

Literature Review: Clinical Trial on the Effectiveness of Melatonin as an Alternative Medicine for COVID-19

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ABSTRACT

Pandemic COVID-19 is one of the horrific events in history. It has left awareness of the need for more effective, cheap, and widely available drugs such as melatonin. This literature review will discuss the effectiveness of melatonin against COVID-19 by reviewing clinical trial research conducted abroad with the aim of providing information that melatonin can be used in Indonesia for COVID-19 treatment therapy.

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1. INTRODUCTION

The COVID-19 pandemic that occurred in recent years is one of the most horrific events in history. Viruses that can infect healthy to susceptible co-morbid populations. This pandemic has caused more than 6 million positive cases and more than 158 thousand people died in Indonesia. The urgency of the pandemic creates the need for specific treatment. The World Health Organization (WHO) has released several treatments that have the potential to reduce the severity of COVID-19 infection in humans, such as chloroquine/hydroxychloroquine, remdesivir, lopinavir and ritonavir, lopinavir and ritonavir plus interferon- β [1]. Moreover, a number of drug names have been mentioned in previous studies with different mechanisms of action, but most of these drugs are potentially toxic and require high costs [2]. Indonesia's COVID-19 guidelines also use similar drugs, such as favipiravir, molnupiravir, nirmatrelvir and others [3]. Even though COVID-19 vaccine which smaller potential side effects and can cause communal immunity, the effectiveness of the vaccine can decrease due to mutations in the virus [4]. scientist quickly realize that there is no truly effective treatment for this disease, especially in patients with comorbidities, moreover the efficacy of vaccines can decrease over time. This has led to a growing awareness of the need for more effective, inexpensive and ready-to-use treatments such as melatonin [5].

Melatonin is a natural hormone in the body that is synthesized by the lymph nodes and released when it is in dark conditions, therefore this hormone is known as the hormone of darkness [6]. Melatonin is a key in various physiological processes of the body, such as immune response, disease prevention, anti-inflammation, preventing aging because it is a strong antioxidant, and most importantly is responsible for circadian rhythms which is a natural process in the body to regulate sleep-wake cycles for 24 hours. O'clock. Lighting at night can naturally reduce melatonin secretion, this can disrupt the body's circadian rhythm which can lead to sleep disturbances and decreased immunity [7]. Melatonin, which is secreted naturally in the body, is a broad-spectrum antiviral that can reduce the severity of the COVID-19 infection [8], [9]. Naturally, melatonin exists in the body, but it can also be obtained exogenously or it is called exogenous melatonin. Exogenous melatonin is available in several medicinal preparations, such as syrup, sublingual tablets, capsules to transdermal patches [7].

Considering that melatonin is not used in Indonesia's COVID-19 guidelines. This literature review will discuss the effectiveness of melatonin against COVID-19 by reviewing clinical trial studies conducted abroad with the aim of providing information that melatonin can be used in Indonesia for the treatment of COVID-19, either used alone or in combination with other drugs.

2. METHOD

The method is literature study by collecting international papers for the last 5 years (2017-2022) via the internet. Literature search using online media, such as Google Scholar, PubMed, ScienceDirect and others. The keywords used in the literature search were “melatonin”, “COVID-19”, “clinical trial”, and “pandemic”. Based on literature search, 8 relevant papers have been found for review and several as supporting papers. Further searches can be seen manually in writing a bibliography.

3. RESULTS AND DISCUSSION

The urgency for effective, inexpensive and ready-to-use treatment has driven the development and research of new drugs, one of which is melatonin. Since the pandemic, there have been many studies that exhibit the efficacy of melatonin for the clinical treatment of COVID-19. Research shows positive results and it is proven that melatonin can be effective in reducing the severity of COVID-19 infection.

Table 1. Clinical Trials of Melatonin Therapy in COVID-19

| Ref. | Methods | Number of Patients | Melatonin Total Dose/Day | Other Drugs | Results |
|------|----------------------------|--------------------|--------------------------|---|---|
| [10] | RCT Double-blind | 44 | 9 mg (3x1) | - | ↓ Respiratory symptoms ↓CRP |
| [11] | RCT Open Label | 158 | 10 mg | Remdesivir Levofloxacin Dexamethasone Enoxaparin | ↓Sepsis ↓Mortality ↓Thrombosis |
| [12] | RCT Double-blind | 60 | 50 mg | - | ↑Oxygen saturation ↓Clinical symptoms ↓CRP ↑TNF-α ↑IL-1β & IL-6 |
| [13] | RCT Open Label | 96 | 3 mg | Chl/HChl Lopinavir Atazanavir Naproxen Azithromycin Methylprednisolone | ↑Sleep quality ↑Oxygen saturation |
| [14] | RCT Open Label | 67 | 21 mg | Corticosteroid Anticoagulant Tocilizumab Remdesivir | ↓CRP ↑Platelets |
| [15] | RCT Double-blind | 314 | 2 mg | - | ↓ Clinical symptoms |
| [16] | RCT Double-blind | 66 | 10 mg | - | ↓ Clinical symptoms ↓Mortality |
| [17] | Retrospective Cohort Study | 20 | 36-72 mg | Chl/HChl Azithromycin Lopinavir/Ritonavir Oseltamivir Na ascorbate Zinc Tocilizumab | ↓Hospitalization ↓ Need for Mechanical Ventilation ↓Mortality |

| | | | | | |
|------|----------------------------|----|-------|---|--|
| [18] | Retrospective Cohort Study | 45 | 15 mg | - | ↓ Hospitalization (ICU) ↓ Mortality |
|------|----------------------------|----|-------|---|--|

Based on studies that have been carried out, various clinical trials have been conducted using several different methods such as the Randomized Clinical Trial Open Label, Randomized Clinical Trial Double-blind, and Retrospective Cohort Study.

Randomized Clinical Trial Open Label is a research method in which each research subject is told information about the treatment or intervention to be given. This method was carried out by Hasan et al., Mousavi et al., and Alizadeh et al.

They conducted studies with different focuses, such as Hasan et al conducting research focusing on the incidence of thrombosis, sepsis and mortality in people with COVID-19. In their study, there were two groups, namely the melatonin group (10 mg dose) and the control group, both groups underwent the same COVID-19 treatment using remdesivir, levofloxacin, dexamethasone, enoxaparin. The results showed significant differences between the melatonin group and the control group in indicators of thrombosis, sepsis, and mortality. Melatonin succeeded in reducing the rate of thrombosis or blood clots, sepsis and mortality in patients.

Mousavi et al. conducted a study focusing on the sleep quality of people with COVID-19. In their study, there were two groups, namely the melatonin group (3 mg dose) and the control group. Both groups underwent the same COVID-19 treatment using atazanavir, methylprednisolone, hydroxychloroquine, naproxen, azithromycin, and lopinavir/ritonavir. The results showed a significant difference between the melatonin group and the control group on sleep quality. This is a good result because sleep is important to increase immunity so that patients can be much more resistant to COVID-19 infection [7]. In addition, this study also showed a significant difference in oxygen saturation. Oxygen saturation in the melatonin group increased compared to the control group.

Alizadeh et al., conducted a study on patients with a nasogastric tube (NGT). Melatonin is used as an adjuvant therapy or additional therapy in addition to the main therapy remdesivir, corticosteroids, anticoagulants and tocilizumab. The melatonin group showed a better decrease in CRP (C-Reactive Protein) and increase in platelets than the control group. A decrease of CRP indicates a reduction in infection and an increase of platelets in the body can speed up the patient's recovery.

Randomized Clinical Trial Double-blind is often applied. In this method, research subjects and researchers are not informed of the treatment and intervention that will be given to the subject. Research using this method was carried out by Farnoosh et al., Ziaei et al., García-García et al., and Fogleman et al. Research is conducted with different focuses.

Farnoosh et al. conducted a study using a low dose of 9 mg melatonin. There was a melatonin group and a control group who were given placebo drugs. Both groups were not on any other COVID-19 therapy treatment. The results showed a decrease in respiratory symptoms and CRP values in the melatonin group.

Ziaei et al. conducted a study by focusing on inflammatory serum parameters present in the body including CRP, TNF- α , IL-1 β and IL-6. The results showed an increase in the inflammatory excretion which indicated a decrease in infection and increased immunity.

García-García et al. conducted a study focusing on melatonin as a prophylactic therapy for health workers. The results showed that there was a significant difference in the clinical symptoms of COVID-19 infection that occurred. The melatonin group showed significantly lower clinical symptoms than the control group.

The results of the study by Fogleman et al. also support the research described previously, that there is an increase in quality of life and a decrease in clinical symptoms in COVID-19 patients.

Another method used is the Retrospective Cohort Study which is a research method by observing something that has happened. Research using this method was carried out by Castillo et al., and Karimpour-razkenari et al.

Castillo et al. conducted a study by observing data on COVID-19 patients at the Manila Hospital in Manila, Philippines. Studies show that patients who take high doses of melatonin have lower duration of hospitalization, need for mechanical ventilation, and mortality than the group who do not take melatonin.

Karimpour-razkenari et al. conducted a study by observing data on ICU inpatients in Iran. Studies show that the group of patients who use melatonin has a lower duration of ICU stay and a reduced mortality rate compared to the group of patients who do not use melatonin.

Melatonin as an Inflammasome Inhibitor

COVID-19 causes severe damage to the lungs, this damage is caused by pyroptosis. Pyroptosis is sudden cell death initiated by inflammatory signals from pro-inflammatories, the main event of cell death in pyroptosis is the death of inflammatory cells such as macrophages. Pyroptosis in macrophages and other inflammatory cells can cause lymphopenia so that it can reduce the ability of immunity. The SARS-CoV-2 virus protein encoded by ORF8b binds directly to the NLRP3 protein complex which is an inflammasome [19]. This reaction will simultaneously release proinflammatory cytokines and disrupt cell membranes and cause inflammation [20]. Previous studies have shown that melatonin can act as an inflammasome inhibitor and protect macrophages from pyroptosis [21].

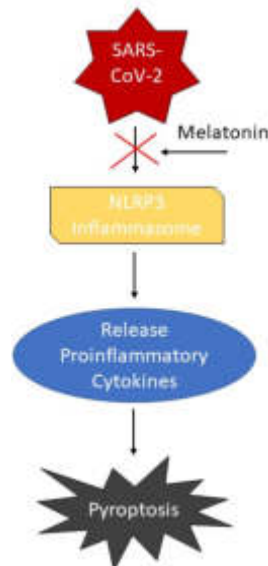


Figure 1. Melatonin Prevents Pyroptosis

Melatonin As Anti-Inflammation and Antioxidant

Sepsis is damage to many organs at once, the cause is infection with viruses, bacteria, fungi and other pathogens. Sepsis occurs frequently in COVID-19 patients and has a common cause, cytokine storm and excess inflammation with oxidative damage. Due to its potent anti-inflammatory and antioxidant effects, melatonin is the recommended drug for treating the cytokine storm caused by viral infections [22], including SARS-CoV-2 infection [23].

Respiratory infections caused by viruses are usually caused by oxidative stress with increased reactive oxygen species (ROS) or reactive nitrogen sepsis (RNS). Viral infections that cause damage to the lungs due to oxidative stress will cause repeated positive feedback. For example, SARS-CoV-2 infection can induce oxidative stress, then oxidative stress can induce PLA2G2D phospholipase gene expression, excessive expression of the PLA2G2D phospholipase gene can reduce natural antiviral immunity in the body, this can cause the virus to infect more strongly [24]. Melatonin has strong antioxidant properties, even 10 times better than commonly used antioxidants such as vitamin C and vitamin E. In addition, melatonin also has high bioavailability and can penetrate the blood-brain barrier and the placenta [25].

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4. CONCLUSION

Many studies have conducted clinical trials of melatonin on COVID-19 patients using a variety of different methods. Research conducted shows that melatonin can be an effective alternative drug therapy for sufferers of COVID-19. It is hoped that this literature review can provide information on the effectiveness of melatonin against COVID-19 and it can be applied to COVID-19 management guidelines in Indonesia.

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