring C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) levels as inflammatory markers. The safety outcomes were all-cause mortality, serious adverse events, adverse events, and withdrawal due to adverse events.

Similar studies showed that the oxygen saturation (SpO_2) level at the end of the study in the group receiving melatonin was 95.81 ± 3.61%. In contrast, the placebo group had a SpO_2 level of 93.65 ± 4.22%, indicating a statistically significant difference. To determine the sample size for the study, a first-type error of 0.05 and a second error of 0.2 were considered, and the sample size was calculated to be approximately 45. However, to account for the possibility of patient dropout, 50 samples were included in the study.

Excel software was used to generate random series. The study used balance block randomization, consisting of 25 blocks of 4. In each block, 2 items were assigned to group A, and 2 were assigned to group B. The order of patients within each block was different. The assignment was done in parallel using a placebo. The drug and placebo were given to the outcome assessor, who divided them according to the randomization section and provided them to the clinical caregiver or researcher (physician).

The blinding method was done so that the attending physician did not know the contents of the envelope. Participants were also unaware of the nature of the drug/placebo. Finally, the outcome assessor collected and provided the information to the data analyzer. The leading researcher generated the random allocation sequence, enrolled participants, and assigned them to interventions.

In this study, after registering the research in the Iranian Clinical Trial Center (IRCT20210411050925N1) and receiving the code of ethics (IR.IUMS.REC.1400.066), the patients with COVID-19 hospitalized in Rasool Akram Research-Treatment Center (PBUH) were examined. First, written consent was obtained from all patients. During hospitalization, nasopharyngeal and oropharyngeal samples were taken for reverse transcription polymerase chain reaction testing of coronavirus. Melatonin 10 mg and placebo were given to the patients at night before bed. The patients in the placebo group received drug treatment according to the Iran national protocol plus placebo, and the melatonin group received therapeutic drugs according to the Iran national protocol plus melatonin. The patients were randomly divided into 2 groups (A and B). The patients were placed in preprepared tables, in the order of the

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time of their participation in the study, in which categories A and B were included. Thus, for group A, an envelope containing melatonin with a therapeutic dose of 10 mg per day, and for group B, a placebo was considered with the same dose of 10 mg per day. The prescribing doctor, the assistant, and the patient were not aware of the contents of the envelopes, and the code of the envelopes was written on the file (double-blind). Patients received melatonin or placebo for 7 days. Inflammatory tests were measured and recorded daily or every 5 days, depending on the type of the test. Improvement of oxygenation, tachypnea, shortness of breath, and change in the number of days of hospitalization in the ICU and the hospital, as well as the survival rate, were evaluated. For both groups of patients, vital signs and blood sugar were checked in the ICU every hour and recorded in the file. Patients were observed for 7 days. In case of any complications, it was recorded in the checklist.

Melatonin can increase or decrease blood pressure, possibly interfering with heart and blood pressure medications. In low doses, melatonin can reduce glucose tolerance and insulin sensitivity in patients with type I diabetes. The drug was administered to diabetic patients treated with insulin, and patients with uncontrolled hypertension or diabetes were not included in the study.

Statistical Analysis

The patient's information was fed into the IBM SPSS software Version 26, a statistical analysis tool used to process data.

The data were then analyzed using various statistical methods. The data were described using central indices, such as mean, which provides information about the mean, and dispersion indices, like standard deviation, which provides information about the spread of the data. To compare quantitative variables, either the Mann-Whitney test or the independent t test was applied. Comparing qualitative variables, however, was done using the chi-square test or Fisher exact test.

The study analyzed the mean of the variables under investigation by conducting a 2-factor repeated measures analysis of variance at 3 different time intervals in those administered medication or placebo. If the significance level was < 0.05, it was considered that the data had statistical importance.

Results

Out of the total number of patients referred to Rasool Akram Hospital, 100 people in 2 groups of 50 were eligible for the study. Six of the patients in the melatonin group and 8 of the patients in the placebo group were excluded from the study due to the patient's lack of consent to continue the treatment. Finally, the data of 44 patients in the melatonin group and 42 patients in the placebo group were included in the study. In the present study, there were 34 women and 52 men. There was no statistically significant difference between the studied groups in terms of patients' sex. (P =0.538). In the melatonin group, 63.6% and in the placebo group, 57.1% were men. The mean age of the patients was 58.02 ± 13.41 years in the melatonin group and 60.95 ± 18.13 years in the placebo group. There was no statistically significant difference between the 2 groups (P = 0.310).

The mean days of hospitalization in the ICU were 11.23 ± 4.73 days in the melatonin group and 11.90 ± 6.52 days in the placebo group, and there was no statistically significant difference between the 2 groups (P = 0.582). The mean days of hospitalization in the melatonin group were 19.70 ± 8.77 days and 21.48 ± 10.85 days in the placebo group, and there was no statistically significant difference between the 2 groups (P = 0.407). The mean oxygen saturation before and after discharge from ICU in the melato-

Table 1. Distribution of Demographic Characteristics and Hospitalization According to the Studied Groups

Variable		Groups		*P* Value
		Melatonin (n=44)	Placebo (n=42)	
Sex	Female	16 (36.4%)	18 (42.9%)	* 0.538
	Male	28 (63.6%)	24 (57.1%)	
Age (years)	mean ± SD	58.02 ± 13.41	60.95 ± 13.18	** 0.310
ICU admission (days)	mean ± SD	11.23 ± 4.73	11.90 ± 6.52	** 0.582
Hospital Admission (days)	mean ± SD	19.70± 8.77	21.48± 10.85	** 0.407
O_2 Saturation in (%)	mean ± SD	81.00 ± 6.73	83.36±8.27	** 0.150
O_2 Saturation out (%)	mean ± SD	91.02±1.17	91.21± 1.26	** 0.467

*Fisher's Exact Test
** Independent Samples Test

Table 2. Repeated-measures ANOVA for Differences in Variables

Variable	Group	First	Second	Third	Between Subjects	Within Subjects
ESR	Melatonin	44.25 ± 26.32	42.45 ± 27.64	21.05 ± 20.05	F=0.460	F=59.35
	Placebo	45.36 ± 24.78	46.05 ± 25.17	25.43 ± 21.05	P=0.499	P<0.001
CRP	Melatonin	22.16 ± 5.91	21.41 ± 6.37	14.57 ± 17.70	F=0.475	F=28.80
	Placebo	21.48 ± 6.71	21.17 ± 6.97	12.40 ± 8.18	P=0.006	P<0.001
LDH	Melatonin	848.84 ± 329.77	999.39 ± 348.95	790.36 ± 386.24	F=0.066	F=1.98
	Placebo	878.21 ± 306.32	1002.24 ± 462.93	808.07 ± 407.95	P=0.798	P=0.163
Fibrinogen	Melatonin	619.43 ± 284.24	623.20 ± 313.93	563.39 ± 270.19	F=14.450	F=14.180
	Placebo	912.62 ± 384.01	876.14 ± 393.58	768.50 ± 334.04	P<0.001	P<0.001
Ferritin	Melatonin	299.95 ± 100.91	301.27 ± 101.97	275.61 ± 127.01	F=6.31	F=4.21
	Placebo	466.83 ± 447.66	482.14 ± 467.84	442.69 ± 416.89	P=0.014	P=0.043

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nin group was 81% ± 6.73%, 91.02% ± 1.17%, and in the placebo group, 83.36% ± 8.27%, 91.21% ± 1.26%, respectively. There was no statistically significant difference between the 2 groups in both stages (P = 0.467 and P = 0.150) (Table 1).

There was no statistically significant difference between the 2 groups in all 3 occasions of evaluating ESR, CRP, and LDH ($P > 0.05$).

The outcomes of the variance analysis with repeated measurements are presented in Table 2. The study focused on comparing the drug-receiving group and the placebo group. The test statistic demonstrated no significant statistical difference in the mean of ESR and LDH (P = 0.499 and P = 0.798, respectively). However, there was a considerable gap in the mean CRP, Fibrinogen, and Ferritin between the 2 groups (P = 0.006, P = 0.001, and P = 0.014, respectively).

Table 2 presents the results of the 2-factor analysis of variance with repeated measurements. The study aimed to compare 2 groups: the drug-receiving and placebo groups. The test statistic revealed that the mean of ESR and LDH was not statistically significant (P = 0.499 and P = 0.798, respectively). However, there was a significant difference in the mean of CRP, Fibrinogen, and Ferritin between the 2 groups (P = 0.006, $P < 0.001$, and P = 0.014, respectively).

Further analysis examined the differences of the studied variables over time. The statistical difference between the 2 groups was significant in the case of ESR, CRP, Fibrinogen, and Ferritin variables ($P < 0.001$, $P < 0.001$, $P < 0.001$, and P = 0.043, respectively). This means that the drug-receiving group showed a different pattern of change over time than the placebo group for these variables.

However, the 2 groups did not show a significant difference in terms of the effect of time on the LDH variable. This suggests that the drug and placebo groups experienced similar changes in the LDH variable over time. The study's findings indicate that the drug significantly impacted CRP, Fibrinogen, and Ferritin but not ESR or LDH.

No adverse drug events were observed in either of the 2 study groups.

Discussion

In addition to the usual treatment approaches, melatonin has attracted the attention of researchers since the onset of the Covid-19 disease. The main reason is its anti-inflammatory, antioxidant, and immune system-modulating functions. In previous studies, the successful performance of melatonin against sleep disorders, respiratory diseases, atherosclerosis, and viral infections (such as respiratory syncytial virus, Venezuelan equine encephalitis virus, hepatitis, and Ebola) has been shown (8). Although the role of melatonin in the antiviral immunity of COVID-19 is unclear, it seems that it can have a protective role in dealing with it through different pathways (9-11).

Studies show that the melatonin level of older people decreases significantly. The nocturnal peak of melatonin in older adults is 11.2 ± 1.6 pg/mL, and in young people is 83 ± 20 pg/mL. Interestingly, the highest level of melatonin is in children between 1 and 3 years old (329.5 ± 42 pg/mL), who are much less likely to get COVID-19 compared with older people. This is the basis of one of the leading hypotheses about the lower severity of COVID-19 in teenagers compared to elderly patients (12, 13).

The intervention group in this study was given oral melatonin tablets of 10 mg each day. There is a shortage of information regarding the benefits and safety of melatonin administration in COVID-19 patients, and there are worries about the adverse effects of greater dosages of the medication in patients who have a high frequency of headache and nausea/vomiting, which may be melatonin side effects.

All of them have contributed to selecting the dose of 10 mg of melatonin for the present study.

According to the available evidence, melatonin can be a valuable supplement for COVID-19 patients. In addition, the significant improvement of blood oxygen saturation in the melatonin group compared with the placebo group can be due to the effect of melatonin on oxygen delivery and its use in tissues as one of the functions of melatonin that have been studied experimentally and clinically (12, 14).

In the present study, blood oxygen saturation in the melatonin group was not significantly improved compared to the placebo group. Also, there was no statistically significant difference between the 2 groups regarding ESR, CRP, and LDH.

Melatonin exhibits a wide range of functions that may have therapeutic potential in COVID-19 patients in treating the disease. Melatonin is a chronobiotic agent with antioxidant, anti-inflammatory, and immunomodulatory properties.

The following justifications could lead to melatonin usage in COVID-19: preventing the spread of SARS-CoV-2, having antiviral properties, preventing circadian disruption, influencing the immune system, antioxidants, and anti-inflammatory agents, treating patients with comorbidities, and serving as an adjuvant to enhance anti-COVID-19 vaccinations (15, 16).

In some studies, intravenous administration of 60 mg of melatonin per day improved septic patients and reduced their mortality to zero. It also reduced hospitalization by 40%. Melatonin had a similar inflammatory response in sepsis and COVID-19 and similar mortality in both groups (25%—20%) in ICU patients compared to the placebo group.

Deep sedated ICU patients with COVID-19 have higher death rates.

Brusco et al study (17) showed that melatonin administration reduced the use of sedatives, pain, restlessness, and anxiety and improved sleep quality. In addition, as a cellular protective agent, melatonin restores the optimal circadian pattern of the sleep/wake cycle and thus improves the clinical condition of the person with COVID-19. The researchers concluded that using melatonin as an adjunctive treatment in ICU patients is recommended and can support the reduction of the length of stay in the ICU. In addition, high safety, the possibility of using oral tablets, the stability of melatonin without refrigeration, and

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low cost make this drug accessible to geographical areas lacking special infrastructure or countries with limited resources. The interest of the mentioned study is mainly focused on the effects on sleep and a specific cellular protective capacity, and a dose of 9 mg is suggested, which is not enough to achieve other effects in the developmental stages of the disease.

In the study of Cardinali et al (18) focusing on the function of melatonin as a potent chronobiotic with mild hypnotic capacity and capable of synchronizing circadian rhythms, it was confirmed that administration of melatonin 2 weeks before vaccination against SARS-CoV-2 improved sleep quality. It ensures that vaccination is done under optimal conditions, keeps the patient's mood and response capacity high, and maintains seroprotection. In addition, melatonin's anti-anxiety and anti-depressant effects ultimately contribute to the effectiveness of the treatment. These are undoubtedly very interesting aspects that indicate its ability to regulate biological rhythms, especially the rhythm of sleep, which changes in affected patients.

Conclusion

A recent study has demonstrated that melatonin administration to patients can significantly reduce inflammation and oxidative stress markers. As a result, it has the potential to be a promising therapeutic option for patients with elevated levels of inflammation and oxidative stress, such as those afflicted with COVID-19. The findings suggest that melatonin supplementation could be a viable treatment option for managing COVID-19 symptoms. Further research is necessary to confirm these findings and determine the optimal treatment dosage and duration. Nonetheless, these results provide a promising avenue for future research and clinical practice.

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Ethical Approval

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Authors' Contributions

Atefe Tirkan: Implementation of the plan
Delaram Eskandari: Implementation of the plan
Maryam Roham: Implementation of the plan
Oldooz Aloosh: Implementation of the plan
Tayeb Ramim: Designing the method and statistical analysis
Hale Afshar: The idea and implementation of the plan

Abbreviations List

CRP: C-reactive protein
ESR: Erythrocyte Sedimentation Rate
LDH: Lactate dehydrogenase
ICU: Intensive care unit
RCRDC: Complex Clinical Research Development Center

Conflict of Interests

The authors declare that they have no competing interests.

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