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Letter to the Editor

Systemic corticosteroids for management of COVID-19: Saving lives or causing harm?

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Abstract

The underlying cause of many complications associated with severe COVID-19 is attributed to the inflammatory cytokine storm that leads to acute respiratory distress syndrome (ARDS), which appears to be the leading cause of death in COVID-19. Systemic corticosteroids have anti-inflammatory activity through repression of pro-inflammatory genes and inhibition of inflammatory cytokines, which makes them a potential medical intervention to diminish the upregulated inflammatory response. Early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the role of corticosteroids was unclear. Corticosteroid use in other indications such as ARDS and septic shock has proven benefit while its use in other respiratory viral pneumonias is associated with reduced viral clearance and increased secondary infections. This review article evaluates the benefits and harms of systemic corticosteroids in patients with COVID-19 to assist clinicians in improving patient outcomes, including patient safety. Dexamethasone up to 10 days is the preferred regimen to reduce mortality risk in COVID-19 patients requiring oxygen support, mechanical ventilation, or extracorporeal membrane oxygenation. If dexamethasone is unavailable, other corticosteroids can be substituted at equivalent doses. Higher doses of corticosteroids may be beneficial in patients who develop ARDS. Corticosteroids should be avoided early in the disease course when patients do not require oxygen support because of potential harms.

Keywords

Corticosteroids, COVID-19, dexamethasone, hydrocortisone, methylprednisolone, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus that causes coronavirus disease 2019 (COVID-19).[1,2] The clinical manifestations of COVID-19 range from asymptomatic infection or mild symptoms to severe viral pneumonia with respiratory failure leading to fatality.[1,3–9] The average incubation time for SARS-CoV-2 is estimated to be 5 days and about 95% of symptomatic patients develop symptoms within 12 days.[4,10] The average time from onset of these symptoms to admission to the hospital and death is about 6–12 and 15 days, respectively.[1,3–9] The underlying cause of many complications associated with severe COVID-19 seems to be inflammatory cytokine storm, where there is increased production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α).[1,11–13] Consequently, many acute phase reactants such as C-reactive protein (CRP), complement factors, fibrinogen, prothrombin, and ferritin may contribute to the

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complications of severe COVID-19.[11,12,14] Neutrophils are the primary source of cytokines and the generation of cytokine storm can lead to acute respiratory distress syndrome (ARDS), which appears to be the leading cause of death in patients with COVID-19 pneumonia, similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[15–17]

Corticosteroids are used to treat autoimmune and inflammatory conditions such as rheumatoid arthritis, asthma, Crohn's disease, and lupus. Systemic corticosteroids (e.g., methylprednisolone, dexamethasone, and hydrocortisone) are given orally or intravenously (IV) and are well distributed throughout the body, and each possesses different relative anti-inflammatory potency and mineralocorticoid effects. Glucocorticoids exert their anti-inflammatory activity by crossing the cellular membrane and binding to the intracellular glucocorticoid receptor. The glucocorticoid receptor complex then goes to the nucleus to repress the genes of pro-inflammatory cytokines or upregulate the genes of anti-inflammatory cytokines.[18] In addition, glucocorticoids antagonize macrophage differentiation and inhibit secretion of inflammatory cytokines (e.g., IL-1, IL-2, IL-6, IL-8, and TNF).[19] These properties make corticosteroids a potential treatment option for the management of cytokine release syndrome associated with respiratory disease (e.g., chronic obstructive pulmonary disease [COPD] and ARDS) or infection (influenza, SARS, MERS, and COVID-19). Corticosteroids seem to be beneficial in patients with sepsis or ARDS, which can be the complications of severe respiratory infections.[20–22] This article reviews the potential harms and benefits of systemic corticosteroids in adult patients with COVID-19.

Literature review

We searched PubMed, EMBASE, and Google Scholar from inception through October 2021 using keyword terms steroid, corticosteroid, dexamethasone, hydrocortisone, methylprednisolone, ARDS, sepsis, respiratory viral infections, influenza, SARS, MERS, COVID-19, and SARS-CoV-2. Studies evaluating the efficacy and safety of corticosteroids for treatment of ARDS, septic shock, and respiratory viral infections (e.g., influenza, SARS, MERS, and COVID-19) published in the English language are included. We also screened English abstracts of non-English studies in order to identify any additional key studies. References of systematic reviews were screened to identify additional studies. End points for efficacy included mortality and clinical status defined as the need for oxygenation or mechanical ventilation, and hospital discharge.

Corticosteroids for ARDS

A serious complication of severe COVID-19 is ARDS, which is associated with high rates of mortality (35%–46%).[23,24] Table 1 provides a summary of corticosteroid studies in patients with ARDS. Prior to 2020, there was no proven pharmacologic treatment for ARDS with mortality benefit.[23] Late initiation of methylprednisolone 2 weeks after ARDS onset was even associated with increased risk of mortality.[29] The 2017 Society of Critical Care Medicine (SCCM) guidelines conditionally recommended the use of corticosteroids in patients with early moderate to severe ARDS (PaO2/FiO2 of <200) within 14 days of onset.[24] Published in 2020, DEXA-ARDS trial enrolled 277 patients with moderate to severe ARDS and found that patients randomized to dexamethasone 20 mg IV once daily for 5 days compared with continued routine intensive care had lower 60-day all-cause mortality (difference −15.3%; 95% confidence interval [CI], −25.9 to −4.9) and more ventilator-free days at 28 days (difference 4.8 days; 95% CI, 2.57–7.03).[32]

A meta-analysis of eight randomized clinical trials (RCTs) with 1091 patients, which included DEXA-ARDS, with moderate heterogeneity (I^2 = 47%) showed that use of glucocorticoids in critically ill adult patients with established respiratory failure secondary to ARDS was associated with a significant reduction of hospital mortality (relative risk [RR] 0.79; 95% CI 0.64–0.98).[33] Subgroup analysis showed a significant reduction in hospital mortality with early (<7 days of ARDS onset) glucocorticoids administration (RR 0.80; 95% CI 0.65–0.98); however, no hospital mortality benefit was seen with late administration of glucocorticoids (RR 0.52; 95% 0.11–2.52). In terms of which glucocorticoids to use in ARDS, methylprednisolone has also shown benefit in ARDS. In patients with early ARDS, prolonged methylprednisolone treatment prevented progression to respiratory failure requiring mechanical ventilation (42% vs. 100%; p = .02) or progression to unresolving ARDS (8% vs. 36%; p = .00).[34] Furthermore, methylprednisolone may have several advantages over hydrocortisone for the treatment of ARDS. Methylprednisolone has higher penetration in lung tissue with longer residence time compared to hydrocortisone. Therefore, the use of glucocorticoids, specifically methylprednisolone and dexamethasone, in ARDS is associated with significant reduction in duration of mechanical ventilation.

Corticosteroids for septic shock

Another complication of severe COVID-19 is septic shock. According to the 2016 Surviving Sepsis Campaign guidelines, corticosteroids (specifically IV hydrocortisone) should only be used for septic shock unresponsive to volume resuscitation and vasopressors.[35] This recommendation is based on the absence of convincing evidence of benefit since several systematic reviews have examined the use of low-dose hydrocortisone in septic shock with contradictory results. Corticosteroid use in the setting of septic shock has been debated for decades, with inconclusive data to support its role. A randomized clinical trial

Table 1: Summary of corticosteroid studies in patients with ARDS.

Study reference	Study design	Patients	Intervention	Results
Bernard et al.[25] (1987)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	99 patients with ARDS	Methylprednisolone 30 mg IV every 6 h for 24 h	• No significant difference in 45-day mortality ($p = .74$)
Meduri et al.[26] (1998)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	24 adult patients with severe ARDS of at least 7 days duration	Methylprednisolone 2 mg/kg IV daily from day 1–14, then 1 mg/kg from day 15–21, then 0.5 mg/kg from day 22–28, then 0.25 mg/kg from day 29–32	• Reduced LIS ($p < .001$) • Decreased MODS score ($p < .001$) • Reduced ICU mortality ($p = .03$)
Confalonieri et al.[27] (2005)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	46 patients with pneumonia and ARDS	Hydrocortisone 200 mg IV bolus, then 10 mg/h continuous infusion for 7 days	• Improved ARDS ($p < .0001$) • Decreased CRP ($p = .01$) • Reduced MODS score ($p = .003$) • Delayed septic shock ($p = .001$) • Reduced length of hospitalization ($p = .03$) • Reduced mortality ($p = .009$)
Annane et al.[28] (2006)	Randomized clinical trial, double-blind, placebo-controlled, multicenter, post-hoc analysis	177 patients with septic shock and ARDS	Hydrocortisone 50 mg IV every 6 h for 7 days plus fludrocortisone 50 mg orally once a day for 7 days	• Reduced mortality ($p = .013$) • Improved number of ventilator-free days ($p = .006$) • The benefits were only apparent in septic shock-associated early ARDS non-responders
Steinberg et al.[29] (2006)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	180 adult patients with ARDS of at least 7 days duration	Methylprednisolone 2 mg/kg IV once, then 0.5 mg/kg every 6 h for 14 days, then 0.5 mg/kg every 12 h for 7 days, then tapering off over 4 days	• No difference in 60-day mortality when initiated in the first 14 days ($p = .26$) • Increased mortality when initiated after 14 days of ARDS ($p = .02$) • Improved number of ventilator-free days at day 28 ($p < .001$)
Meduri et al.[30] (2007)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	91 adult patients with severe ARDS within 72 h of onset	Methylprednisolone 1 mg/kg IV bolus, then 1 mg/kg/day from day 1–14, then 0.5 mg/kg/day from day 15–21, then 0.25 mg/kg/day from day 22–25, then 0.125 mg/kg/day from day 26–28	• Reduced LIS ($p = .004$) • Reduced MODS score ($p = .002$) • Decreased CRP ($p < .0001$) • Reduced duration of mechanical ventilation ($p = .002$) • Reduced duration of ICU stay ($p = .007$) • Reduced ICU mortality ($p = .03$) • No significant difference in in-hospital mortality ($p = .07$)

(continued)

Table 1: (continued)

Study reference	Study design	Patients	Intervention	Results
Tongyoo et al.[31] (2016)	Randomized clinical trial, double-blind, placebo-controlled, single-center	197 adult patients with severe sepsis and ARDS within 12 h of onset	Hydrocortisone 50 mg IV every 6 h for 7 days	• Improved pulmonary physiology (p = .01) • No significant difference in survival (p = .44)
Villar et al.[32] (2020) [DEXA-ARDS]	Randomized clinical trial, open-label, multicenter	277 adult patients with moderate-to-severe ARDS within 1 week of symptoms	Dexamethasone 20 mg IV once daily from day 1–5, then 10 mg once daily from day 6–10	• Improved number of ventilator-free days at day 28 (p < .0001) • Reduced all-cause mortality at day 60 (p = .0047) • Reduced ICU mortality (p = .0166)

LIS, lung injury score; MODS, multiple organ dysfunction syndrome.

showed mortality benefit in patients given corticosteroids in the setting of septic shock.[36] This double-blind trial randomized 151 patients to receive hydrocortisone 50 mg IV every 6 hours with fludrocortisone 50 mcg by mouth daily and 149 patients to receive placebo. The primary outcome of 28-day survival was found to be significantly lower in adrenally insufficient patients (odds ratio [OR] 0.54; 95% CI, 0.31–0.97). This was further stratified in the 2018 APROCCHSS trial, which used the same treatment arms against placebo to investigate 90-day all-cause mortality in 1241 patients with septic shock.[37] Compared to placebo, mortality was reduced in the group receiving hydrocortisone-plus-fludrocortisone therapy (RR 0.88; 95% CI, 0.78–0.99). These two studies were the only landmark trials to show statistically significant mortality benefits with the use of corticosteroids.

Contrary to these, other landmark trials found no statistically significant benefits in regards to mortality, but faster resolution of septic shock was achieved with corticosteroid use. The 2018 ADRENAL trial was a randomized control trial to determine whether administration of hydrocortisone 200 mg IV continuously resulted in a lower 90-day mortality in comparison to a placebo.[38] Although no mortality benefits were seen (OR 0.95; 95% CI, 0.82–1.10), patients had shorter time to resolution of shock (hazard ratio [HR] 1.32; 95% CI, 1.05–1.22). This was further stratified by the APROCCHSS trial, which saw shorter time in weaning from mechanical ventilation and vasopressors.[37] In addition, the CORTICUS trial and a systematic review failed to show a mortality benefit with corticosteroid therapy.[39,40] Other recent systematic reviews and meta-analyses suggest corticosteroid use is associated with reduced mortality.[41,42] While the evidence behind the use of corticosteroids in mortality vary, the proposed benefits in resolution of septic shock allow a compelling argument in the continuation of this practice. With manageable side effects, corticosteroids should be considered in the setting of septic shock.

Corticosteroids for COVID-19

Early on in the pandemic, the potential benefits and harms of corticosteroid therapy in COVID-19 was controversial. A retrospective cohort study from March 2020 found reduced mortality (HR 0.38; 95% CI, 0.20–0.72) among a subgroup of 84 patients with COVID 19 and ARDS who were treated with methylprednisolone.[14] Given the observational nature of the evidence, several randomized clinical trials were conducted to evaluate the efficacy and safety of corticosteroids in COVID-19 (summarized in Table 2), leading to guideline recommendations for using corticosteroids to treat patients with COVID-19.

Dexamethasone

The RECOVERY trial released its preliminary findings on 16 June 2020.[43] This study enrolled 4321 hospitalized patients with COVID-19. Low-dose dexamethasone 6 mg oral or IV once daily for up to 10 days was given to 2104 patients. Compared to usual care alone, dexamethasone reduced 28-day all-cause mortality in patients requiring oxygen therapy or mechanical ventilation (RR 0.83; 95% CI, 0.75–0.93) with 36 patients needed to treat to avoid one death. The sub-group of patients receiving invasive mechanical ventilation had the greatest reduction in mortality (RR 0.64; 95% CI, 0.51–0.81) with a number needed to treat of 9. Reduction in mortality, however, was not seen in patients who did not require oxygen and there was a trend toward increased mortality in this group (RR 1.19; 95% CI, 0.91–1.55) with 3.8% numerically higher rate of death in dexamethasone group, but not statistically significant. In addition, dexamethasone was associated with a lower mortality compared with usual care alone in those with symptom duration > 7 days (RR 0.69; 95% CI, 0.59–0.80), but no significant difference in mortality was found in those with symptom duration of ≤ 7 days (RR 1.01; 95% CI,

Table 2: Summary of corticosteroid studies in patients with COVID-19.

Study reference	Study design	Patients	Intervention	Results
RECOVERY[43] (2020)	Randomized clinical trial, open-label, multicenter	4321 adult patients hospitalized with COVID-19	Dexamethasone 6 mg IV or oral once daily for up to 10 days	• Reduced all-cause mortality at day 28 ($p < .001$) • No mortality benefit in patients not receiving oxygen, with mortality numerically higher in this subgroup • Mortality benefit most pronounced in patients receiving invasive mechanical ventilation • Mortality benefit observed only in patients with symptom duration > 7 days • Reduced need for mechanical ventilation • Increased rate of hospital discharge
CoDEX[44] (2020)	Randomized clinical trial, open-label, multicenter	299 adult critically ill patients in the ICU with COVID-19	Dexamethasone 20 mg IV daily for days 1–5, then 10 mg IV daily for days 6–10	• Study was stopped early due to the results of RECOVERY trial • Improved number of ventilator-free days at day 28 ($p = .02$) • No significant difference in all-cause mortality at day 28 ($p = .31$)
Metcovid[45] (2020)	Randomized clinical trial, double-blind, placebo-controlled, single-center	393 adult patients hospitalized with COVID-19 requiring supplemental oxygen or invasive mechanical ventilation	Methylprednisolone 0.5 mg/kg IV twice daily for 5 days	• Study was stopped early due to the results of RECOVERY trial • No significant difference in 28-day mortality ($p = .629$) • Improved 28-day mortality in patients over 60 years of age ($p = .039$) • Numerically higher rate of mortality in patients under 60 years old, possibly due to early treatment
GLUCOCOVID[46] (2020)	Randomized clinical trial, open-label, multicenter	64 adult patients hospitalized with COVID-19 for at least 7 days of symptoms and requiring oxygen but not yet requiring intensive care or mechanical respiratory support	Methylprednisolone 40 mg IV twice daily for days 1–3, then 20 mg IV twice daily for days 4–6	• Study was stopped early due to the results of RECOVERY trial • No significant difference in 28-day mortality ($p = .482$) • No significant difference in rate of admission to ICU ($p = .880$) • No significant difference in need for invasive mechanical ventilation ($p = .798$)

(continued)

Table 2: (continued)

Study reference	Study design	Patients	Intervention	Results
Edalatifard et al.[47] (2020)	Randomized clinical trial, single-blind, multicenter	62 adult patients hospitalized with severe COVID-19 with SpO2 < 90% (not intubated at baseline), CRP > 10 mg/L, and IL-6 > 6 pg/mL	Methylprednisolone 250 mg IV daily for 3 days prior to intubation	• Significant improvement in survival ($p < .001$) • Improved clinical recovery ($p < .001$) • Reduced need for mechanical ventilation
REMAP-CAP-COVID-19[48] (2020)	Randomized clinical trial, open-label, multicenter	137 adult critically ill patients in the ICU with COVID-19 requiring respiratory or cardiovascular support	Hydrocortisone 50 mg IV every 6 h for 7 days (up to 28 days for shock-dependent patients)	• Study was stopped early due to the results of RECOVERY trial • Hydrocortisone use did not achieve superiority in regards to improvement in 21-day respiratory and organ support-free days
CAPE-COVID[49] (2020)	Randomized clinical trial, double-blind, placebo-controlled, multicenter	149 adult critically ill patients with COVID-19, excluding septic shock	Hydrocortisone 200 mg/day continuous IV infusion for days 1–7, then 100 mg/day for days 8–11, then 50 mg/day for days 12–14	• Study was stopped early due to the results of RECOVERY trial • No significant difference in treatment failure on day 21 ($p = .29$) • Numerically less treatment failure with hydrocortisone use • No significant difference in 21-day mortality ($p = .057$) • Numerically less mortality at 21 days with hydrocortisone use
Ranjbar et al.[50] (2021)	Randomized clinical trial, double-blind, active-controlled, single-center	86 adult hospitalized patients with moderate COVID-19	Methylprednisolone 2 mg/kg IV daily (tapered to half dosage every 5 days)	• No significant difference in mortality ($p = .08$) • Improved clinical status ($p = .001$) • Decreased need for mechanical ventilation ($p = .04$) • Reduced length of hospitalization ($p = .02$)
Ghanei et al.[51] (2021)	Randomized clinical trial, open-label, multicenter	110 patients over the age of 16 years, hospitalized with moderate-to-severe COVID-19	Prednisolone 25 mg daily (tapered to 5 mg per week after discharge for reduction of readmission)	• No significant difference in mortality ($p = .71$) • No significant difference in ICU admission ($p = .79$) • No significant difference in need for mechanical ventilation ($p = .57$) • Reduced length of hospitalization ($p = .03$)
COVID STEROID 2[39] (2021)	Randomized clinical trial, blinded, active-controlled, multicenter	971 adult hospitalized patients with severe COVID-19	Dexamethasone 12 mg IV daily up to 10 days	• No significant difference in number of days alive without life support at day 28 ($p = .07$) • No difference in 28-day mortality ($p = .10$) • No difference in 90-day mortality ($p = 0.09$)

0.87–1.17) with 1.6% numerically higher rate of death in dexamethasone group. After the release of the RECOVERY trial results, several ongoing RCTs assessing corticosteroid therapy in COVID-19 patients halted enrollment as dexamethasone became the standard of care for patients requiring oxygen therapy.

The CoDEX trial evaluated the efficacy of dexamethasone in addition to standard care compared to standard care alone in patients with moderate to severe ARDS due to COVID-19.[44] This open-label study enrolled 299 patients and randomly assigned 151 patients to receive dexamethasone (20 mg IV daily for 5 days, followed by 10 mg IV daily for five more days or until intensive care unit [ICU] discharge) and 148 patients to usual care alone. Higher dose of IV dexamethasone resulted in a statistically significant increase in number of days alive and free of mechanical ventilation over 28 days of follow-up (difference 2.26 days; 95% CI, 0.2–4.38). This finding was not statistically significant for subgroup of patients with symptom duration > 7 days (difference 1.41 days; 95% CI, −1.75–4.58). All-cause mortality at day 28 was a secondary outcome and there was a trend toward greater reduction of 28-day mortality with IV dexamethasone (HR 0.97; 95% CI, 0.72–1.31). The study was stopped early following the release of RECOVERY trial results; therefore, the study was underpowered to detect the effect of corticosteroids on mortality. There was no difference in adverse outcomes between the two groups, including new diagnosis of infection until day 28. Corticosteroid therapy did not seem to increase the need for insulin use for hyperglycemia, although numerically 2.7% more patients required insulin therapy. The dose of dexamethasone in CoDEX was higher than RECOVERY because of the benefits shown in DEXA-ARDS study in patients with ARDS.[32]

The COVID STEROID 2 trial evaluated the effect of 12 mg compared to 6 mg of dexamethasone in adult patients with severe COVID-19.39 This blinded study enrolled 971 patients and randomly assigned 491 patients to receive dexamethasone 12 mg IV daily and 480 patients to receive dexamethasone 6 mg IV daily up to 10 days. About 80% of patients were in the ICU but only about 20% were receiving invasive mechanical ventilation. There was no significant difference between the groups in the primary outcome of number of days alive without life support at day 28 (difference 1.3 days; 95% CI 0–2.6). Mortality rates at day 28 (RR 0.86; 95% CI 0.68–1.08) and day 90 (RR 0.87; 95% CI 0.70–1.07) were secondary outcomes and were not statistically significant between the groups, although there was nonsignificant trend in favor of high-dose group. Serious adverse reactions were similar between the two groups, including invasive fungal infections, bacterial infections, and gastrointestinal (GI) bleeding. Insulin use for hyperglycemia was not reported. The results of this study suggest that doses higher than dexamethasone 6 mg daily are unnecessary for treatment of COVID-19. However, the results may not be applicable to patients who develop ARDS.

Methylprednisolone

After the RECOVERY trial results were released, the question of whether the mortality benefit seen with dexamethasone can extend to other corticosteroids remains. Methylprednisolone has similar glucocorticoid effects as dexamethasone with extra mineralocorticoid activity. However, it likely has higher lung penetration compared to dexamethasone.[53] Metcovid evaluated the use of methylprednisolone for the treatment of COVID-19 in 393 hospitalized patients with clinical and/or radiological suspected COVID-19 with $SpO_2 \leq 94\%$ on room air, or the use of supplemental oxygen or invasive mechanical ventilation.[45] This trial randomized 194 patients to receive IV methylprednisolone 0.5 mg/kg twice daily for 5 days and 199 patients to receive placebo. For the primary outcome of 28-day mortality, there was no statistically significant difference between 5 days of methylprednisolone or placebo (HR 0.92; 95% CI, 0.67–1.28). However, a subgroup analysis found significantly lower 28-day mortality rate in patients over 60 years of age who received methylprednisolone compared to placebo (HR 0.63; 95% CI 0.41–0.98). The patients in this group also had higher CRP median values when compared to younger patients (81.3 [interquartile range {IQR} 67.5-149.8] vs 74.7 [IQR 53.3-89.1]; $p = .0028$), which reflects a more pronounced systemic inflammatory status. Moreover, there was a trend toward higher mortality in patients under 60 years old (HR 1.55; 95%CI, 0.93–2.60), which is hypothesized to be due to early use of corticosteroids in this subgroup. Overall, Metcovid may have been underpowered to detect a significant difference in mortality because it stopped prematurely on 16 June 2020. However, the results of the study suggest that methylprednisolone may benefit patients who are elderly or have more aggressive inflammatory responses.

The GLUCOCOVID trial evaluated methylprednisolone in patients with moderate to severe disease requiring oxygen but not yet requiring intensive care or mechanical respiratory support.[46] This study randomized 35 patients to receive methylprednisolone 40 mg IV twice daily for 3 days, then 20 mg IV twice daily for 3 days plus standard of care and 29 patients to receive standard of care alone. All patients had symptom duration of at least 7 days and evidence of systemic inflammatory response. This intention-to-treat (ITT) analysis included 64 patients and the per-protocol (PP) analysis included 58 patients. There was no statistically significant difference in the primary composite endpoint that included in-hospital all-cause mortality,

escalation to ICU admission, or progression of respiratory insufficiency (RR 0.68; CI 0.37–1.26). In the PP analysis that included 30 patients in the methylprednisolone group and 28 patients in the standard of care group, the primary composite endpoint showed a significant reduction in the methylprednisolone group (RR 0.42; 95% CI, 0.20–0.89), but it was not clear what component was the driver of benefit. There was no significant difference in 28-day mortality in either analysis. Although GLUCOCOVID did not reach target patient enrollment due to early termination of the study after the RECOVERY publication, the PP analysis suggests that methylprednisolone may be beneficial in patients who are not mechanically ventilated and are at risk of developing ARDS.

A small randomized controlled trial evaluated methylprednisolone pulse in hospitalized patients with severe COVID-19.[47] Patients were included if SpO2 < 90% on room air, CRP > 20 mg/L, and IL-6 > 6 pg/mL. The study randomized 34 patients to receive methylprednisolone 250 mg IV daily for 3 days prior to intubation and 28 patients to receive standard care alone. Patients in the methylprednisolone group had significantly improved survival (HR 0.29; CI 0.15–0.56) with three patients needed to treat to avoid one death. However, the study had a very small sample size and was conducted at two centers only with limited external validity. Overall safety profile was similar between the groups, although significantly more patients in the methylprednisolone group required insulin initiation or intensification for hyperglycemia. These results suggest that, similar to dexamethasone, methylprednisolone may be beneficial in hospitalized patients with severe COVID-19 who are not mechanically ventilated. Most recently, a small randomized clinical trial compared methylprednisolone to dexamethasone in hospitalized adult patients with COVID-19.[50] The study randomized 44 patients to receive methylprednisolone 2 mg/kg IV daily (tapered to half dosage every 5 days) and 42 patients to receive dexamethasone 6 mg daily for 10 days. While patients in the methylprednisolone group had better clinical status and decreased length of stay, the study found no statistically significant difference in mortality between the two groups, suggesting that neither therapy is preferred over the other. Nonetheless, this study had a limited sample size and was conducted at a single center, limiting its external validity. Further studies may be needed to determine if methylprednisolone has improved clinical efficacy over dexamethasone.

Hydrocortisone

Hydrocortisone has similar glucocorticoid effects as dexamethasone with extra mineralocorticoid activity, which is used in management of septic shock. The REMAP-CAP-COVID-19 clinical trial enrolled 384 patients with SARS-CoV-2 infection admitted to an ICU for respiratory or cardiovascular organ support due to severe COVID-19.[48] This study randomly assigned 137 patients to receive a fixed dose of hydrocortisone 50 mg IV every 6 h for 7 days, 146 shock-dependent patients to receive hydrocortisone 50 mg IV every 6 h while in shock for up to 28 days, and 108 patients to not receive hydrocortisone. Compared to no hydrocortisone use, neither fixed-dose hydrocortisone nor shock-dependent hydrocortisone use achieved superiority for the primary outcome of improvement in 21-day respiratory and organ support-free days. Although REMAP-CAP-COVID-19 was discontinued prematurely due to the results of RECOVERY trial, there was suggestive, but not statistically significant, benefit for hydrocortisone with 80–93% probability of superiority of hydrocortisone use to no hydrocortisone use. Notably, serious adverse events occurred more frequently in patients who received hydrocortisone, including two events of severe neuromyopathy and fungemia.

The CAPE-COVID clinical trial enrolled 149 critically ill patients with COVID-19, excluding those with septic shock.[49] This study randomly assigned 76 patients to receive low-dose hydrocortisone (200 mg/day continuous IV infusion for 7 days, then 100 mg/day for 4 days and 50 mg/day for 3 days for a total of 14 days) and 73 patients to receive placebo. The primary outcome of treatment failure at day 21, defined as death or persistent dependency on high-flow oxygen therapy or mechanical ventilation, was not significantly different between the groups (difference −8.6%; 95% CI, −24.9 to 7.7), although there was a nonsignificant trend in favor of hydrocortisone. For death at 21 days, there was a nonsignificant reduction in hydrocortisone group (difference −12.7%; 95% CI, −25.7 to 0.3), which is similar to the decreased mortality seen in day 21 of dexamethasone in the subgroup of mechanically ventilated patients from the RECOVERY trial. No serious adverse events were associated with hydrocortisone use. CAPE-COVID was likely underpowered to find a statistically significant and clinically important difference in outcomes, potentially skewing the preliminary results. The doses of hydrocortisone used in both trials had similar glucocorticoid potency as trials including dexamethasone (200 mg vs. 6 mg, respectively). With trends toward improved respiratory support and potential reduced mortality in mechanically ventilated patients, hydrocortisone may be a viable option in the treatment of COVID-19.

Prednisolone

Similar to methylprednisolone, prednisolone has similar glucocorticoid effects as dexamethasone with extra mineralocorticoid activity. Only a small randomized clinical trial has evaluated the efficacy of prednisolone in patients over the age of 16 years hospitalized with COVID-19.[51]

This multicenter study randomized 51 patients to receive prednisolone 25 mg daily (gradually tapered to 5 mg per week after discharge for reduction of readmission) and 59 patients to receive standard care alone. It is not clear how long patients received weekly prednisolone after discharge so no conclusion can be drawn regarding readmission. The study did not find a statistically significant difference in mortality between the groups, although there was a non-significant trend in favor of prednisolone. This study was stopped early in August of 2020 and is likely underpowered to find a significant difference between the groups. There were no significant differences in adverse events between the groups. The results of this study suggest that, similar to methylprednisolone and hydrocortisone, prednisolone may be a viable option in the treatment of COVID-19 for patients who do not have access to dexamethasone.

Meta-analysis of systemic corticosteroids for COVID-19

During the COVID-19 pandemic, rigorous data regarding systemic corticosteroids were released. The World Health Organization (WHO) provided a prospective meta-analysis in order to estimate the association between corticosteroids and mortality in the setting of COVID-19.[54] A total of 1703 critically ill patients with COVID-19 were included in this meta-analysis with low heterogeneity (I^2 = 16%) to assess all-cause mortality at 28 days after randomization. Mortality rate was 32.7% with corticosteroids compared to 41.5% with usual care (OR 0.66, 95% CI, 0.53–0.82) with 12 patients needed to treat to avoid one death. In a subgroup analysis, the results were significant for patients having symptoms > 7 days, but there was no signal for harm for those who had symptoms for ≤ 7 days. Dexamethasone was shown to decrease mortality significantly but not its counterparts. However, as trials were discontinued prematurely, meta-regression analyses showed similar association of hydrocortisone and methylprednisolone to mortality as dexamethasone. These results have been replicated in other systematic reviews and meta-analyses.[55–57]

Potential harms of corticosteroids

Early treatment of COVID-19

A concern regarding the use of corticosteroids in COVID-19 is the optimal time to initiate corticosteroid therapy, given that early administration may suppress immune activation and reduce viral clearance.[58] Earlier studies evaluating corticosteroid use in SARS and MERS suggested that use of corticosteroids, especially when initiated early within 7 days of illness, is associated with delayed viral clearance and emergence of secondary infections.[22,59,60] In the RECOVERY trial, the mortality benefit of corticosteroid therapy was only evident in those with symptom duration of 7 days or more.[43] In patients with symptom duration of less than 7 days, there was a signal for 1.6% numerically higher rate of death in dexamethasone group.[43] There was also no evidence to support dexamethasone in patients who were not receiving respiratory support. In the Metcovid trial, a trend toward increased mortality was seen in patients under 60 years of age, which had lower CRP levels, indicating lower inflammatory status and lower severity of disease.[45] Harm seen with methylprednisolone in these patients is likely due to increasing the viral load from early administration of corticosteroids in COVID-19.

Treatment of influenza pneumonia

The 2018 IDSA guidelines for management of seasonal influenza do not recommend corticosteroid adjunctive therapy for the treatment of suspected or confirmed seasonal influenza, influenza-associated pneumonia, respiratory failure, or ARDS, unless clinically indicated for other reasons (e.g., exacerbation of asthma, COPD, adrenal insufficiency, or refractory septic shock).[61] There is no randomized clinical trial evaluating the efficacy and safety of corticosteroids in patients with influenza. Meta-analyses of observational studies have shown that systemic corticosteroid use is associated with increased mortality in patients with influenza.[62–66] A meta-analysis of 10 observational studies (1497 patients) with moderate heterogeneity (I^2 = 40%) found significantly higher odds of mortality (OR 2.12; 95% CI, 1.36–3.29) with corticosteroid treatment of presumed influenza-associated complications (majority of patients were hospitalized).[62] The results were consistent when the analysis was limited to four homogeneous (I^2 = 0%) studies (OR 2.82; 95% CI, 1.61–4.92). The corticosteroid regimens were not reported in all studies. Similar results were found in a Cochrane review of 30 studies (99,224 patients) with high heterogeneity (I^2 = 68%) showing that corticosteroids were associated with increased mortality (OR 3.90; 95% CI 2.31–6.60).[67]

In addition to increased mortality, a meta-analysis of 19 studies (4916 patients) with significant heterogeneity (I^2 = 54%) showed that corticosteroid use in patients with influenza was associated with increased nosocomial co-infection (OR 3.16; 95% CI, 2.09–4.78).[64] In addition, meta-analysis of two studies with low heterogeneity (I^2 = 0%) showed increased length of mechanical ventilation and length of ICU stay with corticosteroid use.[64] Regimens used as well as the timing of corticosteroids were unknown. Other meta-analyses have also shown longer ICU stay and higher rate of secondary infections.[65,66] The timing of corticosteroid initiation and the dose may be significant because an observational study of 83 hospitalized patients

showed that early use of corticosteroids within 72 h of influenza-like illness onset (17 patients) was associated with increased risk of subsequent critical disease or death and for every 10 mg increase in corticosteroids, the OR was 1.3 (95% CI, 1.01–1.4).[68] A retrospective observational study using propensity score analysis suggested that there may be increased risk of mortality even if the corticosteroids are used within 7 days of hospitalization for influenza.[69] Another observational study of 2141 hospitalized patients with influenza showed that low-to-moderate-dose (25–150 mg/day methylprednisolone equivalent) was actually associated with lower mortality compared to no treatment (HR 0.64; 95% CI, 0.43–0.96).[70] However, high-dose corticosteroid therapy resulted in no difference in mortality but in the subgroup of patients with mild disease ($PaO_2/FiO_2 \geq 300$ mmHg) 60-day mortality was increased (HR 3.02; 95% CI, 1.06–8.58).

Lastly, multiple observational studies have shown that systemic corticosteroid use is associated with prolonged influenza viral shedding.[71–73] This may lead to emergence of antiviral resistance due to increased viral replication.[74] While rare, coinfection with SARS-CoV-2 and influenza can occur.[75] It is important to avoid early and high-dose corticosteroids in these patients and only treat them with corticosteroids once they require oxygen supplementation or mechanical ventilation. Outpatient treatment of such patients with oral corticosteroids could increase viral replication for both viruses, lead to secondary bacterial or invasive fungal coinfections, and potentially increase the risk of mortality.[76]

Adverse effects

While long-term use of corticosteroids is associated with many adverse effects (e.g., hyperglycemia, infections, gastric ulcer, osteoporosis, venous thromboembolism, and psychoses), the risk of short-term use is less understood.[77] Stress ulcers occur in response to severe physiological stress in critically ill patients, likely involving a decreased mucosal blood flow, allowing physiological factors to invoke ulceration.[78] The evidence is insufficient to conclude that corticosteroids are associated with GI bleeding or perforation.[79] The risk of bleeding due to the sole initiation of corticosteroids seems low in the critical care setting and concomitant gastric protection is unnecessary for patients whose only indication is the use of corticosteroids.[80] Hyperglycemia, present at the initiation of steroids, generates a need for large amounts of insulin in patients with diabetes, with insulin requirements gradually reduced as further glycemic control is reached. However, the effects of steroids are transient and reversible. As fluctuations in serum glucose levels have been associated with increased mortality and hospital stay, higher risk of infection, and poor wound healing, vigilance of glucose trends is critical.[81,82]

With steroids being widely used for treatment during the COVID-19 pandemic, its safety is being put to the test. In the various trials, there were no significant adverse effects solely attributed to the study treatment. For example, in CAPE COVID, three serious adverse events were reported (cerebral vasculitis, pulmonary embolism, abdominal hemorrhage).[46] However, there is insufficient evidence to support that steroids were the culprit as patients also had conflicting diagnoses such as pulmonary embolism, or therapeutic anticoagulation. To further support this, nosocomial infections were seen in 37% in the hydrocortisone arm and 41% in the placebo arm (HR 0.81; 95% CI, 0.49–1.35). Assessing the RECOVERY trial, four serious adverse events were deemed by investigators as related to dexamethasone: hyperglycemia, GI hemorrhage, and psychosis. Although rates of adverse events seem relatively low, potential side effects should be assessed in regards to improving patient outcomes.

Discussion

Relevance to patient care and clinical practice

Rapid transmission of SARS-CoV-2 has resulted in a large number of patients with severe COVID-19 and its complications, requiring urgent treatment and prevention measures. Corticosteroids have become the standard of care in patients with COVID-19 requiring oxygen supplementation or respiratory support to decrease the risk of mortality. Early treatment of patients with COVID-19 who do not require oxygen supplementation or respiratory support (the first week of disease course) may be harmful and is associated with delayed viral clearance and increased risk of mortality. Low-dose corticosteroids (e.g., dexamethasone 6 mg/day, methylprednisolone 32 mg/day, or prednisone 40 mg/day) given at least 7 days after symptom onset for up to 10 days can reduce the risk of mortality in patients requiring oxygen supplementation or respiratory support. Patients who develop ARDS, typically 8–12 days after COVID-19 symptom onset, may benefit from higher doses (e.g., dexamethasone 20 mg daily for 5 days, followed by 10 mg daily for five more days) and treatment should be started within 7 days of ARDS onset and continued for at least 7 days. These findings assist clinicians in selecting appropriate patients who will benefit from systemic corticosteroid treatment and improving patient safety by eliminating inappropriate use of systemic corticosteroid in patients who are at risk of harm.

Limitations

As a narrative review, this article selected studies to describe a problem of interest to clinicians and patients. Our aim was to emphasize the potential harms of using

corticosteroids inappropriately and helping clinicians identify the time window where patients are most likely to benefit from use of systemic corticosteroids. While we performed a comprehensive search of the literature using three databases, we did not perform a systematic review with predetermined research questions. We relied on articles published in the English language, which can potentially lead to selection bias; however, we screened English abstracts of articles published in other languages to identify any studies that could potentially influence our conclusions. We used our clinical judgment to include or exclude studies rather than pre-defined inclusion and exclusion protocol. We also did not grade the quality of the evidence, although we discussed limitations of the included studies.

Conclusion

Complications of severe COVID-19 (e.g., pneumonia and ARDS) involve inflammatory cytokine storm in the late phase of the disease course. Systemic corticosteroids are widely available and inexpensive. There are pharmacokinetic and pharmacologic differences between various corticosteroids. Dexamethasone at a dose of 6 mg once daily up to 10 days is the preferred regimen to reduce the risk of mortality in COVID-19 patients requiring oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), given the lack of proven efficacy for other corticosteroids. However, if dexamethasone is not available, other corticosteroids may be substituted at equivalent doses because the mortality benefit is likely to be a class effect given the fact that other randomized clinical trials evaluating other corticosteroids were underpowered because they stopped early as a result of RECOVERY trial findings. It is very likely that the benefit is due to glucocorticoid rather than mineralocorticoid effects, since dexamethasone lacks mineralocorticoid activity, hence fludrocortisone is not recommended for this use. Higher doses of corticosteroids may be beneficial in patients who develop ARDS. In the absence of other indications, it is important to avoid corticosteroids early in the disease course when patients do not require oxygen support because of potential harms and lack of benefits.

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