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A Pilot Study on Controlling Coronavirus Disease 2019 (COVID-19) Inflammation Using Melatonin Supplement

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ABSTRACT

No effective antiviral drugs and vaccines are available for the treatment of patients with severe coronavirus 2019 (COVID-19). Therefore, available, safe, and inexpensive drugs and supplements such as melatonin are among the proposed options for controlling inflammation.

We did a randomized, single-blind study in Imam Khomeini Hospital between June 30, 2020, and August 5, 2020. Mild to moderate COVID-19 patients aged 25-65 years were eligible to enter the study based on chest CT scan, clinical symptoms, and physician diagnosis. The intervention group was prescribed 6 mg of oral melatonin for 2 weeks, which consumed half an hour before bedtime every night in low light conditions. Clinical symptoms and C-reactive protein (CRP) were measured before and after treatment in the melatonin received and control (regular medications) groups. Among screened patients with COVID-19, 14 patients were assigned to receive melatonin, and 17 patients were considered as controls.

A significant difference (p=0.005) between CRP 1 and CRP 2 levels (before and after using melatonin) was found in the melatonin group while this difference (p=0.069) was not significant in the control group. Also, the percentage of recovery (based on symptoms) in patients who took melatonin was higher than that of patients in the control group (85.7% VS 47.1%).

The result of this study confirmed the effectiveness of melatonin in mild to moderate outpatients with COVID-19. More clinical trials on elderly, diabetic, obese patients and severe cases are suggested in future studies.

Keywords: COVID-19; Inflammation; Melatonin

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INTRODUCTION

The most serious problem of patients with Coronavirus disease 2019 (COVID-19) is an excessive

inflammatory response.[1] The clinical features of the disease are varying from simple symptoms such as cough, fever, headache, diarrhea, and shortness of breath to more severe situations like acute respiratory problems, septic shock, and organs failure.[2] The upregulation of interleukin (IL)-1β, IL-6, IL-10, IL-8, tumor necrosis factor-alpha (TNF-α), and NOD-like receptor protein 3 (NLRP3) inflammasome leading to cytokine storm has been demonstrated in patients with acute respiratory distress syndrome and acute lung injury (ARDS/ALI).[3,4] The role of NLRP3 inflammasome activation has been shown in heart and kidney fibrosis also, kidney and heart failure have been reported in some patients with COVID-19.[5]

Up to now, no promising anti-virus treatments are available. Thus, inhibition of NLRP3 Inflammasomes and inflammation in this disease can be of special importance. Administrating a cheap, practical, and available treatment is an urgent matter. Previously, melatonin has been effectively used as an immunomodulator and anti-inflammatory treatment in several viral infections and respiratory diseases.[6,7] Moreover, melatonin plays role in controlling different mechanisms including normal nervous system aging, neuropathological aging and longevity, circadian rhythm, and mitochondrial metabolism.[8] It is postulated that the most potent approaches to overcome COVID-19 and other viral pandemics are those that trigger and reverse the aging process.[8]

Multiple reviews have been recently published proposing the beneficial effects of melatonin on COVID-19.[8-15] However, no clinical data are available about the effectiveness of melatonin on patients with COVID-19. Herein, a preliminary study was performed to find out the effectiveness of melatonin on outpatients with COVID-19 who were referred to Imam Khomeini Hospital, Tehran, Iran.

MATERIALS AND METHODS

Study Design

This was an investigator-initiated, randomized, single-blinded trial to assess the effectiveness of oral melatonin in adults (aged 25 to 65 years) admitted to the hospital as outpatients with mild to moderate COVID-19. The trial was done at Imam Khomeini Hospital, Tehran, Iran. The physician who was aware of the intervention groups was in contact with the patients and followed up with them.

Ethical approval was obtained from the Ethics Committee of the Ministry of Health (IR.TUMS.VCR.REC.1399.068) and this trial was approved by the Iranian Registry of Clinical Trials (IRCT20200922048804N1). Also, written informed consent was obtained from all patients.

Patients

Forty patients entered the intervention and control groups randomly and in parallel by the physician. Both male and female patients with mild to moderate COVID-19 (aged 21 to 60 years) were diagnosed by a physician, chest imaging, and clinical symptoms.

Patients (if needed) received medications prescribed by the physician (hydroxychloroquine, acetaminophen, and naproxen).

Exclusion criteria included pregnancy or breastfeeding, depression, chronic obstructive pulmonary disease (COPD), sleep apnea and seizure, severe kidney problem (eGFR<30 mL/min), and severe liver problem. Also, patients who received fluvoxamine, benzodiazepine, or zolpidem, as well as the patients who received drugs that extend QT, and patients who had an allergy to melatonin were excluded from the study. In both groups, patients who had diabetes, heart disease, hypertension, and obesity were excluded.

Procedures

The intervention group was prescribed 2 tablets (6 mg) per day of melatonin for 2 weeks as a supplement to the regular medication. Melatonin was consumed half an hour before bedtime every night in low light conditions. The control group received regular medications. Patients in both groups (if needed) received medications prescribed by physicians (hydroxychloroquine, acetaminophen, and naproxen) and patients in both groups were followed up by the physician after 7 and 14 days.

Outcomes

The primary outcomes of the disease in the patients were considered from the date of their admission to the respiratory triage. The questionnaires were filled out about patients' symptoms under physician supervision. Their C-reactive protein (CRP 1, first time) and oxygen saturation were measured at the time of admission as well as lung CT scan if applicable.

Secondary outcomes were measured in patients after using prescribed medications and melatonin respectively. The improvement of the disease was based on CRP 2 (after 14 days) measurement and elimination of symptoms after 14 days of intervention without complications, the requirement of oxygen supplement, or intensive care unit involvement. The adverse events were hospitalization or continuous disease symptoms in patients.

Statistical Analysis

The data analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY). The frequency and percentage of categorical variables were calculated. To determine the normality of quantitative variables, the Shapiro-Wilk test was applied. To describe the quantitative data, the mean and standard deviation or median (Q1, Q3) were determined. The Chi-Square and Fisher Exact tests were used to test the association between two qualitative variables. To assess the difference of a quantitative variable between two independent groups, Mann Whitney was utilized. Moreover, Wilcoxon signed-rank test was used to evaluate the difference between non-normal quantitative data before and after melatonin use. A p-value less than 0.05 was regarded as significant. The graphs were drawn by GraphPad Prism Version 8 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Between June 30, 2020, and August 5, 2020, among screened patients with COVID-19, 60 patients were eligible to enter the study, 20 were not agreed to participate in the trial. Twenty patients were assigned to receive melatonin and 20 were considered as controls. One patient in the melatonin group was excluded due to the development of clinical symptoms leading to his hospitalization before using melatonin and 5 more patients did not start their assigned treatment so were not included in the analyses. Three patients in the control groups withdrew their previously written informed consent after leaving the hospital.

The mean±SD age of melatonin and control groups were 37.5+8.2 and 34.5+8.2, respectively. Sex distribution was 35.7% female versus 64.3% male in the melatonin group and 52.9% female versus 47.1% male in the control group. Sixty-four percent of the melatonin group and 65% of the control group had contact with infected COVID-19 patients. The most common symptoms among patients in 2 groups were myalgia, fever, cough, and chill. The results of CRP 1 and CRP2 showed no significant difference between the melatonin and the control groups. However, a significant difference (p=0.005) between CRP 1 and CRP 2 levels (before and after using melatonin) was found in the melatonin group while no significant difference (p=0.069) was observed in the control group (Figure 1). The percentage of recovery (based on symptoms) in patients who took melatonin was higher than that of patients in the control group (85.7 VS 47.1%). Interestingly, the percentage of symptoms improvement in males was higher than in females (Melatonin group: 88.9 VS 80% and control group:

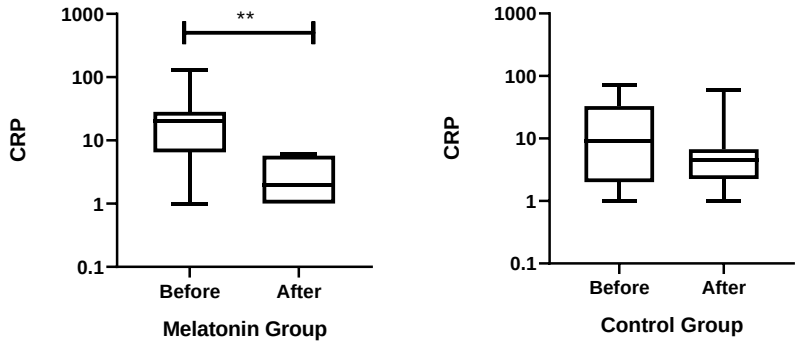

Figure 1. The box and whisker (5-95 percentiles) plot of C-reactive protein (CRP) before and after 14 days consumption of 2 tablets (6 mg) per day of melatonin for 2 weeks in melatonin (n==14) and control groups (n=17). The control group received regular medications. **p<0.01

62.5 VS 33.3%). On the other hand, the percent of normal CRP in females was more than males (80 VS 71.4%) in the melatonin group while it was lower than males in the control group (66.7 VS 75%) at the end of the study although these differences were insignificant.

The demographic and clinical data of the patients are presented in Table 1.

Table 1. The demographic and clinical data of the patients with Coronavirus disease 2019 (COVID-19) in the melatonin and control groups

	Melatonin group(n=14)	Control group (n=17)	*p*
Men (%)	64.3	47.1	0.47
Women (%)	35.7	52.9	
Age (Mean± SD)	37.57+8.2	34.53+8.2	0.49
Contact history (%)	64	65	1.00
Fever (%)	78.6	58.8	0.28
Cough (%)	71.4	70.6	1.00
Sore throat (%)	50	47.1	1.00
Myalgia (%)	85.7	70.6	0.41
Headache (%)	50	29.4	0.28
Chill (%)	64.3	35.3	0.15
Rhinitis (%)	21.4	11.8	0.63
No smell (%)	28.6	35.3	1.00
No taste (%)	7.1	29.4	0.18
Vomiting (%)	35.7	25.0	0.69
Diarrhea (%)	42.9	47.1	1.00
Chest pain (%)	42.9	29.4	0.47
Respiratory distress (%)	35.7	29.4	1.00
Pulse oximetry <93% (%)	7.1	0%	0.45
CRP1 (Before medication) Median (Q1, Q3)	20.50 (6.5, 28.25)	9 (2,33)	0.65
CRP2 (After medication) Median (Q1, Q3)	2(1,5.75)	4(2,6.5)	0.19
Non-normal CRP 1(%)	78.6	70.6	0.69
Non-normal CRP 2(%)	25	29.4	1.00
The recovered patients (%)	85.7	47.1	0.057

DISCUSSION

The current trial found that oral melatonin significantly improved symptoms in the patients after 14 days of consumption compared to the control group. Also, a significant difference in CRP1 and CRP2 was obtained in the melatonin group. The safety and versatile functions of melatonin had been described in aging, sepsis, and inflammatory diseases in many reviews.[16-19]

Previously, the effectiveness of melatonin was confirmed in inhibition of the inflammatory response during sepsis in a murine model.[20] Also, it was shown that melatonin diminished airway inflammation through inhibition of NLRP3 inflammasome and IL-1β in rats with COPD and virally infected bats.[21,22] Meanwhile, a low-level correlation of serum melatonin to an increased level of IL-1β in patients with pulmonary hypertension suggested that melatonin may attenuate inflammasome.[23] Likewise, reduced blood coagulation activity was reported in young adults previously.[24] Herein, patients without any comorbidity including old age, hypertension, obesity, and diabetes have entered the study to evaluate the effectiveness and safety of 6mg melatonin. Previous studies positively demonstrated the effect of melatonin in modulating

inflammation in obesity, hypertension, and diabetes.[9,25,26] Therefore, it is speculated that melatonin may have a more significant effect on obese, diabetic, and elderly patients with COVID-19. Moreover, the inverse relation of melatonin was shown in the vascular system, nervous system, and kidney diseases through inhibition of inflammasome NLRP3 pathway and cytochrome C release from mitochondria in animal models.[25] Thus, reported multiorgan conflict in more severe cases of COVID-19 may lead us to this idea that melatonin would be a suitable and safe adjutant to consider in new trials.

Limitations of our study include low sample size due to evaluation of its safety and we consider this trial as a preliminary study to encourage patients for more collaboration in forthcoming trials. In the current study, CRP and clinical symptoms were evaluated in the patients though; measuring other immunological features such as cytokines levels and characterizing immune cells will give a better understanding of melatonin effects.

Although many review papers are available about melatonin utility, this study is among a few clinical trials using melatonin in patients and units now, only 2 clinical trials in COVID-19 patients were published in PubMed and hopefully, their results give more pieces of evidence about melatonin application.[27,28]

Taken together, the result of this study shows the effectiveness of melatonin in mild to moderate outpatients with COVID-19. More clinical trials on elderly, diabetic, obese patients, and severe cases are suggested. Also, more molecular and functional studies in the human will shed the light on melatonin assumption in pandemic diseases such as COVID-19.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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