Strategic Integration of Melatonin to Enhance Corticosteroid Therapy in Long COVID-19 Cardiovascular Care: A Lifesaving Opportunity

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Abstract

We applaud Kakad et al. for their convincing analysis of melatonin's potential as a treatment for long-term COVID-19 (LC19), emphasizing its pleiotropic effects. Due to oxidative stress and chronic inflammation, LC19 has caused millions of people to suffer from cardiovascular problems such myocarditis and thrombosis. Even while corticosteroids are still a mainstay of treatment, long-term usage of them can have serious adverse effects, such as disruption of metabolism and disturbed sleep. In this letter, we present a novel chronotherapeutic strategy that combines evening melatonin supplementation with morning corticosteroid delivery that is timed to coincide with natural cortisol peaks. This approach seeks to minimize side effects brought on by corticosteroids while maximizing the anti-inflammatory and cardioprotective benefits of both drugs. The cardioprotective, anti-inflammatory, and antioxidant qualities of melatonin enhance corticosteroid treatment, potentially lowering dosages and improving patient results. In order to continue this strategy through coordinated, multi-center trials and guarantee thorough assessment and application of this potential therapeutic paradigm, we also support the creation of a Global LC19 Chronotherapy Consortium.

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Short title : Strategic Melatonin-Corticosteroid Integration in Long COVID-19

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Long COVID-19 (LC19) has left millions of survivors grappling with cardiovascular complications, particularly myocarditis and thrombosis, which significantly elevate mortality risk through mechanisms of sustained inflammation and oxidative stress **(1, 2)** . Corticosteroids have become a principal therapeutic approach, with meta-analyses validating their effectiveness in decreasing mortality in critically ill patients **(3, 4)** . However, their long-term administration often results in significant side effects, including metabolic disorders and sleep disruption, which can limit treatment adherence and effectiveness.

In this article, we propose a novel chronotherapeutic solution: morning administration of corticosteroids, aligned with natural cortisol peaks**(5)** , complemented by evening melatonin doses **(6)** . This strategic timing could enhance therapeutic outcomes through two mechanisms: First, optimizing the anti-inflammatory effects of corticosteroids through circadian alignment, and second, leveraging melatonin's established antioxidant and cardioprotective properties while mitigating corticosteroid-induced sleep disturbances.

Meta-analyses have established corticosteroids as a cornerstone treatment for COVID-19, demonstrating significant reductions in mortality rates among critically ill patients **(4)** . Their therapeutic action centers on suppressing the excessive inflammatory response that characterizes severe disease progression **(3)** . Regarding LC19's cardiovascular manifestations, corticosteroids directly address myocarditis through immunosuppression and reduce thrombotic risk by dampening systemic inflammation. Despite these benefits, prolonged corticosteroid administration presents substantial challenges. Sleep disruption occurs through interference with the hypothalamic-pituitary-adrenal axis, while metabolic effects manifest as weight gain and glucose dysregulation **(5)** . Beyond diminishing quality of life, corticosteroid-induced circadian and metabolic disturbances can heighten cardiovascular risk **(5)** .

Melatonin's established safety profile and diverse therapeutic properties position it as an ideal complement to corticosteroid therapy. Melatonin offers cardioprotection via multiple pathways distinct from its chronobiological benefits. It enhances mitochondrial bioenergetics, promotes autophagy of dysfunctional cardiac cells, and reduces apoptosis, thereby preserving cardiac tissue integrity **(7)** . Additionally, melatonin's inhibition of NLRP3 and activation of NRF2 pathways provides anti-inflammatory and antioxidant effects that could potentially allow for reduced corticosteroid dosing **(7)** . In the context of thrombotic complications, melatonin's antithrombotic properties offer further benefits. It improves endothelial function, reduces platelet aggregation, and enhances fibrinolytic capacity through downregulation of plasminogen activator inhibitor-1 **(8, 9)** . These effects directly address the prothrombotic environment characteristic of LC19, while complementing the anti-inflammatory action of corticosteroids.

The optimal timing of corticosteroid and melatonin administration aligns with natural circadian rhythms to maximize therapeutic benefits. Morning corticosteroid dosing coincides with peak endogenous cortisol production, enhancing anti-inflammatory effects while minimizing circadian disruption **(5)** . Evening melatonin restores cortisol secretion patterns altered by LC19 and corticosteroid therapy. With aging and in post-infectious states, melatonin production typically declines while cortisol peaks shift earlier, disrupting the natural endocrine balance **(10)** . Exogenous melatonin administration has demonstrated the ability to rectify early-onset cortisol production, potentially optimizing the therapeutic window for corticosteroid treatment. This timing-based approach may enhance treatment efficacy while reducing the required corticosteroid dosage, thereby minimizing side effects.

The translation of this promising chronotherapeutic approach into clinical practice demands innovative and immediate action from the global research community. We propose establishing a Global LC19 Chronotherapy Consortium (GLCC) to unite experts in chronobiology, cardiovascular medicine, clinical pharmacology, machine learning, and big data science. The consortium would leverage advanced monitoring systems and telemedicine for comprehensive clinical data collection. This digital infrastructure, combined with patient-centered trial designs and input from patient advocacy groups, would not only support rigorous clinical investigation but also facilitate seamless implementation across diverse healthcare settings. While our theoretical framework is promising, we acknowledge that clinical translation may yield varying results across

different patient populations and healthcare contexts. The accessibility and safety profiles of both agents present a unique opportunity to address health equity concerns, particularly in resource-limited regions. We urgently call upon research institutions, funding bodies, and healthcare systems worldwide to embrace this initiative through coordinated, technology-enabled, multi-center trials that can definitively establish the role of chronotherapeutic optimization in LC19 treatment. However, these investigations must maintain rigorous methodological standards and critical evaluation of outcomes, as the complexity of chronobiological interventions may present unexpected challenges. The time for action is now - millions of patients await evidence-based solutions, and we stand at a crucial intersection where theoretical understanding, technological capability, and global health needs converge to potentially transform the landscape of LC19 cardiovascular care.

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