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Review Article

Evolving perspectives on corticosteroid use in COVID-19: From pre- to post-vaccination era

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A B S T R A C T

In treating severe COVID-19, especially for patients requiring respiratory support, corticosteroids such as dexamethasone are crucial because of their anti-inflammatory properties that counter the "cytokine storm," which exacerbates respiratory issues and can lead to acute respiratory distress syndrome. The RECOVERY trial indicated that dexamethasone significantly reduced mortality in patients on invasive mechanical ventilation and those receiving oxygen, but no survival benefit was observed in mild cases without oxygen support. The effectiveness of corticosteroids depends on the timing, dosage, and disease severity, with early administration or higher doses linked to increased mortality. They may also prolong viral shedding and increase the risk of secondary infections and complications such as hyperglycaemia and osteonecrosis. With widespread vaccination, the necessity for corticosteroids has decreased, as vaccinated individuals generally experience milder symptoms, although severe illness persists among the unvaccinated and those with breakthrough infections. Corticosteroids are commonly used for severe cases in Asia and Central Asia, which is consistent with WHO recommendations. Their adoption is influenced by the regional healthcare infrastructure, resources, and cultural factors. Future research should refine corticosteroid use by considering new variants and patient-specific factors and optimise combination therapies for better safety and efficacy.

Keywords: Corticosteroids, COVID-19, Dexamethasone, Cytokine storm, Acute respiratory distress syndrome, Mortality

Introduction

Severe acute respiratory syndrome coronavirus 2 is the causative agent of coronavirus disease (COVID-19), a transmissible disease that predominantly affects the respiratory system and may result in severe complications, such as kidney failure.[1–4]

Corticosteroid medication, especially dexamethasone, is essential in treating hospitalised severe symptoms in patients with coronavirus disease (COVID-19). These anti-inflammatory drugs help counteract the hyperinflammatory "cytokine storm" that exacerbates respiratory issues.

Corticosteroids suppress the overactive immune response in severe COVID-19 cases, reduce inflammation, and prevent acute respiratory distress syndrome (ARDS).[5] This modulation is critical for preventing extensive lung damage caused by cytokine storms.[6]

The RECOVERY trial showed that dexamethasone reduced mortality in patients needing respiratory support, proving its efficacy in severe cases.[7] Observational data suggest that this benefit is more significant in patients with high levels of inflammatory markers and severe symptoms.[8] In contrast, corticosteroids show limited benefits in mild cases that do not require oxygen.[8]

For severely and critically ill patients with COVID-19, particularly those needing mechanical ventilation or supplemental oxygen, corticosteroid therapy is recommended.[9,10] Treatment usually involves low-to-moderate doses for a limited period to minimise adverse effects.[5]

In hospitalised patients, corticosteroids are associated with lower mortality and reduced disease progression to severe stages,[7] underscoring their importance in treatment protocols for severe COVID-19.[5]

However, corticosteroids can cause immunosuppression, increasing the risk of secondary infections such as candidemia.[11] Prolonged use may lead to complications, such as hyperglycemia and osteonecrosis, necessitating careful monitoring of dosage and duration.[12]

Current research seeks to optimise dosing regimens and combination therapies to enhance corticosteroid effectiveness across various patient groups, including those with comorbidities and different COVID-19 variants.[7,8] Studies have also explored corticosteroid use in specific populations, such as pregnant women, where balancing maternal benefits and foetal risks is crucial.[10]

Corticosteroid therapy, notably dexamethasone, is vital for managing severe COVID-19 in hospitalized patients. Adhering to guidelines is essential for benefits and minimising risks. Ongoing research is likely to refine treatment approaches to improve patient outcomes.

Corticosteroids are administered to reduce the inflammatory response and minimiselung damage. However, their use in ARDS patients remains controversial. Few drugs have proven effective in reducing COVID-19 mortality. This study investigated the role of corticosteroid therapy in hospitalised COVID-19 patients over 18 years of age.

Administration of corticosteroids in patients with COVID-19

The effectiveness of corticosteroids in treating COVID-19 remains inconclusive due to limitations in existing studies.[13] The WHO recommends corticosteroids for severe or critical cases, with individualised risk-benefit assessments.[14] A study found that severe and critical patients with COVID-19 exhibited impaired interferon responses, leading to poor viral clearance and heightened inflammation.[15,16] Corticosteroids may benefit these patients by reducing inflammation, promoting lipolysis, decreasing pulmonary vascular permeability, and enhancing epithelial barrier function.[17,18]

Awadhesh et al. (2020) reviewed five Spanish studies on corticosteroid efficacy in hospitalised adults with severe and critical COVID-19, concluding that low-dose corticosteroids are more beneficial.[13,19] A quasi-experimental study in Michigan evaluated early methylprednisolone administration in patients with moderate-to-severe COVID-19, finding lower mortality, ICU transfer, and mechanical ventilation rates in corticosteroid-treated patients.[20]

The RECOVERY trial, a prospective study conducted in the UK with 2104 hospitalised COVID-19 patients of varying severity, demonstrated a significantly lower 28-day mortality rate in the dexamethasone group than in the usual treatment group.[21] Dexamethasone significantly reduced mortality in patients on invasive mechanical ventilation (29.0% vs. 40.7%, $p<0.003$) and in those receiving supplemental oxygen with or without noninvasive ventilation (21.5% vs. 25.0%, RR, 0.80 [95% CI: 0.70 to 0.92], $p<0.0021$) over 28 days. No survival benefit was observed in patients with milder disease who did not require oxygen support (17.0% vs. 13.2%, $p=0.14$). Dexamethasone-treated patients had shorter hospital stays (median, 12 days vs. 13 days, $p=0.002$) and an 11% higher probability of discharge within 28 days, with positive responses within the first week of therapy.[21-23]

Group et al. conducted a meta-analysis of seven randomised clinical trials involving 1,703 patients to evaluate the efficacy of dexamethasone in severe and critical COVID-19 cases.

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Their findings indicated that systemic corticosteroids, compared to standard treatment, reduced 28-day all-cause mortality (OR, 0.66 [95% CI: 0.53-0.82]; P < 0.001).[24]

Tomazini et al. (2020) reported results from a multicenter randomised clinical trial in 41 Brazilian ICUs, comparing dexamethasone with standard care in COVID-19 patients with moderate to severe ARDS. Intravenous dexamethasone, combined with standard therapy, increased ventilator-free days at 28 days (6.6 vs 4.0 days, 95% CI, 0.2-4.38; p=0.04).[25]

The CAPE COVID study, a randomized, placebo-controlled, double-blind trial in nine French ICUs, assessed low-dose hydrocortisone (200 mg/day infusion) in 149 adults with severe COVID-19-related respiratory issues. The primary outcome, treatment failure at day 21 (death or continued respiratory support), was less frequent in the hydrocortisone group (42.1% vs 50.7%, p=0.29).[26,27]

Callejas Rubio et al. examined corticosteroid pulses for COVID-19-associated cytokine release syndrome (CRS) across five Spanish hospitals. CRS was defined as an elevated IL-6 level of > 40 pg/ml and/or specified markers. Among the 92 patients with CRS, 60 (65.2%) received only corticosteroid pulses (group 1), 23 (25%) received pulses and tocilizumab (group 2), and 9 (9.8%) received tocilizumab alone (group 3). Group 2 had a lower 28-day mortality rate compared to groups 1 and 3 (4.4% vs 8.8% and 11.1%, CI 95%, p= 0.065).[28]

The timing, dosage, and disease severity significantly impact corticosteroid treatment outcomes in patients with COVID-19.[21,29] Early administration (within three days) and higher doses (>200 mg hydrocortisone) have been associated with increased 28-day mortality.[29] The RECOVERY study, which demonstrated reduced mortality in severe cases, used 150 mg of hydrocortisone. Corticosteroids delayed the clearance of SARS-CoV-2 RNA.[21,29] Early low-dose corticosteroids may benefit patients with moderate-to-severe COVID-19 pneumonia, particularly those requiring mechanical ventilation, by influencing SARS-CoV-2 excretion.

Initial corticosteroid therapy has not been proven effective in moderate COVID-19. Researchers are investigating inflammatory marker profiles to gauge severity and provide insights into the timing and effectiveness of corticosteroid treatment.[30]

Tlayjeh et al. conducted a meta-analysis of 19 trials with 16,977 hospitalised COVID-19 patients to evaluate corticosteroid efficacy.[31] Their findings showed that corticosteroids did not significantly reduce short-term mortality (adjusted RR: 0.91, 95% CI: 0.71-1.16, I2 = 82.23%). They observed a reduced risk of the composite outcome of death, ICU admission, and mechanical ventilation in four small cohort studies (pooled adjusted SHR 0.41, 95% CI 0.23-0.73) and noted that corticosteroids might delay viral shedding (adjusted RR 1.47, 95% CI 1.11-1.93). However, the meta-analysis data from Tlayjeha et al. had very low confidence owing to study heterogeneity.[31]

Potential risks associated with corticosteroid use in COVID-19

Corticosteroids have been associated with various adverse effects under different conditions. In ICU patients with SARS-CoV-2 pneumonia, these drugs increase viral shedding, though the clinical impact on transmission is unclear.[31–34] Coronaviruses evade detection and modify the immune response early during infection. Corticosteroids during this initial phase may suppress the host's antiviral defence by enhancing viral replication and causing cytopathic injury to alveolar epithelial cells.[35]

Corticosteroid therapy also increases gluconeogenesis, proteolysis, and lipolysis while directly inhibiting pancreatic beta cells. These drugs can increase insulin resistance by 60-80% through interference with the GLUT-4 receptor signaling pathway. While these effects are usually transient and reversible upon discontinuation, corticosteroids may worsen dysglycaemia and reveal latent diabetes.[36,37]

Short-term corticosteroid use is unlikely to significantly aggravate diabetes or glycaemic control. Most clinical trials for COVID-19 use brief regimens: dexamethasone for 10 days (RECOVERY) or methylprednisolone for 3–7 days. The anticipated hyperglycemia from corticosteroid use in COVID-19 patients requires consideration, and corrective measures should be taken.(19, 25)[38,39]

COVID-19, like other severe illnesses, exacerbates adrenal insufficiency, particularly in patients with preexisting adrenal hypofunction. Suppression of the hypothalamic-pituitary-adrenal axis is expected in critically ill patients with COVID-19, and corticosteroids may be beneficial. However, the potential risks associated with corticosteroid use in COVID-19 have not been thoroughly evaluated.[40]

Impact of vaccination on corticosteroid efficacy in severe covid-19 cases

The impact of corticosteroid therapy in COVID-19 patients has evolved significantly with widespread vaccination, reflecting the changing nature of the pandemic.

Before vaccination

Before vaccines, corticosteroids, such as dexamethasone, were primarily used for severe COVID-19 cases involving respiratory distress or the need for oxygen or mechanical ventilation. The goal is to reduce mortality by mitigating the hyperinflammatory response, known as a cytokine storm.[5,6] Research, such as the RECOVERY trial, showed that

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systemic corticosteroids could lower mortality in critically ill COVID-19 patients.[7]

Corticosteroids reduce inflammation and prevent progression to ARDS.[1] Case studies have indicated that early administration of corticosteroids in severe COVID-19 pneumonia improved clinical outcomes by mitigating the cytokine storm.[6,10]

Post-Vaccination

Vaccines have led to fewer severe cases, changing the demographics of hospitalised patients WITH COVID-19. Vaccinated individuals often have milder symptoms, which reduce the need for corticosteroids.[41] However, severe illness remains a risk for unvaccinated individuals and those with breakthrough infections, highlighting the importance of corticosteroids in such cases.[7]

Corticosteroids remain crucial for severe COVID-19 cases, especially in unvaccinated individuals or those with severe breakthrough infections. The focus remains on patients requiring respiratory support, where corticosteroids offer significant benefits.[7,42]

New variants have influenced disease severity and treatment outcomes, but corticosteroids remain effective in severe cases caused by hyperinflammatory variants, underscoring their importance.[7]

Vaccinated individuals with severe breakthrough infections may benefit from corticosteroids, albeit less frequently. Corticosteroids alleviate inflammatory responses, considering the reduced risk of severe illness due to vaccination.[7,43]

While beneficial, corticosteroids can cause immunosuppression, increasing the risk of secondary infections such as candidemia.[11] Additionally, prolonged use can lead to corticosteroid-induced osteonecrosis, necessitating careful monitoring of dosage and treatment duration.[12]

Role in Asia and Central Asia

Corticosteroids, particularly dexamethasone, are widely used in Asia and Central Asia to treat severe COVID-19 cases, aligning with the WHO guidelines and global evidence supporting their efficacy in reducing mortality. However, regional disparities in healthcare infrastructure, resource availability, and cultural factors affect the adoption and implementation of corticosteroid therapy.

Some countries have conducted local studies to understand corticosteroid effectiveness in their populations, considering genetic variations and prevalent comorbidities, leading to adjustments in treatment protocols.[9,40] COVID-19 variants necessitate adaptation to treatment strategies; however, corticosteroids remain crucial for managing severe cases. The impact of vaccination rates on corticosteroid use varies by region, with high vaccination rates potentially reducing the incidence of severe cases requiring corticosteroid treatment.[9,45] Ongoing efforts to improve healthcare access and incorporate local research findings are essential to optimise corticosteroid treatment in these regions.

Conclusions

Corticosteroids significantly reduced mortality in severe COVID-19 cases, especially in patients requiring respiratory support. The RECOVERY trial confirmed the effectiveness of dexamethasone in controlling cytokine storms, lowering death rates, and improving outcomes in critically ill patients. However, risks such as immune suppression and high blood sugar levels necessitate careful dosing, particularly in vulnerable patients. Corticosteroids remain crucial in the post-vaccine era, particularly in unvaccinated individuals with severe infections. Despite reduced hospitalisations due to vaccination, these medications are essential for severe cases in areas with low vaccination rates and high disease prevalence. Future research should refine corticosteroid use by considering new variants and patient-specific factors and optimising combination therapies for enhanced safety and efficacy.

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