中文題目：Melatonin 對於 COVID-19 病人臨床療效之系統性回顧與統合分析

英文題目：The clinical and laboratory efficacy of melatonin in the treatment of patients with COVID-19: systematic review and meta-analysis

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Background

COVID-19 virus triggers a cytokine storm that related with disease severity. The exaggerated immune response even results in patient multi-organ dysfunction and death. Melatonin, a hormone produced by the pineal gland, has been found to have anti-inflammatory and Immunomodulation effects. One recent meta-analysis revealed use melatonin can effectively reduce inflammatory markers (TNF-α and IL-6 level). However, the effect of melatonin in improving COVID-19 clinical outcome is still conflicting. With new evidence available, this study aimed to pool all the data from COVID-19 patients with melatonin intervention, using a meta-analysis to provide reliable and quantitative results on the effect of melatonin in treating patients with COVID-19.

Methods

PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched without publication year and language limitation from inception to 10 August 2022 (PROSPERO CRD42022351424). Randomized controlled trials (RCTs) of melatonin, enrolling adult COVID-19 patients, were included. The primary outcome was mortality; the secondary outcomes were recovery rate of clinical symptoms, the level of inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and neutrophil to lymphocyte ratio (NLR). They were expressed as the risk ratio (RR) or mean difference (MD) and 95% confidence intervals (CI), which used a random-effects model to pool effect sizes. We conducted a subgroup analysis based on treatment duration if significant heterogeneity exists within mortality.

Results

A total of eight RCTs involving 650 subjects were included. Eight studies with the primary outcome were analyzed, all of which used melatonin as the intervention. The

pooled results showed no significant difference in mortality between melatonin and placebo groups, with high heterogeneity across studies identified (RR 0.31, 95% CI 0.02 to 4.99, p = 0.02; I^2 = 90%). Subgroup analyses revealed statistically significant effects within subgroups of a duration of treatment above 10 days (RR 0.07, 95% CI 0.01 to 0.53, p = 0.01). As for other COVID-19-associated secondary outcomes, a significant difference was revealed in the level of CRP between the intervention and control groups (MD -6.06, 95% CI -11.32 to -0.79, p = 0.02; I^2 = 90%). By contrast, there is no statistical significance in the level of ESR (MD 7.34, 95% CI -10.24 to 24.92, p = 0.41; I^2 = 80%) nor NLR (MD 0.37, 95% CI -1.73 to 2.47, p = 0.35; I^2 = 43%). Change in the level of CRP (MD 0.95, 95% CI -10.21 to 12.12, p = 0.87; I^2 = 93%) and ESR (MD 26.42, 95% CI -29.79 to 82.63, p = 0.36; I^2 = 98%) both demonstrate no statistical significance. No significant difference was discovered in the recovery rate of clinical symptoms (RR 1.14, 95% CI 0.90 to 1.46, p = 0.28; I^2 = 70%). None of the included studies found serious adverse effects from melatonin use.

Conclusion

Melatonin supplementation showed a significant reduction in the mortality of COVID-19 patients in the group with a treatment course above 10 days. Regarding the inflammatory markers, statistical significance was observed in decreasing CRP but not in ESR or NLR. There is no significant difference in the recovery rate of COVID-19-related symptoms. Further studies with larger sample sizes are warranted to elucidate the correlation between the clinical and laboratory benefits of melatonin on COVID-19 patients.