

# Perioperative melatonin in COVID-19 patients: benefits beyond sedation and analgesia

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## Abstract

Cytokine storm in coronavirus disease 2019 (COVID-19) patients leads to acute lung injury, acute respiratory distress syndrome, multi-organ dysfunction, shock, and thrombosis thus contributing to significant morbidity and mortality. Several agents like steroids, ascorbic acid, vitamins (C, D, E), glutathione, N-acetylcysteine have been used and several studies are underway to identify its efficacy in addressing undesirable effects due to COVID-19 illness. Among several experimental modalities based on expert opinion and anecdotal data, melatonin is one molecule that appears promising. Owing to its anti-inflammatory, anti-oxidant, and immunomodulatory properties, melatonin can be an important agent used as a component of multimodal analgesia in COVID-19 patients, suspected patients, and patients with exposure to positive patients undergoing emergency or urgent surgeries. Further research is required to know the optimal time of initiation, dose, and duration of melatonin as an adjunct.

**Key words:** anesthesia; antioxidants; COVID-19; cytokine; inflammation; melatonin; multimodal analgesia; perioperative; surgery

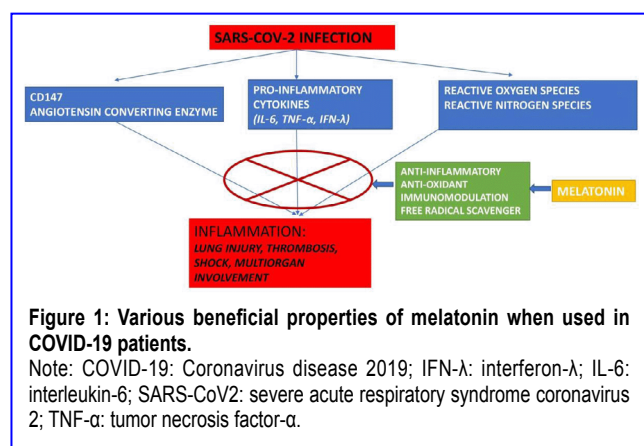
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## THE SPECTRUM OF COVID-19 INFECTION

In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, there are marked inflammatory and immune responses leading to cytokine storm. This is because of the imbalance between the pro-inflammatory and anti-inflammatory mediators in the lung parenchyma. This eventually leads to apoptosis of epithelial cells and endothelial cells; subsequently, vascular leakage, abnormal T cell, and macrophages responses ensue and induce acute lung injury (ALI), acute respiratory distress syndrome (ARDS), multi-organ dysfunction, or even death.<sup>1,2</sup> The components of a cytokine storm are interferons, interleukins, chemokines, colony-stimulating factors, and tumor necrosis factor- $\alpha$ .<sup>3</sup> SARS-CoV-2 infection intrudes the host cells via S-spike protein by binding to angiotensin-converting enzyme 2 for internalization which is aided by transmembrane serine protease 2 protease. Once internalized, the viruses attack pulmonary parenchyma, myocytes, and endothelial cells of vasculature which leads to a cascade of inflammatory changes like tissue edema, degeneration, and necrosis. Proinflammatory cytokines like interleukin-6, interleukin-10 and tumor necrosis factor  $\alpha$ , granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 $\alpha$ , and increased expression of programmed cell death 1, T-cell immunoglobulin, and mucin domain 3 are responsible for the insult. The systemic inflammation owing to this leads to ARDS, lowering of immunity, myocardial cell damage, and gastrointestinal system insults like diarrhea, vomiting, and abdominal pain.<sup>4,5</sup> Several modalities have been used by clinicians to address the cytokine storm to reduce the damage caused by them. The most commonly used modalities are corticosteroids, immunoglobulins, interleukin antagonists, interferon- $\alpha$ , blood purification therapy like convalescent plasma.<sup>6</sup> One such drug under investigation

with a lot of promise appears to be melatonin (**Figure 1**). We searched PubMed, Google Scholar database, and clinicaltrials.gov using keywords: COVID-19; cytokine; melatonin; anesthesia; inflammation; antioxidants; surgery to investigate proven efficacy of melatonin in the perioperative period as an antioxidant, immunomodulator, adjunct to multimodal analgesia, and anti-COVID-19 properties.



## CD147 AND ITS IMPLICATION IN COVID-19

CD147 is a type I transmembrane protein that is implicated with unfavorable outcomes during viral infections including SARS-CoV-2. This is mediated through pro-inflammatory cytokines like interleukin-6, interferon- $\lambda$ , tumor necrosis factor- $\alpha$ , and monocyte chemo-attractant protein-1. CD147 has also been found responsible for conditions like multiple sclerosis, myocardial infarction, and cancer proliferation.<sup>7,8</sup> In SARS-CoV-2 infections, CD147, along with angiotensin-



converting enzyme, has been implicated in activation of inflammation. COVID-19 infection has an initial pulmonary phase in which there is viral replication and inflammation. The inflammasome is an important element in the cytokine storm and that reactive oxygen species (ROS) is a potent ligand and direct mediator for triggering NOD-like receptors P3 inflammasome.<sup>9</sup> With the activation of ROS and inflammasome along with inflammatory cytokines, there are systemic inflammatory effects like thrombosis, lung injury, and myocardial injury.<sup>10</sup> Mitochondria of the cell are the main target of ROS produced due to inflammation. The balance between oxidase and antioxidant determines the generation and elimination of ROS. Increased production of free radical, enhanced activity of mitochondrial inducible nitric oxide synthase, enhanced nitric oxide production, decreased respiratory complex activity, malfunctioning of the electron transport system, and opening of mitochondrial permeability transition pores lead to impaired mitochondrial function.<sup>11</sup>

## MELATONIN – CLINICAL PHARMACOLOGY

Melatonin (5 methoxy-N acetyltryptamine) is a hormone secreted by the pineal gland. Supplemental melatonin has been used by clinicians to manage sleep disorders, delirium, and as an anti-inflammatory agent in diseases like atherosclerosis, respiratory diseases, and viral infections. The anti-oxidative effect of melatonin along with its anti-inflammatory actions like up-regulating anti-oxidative enzymes (e.g., superoxide dismutase), down-regulating pro-oxidative enzymes (e.g., nitric oxide synthase) is well known.<sup>12-15</sup> Melatonin also interacts directly with free radicals, functioning as a free radical scavenger. Another favorable effect of melatonin is its immunomodulatory effects.<sup>16</sup> This is supposed to be due to its anti-inflammatory effects in certain conditions and also antioxidative effects.

Melatonin exerts anti-inflammatory effects through various pathways. Sirtuin-1 mediates anti-inflammatory actions of melatonin by inhibiting high mobility group box chromosomal protein 1, and down-regulating the polarization of macrophages towards the pro-inflammatory type.<sup>17</sup> Nuclear factor kappa-B (NF- $\kappa$ B) has pro-inflammatory and pro-oxidative activities in ALI. The anti-inflammatory effect of melatonin suppresses NF- $\kappa$ B activation by down-regulating NF- $\kappa$ B activation in T cells and lung tissue. Experimental research suggests close interaction of sirtuin-1, NF- $\kappa$ B, and nuclear factor erythroid 2-related factor 2 suggests their participation in the coronavirus-induced ALI/ARDS.<sup>18</sup> Melatonin directly scavenges oxygen free radicals, upregulates the expression of antioxidant, and downregulates the expression of oxidase. Therefore, melatonin is also referred to as a mitochondria-targeted antioxidant.<sup>19</sup>

Melatonin does not have any antiviral effects. However, the anti-inflammatory and anti-oxidant properties of melatonin have been found beneficial in a series of patients with viral lung infections. In a dose ranging from 3 to 10 mg per day, oral melatonin has been found safe in critically ill patients.<sup>20</sup> Melatonin deficiency in older adult patients is considered as a factor responsible for adverse outcomes as the deficiency leads to immunosuppression.

## MELATONIN AS ADJUVANT IN COVID-19 TREATMENT

Reducing inflammation and enhancing immunity is important in COVID-19 patients to prevent mortality and morbidity. The use of antiviral drugs in early stages when viral replication and infectivity is high appears to be beneficial. Once that stage is crossed, i.e., from the second-week cytokine storm sets in which is responsible for ALI/ARDS, multiorgan dysfunction, and other adverse events like thrombosis.

The safety of melatonin as an adjuvant to multimodal analgesia is well established. Melatonin has antinociceptive properties and has been shown efficacious in managing acute postoperative pain and chronic neuropathic pain as a component of multimodal analgesia.<sup>21-23</sup> Due to its anti-inflammatory, antioxidant, and antinociceptive effects, anesthesiologists can consider starting oral melatonin to COVID-19 positive patients who are coming for emergency or urgent surgeries. When administered orally, the T<sub>max</sub> of oral melatonin is about 50 minutes in healthy volunteers. Ramlall et al.<sup>24</sup> retrospectively reviewed data from 791 intubated patients with COVID-19. Authors concluded that patients who were treated with melatonin after intubation had a statistically significant positive outcome (demographics and comorbidities adjusted hazard ratio: 0.131, 95% confidence interval: 0.076 to 0.223). However, the authors did not mention the dose and duration of melatonin therapy in these patients. There are several ongoing studies which are currently ongoing which is investigating the dose, efficacy, safety, and duration of melatonin use in critically ill COVID-19 patients.<sup>25-27</sup> A study has suggested a dose ranging from 5–8 mg/kg per day in COVID-19 patients for its anti-inflammatory and immunomodulatory effects.<sup>28</sup> In critically ill patients, bioavailability will be affected by gut malabsorption and factors affecting the first-pass metabolism. Based on a systematic review done by Harpsøe et al.<sup>29</sup> the authors concluded that the bioavailability of oral melatonin is 15%. Results of ongoing studies could guide clinicians regarding the safest possible dose and acceptable duration of melatonin use in critically ill COVID-19 patients. Lower segment caesarean sections posed a unique challenge during the COVID-19 pandemic both while dealing with positive patients and also while dealing with reverse transcriptase polymerase chain reaction negative or suspected patients. Reports which are available from several centers have mentioned that there was an increased rate of caesarean section during the pandemic.<sup>30</sup> The safety and efficacy of preoperative melatonin was explored earlier by Khezri et al.<sup>31</sup> in patients undergoing caesarean section and it was found that the time to rescue analgesia was prolonged though not significant statistically. In this pandemic, researchers can utilize the opportunity to determine the optimal dose of melatonin as premedication before caesarean section and also the anti-inflammatory, anti-oxidant properties of melatonin in COVID-19 parturients undergoing surgery.

## CONCLUSION

Melatonin is a safe drug that could be used in therapeutic doses at any stage when reverse transcriptase polymerase chain reaction is positive for COVID-19 as there are no recommendations right now for the optimal time of starting melatonin. Anesthesi-



ologists could consider using melatonin as a part of multimodal analgesia when dealing with COVID-19 patients, suspected patients, or patients who have history of exposure as it could provide additional benefit. Further, ongoing studies could reveal the optimal time of starting, safest possible dose, and duration of melatonin therapy to provide anti-inflammatory and anti-oxidative benefits in COVID-19 patients.

#### Author contributions

Conception of the idea, research design, manuscript writing and editing, review of the literature are all by the author.

#### Conflicts of interest

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