1-1-2022

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Recommended Citation

Joshi S, Smith Z, Soman S, Jain S, Yako A, Hojeij M, Massoud L, Alsaadi A, Williams J, Kenney R, Miller J, Alangaden G, and Ramesh M. Low- Versus High-Dose Methylprednisolone in Adult Patients With Coronavirus Disease 2019: Less Is More. Open Forum Infect Dis 2022; 9(1):ofab619.

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Open Forum Infectious Diseases

MAJOR ARTICLE

Low- Versus High-Dose Methylprednisolone in Adult Patients With Coronavirus Disease 2019: Less Is More

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Background. Corticosteroids use in severe coronavirus disease 2019 (COVID-19) improves survival; however, the optimal dose is not established. We aim to evaluate clinical outcomes in patients with severe COVID-19 receiving high-dose corticosteroids (HDC) versus low-dose corticosteroids (LDC).

Methods. This was a quasi-experimental study conducted at a large, quaternary care center in Michigan. A corticosteroid dose change was implemented in the standardized institutional treatment protocol on November 17, 2020. All patients admitted with severe COVID-19 that received corticosteroids were included. Consecutive patients in the HDC group (September 1 to November 15, 2020) were compared to the LDC group (November 30, 2020 to January 20, 2021). High-dose corticosteroids was defined as 80 mg of methylprednisolone daily in 2 divided doses, and LDC was defined as 32–40 mg of methylprednisolone daily in 2 divided doses. The primary outcome was all-cause 28-day mortality. Secondary outcomes included progression to mechanical ventilation, hospital length of stay (LOS), discharge on supplemental oxygen, and corticosteroid-associated adverse events.

Results. Four-hundred seventy patients were included: 218 (46%) and 252 (54%) in the HDC and LDC groups, respectively. No difference was observed in 28-day mortality (14.5% vs 13.5%, $P = .712$). This finding remained intact when controlling for additional variables (odds ratio, 0.947; confidence interval, 0.515–1.742; $P = .861$). Median hospital LOS was 6 and 5 days in the HDC and LDC groups, respectively ($P < .001$). No differences were noted in any of the other secondary outcomes.

Conclusions. Low-dose methylprednisolone had comparable outcomes including mortality to high-dose methylprednisolone for the treatment of severe COVID-19.

Keywords. 28-day mortality; COVID-19; hypoxia; methylprednisolone; SARS-CoV-2.

The use of corticosteroids in hospitalized hypoxic patients with coronavirus disease 2019 (COVID-19) has become the standard of care based on improvement in clinical outcomes from a robust body of literature [1–5]. It is well known that pharmacodynamic differences exist between corticosteroids, and their effects vary when different doses are used [6].

Early reports from China described a mortality benefit with methylprednisolone in patients with COVID-19 and acute respiratory distress syndrome (ARDS) [7]. Based on this information, in March 2020, our center initiated a protocol using 80 mg (1 mg per kg) of methylprednisolone daily for patients with severe COVID-19 [8]. Methylprednisolone was selected as the corticosteroid due to prior trial data in ARDS, favorable pharmacokinetic properties, and pharmacogenomic data suggesting it may be the optimal corticosteroid in COVID-19 [9–12]. After publication of randomized clinical trials in the subsequent months, evidence-based guidelines (such as the National Institutes of Health treatment guidelines) recommended adopting trial regimens or administering an alternate corticosteroid at an equivalent glucocorticoid dose (Supplement Table 1) [1]. Based on these recommendations, in November 2020, our center modified treatment protocol to a lower dose of 32–40 mg (0.5 mg per kg) of methylprednisolone daily.

Although corticosteroids improve outcomes in severe COVID-19, the optimal dose is undefined. Methylprednisolone has been used in varying doses ranging from 40 to 500 mg per day [4, 13–15]. This study compares outcomes, including 28-day mortality, of high- versus low-dose methylprednisolone within our standardized institutional treatment protocol in those with severe COVID-19.

METHODS

Patient Consent Statement

This study does not include factors necessitating patient consent because it is based on an observational cohort (pre- and

Received 14 September 2021; editorial decision 3 December 2021; accepted 7 December 2021; published online 8 December 2021.

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofab619

poststudy design). The design of the work has been approved by the institutional review board of the Henry Ford Health System.

Study Population

Patients were eligible for inclusion in this study if they were admitted to Henry Ford Hospital (HFH), age >18 years, had laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and had severe COVID-19, defined as hypoxia requiring supplemental oxygen [16]. Patients who were excluded from this study were those who died within 24 hours, received less than 48 hours of corticosteroids, and lacked a 28-day follow up. A confirmed case of COVID-19 was defined as having a positive reverse-transcription polymerase chain reaction assay for SARS-CoV-2 by nasopharyngeal sample.

Study Design

This was a single-center, quasi-experimental study at HFH, an 877-bed quaternary care hospital in Detroit, Michigan. We experienced a surge of COVID-19 admissions from September 2020 to February 2021. The treatment protocols for severe COVID-19 remained unchanged during the surge, except for a reduction in the dose of methylprednisolone initiated on November 17, 2020 (see below). Consecutive patients that met study criteria were included in the high-dose corticosteroid (HDC) group from September 1, 2020 to November 15, 2020 and were compared with consecutive patients in the low-dose corticosteroid (LDC) group from November 30, 2020 to January 20, 2021. A 2-week washout period was completed from November 17 to November 30, 2020.

Corticosteroid Groups

High-dose corticosteroid was defined as 80 mg of methylprednisolone daily in 2 divided doses, intravenous or oral, for up to 7 days. Low-dose corticosteroid was defined as methylprednisolone, 40 mg intravenous or 32 mg oral, in 2 divided doses for up to 7 days. Dosing was based on availability of corticosteroid formulation; methylprednisolone was available in 16-mg tablets and 20-mg intravenous formulation. Choice of oral versus intravenous corticosteroid administration was at the discretion of the primary team. Corticosteroids were discontinued upon resolution of symptoms.

Standard of Care

During this study period, standard of care was composed of supplemental oxygen (nasal cannula, high-flow nasal cannula, noninvasive positive pressure ventilation, or mechanical ventilation), remdesivir, and corticosteroid administration. Other therapies including antibiotics, tocilizumab, vasopressor support, renal replacement therapy, and venous thromboembolism prophylaxis were at the discretion of the primary team.

Data Collection

Data were collected from HFH's electronic medical record. All information was entered in a standardized case report form. Demographic, clinical, laboratory, treatment, and outcome data were obtained.

Primary Outcome

The primary outcome was all-cause, 28-day mortality. Twenty-eight-day mortality data were available through updated medical records, and all patients were cross-referenced with data from the Michigan Health Information Network [17].

Secondary Outcome

Secondary outcomes were progression to mechanical ventilation, length of hospital stay, discharge on supplemental oxygen, and corticosteroid-associated adverse events (bacteremia, hospital-acquired pneumonia/ventilator-associated pneumonia, candidemia, and hyperglycemia).

Healthcare-associated infections were defined by standard National Healthcare Safety Network criteria [18]. Hyperglycemia was defined as glucose greater than 200 mg/dL and with additional insulin use.

Statistical Analysis

We reported continuous variables as median and interquartile range (IQR) and performed comparisons using the Mann-Whitney *U* test or *t* test, as appropriate. Categorical data were reported as number and percentage (no., %), and comparisons were performed using the χ^2 test or Fisher's exact test, as appropriate. No imputation was made for missing data points. A 2-sided $\alpha < .05$ was considered statistically significant. We performed bivariable and a priori multivariable logistic regression analysis to test the association between 28-day mortality and exposure to the HDC or LDC protocol. Covariates in the bivariable analysis with a $P < .1$ and clinical rationale were included in the multivariable regression model that was restricted to an event-to-variable ratio of 10:1. We constructed a Kaplan-Meier curve that plotted the proportion of patients who survived over 28 day based on their exposure to the HDC or LDC protocol (Supplemental Figure 1). Statistical analysis was performed using IBM SPSS version 25 (Chicago, IL) and SAS 9.4 (Cary, NC).

RESULTS

During the study period, there were 784 patients admitted who were diagnosed with COVID-19. Of these, 470 patients had severe COVID-19 and met inclusion criteria; 218 patients (46%) in the HDC group and 252 patients (54%) in the LDC group. All patients within both study groups received 48 hours or more of corticosteroid therapy. The median age of the HDC and LDC group was 63 (IQR, 52–73) and 65 (IQR, 53–75) years, respectively. Black patients comprised 45.0% of the HDC group and

48.4% of the LDC group. Patient characteristics were comparable, apart from cardiovascular disease (Table 1). Severity of illness at presentation was also similar.

Median time from diagnosis to corticosteroid administration was 1 day for both groups. Oral corticosteroids were used more than intravenous corticosteroids in the LDC group (82.9% and 23.8%) compared to the HDC group (61.0% and 57.3%). The median duration of corticosteroid treatment was 5 days in both study groups.

Twenty-eight-day mortality was comparable in both groups (14.5% vs 13.5%, $P = .712$) (Table 2). Multivariate analysis after adjusting for age >60, gender, race, cardiovascular disease, baseline intensive care unit status, antibiotic use, and tocilizumab use showed no difference among the HDC and LDC groups (odds ratio, 0.947; confidence interval, 0.515–1.742; $P = .861$).

Median duration of hospital length of stay was 6 days and 5 days in the HDC and LDC groups ($P < .001$). Other secondary outcomes including need for mechanical ventilation and supplemental oxygen upon discharge were similar. Corticosteroid-associated adverse events were comparable.

DISCUSSION

In a cohort of patients with severe COVID-19 treated with methylprednisolone, a reduction in dose did not impact 28-day mortality. Our mortality rates were lower than those reported in randomized trials done early in the pandemic and may reflect differences in study populations and improvement in supportive care over time [19–22]. No differences were observed in corticosteroid-associated adverse events between groups similar to previous reports with varying corticosteroid doses [3, 5]. Rates of hyperglycemia were similar to clinical trials that included comparable patients with diabetes [20].

Methylprednisolone doses greater than 1.36 mg per kg per day have been associated with worse outcomes [13]. Both

Table 1. Patient Characteristics of the High-Dose and Low-Dose Corticosteroid Groups

Characteristics	Total (n = 470)	HDC (n = 218)	LDC (n = 252)	*P* Value
Demographics				
Median age (IQR), years	64 (53–74)	63 (52–73)	65 (53–75)	.295
Male sex, no. (%)	245 (52.1%)	110 (50.5%)	135 (53.6%)	.518
Race, no. (%)				
Black	220 (46.8%)	98 (45.0%)	122 (48.4%)	.454
White	103 (21.9%)	53 (24.3%)	50 (19.8%)	.199
Other	147 (31.3%)	67 (30.7%)	80 (31.7%)	.886
Median BMI (IQR), kg/m^2	30.7 (26.3–36.2)	30.2 (26.2–35.7)	31 (26.6–37.1)	.395
Coexisting Conditions, No. (%)				
Cardiovascular disease	339 (72.2%)	140 (64.2%)	199 (79.0%)	<.001
Chronic kidney disease	103 (21.9%)	42 (19.3%)	61 (24.2%)	.197
Diabetes	195 (41.5%)	81 (37.2%)	114 (45.2%)	.076
Immunodeficiency	50 (10.6%)	20 (9.2%)	30 (11.9%)	.338
Lung disease	160 (34.0%)	65 (29.8%)	95 (37.7)	.072
Malignancy	61 (13/0%)	32 (14.7%)	29 (11.5%)	.308
Severity of Illness on Admission				
Median qSOFA in ED (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	.870
Direct admission to ICU from ED, no. (%)[a]	77 (16.4%)	41 (18.8%)	36 (14.3%)	.187
Mechanical ventilation in ED, no. (%)	10 (2.1%)	4 (1.8%)	6 (2.4%)	.688
Treatment				
Remdesivir, no. (%)	330 (70.2%)	147 (67.4%)	183 (72.6%)	.220
Antibiotic, no. (%)	193 (41.1%)	120 (55.0%)	73 (29.0%)	<.001
Tocilizumab, no. (%)	12 (2.6%)	12 (5.5%)	0 (0%)	<.001
Corticosteroids[b]	470 (100%)	218 (100%)	252 (100%)	
Median time from diagnosis to corticosteroid administration (IQR), days	1 (1–2)	1 (1–2)	1 (1–2)	.871
Oral corticosteroids, no (%)	342 (72.8%)	133 (61.0%)	209 (82.9%)	<.001
Intravenous corticosteroids, no (%)	185 (39.4%)	125 (57.3%)	60 (23.8%)	<.001
Median duration of corticosteroids (IQR), days	5 (3–7)	5 (3–7)	5 (3–6)	.072

Abbreviations: BMI, body mass index; ED, emergency department; HDC, high-dose corticosteroid; ICU, intensive care unit; IQR, interquartile range; LDC, low-dose corticosteroid; qSOFA, quick Sequential Organ Failure Assessment.

Definitions: lung disease = asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, interstitial lung disease, pulmonary hypertension; cardiovascular disease = coronary artery disease, hypertension.

[a]Admission to ICU = use of high-flow nasal cannula, noninvasive positive pressure ventilation, mechanical ventilation.

[b]Some patients received sequential intravenous followed by oral corticosteroids; 27 and 31 patients received dexamethasone or prednisone (methylprednisolone equivalents) in the HDC and LDC groups, respectively.

Table 2. Patient Outcomes

Outcomes	HDC (n = 218)	LDC (n = 252)	*P* Value
Primary Outcome			
28-day mortality, no. (%)	32 (14.7%)	29 (13.5%)	.712
Secondary Outcomes			
Mechanical ventilation, no. (%)	28 (12.8%)	19 (7.5%)	.056
Median hospital length of stay (IQR), days	6 (4–11)	5 (3–7)	<.001
Discharged on supplemental oxygen, no. (%)	36 (16.5%)	51 (20.2%)	.300
Adverse Events			
Bacteremia, no. (%)	7 (3.2%)	10 (4.0%)	.661
Candidemia, no. (%)	4 (1.8%)	1 (0.4%)	.130
HAP/VAP, no. (%)	18 (8.3%)	18 (7.1%)	.651
Hyperglycemia, no. (%)	93 (42.7%)	112 (44.4%)	.697

Abbreviations: HAP, hospital-acquired pneumonia; HDC, high-dose corticosteroid; IQR, interquartile range; LDC, low-dose corticosteroid; VAP, ventilator-associated pneumonia.

groups in the current study received a lower dose than this threshold. Without evidence of superior efficacy with high-dose methylprednisolone, it seems prudent to use the minimal effective dose until more data are available [23].

Dexamethasone, hydrocortisone, and methylprednisolone have been studied in COVID-19 clinical trials [3–5]. The largest trial to date that first reported the benefits of corticosteroids in COVID-19 used a regimen of 6 mg of dexamethasone daily for up to 10 days [19]. Many guidelines adopted this trial regimen as the preferred corticosteroid regimen for COVID-19. If an alternate corticosteroid is used, it is recommended to provide a daily dose equivalent to 6 mg of dexamethasone [1]. However, limited data from smaller trials have reported that methylprednisolone may be the preferred corticosteroid when compared with dexamethasone, but the total corticosteroid dose equivalency between the 2 agents has varied [24, 25]. These preliminary findings support a pharmacogenomic analysis suggesting that methylprednisolone may be the optimal corticosteroid [12]. Future research is warranted to identify whether corticosteroid agents selection may play a role in patient outcomes.

Most patients in the present study received oral methylprednisolone during their treatment course within 1 day of hospitalization for a median duration of 5 days. A majority of randomized clinical trials for COVID-19 used intravenous corticosteroids [3]. Our finding that oral corticosteroids are efficacious is consistent with previous literature [19]. Duration of corticosteroid use in randomized trials for COVID-19 ranged from 5 to 14 days [3]. The median duration of corticosteroids treatment in the present study was shorter by 2 days compared with trials that allowed for discontinuation of corticosteroid upon symptom resolution [19]. These findings highlight the importance of early initiation of oral methylprednisolone in severe COVID-19 and utilizing a short course when symptoms resolve.

The current study has limitations. A quasi-experimental study design was used due to the changes in methylprednisolone dosing in the early and later months of the pandemic. However, methylprednisolone usage in COVID-19 was consistent due to the use of a standardized institutional protocol with a clear time point of when methylprednisolone dosing was reduced. A wash out period of 2 weeks was used between study groups to allow clinicians to adjust to the new dosing. It is notable that the mortality rate in our present study remained similar to our earlier study in March 2020, which suggests a minimal effect of maturation bias [8]. Our results are limited in that they are from real-world clinical practice and unmeasured confounding cannot be ruled out.

CONCLUSIONS

In conclusion, an early, short course of low-dose oral methylprednisolone in hospitalized patients with severe COVID-19 had comparable outcomes to high-dose methylprednisolone. Further research is needed to clarify an optimal corticosteroid dose while the world continues to face threats of COVID-19 variants.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Financial support. This work was funded by an internal source (Division of Infectious Diseases, Henry Ford Hospital).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Acknowledgments

We acknowledge our patients and frontline healthcare workers during the coronavirus disease 2019 pandemic.

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