Corticosteroid Administration and Impaired Glycemic Control in Mechanically Ventilated COVID-19 Patients

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Abstract

Objective. Recent clinical trials confirmed the corticosteroid dexamethasone as an effective treatment for patients with COVID-19 requiring mechanical ventilation. However, limited attention has been given to potential adverse effects of corticosteroid therapy. The objective of this study was to determine the association between corticosteroid administration and impaired glycemic control among COVID-19 patients requiring mechanical ventilation and/or veno-venous extracorporeal membrane oxygenation. *Design.* Multicenter retrospective cohort study between March 9 and May 17, 2020. The primary outcome was days spent with at least 1 episode of blood glucose either >180 mg/dL or <80 mg/dL within the first 28 days of admission. *Setting.* Twelve hospitals in a United States health system. *Patients.* Adults diagnosed with COVID-19 requiring invasive mechanical ventilation and/or veno-venous extracorporeal membrane oxygenation. *Interventions.* None. *Measurements and Main Results.* We included 292 mechanically ventilated patients. We fitted a quantile regression model to assess the association between steroid administration ≥320 mg methylprednisolone (equivalent to 60 mg dexamethasone) and impaired glycemic control. Sixty-six patients (22.6%) died within 28 days of intensive care unit admission. Seventy-one patients (24.3%) received a cumulative dose of least 320 mg methylprednisolone equivalents. After adjustment for gender, history of diabetes mellitus, chronic liver disease, sequential organ failure assessment score on intensive care unit day 1, and length of stay, administration of ≥320 mg methylprednisolone equivalent was associated with 4 additional days spent with glucose either <80 mg/dL or >180 mg/dL (B = 4.00, 95% CI = 2.15-5.85, *P* < .001). *Conclusions.* In this cohort study of 292 mechanically ventilated COVID-19 patients, we found an association between corticosteroid administration and higher incidence of both hyperglycemia and hypoglycemia.

Keywords

COVID-19, mechanical ventilation, corticosteroids, dexamethasone, hypoglycemia, hyperglycemia, glycemic control

Highlights

- Dexamethasone has become widely used for mechanically ventilated COVID-19 patients.
- Limited attention has been given to adverse effects of corticosteroid therapy.
- Corticosteroids are associated with hyperglycemia and hypoglycemia related to insulin treatment in COVID-19.

Introduction

Hyperglycemia is common in critical illness, which is associated with increased mortality, and is potentially dangerous in all critically ill patients, including those with coronavirus disease 2019 (COVID-19).[1-3] Hyperglycemia appears to be an independent risk factor for admission to the intensive care unit (ICU) in COVID-19 patients.[4] The most common treatment for significant hyperglycemia in ICU patientsis an intravenous insulin infusion.[2] However,

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insulin administration carries the risk of hypoglycemia, which can lead to higher mortality in critically ill patients than hyperglycemia.[2,5]

The optimal glucose range for critically ill patients was previously a topic of great debate. Earlier studies suggested tight glucose control may improve morbidity and mortality for critically ill patients.[6,7] However, recent randomized trials showed that tight glucose control is associated with greater morbidity and mortality related to the development of iatrogenic hypoglycemia.[1,5,8] As a result, the American Association of Clinical Endocrinologists and the American Diabetes Association consensus statement from 2011 recommended initiating insulin therapy for glucose values >180 mg/dL and targeting a blood glucose value of 140 to 180 mg/dL for critically ill patients.[9] These targets have been incorporated into ICUs worldwide.

The randomized clinical trial from the Recovery Collaborative Group[10] demonstrated a significant reduction in mortality for patients with COVID-19 requiring mechanical ventilation who received the corticosteroid dexamethasone 6 mg daily for up to 10 days. These results provided new hope for an inexpensive and widely available therapeutic intervention to help the sickest patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[11] Several subsequent trials have validated the beneficial effects of corticosteroids in critically ill COVID-19 patients. These include the CoDEX,[12] CAPE COVID,[13] and REMAP-CAP[14] trials. A meta-analysis of 7 randomized clinical trials revealed corticosteroids decrease 28-day mortality in critically ill COVID-19 patients.[15] As a result, the use of dexamethasone for such patients was recently endorsed by several guideline panels, including the National Institutes of Health.[16]

While these findings are changing clinical practices worldwide, limited attention has been given to potential adverse effects of corticosteroid therapy, such as impaired glucose control.[17] Awareness of the risk of impaired glycemic control (including hyperglycemia and iatrogenic hypoglycemia, presumably due to insulin administered to treat steroid-induced hyperglycemia) is critical for the optimal care of severe COVID-19 patients receiving steroids. In this study, we hypothesized that the administration of corticosteroids would result in impaired glycemic control among COVID-19 patients requiring mechanical ventilation. To test this hypothesis, we performed an observational cohort study at a large health care system in the United States.

Materials and Methods

We obtained approval from the Institutional Review Board (Colorado Multiple Institutional Review Board #20-0677) on April 3, 2020, which included a waiver of informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.[18]

Design, and Setting

We sought to identify if the administration of systemic corticosteroids is associated with days spent with at least 1 episode of hyperglycemia (blood glucose >180 mg/dL) or hypoglycemia (<80 mg/dL) (primary outcome), 28-day mortality, duration of mechanical ventilation to day 28, and ventilator-free days to day 28 (secondary outcomes) in a cohort of COVID-19 patients requiring mechanical ventilation and/or veno-venous extracorporeal membrane oxygenation. This observational cohort study included 12 hospitals within a large United States health care system. We designed the study to incorporate both automated data collection and manual chart review from the electronic health record (EHR).

Participants, Covariates, and Outcomes

Patients with COVID-19 who required invasive mechanical ventilation and/or veno-venous extracorporeal membrane oxygenation and were admitted between March 9, 2020, and May 17, 2020, to 1 of the health systems' ICUs were eligible for inclusion in this study. Exclusion criteria were age <18 years old; administration of a corticosteroid during index hospital admission other than dexamethasone, methylprednisolone, hydrocortisone, or prednisone; and if patients or their proxies indicated that they objected to observational data collection for research (Figure 1). We excluded 6 of the 298 patients initially screened due to missing height or weight measurements for body mass index calculations.

We obtained patient characteristics from the EHR. These include baseline demographics, chronic comorbidities, components of the sequential organ failure assessment (SOFA) score, glucose levels, and administered medications—including insulin and corticosteroids (Table 1). We chose chronic comorbidities according to published guidelines from our group[19,20] and others,[21,22] based on relevant preexisting International Classifications of Diseases codes (ICD-10) information. We obtained ICD-10 codes from the EHR. Comorbidities included any history of cardiac disease, pulmonary disease, hypertension, diabetes mellitus, renal disease, liver disease, and solid malignancies.[19,20] We calculated SOFA scores within the first 8 hours of ICU admission. We obtained initial platelet count, first recorded Glasgow Coma Scale score, initial creatinine, initial bilirubin, and lowest mean arterial pressure or highest dose of vasoactive agents from the EHR.[19,20,23] All blood glucose values measured during the first 28 days of the index admission were obtained. We assessed 28-day mortality by collecting the date of death recorded in the
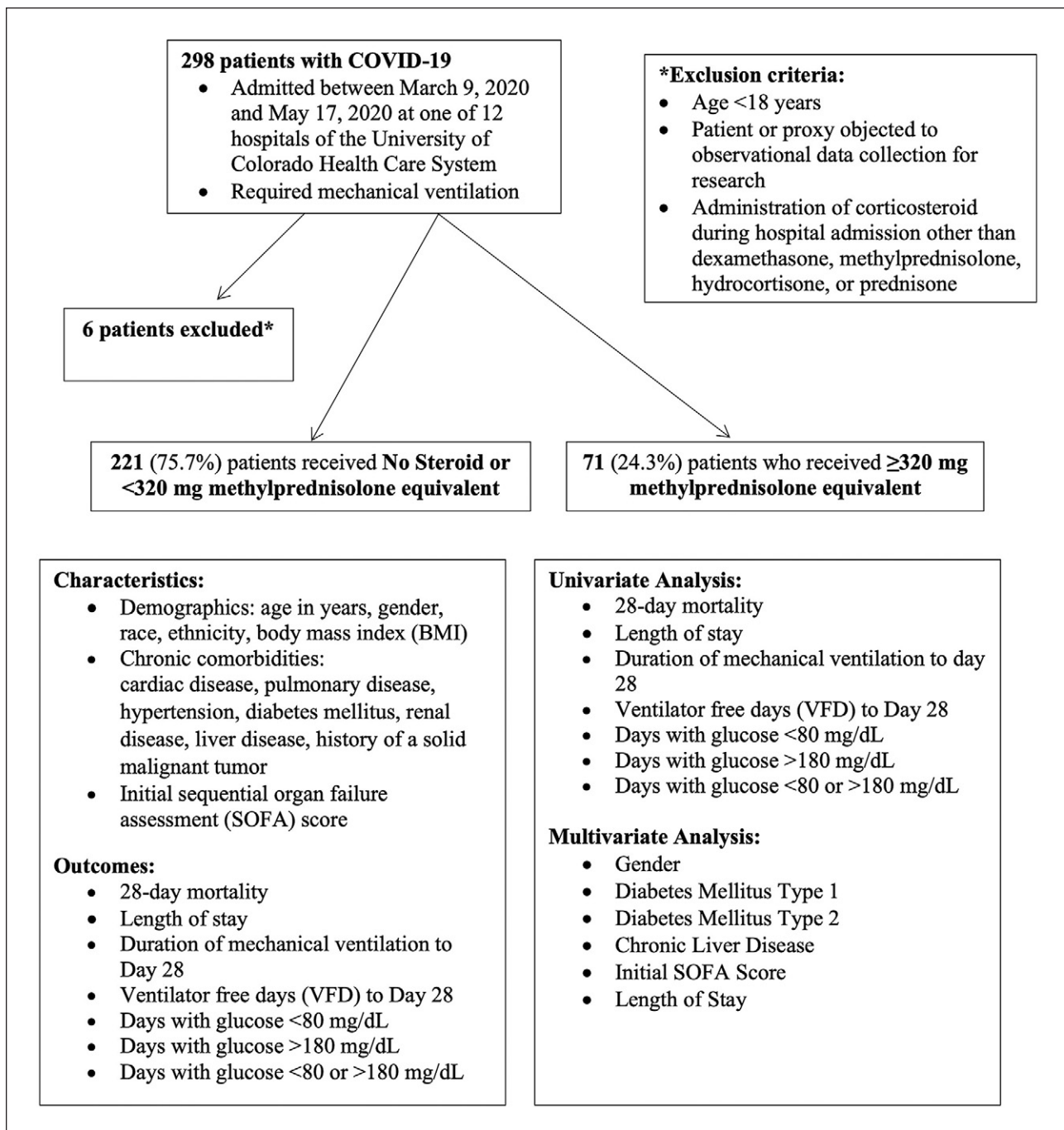
Figure 1. Flow diagram of study cohort.

EHR if this occurred within 28 days of initial ICU admission. We obtained duration of mechanical ventilation during the first 28 days of admission via chart review.[19,20]

Following published literature,[24,25] days were counted toward invasive mechanical ventilation if any of the following conditions were met: (1) the patient was mechanically ventilated within the first 28 days of ICU admission (mechanical ventilation), (2) the patient was reintubated within 48 hours of attempted extubation (failure to extubate), (3) the patient had a tracheostomy and required noninvasive ventilation (mechanical ventilation), or (4) the patient had a tracheostomy and was unable to tolerate a lack of invasive/noninvasive ventilation for greater than 48 hours (failure to wean). Day 1 of mechanical ventilation was the day of ICU admission. This allows for a direct comparison of the time from ICU admission to extubation

Table 1. Patient Demographics and Comorbidities.[a]

Characteristic	Total (n = 292)	≥320 mg ME (n = 71)	No steroid or <320 mg ME (n = 221)	P
Age, years, median (IQR)	58 (48-68)	58 (52-68)	58 (47-69)	.30
Male gender, n (%)	189 (64.7)	54 (76.1)	135 (61.1)	.02
Race, n (%)				.06
White/Caucasian	102 (34.9)	28 (39.4)	74 (33.5)	
Black/African American	51 (17.5)	6 (8.5)	45 (20.4)	
Multiple races or other	139 (47.6)	37 (52.1)	102 (46.2)	
Ethnicity, n (%)				
Non-Hispanic	168 (57.5)	34 (47.9)	134 (60.1)	.07
Hispanic	124 (42.5)	37 (52.1)	87 (39.9)	
Comorbidities, n (%)				
Chronic cardiac disease	143 (49.0)	34 (47.9)	109 (49.3)	.89
Hypertension	194 (66.4)	48 (67.6)	146 (66.1)	.89
Chronic pulmonary disease	101 (34.6)	26 (36.6)	75 (33.9)	.67
Diabetes mellitus type 1	2 (0.7)	0 (0.0)	2 (0.9)	1.00
Diabetes mellitus type 2	142 (48.6)	34 (47.9)	108 (48.9)	.89
Chronic kidney disease	83 (28.4)	16 (22.5)	67 (30.3)	.23
Chronic liver disease	38 (13.0)	3 (4.2)	35 (15.8)	.01
History of solid malignant tumor	32 (11.0)	7 (9.6)	25 (11.3)	.83
Required insulin infusion, n (%)	91 (31.2)	26 (36.6)	65 (29.4)	.30
BMI, kg/m², median (IQR)	29 (26-35)	29 (26-33)	30 (26-36)	.27
SOFA score,[b] median (IQR)	7 (5-10)	7 (5-10)	7 (5-10)	.40
Days receiving any steroids, median (IQR)	0 (0-5)	9 (6-11)	0 (0-1)	n/a[c]

Abbreviations: n, number of subjects; ME, methylprednisolone equivalent; IQR, interquartile range; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; n/a, not applicable.

[a]For categorical variables, column percentages are in parentheses and *P* values are derived from Fisher's exact test. For the continuous variables age, BMI, and SOFA score, median and IQR are reported.

[b]SOFA score was calculated on intensive care unit admission.

[c]A *P* value was not calculated for this variable because the cohort was defined by steroid administration.

and the time from ICU admission to death. Patients who died within the first 28 days of admission received a count of 28 days of invasive mechanical ventilation, that is, 0 ventilator-free days.[19,20,24,25]

We obtained systemic corticosteroid administration, including date, duration of therapy, daily dose, and total dose via chart review. Steroid administration, timing, and dosing were at the sole discretion of the patient's ICU team. We calculated methylprednisolone equivalent doses for patients receiving any of the 4 previously described corticosteroids. The Recovery trial[10] used dexamethasone 6 mg daily for up to 10 days, which we chose to use as our reference dose. Based on the recommended dexamethasone dose (6 mg × 10 days) for treatment of COVID-19 pneumonia,[10] we dichotomized the total amount of any steroids a patient received as <320 or ≥320 mg methylprednisolone equivalents. We calculated these based on established conversion formulas: 6 mg dexamethasone × 10 days × 5.333 mg methylprednisolone per mg dexamethasone = 320 mg methylprednisolone.[26] Based on consensus guidelines from the American Association of Clinical Endocrinologists and American Diabetes Association,[9,27-29] impaired glucose control was quantified

as the number of days to day 28 with any blood glucose value either >180 mg/dL or <80 mg/dL. These days were counted from ICU admission, regardless of the timing of steroid administration.

Statistical Analysis

We used descriptive statistics to summarize results. These included median, interquartile range (IQR), counts, and percentages as appropriate. Since all continuous variables displayed nonnormal distribution by visual estimation as well as by Kolmogorov-Smirnov test, we compared these using Mann-Whitney *U* tests in the univariate analysis. We compared the secondary outcome 28-day mortality using Fisher's exact test. Next, we evaluated the association between receiving 320 mg or greater methylprednisolone equivalents and days spent with glucose <80 mg/dL or >180 mg/dL using quantile regression analysis. Gender, history of diabetes mellitus type 1 or 2, chronic liver disease, SOFA score on ICU day 1, and length of stay were chosen as covariates in the model based on statistical significance in the univariate analysis or relevance based on published literature.[5,30-32] The

Table 2. Univariate Analysis of Outcomes.

Outcome, median (IQR)	Total (n = 292)	≥320 mg ME (n = 71)	No steroid or <320 mg ME (n = 221)	P^a
Days with glucose <80 mg/dL	0 (0-2)	1 (0-2)	0 (0-2)	.048
Days with glucose >180 mg/dL	5 (1-15)	10 (3-16)	4 (0-13)	.002
Days with glucose <80 or >180 mg/dL	6 (2-17)	12 (4-18)	5 (1-14)	.002
28-day mortality, number (%)	66 (22.6)	16 (22.5)	50 (22.6)	1.00
Length of stay, days	21 (13-33)	25 (19-38)	20 (11-31)	.001
Duration of MV to day 28	18 (9-28)	28 (13-28)	15 (9-28)	.001
Ventilator-free days to day 28	10 (0-19)	0 (0-15)	13 (0-19)	.001

Abbreviations: IQR, interquartile range; n, number of subjects; ME, methylprednisolone equivalent; MV = mechanical ventilation.
[a]P values signify 2-sided P values from Fisher's exact test for 28-day mortality; and from Mann-Whitney *U* test for length of stay, duration of MV, ventilator-free days, and all 3 glucose variables.

reference groups for the binary independent variables used in the mode were women for gender and the absence of the respective condition for the others. We performed statistical analysis using the software program SPSS, Version 26 (IBM Corporation).

Results

A total of 292 mechanically ventilated patients, who tested positive for COVID-19,were included. For events occurring before April 3, we collected data retrospectively. We collected data prospectively for events occurring on or after April 3. Baseline demographics and patient comorbidities are summarized in Table 1. These include age in years, self-reported gender, body mass index in kg/m², race, and ethnicity. A total of 117 patients received any dose of systemic corticosteroids and 71 patients (60.7%) received ≥320 mg methylprednisolone equivalents. Of these patients 34 (47.9%) received their first dose of systemic corticosteroids within the first 7 days of ICU admission. The median time from ICU admission to first systemic corticosteroid administration was 8 days and ranged from day 1 to day 28. The median duration of corticosteroid administration for patients who received 320 mg or greater methylprednisolone equivalents was 9 days (IQR = 6-11; Table 1). Only 2 out of 292 patients received any dose of corticosteroids more than 28 days after ICU admission. Patients who received 320 mg or greater methylprednisolone equivalents were less likely to have chronic liver disease (4.2% vs 15.8% *P* = .01) and more likely to be male (76.1% vs 61.1%; *P* = .02). There were no other statistically significant differences in demographics and comorbidities.

The 139 patients who spent at least 1 day with a glucose <80 mg/dL spent a median of 2 days (IQR = 1-3) with hypoglycemia. The 223 patients who spent at least 1 day with a glucose >180 mg/dL spent a median of 8 days (IQR = 5-15)with hyperglycemia. A total of 247 patients spent at least 1 day with either hypoglycemia or hyperglycemia and 117 patients spent at least 1 day in both categories.
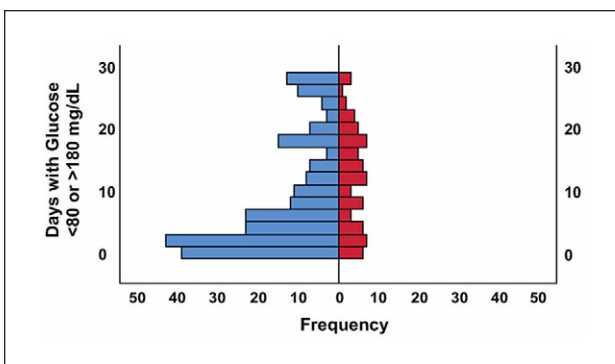

Figure 2. Patients who received ≥320 mg methylprednisolone equivalents (red) versus those who did not (blue) stratified by quantity of days spent with glucose <80 mg/dL or >180 mg/dL.

Based on univariate analysis, administration of ≥320 mg methylprednisolone equivalent was associated with a significant increase in days with glucose <80 mg/dL (*P* = .048) as well as days with glucose >180 mg/dL (*P* = .002) and days with glucose <80 mg/dL or >180 mg/dL (*P* = .002, Table 2). Administration of ≥320 mg methylprednisolone equivalent was also associated with a significantly longer duration of mechanical ventilation to day 28 (*P* = .001), a longer length of stay (*P* = .001), and fewer ventilator-free days to day 28 (*P* = .001). There was no difference in 28-day mortality between the 2 groups. The quantity of days patients spent with glucose <80 mg/dL or >180 mg/dL stratified by steroid dose is displayed in Figure 2.

Results from the univariate analysis were used to inform adjustment variable selection for the quantile regression model (Table 3). Since our study was underpowered to detect differences for less common clinical outcomes, secondary outcomes were not included in the quantile regression. Diabetes mellitus type 1 and type 2 as well as length of stay were significantly associated with the primary outcome. After adjustment for gender, history of diabetes mellitus, chronic liver disease, SOFA score on

Table 3. Quantile Regression Analysis for Days With Glucose <80 mg/dL or >180 mg/dL as the Dependent Variable.[a]

Characteristic	B coefficient	95% CI	P
Intercept	−1.75	−4.35 to −0.85	.19
Methylprednisolone equivalent ≥320 mg	4.00	2.15 to 5.85	<.001
Gender (male)	−0.25	−1.89 to 1.39	.76
Diabetes mellitus type 1	26.50	17.09 to 35.91	<.001
Diabetes mellitus type 2	10.00	8.44 to 11.56	<.001
Chronic liver disease	−0.50	−2.80 to 1.80	.67
SOFA score on ICU day 1	<0.001	−0.18 to 0.18	1.00
Length of stay (days)	0.25	0.16 to 0.34	<.001

Abbreviations: SOFA, Sequential Organ Failure Assessment Score; ICU, intensive care unit.
[a]Model quality parmameters (*q* = 0.5): Peudo R^2 = 0.33, mean absolute error = 4.86.

ICU day 1, and length of stay, administration of ≥320 mg methylprednisolone equivalent was associated with 4 additional days spent with glucose either <80 mg/dL or >180 mg/dL (B = 4.00, 95% confidence interval = 2.15-5.85, *P* < .001).

Discussion

Our results indicate that administration of ≥320 mg methylprednisolone equivalents was independently associated with, on average, 4 additional days with glucose either <80 mg/dL or >180 mg/dL in critically ill patients with COVID-19 requiring mechanical ventilation.

Our findings demonstrate an association between corticosteroid administration and impaired glucose control in mechanically ventilated COVID-19 patients, thereby confirming our hypothesis. Given the benefit observed with dexamethasone administration to mechanically ventilated COVID-19 patients and the widespread adoption of corticosteroid use in this population, these findings are particularly timely.[10,12] To our knowledge, this is the first study to report on the glycemic control consequences of corticosteroids in COVID-19 patients.

The variety of corticosteroids utilized in this study reflects its timing. The Recovery trial,[10] which prompted the widespread administration of dexamethasone to critically ill COVID-19 patients, was published in July 2020. Our cohort included patients admitted through May 17, 2020. Therefore, all included patients were admitted for 28 days before the results of the Recovery trial were published. It is likely that some corticosteroids were administered primarily for shock instead of COVID-19 pneumonia. For unadjusted results, severity of illness was not adjusted for and, hence, may explain the worse outcomes in the dexamethasone group.

While it may seem evident that corticosteroid administration is associated with impaired glucose control, there are several reasons why this is important to clinical practice. Hyperglycemia frequently occurs in critically ill patients and has already been established as a common issue in COVID-19 patients.[3] In fact, many COVID-19 patients who require critical care initially present with diabetic ketoacidosis.[3] The most common treatment for significant hyperglycemia in critically ill patients is an intravenous insulin infusion.[2] Nearly one-third of the patients included in this study required an insulin infusion to treat hyperglycemia. Such aggressive treatment can lead to overcorrection resulting in hypoglycemia.[1,5-8] Hypoglycemia in the ICU has a well-established link with increased mortality.[5] Clinicians should therefore treat steroid-associated hyperglycemia judiciously. The risk of insulin-induced hypoglycemia following steroid-associated hyperglycemia may increase the risk for iatrogenic morbidity and mortality in COVID-19 patients and deserves further attention.

Limitations

The limitations of this study stem mainly from its retrospective design and size. In our study, there was wide variability in the timing of corticosteroid administration in relation to the disease course. Since the National Institute of Health COVID treatment guidelines now recommend administration of dexamethasone for 6 mg a day for up to 10 days in mechanically ventilated patients,[16,17] it is possible that the rates of hyperglycemia identified in this study may not be entirely relevant to current recommended practice. Similarly, the steroid type administered in our study was not standardized. Steroid-induced insulin resistance is dependent both on steroid type and duration of use, with longer-acting steroids exhibiting increased duration of hyperglycemia.[16] It is unclear whether the steroids included in our study (dexamethasone, methylprednisolone, hydrocortisone, and prednisone) influence hyperglycemia similarly, since they have different half-lives and dosing considerations. The influence of this steroid heterogeneity on the exploratory outcomes, duration of mechanical ventilation, and length of stay is, therefore, unclear.

Our study was not powered to assess whether time spent with hypoglycemia or hyperglycemia was able to predict length of stay or mortality. As immunosuppressant agents, corticosteroids could theoretically facilitate bacterial superinfection or delayed viral clearance and increase length of stay. Furthermore, other clinical outcomes such as delirium or postoperative cognitive dysfunction were difficult to ascertain in a valid fashion from chart review alone. Large, prospective clinical studies are needed to investigate suchquestions.

This study includes patients from a single health system in one region of the United States. A lack of geographic diversity may limit the external validity and generalizability of our findings to other settings.

An additional limitation of our study is the steroid dose and the timing used to define our treatment group. We chose a steroid dose equal to or greater than the upper dosing limit of the Recovery trial. The median dose of methylprednisolone administered in the Recovery trial was 224 mg. It is, therefore, possible that hyper- and hypoglycemic events in our study may not be entirely reflective of current practice, since it is well established that higher steroid doses correlate with elevations in hyperglycemia.[17] This should be considered as well when scrutinizing our exploratory outcomes of mechanical ventilation and length of stay, as higher doses of steroids can pose harm, such as decreasing immunity.[33] Additionally, the median time from ICU admission to corticosteroid receipt in our study was 8 days, implying not every patient received steroids immediately. This is partially mitigated by a median duration of 9 days of steroid administration. In fact, only 2 patients received any dose of steroids more than 28 days after ICU admission. Therefore, the vast majority of patients in our study had completed their steroid course by day 28. Finally, although both groups underwent mechanical ventilation and, thus, were considered critically ill, it is possible that patients with worse disease courses were prescribed steroid treatment at a greater frequency. Therefore, it is plausible that hyper- and hypoglycemic events in the treatment group can be explained by illness severity and not corticosteroid administration alone. However, adjustment for SOFA scores in our multivariable analysis mitigated this effect to some extent. Confounders for which we did not account for include nutrition, individual responses to insulin administration, and medications that could indirectly influence glycemic control.

Conclusions

Administration of corticosteroids ≥320 mg methylprednisolone equivalents to critically ill COVID-19 patients requiring mechanical ventilation is associated with impaired glucose control. These findings raise the potential for adverse events associated with the use of steroids for COVID-19 patients requiring mechanical ventilation. Future studies should examine the frequency of iatrogenic insults to glycemic control, especially the potential of insulin-associated hypoglycemia following steroid administration in critically ill COVID-19 patients.

Author Contributions

DJD contributed to the conception of the work, the acquisition, and interpretationof data, drafting the manuscript, and revising it critically for important intellectual content, and approved the final version to be published. MK, CW, and KT contributed to the acquisition and interpretation of data, revising the manuscript critically for important intellectual content, and approved the final version to be published. AAG and AFB contributed to the interpretation of data, revising the manuscript critically for important intellectual content, and approved the final version to be published. ANQ contributed to the interpretation of data, drafting the manuscript, and revising it critically for important intellectual content, and approved the final version to be published. KB contributed to the conception of the work, the acquisition, analysis, and interpretation of data, revising the manuscript critically for important intellectual content, secured funding for the study, and approved the final version to be published.

Declaration of Conflicting Interests

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