

Corticosteroids in COVID-19: We Should Be Mindful of Their Acute Toxicities

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has wreaked havoc across the globe. As of May 2021, this disease has claimed nearly 3.5 million lives and affected >165 million people globally.¹ A variety of treatment modalities and drugs have been tried in the management of severe COVID-19, most of them as a desperate measure. In line with the outcomes from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial and prospective meta-analysis, the World Health Organization (WHO) recommended use of systemic corticosteroid therapy in patients with severe and critical COVID-19.² At present, the treatment protocol for the majority of hospitalized cases of COVID-19 revolves around corticosteroid-based regimens. Corticosteroids are listed in the WHO model list of essential medicines and are readily available across the world at low cost; thus, the chance of abuse, overuse, and misuse is high.

Corticosteroids have been used for more than half a century to treat a diverse range of conditions by modulating the immune response. Steroids have pleiotropic effects and have been shown to prevent and attenuate inflammation by genomic and nongenomic mechanisms. Endothelial damage by SARS-CoV-2 leads to systemic hyperinflammation and multiorgan dysfunction, forming the basis for steroid use in COVID-19 patients.³ Use of steroids is associated with numerous adverse effects in the long term. However, there are several toxicities related to short-term steroid use that are critical and often neglected. This seems the right time to discuss these acute adverse effects of steroids that we may see in current clinical practice.

Because systemic steroids are used in COVID-19 patients on oxygen supplementation, clinicians should be vigilant about immediate hypersensitivity reactions associated with steroid use, including anaphylaxis, which may be life-threatening. The exact incidence of such re-

actions is unknown, but it is estimated to occur in fewer than 1% of patients receiving systemic steroids.^{4,5} This is important clinically, as the presentation of allergy may be confused with that of progressively worsening COVID-19. Another major concern is that of acute infection and reactivation of latent infections. Evidence is that steroid use in COVID-19 patients is associated with bloodstream infection, COVID-associated pulmonary aspergillosis, mucormycosis, *Strongyloides* infection, and other various secondary infections.⁶ This susceptibility may be because of immune-modulating effects of both COVID and corticosteroids. Moreover, patients on steroids may not manifest signs and symptoms of infection as distinctly and early, and many of them may eventually land up in sepsis, leading to increased morbidity and mortality.

The majority of COVID-19 patients have underlying comorbid conditions, especially diabetes and cardiovascular diseases. Steroid use in diabetics may disrupt glycemic control and lead to diabetic ketoacidosis and a nonketotic hyperosmolar state. Steroids can exacerbate hypertension, and its use is associated with increased rates of myocardial infarction, acute decompensation of heart failure, arrhythmias, and all-cause mortality.⁷ Pulse administration of corticosteroids is also being used for managing severe COVID-19. Note that severe cardiovascular toxicity and even sudden deaths have been reported while using pulse infusion

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of steroids.^{8,9} Cardiac monitoring is advocated. Acute systemic steroid use can also lead to acute glaucoma and central serous chorioretinopathy. Clinicians should be vigilant about these conditions.

Steroid use is associated with gastrointestinal (GI) problems such as gastritis, peptic ulcer, and GI bleeding. These are also implicated in acute visceral perforation and acute pancreatitis. Corticosteroids can cause myriad neuropsychiatric effects. Acutely, they can cause exacerbation of preexisting psychiatric illnesses, mood disorders, steroid dementia, akathisia, and pseudotumor cerebri.¹⁰ Acute psychosis, mania, and euphoria are also related to acute steroid use in high dosages.¹¹ Steroids also cause myopathy, which may be difficult to distinguish from COVID-19-related critical illness neuropathy and myopathy. Moreover, early initiation of steroids in critically ill patients was associated with a significant delay in viral clearance in patients with SARS and Middle East respiratory syndrome infection, and this may be the case with COVID-19 as well.^{12,13} Further research is needed to assess the effect of steroids in SARS-CoV-2 clearance.

Another critical problem of steroid use in COVID-19 is that of thrombosis and associated cerebrovascular disease. The risk of stroke varies according to the severity of COVID-19 and may be as high as 6% in severe cases.¹⁴ It is hypothesized that SARS-CoV-2 infection-induced endothelial injury leads to a hypercoagulable state. Corticosteroids supposedly increase clotting factor and fibrinogen concentration and are thus implicated in clinical thrombosis in patients with COVID-19.¹⁵

Corticosteroids are potent immunomodulatory drugs. Current evidence suggests low-dose, short-course use in COVID-19 patients requiring oxygen supplementation or ventilatory support. The National Institutes of Health recommends steroid use in hospitalized patients who require supplemental oxygen, in patients who require oxygen delivery through a high-flow device or noninvasive ventilation, and in those who require invasive mechanical ventilation or extracorporeal membrane oxygenation.¹⁶ As discussed, steroids can have severe adverse effects even when used for short duration. Its consequences in virus clearance are still unknown. With the easy availability of corticosteroids, it is highly possible that this drug might be overused or misused by clinicians and the general public. Although corticosteroids have shown benefit in COVID-19, the risk they bear should not be belittled. Judicious, evidence-based use of steroids by assessing the risk-benefit ratio and taking into account the patient's preexisting conditions is recommended. People are generally concerned about the long-term harm associated with steroid use. But corticosteroid use may have acute, life-threatening consequences.

Knowledge of its acute toxicities seems highly relevant in the present context.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

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