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Do Corticosteroids Reduce Mortality or Progression to Severe Disease for Non-Oxygen Requiring Patients Infected With COVID-19?

TAKE-HOME MESSAGE

In patients infected with COVID-19 not requiring supplemental oxygen, systemic corticosteroids are associated with a small increase in mortality and progression to severe disease.

METHODS

DATA SOURCES

Two independent investigators searched PubMed, Embase, Web of Science, and medRxiv databases from December 2019 to May 2021 using the terms COVID-19 (or synonyms) AND corticosteroids (or synonyms) OR dexamethasone OR methylprednisone OR hydrocortisone. The authors also examined the relevant article and related citation lists from PubMed. They did not restrict by country or publication language; however, they also did not report searching gray literature. The authors performed the search in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.¹

STUDY SELECTION

Two independent investigators selected randomized controlled trials and prospective or retrospective observational studies that used propensity score matching. They included studies evaluating the effectiveness of systemic corticosteroids in COVID-19 patients who did not require oxygen at the time of

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Sahu AK, Mathew R, Bhat R, et al. Steroids use in non-oxygen requiring COVID-19 patients: a systematic review and meta-analysis. *QJM*. 2021;114:455-463.**

Results

Select outcome measures for corticosteroids versus no corticosteroids.

Outcome	No. of Studies*	Corticosteroids		OR (95% CI)
		Yes, n (%)	No, n (%)	
Mortality	2 RCT, 1 PSM	91/586 (15.5)	145/1131 (12.8)	1.35 (1.01, 1.79)
Progression to severe disease	2 PSM	11/90 (12.2)	2/90 (2.2)	5.97 (1.27, 27.99)

CI, confidence interval; OR, odds ratios; PSM, propensity score matching; RCT, randomized controlled trial.

*Although the review included 7 studies in total, not all evaluated mortality or progression to severe disease.

The authors screened 2,990 studies and reviewed 145 full-text articles. After exclusions, they included 7 studies: 4 randomized controlled trials and 3 retrospective propensity score matching studies. These studies included 2,214 laboratory-confirmed COVID-19 patients not requiring supplemental oxygen, 833 receiving systemic corticosteroid treatment, and 1,381 without.

Although 6 of the 7 studies examined methylprednisolone,⁶⁻¹¹ the study that contributed the most patients to the meta-analysis used a 6 mg/day dose of oral or intravenous dexamethasone for 10 days.¹²

Systemic corticosteroid administration was associated with increased mortality and progression to severe disease (Table). In

enrollment or exposure. The authors examined the following outcomes: mortality, progression to severe disease, fever duration, viral clearance, and hospital length of stay. They excluded case reports, letters, editorials, and reviews. They also excluded studies evaluating inhaled or intranasal corticosteroids. A third reviewer resolved discrepancies.

DATA EXTRACTION AND SYNTHESIS

The authors reviewed studies using the National Health Commission of China or World Health Organization definitions for mild or moderate COVID-19.^{2,3} A single reviewer extracted the data, and a second reviewer verified the data independently. They assessed the risk of bias for randomized controlled trials using the Cochrane Risk of Bias tool⁴ and methodological quality for propensity score matching observational studies using the Risk of Bias Assessment Tool for Non-randomized Studies.⁵ Two authors performed the quality assessment separately, with disagreements addressed by consensus in the presence of a third reviewer. They calculated pooled odds ratios using a random-effects model and estimated heterogeneity between studies with I^2 statistics.

In addition, systemic corticosteroid administration was associated with a longer duration of fever (standardized mean difference, 0.46; 95% confidence interval (CI), 0.15 to 0.76), a longer hospital length of stay (0.83; 95% CI, 0.61 to 1.05), and a shorter duration of viral clearance (0.20; 95% CI, 0.04 to 0.36).

Commentary

Not all patients with COVID-19 benefit from systemic corticosteroids. Systemic corticosteroids lower the 28-day all-cause mortality in critically ill COVID-19 patients who require supplemental oxygen.¹³ However, a mortality benefit has not been observed in those who do not require supplemental oxygenation.^{6,7,12} Furthermore, this review suggests that systemic corticosteroids are harmful in this nonhypoxemic cohort of COVID-19 patients, associated with higher mortality and progression to severe disease.¹⁴ Although uncommon with COVID-19,¹⁵ the authors suggest that corticosteroids may increase the risk of secondary bacterial infections.

However, this study has several limitations. First, this review excluded inhaled corticosteroids, and the route of administration may be significant. Inhaled budesonide has been shown to reduce recovery time^{16,17} and the need for urgent medical care¹⁶ among nonhospitalized COVID-19 patients. However, this recovery time benefit is not consistent among other inhaled corticosteroids, particularly ciclesonide.^{18,19}

Additionally, despite a large number of patients, this meta-analysis includes a small number of studies, and all the studies had either a high or unclear risk of bias, which might compromise the validity of the results. Furthermore, the meta-analysis included propensity score matching observational studies, making the results susceptible to confounding. Next, the review does not address COVID-19 patients

with concurrent asthma or chronic obstructive pulmonary disease exacerbations in whom systemic corticosteroids remain indicated despite normoxia.^{20,21} Also, only 3 studies explicitly excluded patients on chronic systemic corticosteroids.^{6,8,9} Chronic systemic corticosteroid use is a risk factor for severe COVID-19 infection in, for example, asthma and chronic liver disease patients^{22,23}; therefore, possible selection of these high-risk patients into the corticosteroid groups in the propensity score matching studies could have biased the results against corticosteroids. Lastly, the authors excluded studies from their analysis in which no patients died or progressed to severe disease in either treatment group. This exclusion may have introduced some selection bias where only studies with sicker patients were assessed, and sicker patients may have been more likely to get corticosteroids in the propensity score matching studies, making the corticosteroid group appear worse. In addition, the pooled mortality in this review was 13.7%, which is higher than the 1.2% to 7.0% overall COVID-19 mortality found in other studies.²⁴⁻²⁷ Therefore, illness severity may have confounded the results. Nevertheless, the a priori choice of mortality as an end point in these less critically ill patients with COVID-19 infections is less logical than in sicker cohorts.^{13,28}

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