International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn22208

Major clinical outcomes of melatonin use in COVID-19 patients: a systematic review

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DOI: https://doi.org/10.54448/ijn22208
Received: 02-04-2022; Revised: 04-24-2022; Accepted: 05-15-2022; Published: 05-25-2022; IJN-id: e22208

Abstract

Introduction: In the context of the Sars-Cov-2 (COVID-19) pandemic, as well as other viral infections, these viruses can lead to significant morbidity and mortality. Thus, in the context of melatonin science in viral infections such as influenza and COVID-19, there is a growing realization that the regulation of melatonin pathways, both pineal and systemic, may be an important aspect of the regulation of viruses in cellular functions. **Objective:** It was to list the main results of clinical studies of the use of melatonin in patients infected with Sars-Cov-2 through a systematic review. **Methods:** The rules of the Systematic Review-PRISMA Platform. The search was carried out from December 2021 to April 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** It was found 164 articles. A total of 86 articles were fully evaluated and 30 studies were developed in a systematic review. Melatonin is known as an anti-inflammatory agent and immune modulator that may address the progressive pathophysiology of coronavirus disease 2019 (COVID-19). According to the objective and results obtained in the present study that evaluated the treatment in patients with COVID-19, the use of melatonin can help reduce thrombosis, sepsis and mortality. Furthermore, the combination of 3.0 mg oral melatonin tablets and standard care can substantially improve sleep quality and blood oxygen saturation in hospitalized patients. Clinical symptoms such as cough, dyspnea and fatigue, as well as the polymerase chain reaction (PCR) level and lung involvement in patients receiving melatonin can improve significantly. Also, the mean time of patients' hospital discharge and return to initial health was significantly shorter in patients who received melatonin compared to the control group. There was evidence of benefit of sustained-release melatonin 2 mg in therapy in patients, as well as evidence that the use of melatonin was associated with a reduced probability of a positive SARS-CoV-2 test result compared to the use of blockers of the angiotensin II receptor or angiotensin-converting enzyme inhibitors.

Keywords: Melatonin. Immunomodulation. Inflammatory process. SARS-CoV-2. COVID-19. Clinical trials.

Introduction

In the context of the Sars-Cov-2 (COVID-19) pandemic, as well as other viral infections, these viruses can lead to significant morbidity and mortality. Due to its importance and the lack of effective therapeutic approaches, further attempts should be made to discover suitable alternative or complementary treatments, such as the use of melatonin **[1]**. Melatonin or N-acetyl-5-methoxytryptamine is a hormone produced by the pineal gland. It is synthesized from serotonin by the initial conversion of tryptophan into serotonin which produces N-acetylserotonin, whose molecule will then be converted into melatonin **[2,3]**. This hormone functions as a circadian rhythm regulator and is also a potent antioxidant and anti-inflammatory **[4]**.

Thus, in the context of melatonin science in viral infections such as influenza and COVID-19, there is a growing realization that the regulation of melatonin pathways, both pineal and systemic, may be an

important aspect of the regulation of viruses in cellular functions. In this sense, viral suppression by melatonin can reduce the action of neutrophils. As a mechanism of action, melatonin induces the circadian gene, Bmal1, which disinhibits the pyruvate dehydrogenase complex (PDC), counteracting the viral inhibition of Bmal1/PDC **[5,6]**. PDC drives the mitochondrial conversion of pyruvate to acetyl-coenzyme A (acetyl-CoA), thereby increasing the tricarboxylic acid cycle, oxidative phosphorylation, and ATP production. Suppression of pineal melatonin attenuates this by preventing the circadian "reset" of mitochondrial metabolism **[7]**.

In this sense, this is especially relevant in immune cells, where the shift in metabolism from glycolytic to oxidative phosphorylation changes the phenotypes of reactive to quiescent cells. Acetyl-CoA is a necessary co-substrate for arylalkylamine N-acetyltransferase, providing an acetyl group for serotonin and thus initiating the melatoninergic pathway. Consequently, pineal melatonin regulates mitochondrial melatonin and immune cell phenotype. Control of the pineal and mitochondrial melatonin pathway by virus and cytokine storms, therefore, regulates immune responses **[8]**.

Furthermore, melatonin can modulate inflammatory processes by eliminating nitrogen oxide, a molecule involved in tissue injury as a secondary inflammatory mediator. There are reports that melatonin can reduce the synthesis or inhibit other pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-a), interleukin 6 (IL-6), and interleukin 8 (IL-8) **[8]**. In this sense, metabolic and liver diseases become targets of studies with melatonin, aiming to clarify its association with molecular mechanisms, and possible use in clinical practice.

Also, melatonin has endocrine and paracrine actions and binds to three receptors, central and peripheral, at various sites in the body **[9]**. The high-affinity receptors MT1 and MT2 or MTNR1A and MTNR1B belong to the family of membrane-bound receptors with G protein activation by PKC and cyclic GMP reduced monophosphate (cGMP), respectively. MT3, a nuclear receptor of the retinoic acid family (RZR/ROR), recently discovered, has a quinone reductase-like structure whose function is not yet fully understood **[10]**.

Furthermore, changes caused by virus and cytokine storms also increase intestinal permeability and dysbiosis, thereby suppressing levels of short-chain fatty acid, and butyrate and increasing circulating lipopolysaccharide (LPS). Changes in butyrate and LPS can promote viral replication and severity of host symptoms through impacts on the melatonin pathway **[11]**.

In this regard, evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response likely contribute to the pathology of COVID-19, which brings about a cytokine storm. In this way, melatonin, being an anti-inflammatory and antioxidant molecule, can protect against the virulence of COVID-19, as well as any other viral infection. In this sense, melatonin can reduce vessel permeability, and anxiety, use sedation and improve sleep quality **[12]**.

Therefore, the present study aimed to list the main results of clinical studies on the use of melatonin in patients infected with Sars-Cov-2 through a systematic review.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-HTTP://www.prisma-statement.org/) were followed **[13]**.

Data Sources And Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Melatonin. Immunomodulation. Inflammatory process. SARS-CoV-2. COVID-19. Clinical trials*". The search was carried out from December 2021 to April 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality And Risk Of Bias

The quality of the studies was based on the GRADE instrument **[14]** and the risk of bias was analyzed according to the Cochrane instrument **[15]**.

Results and discussion

Findings Summary

It was found 164 articles. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the topic of this article. A total of 86 articles were fully evaluated and 30 studies were included and developed in the systematic review. A total 18 studies did not meet the GRADE, and 38 studies were excluded due to risk of bias that could compromise the results (**Figure 1**).

Figure 1. Article selection (Systematic Review).

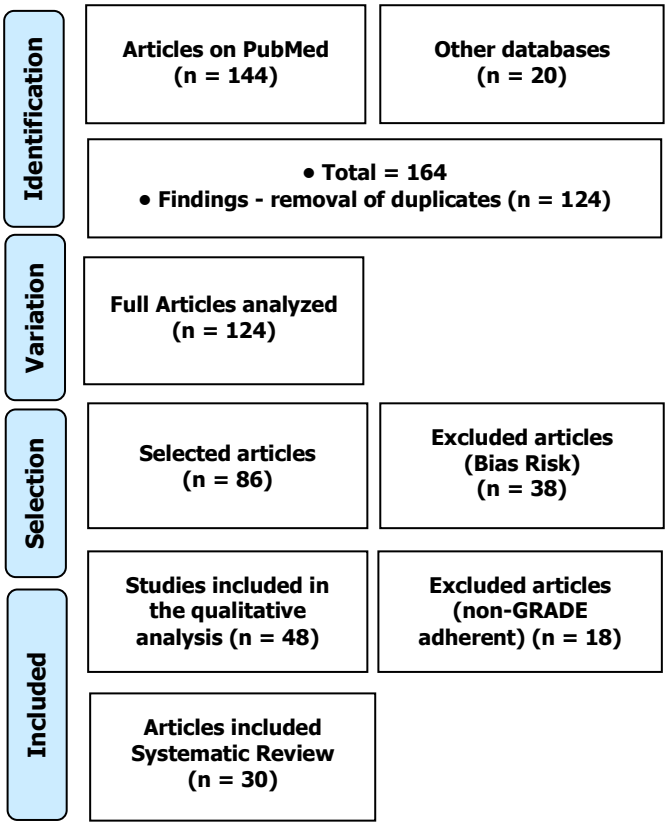
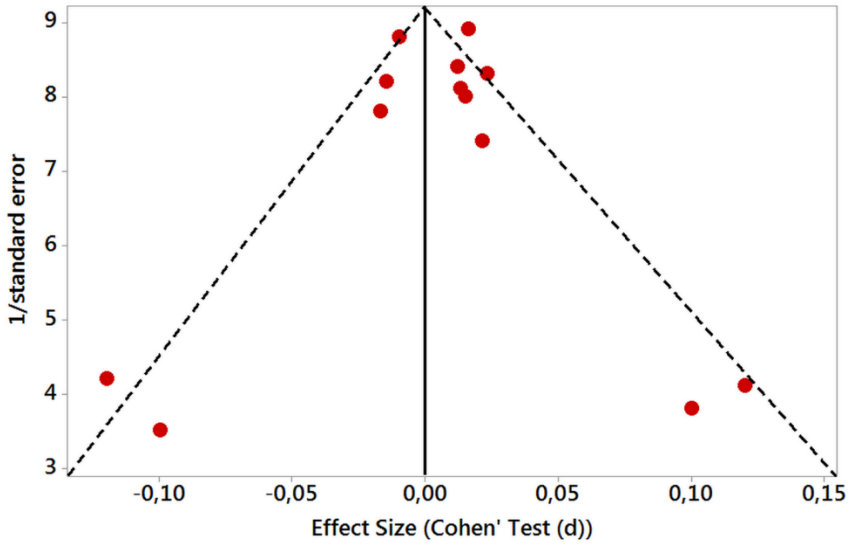


Figure 2 presents the results of the risk of bias in the studies using the Funnel Plot, through the calculation of the Effect Size (Cohen's Test). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). The number of clinical studies evaluated was n=13. The graph showed symmetrical behavior, not suggesting a significant risk of bias in the studies with small sample sizes that are shown at the bottom of the graph.

Melatonin and Endocrine Action

By presenting the characteristic of an amphiphilic molecule, melatonin can cross cells, organelles, and nuclear membranes and directly interact with intracellular molecules in the so-called non-receptor-mediated actions **[16]**. Melatonin is an effective antioxidant, as well as stimulates the transcription and activity of antioxidant enzymes and binds to transition metals that inhibit hydroxyl formation. Furthermore, melatonin protects lipids, proteins, and DNA against oxidative damage **[17]**.

Figure 2. The symmetrical Funnel Plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph. N=13 clinical studies.



Thus, the antioxidant properties of melatonin are essential for mitochondrial functions in regulating the activities of respiratory complexes I and IV and protecting mitochondrial DNA against chromosomal/chromatid alterations and mutations **[18]**. Melatonin also regulates the ubiquitin-proteasome system in protein degradation **[19]**. Furthermore, melatonin inhibits Ca2+/calmodulin which is dependent on protein kinase II activity and autophosphorylation by direct interaction with Ca2+ activated calmodulin, acting as an antagonist **[20]**.

Main Results of Clinical Studies – Melatonin Vs. COVID-19

Based on the literature findings of the present study, a retrospective observational study of 791

intubated patients with COVID-19 showed that patients treated with melatonin had a lower risk of life, suggesting an anti-inflammatory benefit **[21]**. This is because melatonin regulates the expression of silent information regulator 1 (Sirt1), a deacetylase that is known to suppress the activity of pro-inflammatory nuclear factor kappa B (NF-kappaB), and also upregulates erythroid nuclear factor 2 related to factor 2 (Nrf2), which promotes the transcription of a variety of antioxidant proteins **[22-24]**. Thus, a nutraceutical regimen including vitamin D, zinc, and melatonin supplementation may have general utility for the prevention and treatment of RNA virus infections such as COVID-19 and influenza **[25]**.

Furthermore, studies have shown that current melatonin supplementation is associated with a significant 28% reduction in the risk of serologically detectable COVID-19. Among black Americans, this risk reduction was a remarkable 52% **[26]**. However, it is still unclear about this decrease in viral load, especially since Sirt1 activity, which melatonin promotes, is known to regulate transcriptional expression of ACE2 (receptor for COVID-19) **[27,28]**.

Also, a prospective randomized clinical trial analyzed the effect of melatonin on thrombosis, sepsis, and mortality rate in adult patients with severe COVID-19 infection. A total of 158 patients with severe COVID-19 were included in the study, in which 82 patients were in the melatonin group (10 mg of melatonin and standard therapy) and 76 in the control group (standard therapy). Compared with the control group, thrombosis and sepsis developed significantly less frequently in the melatonin group during the second week of infection, while mortality was significantly higher in the control group. Therefore, the use of melatonin may help to reduce thrombosis, sepsis, and mortality in patients with COVID-19 **[29]**.

Besides, another randomized clinical trial evaluated the effectiveness of adding melatonin to the treatment protocol for hospitalized patients with COVID-19. One group received melatonin (3.0 mg) plus standard care, the other group standard care only. A total of 96 patients were recruited and allocated to the melatonin arm (n=48) or control group (n=48). Baseline characteristics were similar between treatment arms. There was no significant difference in symptoms on day 7. Mean Leeds Sleep Assessment Questionnaire scores were significantly higher in the melatonin group. There was no significant difference in laboratory data, except for blood oxygen saturation, which significantly improved in the melatonin group compared to the control group (95.81% vs. 93.65% respectively). Therefore, the combination of oral 3.0 mg melatonin tablets and standard care can substantially improve sleep quality and blood oxygen saturation in hospitalized patients with COVID-19 **[30]**.

In addition, another randomized clinical trial evaluated the clinical efficacy of the adjuvant use of melatonin in patients with COVID-19. This study included 74 hospitalized patients with mild to moderate COVID-19. Patients were randomized in a 1:1 ratio to receive standard care and standard care plus melatonin at a dose of 3 mg three times daily for 14 days. Clinical, laboratory and radiological findings were evaluated and compared between two study groups at baseline and post-intervention. A total of 24 patients in the intervention group and 20 patients in the control group completed treatment. Compared with the control group, clinical symptoms such as cough, dyspnea, and fatigue, as well as the PCR level and lung involvement in the group receiving melatonin improved significantly. The mean time of patients' hospital discharge and return to initial health was significantly shorter in the group receiving melatonin compared to the control group. No deaths and adverse events were observed in either group **[31]**.

Furthermore, a retrospective observational clinical study looked at the effect of insomnia treatment in patients admitted for COVID-19 who received a 2 mg extended-release melatonin therapy versus an off-therapy group of patients. It was evaluated 40 patients on melatonin therapy versus a control group of 40 patients off therapy. Patients in the 2 mg extended-release melatonin group had a shorter duration of therapy with non-invasive ventilation (5.2 ± 3.0 vs. 12.5 ± 4.2), with a shorter length of stay in sub-intensive therapy (12.3 ± 3.0). 3.2 vs. 20.1 ± 6.1) and, therefore, shorter total hospital stay (31.3 ± 6.8 vs. 34.3 ± 6.9). In addition, a lower incidence of delirium was found (2.2 ± 1.1 vs. 3.3 ± 1.3; $p < 0.001$) in the group that received melatonin. Therefore, there has been evidence of the benefits of sustained-release melatonin 2 mg in COVID-19 therapy **[32]**.

Finally, one study prioritized possible treatments through an observational study corresponding to the propensity score (PS) of 26,779 individuals from a COVID-19 registry. Melatonin use was identified to be significantly associated with a 28% reduced probability of a positive SARS-CoV-2 laboratory test result confirmed by reverse transcription, and polymerase chain reaction assay. Using a PS-compatible active user comparator design, it was evidenced that the use of melatonin was associated with a reduced probability of a positive SARS-CoV-2 test result compared to the use

of angiotensin II receptor blockers or inhibitors of the angiotensin-converting enzyme. Importantly, melatonin use is associated with a 52% reduced probability of a positive SARS-CoV-2 laboratory test result in African Americans after adjustment for age, sex, race, smoking history, and various comorbidities disease using PS correspondence **[33]**.

Conclusion

Melatonin is known as an anti-inflammatory agent and immune modulator that may address the progressive pathophysiology of coronavirus disease 2019 (COVID-19). According to the objective and results obtained in the present study that evaluated the treatment in patients with COVID-19, the use of melatonin can help reduce thrombosis, sepsis, and mortality. Furthermore, the combination of 3.0 mg oral melatonin tablets and standard care can substantially improve sleep quality and blood oxygen saturation in hospitalized patients. Clinical symptoms such as cough, dyspnea, and fatigue, as well as the PCR level and lung involvement in patients receiving melatonin can improve significantly. Also, the meantime of patients' hospital discharge and return to initial health was significantly shorter in patients who received melatonin compared to the control group. There was evidence of the benefit of sustained-release melatonin 2.0 mg in therapy in patients, as well as evidence that the use of melatonin was associated with a reduced probability of a positive SARS-CoV-2 test result compared to the use of blockers of the angiotensin II receptor or angiotensin-converting enzyme inhibitors.

Acknowledgement

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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