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LETTER TO THE EDITOR

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Could melatonin be used in COVID-19 patients with laryngopharyngeal reflux disease?

To the Editor,

The study by Jiang et al[1] to determine the impact of laryngopharyngeal reflux disease (LPRD) on the clinical outcomes in hospitalized patients with novel coronavirus disease 2019 (COVID-19) is first of its kind study in the literature. While available studies have mostly focused on the effect of cardiovascular comorbidities, the authors' work raises the concurrent gastrointestinal-related issues in patients with COVID-19.

Specifically, the authors noted that COVID-19 patients with LPRD experienced significantly higher odds of having a severe course of the disease (odds ratio, 11.411; 95% confidence interval, 2.95-42.09) as well as a critical course of the disease (odds ratio, 19.61; 95% confidence interval, 1.38-277.99). Though the precision of effect size estimation may be too low to make a definitive conclusion, we feel that preemptive interventions should be taken to reduce the risk of progression of COVID-19 in patients with LPRD. One such possible intervention is melatonin. The effects of melatonin in this context is twofold: alleviating symptoms of LPRD and mitigating cytokine storm syndrome in COVID-19.

In healthy individuals, the lower esophageal sphincter is among the barriers to reflux encroaching on the larynx, which is located at the gastroesophageal junction whose contracture leads to circular closure and prevention of egress of stomach acid.[2] The incompetence of the lower esophageal sphincter allows reflux of gastric contents into the esophagus and subsequently into the larynx and pharynx, causing symptoms of LPRD. In this sense, strengthening of lower esophageal sphincter could be achieved with melatonin treatment. It was demonstrated in a clinical trial[3] that patients with gastroesophageal reflux disease (GERD) receiving melatonin with a dosing regimen 3 mg once daily, with or without omeprazole had an improvement in the tone of the lower esophageal sphincter, in the forms of a significant increase in lower esophageal sphincter pressure, a significant increase in the residual pressure, a significant decrease in the relaxation duration, and a significant increase in the relaxation percentage, compared to healthy controls without gastroesophageal reflux disease. Though the study was performed in patients with GERD, we believe that it could be extrapolated to patients with LPRD considering common pathophysiology of lower esophageal sphincter incompetence.[4]

As more has been unraveled, we have now understood that the pathophysiology of COVID-19 involves the overproduction of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and IL-1β, leading to enhanced vascular hyperpermeability, subsequent multiorgan failure, and eventual death, which has been termed as cytokine storm syndrome by researchers.[5] Therefore, current investigational interventions aim to target such an overactive cytokine response in COVID-19 to prevent the progression of the disease. The anti-inflammatory effect of melatonin supports its use in mitigation of cytokine storm syndrome in COVID-19 patients, where suppression of nuclear factor-κB pathway in lung tissue by melatonin led to reduced production of pro-inflammatory cytokines including TNF-α and IL-10, as demonstrated in a mice model with acute lung injury.[6] There are also promising results with melatonin in human studies with regard to the attenuation of circulating cytokines levels. A systematic review and meta-analysis[7] of clinical trials included 22 data sets with a total of 749 patients reported a significant reduction in TNF-α and IL-6 levels (weighted mean difference = −2.24 pg/mL; 95% confidence interval, −3.45, −1.03) with melatonin supplementation. Furthermore, in the acute care setting among patients undergoing coronary artery bypass grafting, melatonin intake of 5 mg once daily for a few days resulting in a reduced level of pro-inflammatory TNF-α.[8]

Nevertheless, a high dose of melatonin may lead to somnolence, which could promote aspiration and possibly secondary bacterial aspiration pneumonia in COVID-19 patients, though a dosing regimen as high as 10 mg once daily has been found to be safe among patients in the intensive-care units.[9] The aforementioned beneficial effects of melatonin warrant a clinical trial to determine its efficacy in patients with COVID-19, especially those with LPRD, since they may have a more severe manifestation of the disease, where melatonin treatment could address both symptoms of LPRD and mitigate the progression of COVID-19.

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