Clinical Outcomes Associated with Methylprednisolone in Mechanically Ventilated Patients with COVID-19

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Article summary: In a propensity-matched cohort study, ventilator-free days and the probability of extubation were both significantly increased in patients receiving methylprednisolone at 28-day follow-up. The incidence of hyperglycemia and positive cultures were not increased.

Abstract

Background: The efficacy and safety of methylprednisolone in mechanically ventilated patients with acute respiratory distress syndrome due to coronavirus disease 2019 (COVID-19) are unclear. In this study, we evaluated the association between use of methylprednisolone and key clinical outcomes.

Methods: Clinical outcomes associated with the use of methylprednisolone were assessed in an unmatched, case-control study; a subset of patients also underwent propensity-score matching. Patients were admitted between March 1 and April 12, 2020. The primary outcome was ventilator-free days by 28 days after admission. Secondary outcomes included extubation, mortality, discharge, positive cultures, and hyperglycemia.

Results: A total of 117 patients met inclusion criteria. Propensity matching yielded a cohort of 42 well-matched pairs. Groups were similar except for hydroxychloroquine and azithromycin use, which were more common in patients who did not receive methylprednisolone. Mean ventilator free-days were significantly higher in patients treated with methylprednisolone (6.21±7.45 versus 3.14±6.22; *P* = 0.044). The probability of extubation was also increased in patients receiving methylprednisolone (45% versus 21%; *P* = 0.021), and there were no significant differences in mortality (19% versus 36%; *P* = 0.087). In a multivariable linear regression analysis, only methylprednisolone use was associated with higher number of ventilator-free days (*P* = 0.045). The incidence of positive cultures and hyperglycemia were similar between groups.

Conclusions: Methylprednisolone was associated with increased ventilator-free days and higher probability of extubation in a propensity-score matched cohort. Randomized, controlled studies are needed to further define methylprednisolone use in patients with COVID-19.

Keywords: SARS-CoV-2, COVID-19, methylprednisolone, intubated

Introduction

In December 2019, the outbreak of a novel respiratory virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China marked the beginning of a global pandemic that has since led to over four million cases and 300,000 deaths worldwide [1]. The clinical manifestations of coronavirus disease 2019 (COVID-19) are varied and range from asymptomatic disease to acute respiratory distress syndrome (ARDS) with septic shock and multiorgan failure [2, 3]. The reported mortality among critically-ill patients with COVID-19 has varied significantly. An early study reported 61.5% mortality among critically-ill patients [4], while a more recent study reported an overall mortality of 25.8% in a critically-ill cohort [5].

Emerging data and analogy to other coronaviruses indicate that a dysregulated immune response to SARS-CoV-2 infection results in a cytokine storm-like syndrome that precipitates the severe clinical manifestations in COVID-19 [6]. Corticosteroids inhibit expression of the cytokines involved in the inflammatory response [7] and may improve outcomes in patients with severe ARDS [8, 9]. Consequently, there is considerable interest in using corticosteroids to treat severe COVID-19.

More data are needed to further define the role of corticosteroids in emerging coronavirus infections. Prior studies on the use of corticosteroids in severe acute respiratory syndrome coronavirus (SARS) and Middle Eastern respiratory syndrome coronavirus (MERS) were inconclusive. These studies failed to show improved mortality, and one study showed delayed viral clearance [10, 11]. Early reports out of Wuhan, China describing the effect of corticosteroids in COVID-19 have demonstrated variable results [12, 13]. The recently published RECOVERY trial demonstrated improved mortality in patients that received dexamethasone; however, it did not examine other corticosteroids and included all hospitalized patients, including patients who were not critically ill [14]. We sought to further evaluate the effect of corticosteroids in cases of severe COVID-19 and to assess adverse effects, such as hyperglycemia and secondary infections. In this retrospective, observational, case-control study, we investigated the effect of methylprednisolone on critically-ill, mechanically ventilated patients with COVID-19.

Materials and Methods

Study design. This study retrospectively evaluated consecutive adult patients with COVID-19 pneumonia requiring intubation and mechanical ventilation. All patients were admitted to a quaternary care medical center in New York City, comprised of a large academic hospital and a smaller community hospital, between March 1, 2020 and April 12, 2020. The study was approved by the Columbia University Irving Medical Center Institutional Review Board with a waiver for informed consent. Patients were eligible for inclusion if they tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal and/or oropharyngeal swab specimen within 48 hours after admission and subsequently required mechanical ventilation. Patients were excluded if they died less than five days after hospital admission, if they weighed more than 200 kg, or if they received steroids other than methylprednisolone for greater than 24 hours. Patients more than 200 kg were excluded to account for our weight-based dosing protocol that recommended a maximum dose of 80 mg. Those who died prior to hospital day five were excluded because most patients in the study period were not evaluated for steroid treatment until at least four days into their hospital course.

Those included in the methylprednisolone group received greater than 24 hours of methylprednisolone initiated within the first 14 days after admission. Our hospital dosing protocol for methylprednisolone was one mg/kg/day with a max dose of 80 mg per day, with recommended duration of five days, although the course could be extended at the discretion of the treating physician. Our protocol also recommended that steroids only be started in patients at least five to seven days after symptom onset and only in those with evidence of systemic inflammation. Early in the pandemic, our hospital guidelines permitted the use of hydroxychloroquine and azithromycin for patients with vital sign abnormalities or risk factors for disease progression. This recommendation was later removed after publication of new findings showing minimal benefit with these agents [15].

The primary outcome evaluated was ventilator-free days at hospital day 28. Ventilator-free days were defined as days after extubation, with days prior to intubation not included. Patients who died within 28 days were assigned zero for this outcome, as were those who were not extubated during the follow-up period [16]. Secondary outcomes included extubation, death, and hospital discharge at both 28 and 60 days after admission. Extubation was defined as either removal of the endotracheal tube or discontinuation of mechanical ventilation without relapse in patients who had undergone tracheostomy. Safety outcomes were also assessed, including hyperglycemia and all positive clinical cultures (except for coagulase-negative *Staphylococcus* isolated from a single blood culture). Hyperglycemia was defined as days with a blood glucose ≥ 180 mg/dL during the first 21 days, chosen to reflect the time period during which most patients received steroids. Positive cultures from any source during the first 28 days served as a proxy for secondary infections, given the difficulty of discerning between colonization and infection in this patient population.

Data points collected at the time of admission included patient demographics, chronic comorbidities summarized using the Charlson comorbidity index (CCI) [17], laboratory values, and the reported date of symptom onset. The sequential organ failure assessment (SOFA) score [18] was calculated on the day of intubation. Days from admission to intubation were also documented. The use of additional agents with antiviral and immunomodulatory effects targeting SARS-CoV-2 was also noted. PaO_2/FiO_2 (PF) ratios, high-sensitivity C-reactive protein (CRP) values, and use of vasopressors were recorded during the first 48 hours after admission.

Statistics. Patients who received methylprednisolone were analyzed as cases, and those who did not served as controls. We performed unmatched, case-control analysis of all patients meeting criteria for inclusion. We then used propensity scoring to create well-matched groups by using 1:1 nearest-neighbor matching without replacement. Covariates included in the propensity score matched analysis were the following: body mass index ≥ 30 kg/m^2, age ≥ 65 years, gender, admission CRP ≥ 150 mg/L, admission D-dimer ≥ one mcg/mL, PF ratio < 200 at hospital day two, SOFA score on the day of intubation, CCI score, and days from symptom onset to admission. Dichotomous cutoffs were chosen in order match specific populations (i.e. elderly or obese

patients) or because our system reported laboratory values with a specified upper limit that precluded continuous analysis. Patients who did not have a match within 0.2 propensity score standard deviations were excluded from the analysis. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. Variables with *P* values < 0.1 in univariable analysis were considered for inclusion into a multivariable linear regression model identifying factors associated with ventilator-free days. Methylprednisolone use was also included *a priori*. Statistical analyses were performed using IBM SPSS Statistics, version 26 (SPSS Inc., Chicago, Ill., USA).

Results

Patient characteristics. 142 patients with COVID-19 who required mechanically ventilation were identified during the study period. Of these, 25 were excluded from the analysis: 13 died within five days of admission; seven received other steroids; four received methylprednisolone starting more than 14 days after admission; and one weighed > 200 kg. A total of 117 patients were included in the overall analysis. The median patient age was 63 years (interquartile range [IQR], 52-71) and 67% of patients were male. The median body mass index (BMI) was 30 kg/m^2 (IQR, 26-35). The median time from symptom onset to admission was seven days (IQR, 3-8). Median time from admission to intubation was one day (IQR, 0-2). On the day of intubation, the median SOFA score was 11 (IQR, 8-12). The median CCI at admission was three (IQR, 1-4). 33 patients died by hospital day 28 (28%).

48 patients that received methylprednisolone were identified. The median dose was 80.0 mg/day (IQR, 78.8-80.0) or 1.0 mg/kg/day (IQR 0.8-1.0). The median time from hospital admission to initiation of methylprednisolone was four days (IQR, 2-6). Methylprednisolone was continued for a median course of five days (IQR, 4-6).

42 well-matched pairs were identified and included in the propensity-matched analysis (Table 1). For most variables, the matched groups were comparable at baseline; however, patients who received steroids were

less likely to have received hydroxychloroquine (91% versus 100%, *P* = 0.040) or azithromycin (45% versus 88%; *P* < 0.001). There was also a trend toward higher median LDH levels in the steroid group (637 U/L [IQR, 459-840] versus 521 U/L [IQR, 423-663]; *P* = 0.089), as well as in use of tocilizumab (29% versus 12%; *P* = 0.057). Other key variables such as age, BMI, gender, CCI, SOFA score, and days from symptom onset to admission were similar between groups (Table 1).

Clinical outcomes. Within the matched cohorts, the primary outcome of ventilator-free days was significantly higher in the steroid group (mean ± standard deviation, 6.21±7.45 versus 3.14±7.45; *P* = 0.044) (Table 2). The probability of extubation by day 28 was significantly higher in patients who received steroids (45% versus 21%; *P* = 0.021), and there was a statistically non-significant trend toward reduced mortality (19% versus 36%; *P* = 0.087). Mortality was still numerically lower at the end of the 60-day follow-up period but the difference remained non-significant. There were also no significant differences in hospital discharge between those who received steroids and those who did not at day 28 (17% versus 19%; *P* = 0.776) or day 60 (45% versus 36%; *P* = 0.374). Regarding safety outcomes, the proportion of patients with positive cultures was similar between steroid and control patients at hospital day 28 (52% versus 45%; *P* = 0.513). Days with blood glucose values ≥ 180 mmol/L over the first 21 days were also similar (9 [IQR, 3-17] versus 8 [2, 14]; *P* = 0.415).

In a multivariable, linear regression model including matched pairs (Table 3), the use of methylprednisolone was found to be independently associated with a higher number of ventilator-free days (*P* = 0.045) after controlling for lactate dehydrogenase (LDH). The use of hydroxychloroquine, azithromycin, or tocilizumab was not significantly associated with the primary outcome. After controlling for age, SOFA score, white blood cell count (WBC), LDH, and D-dimer, the use of methylprednisolone (*P* = 0.015) was independently associated with improved outcome within the overall cohort, while treatment with hydroxychloroquine, azithromycin, or tocilizumab was not.

Discussion

Our study evaluated the association of methylprednisolone treatment with duration of mechanical ventilation and mortality in intubated, critically-ill patients with COVID-19. All patients had bilateral infiltrates and hypoxemic respiratory failure consistent with ARDS. We observed an increase in the number of ventilator-free days and the likelihood of extubation, as well as a statistically non-significant trend towards improved mortality, in the corticosteroid group when compared to control patients in a propensity-matched cohort by day 28. Numerically fewer patients died by day 60 but the difference was not statistically significant. Few patients were discharged by day 28, but there was a trend toward earlier discharge by hospital day 60 in those who received methylprednisolone.

Conflicting results on the benefit and safety of corticosteroids in other viral pneumonias led to early recommendations by the WHO against routine use in the management of COVID-19 [19]. A systematic review found that corticosteroids used to treat influenza were associated with increased mortality [20]. In a study of patients with MERS-CoV, there was no effect of corticosteroids on mortality, and there was a delay in viral clearance [11]. A systematic review of the literature on corticosteroid use in SARS-CoV yielded inconclusive results, with some studies trending towards harm [10]. Steroid dosing regimens have varied significantly among studies. For example, in one study SARS-CoV patients, doses as high as 160 mg of methylprednisolone per day were used [21], while in another study of patients with ARDS receiving less potent corticosteroid doses, treatment duration was as long as 32 days [8]. Several other studies have shown no mortality benefit associated with corticosteroids in patients with ARDS, and one larger study found an increase in mortality when methylprednisolone was initiated more than two weeks after the onset of ARDS [22, 23].

Corticosteroids and other immunomodulators have also been studied as a potential treatment for ARDS. Prior studies have shown that infection with SARS-CoV and MERS-CoV can result in a cytokine release syndrome leading to massive inflammatory cell infiltration, acute lung injury, and ARDS [24], and a similar process has been theorized as the cause of ARDS in COVID-19 [6]. Recent studies have shown improved outcomes in patients with ARDS who received corticosteroids [8, 9]. In one multicenter, randomized, controlled trial,

mechanically ventilated patients with ARDS who received dexamethasone had a significant increase in the number of ventilator-free days and a significant reduction in mortality compared to the control group [9]. In a small, observational study among patients with ARDS from severe COVID-19, treatment with methylprednisolone reduced mortality from 61.8% to 46.0% [25], although these results should be interpreted with caution given the limited quality of the trial design. Most recently, the RECOVERY trial found that patients with COVID-19 who received dexamethasone six mg daily for 10 days experienced a mortality benefit. Although this benefit was greatest in the subset of patients that required mechanical ventilation, the trial only evaluated outcomes through hospital day 28 and did not assess other corticosteroids, such as methylprednisolone [14].

The earlier time to recovery seen in our study suggests that corticosteroids may have a favorable effect on the hyperinflammatory state in patients with COVID-19. We observed a significant increase in both ventilator-free days and in the likelihood of extubation by day 28. There was also a numerical increase in earlier discharge by day 60, but this difference was not statistically significant. Additional studies examining the pathophysiology of ARDS in COVID-19 are needed to determine the interplay between the immune response and disease progression and how this is affected by different management strategies.

Concerns have been raised regarding the incidence of hyperglycemia in patients who are treated with corticosteroids [26, 27]. Our study did not detect a difference in days with blood glucose values ≥ 180 mmol/L by day 21. An additional concern is the potential for secondary infections. This finding was noted in a review of patients with influenza pneumonia who were treated with corticosteroids [19], although another study found that corticosteroids did not increase the type or incidence of infectious complications among patients with ARDS admitting to intensive care [9]. Our study did not detect a difference in incidence of positive cultures at day 28 in patients who received methylprednisolone compared to those who did not.

The optimal dose and duration of methylprednisolone treatment in patients with viral pneumonia and ARDS remains unknown. Our hospital protocol for use of methylprednisolone in treatment of COVID-19 was one mg/kg/day with a maximum daily dose of 80 mg, with median duration of four to six days. The corticosteroid regimen used in our study was similar to regimens used in prior studies that found improved clinical outcomes in patient with ARDS [9, 13]. The RECOVERY trial used a dexamethasone dose that was approximately half the equivalent methylprednisolone dose used in our patients with a duration of 10 days compared to the four to six days use in this study

There are several limitations to our study. First, our study only included patients with COVID-19 requiring mechanical ventilation, which limits the generalizability to less critically-ill patients. However, several recent studies have highlighted the benefits of early corticosteroids in patients with moderate COVID-19 [14, 28, 29]. Our study was conducted at a single hospital center with limited sample size, and efforts at propensity matching to reduce selection bias may not have accounted for all the variables determining which patients received corticosteroids. Rapidly changing practice patterns at our hospital throughout the course of the pandemic may also have influenced our results. During the second month of the pandemic, there was a higher threshold for intubation. However, in our study the timing of intubation was similar between groups, reflecting the overall early enrollment of these patients. Similarly, the threshold to admit patients was also raised later in the outbreak, which may have resulted in prolonged time to admission, although no differences were noted between groups in our study. Our hospital guidelines regarding management of COVID-19 were updated several times during the period of our study, as reflected in the differences seen in the use of hydroxychloroquine and azithromycin. These treatments had no significant associations the primary outcomes in multivariable analysis. Finally, there were also changes to the prevention and management of venous thromboembolism during the study period. However, none of those changes were routine or protocolled at the time. Our ability to distinguish true infection from colonization or contamination was limited by chart review and by diagnostic limitations in the setting of the pandemic. Thus, we defined any positive culture as a possible proxy for infection (except for coagulase-negative *Staphylococcus* isolated from a single blood culture). Although we observed a trend towards improved mortality both at day 28 and day 60 in patients treated with methylprednisolone, our study may have been underpowered to detect a significant difference in

mortality between the two groups. Given the limitations of our study design, a randomized-controlled trial is needed to better able to evaluate survival benefits associated with methylprednisolone.

In conclusion, our study adds to a growing body of literature regarding the use of corticosteroids for treatment of COVID-19. We found that treatment with methylprednisolone increased the number of ventilator-free days and probability of extubation compared with a propensity matched control group among patients with severe COVID-19 requiring mechanical ventilation, but we did not detect a significant difference in mortality. A randomized-controlled trial is necessary to further define the role of methylprednisolone in this emerging disease.

NONE OF THE AUTHORS HAS ANY POTENTIAL CONFLICTS TO DISCLOSE.

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Table 1. Baseline demographics and clinical characteristics.

	Overall cohort (117)[a]			Propensity-matched cohort (84)[a]		
	Control (69)	**MP (48)**	***P***	**Control (42)**	**MP (42)**	***P***
Demographics						
Age (years)	63 (56-73)	60 (46-69)	0.040	62 (55-70)	60 (46-68)	0.166
Male	48 (70)	32 (67)	0.740	30 (71)	28 (67)	0.637
BMI (kg/m^2)	30 (26-35)	31 (27-35)	0.733	31 (27-36)	31 (26-37)	0.872
Charlson comorbidity index score	3 (2-4)	3 (1-4)	0.238	3 (1-4)	3 (1-4)	0.598
Sequential organ failure assessment score	10 (8-12)	11 (9-13)	0.059	9 (9-12)	11 (9-13)	0.392
Days from symptom onset to admission	7 (4-8)	6 (3-7)	0.464	6 (4-8)	6 (3-8)	0.847
Days from admission to intubation	0.5 (0.1-2.3)	1.0 (0.0-2.3)	0.425	0.5 (0.1-1.9)	1.0 (0.0-2.0)	0.935
Laboratory values at admission						
White blood cells x10^3/µL	8.1 (5.9-10.6)	9.5 (7.3-12.5)	0.044	8.1 (6.0-10.4)	9.1 (7.2-12.4)	0.138
Serum creatinine (mg/dL)	1.2 (0.9-1.5)	1.1 (0.9-2.0)	0.883	1.2 (0.9-1.7)	1.1 (0.9-2.0)	0.897
Blood glucose (mmol/L)	149 (114-224)	137 (188-241)	0.733	149 (115-232)	137 (120-265)	0.655
Lactate dehydrogenase (U/L)	502 (386-664)	610 (444-839)	0.037	521 (423-663)	637 (459-840)	0.089

Procalcitonin (ng/mL)	0.4 (0.2-0.7)	0.5 (0.3-1.5)	0.246	0.4 (0.2-0.8)	0.5 (0.2-1.1)	0.455
D-dimer ≥ 1 μg/mL	53 (77)	40 (83)	0.008	38 (91)	37 (88)	0.603
Ferritin ≥ 1000 ng/mL	34 (29)	19 (40)	0.574	21 (50)	16 (28)	0.401
C-reactive protein ≥ 150 mg/L	48 (70)	38 (79)	0.247	29 (69)	31 (74)	0.629
Other agents						
Hydroxychloroquine	69 (100)	43 (90)	0.010	42 (100)	38 (91)	0.040
Azithromycin	60 (87)	22 (46)	<0.001	37 (88)	19 (45)	<0.001
Remdesivir	1 (1)	1 (2)	1.000	0 (0)	1 (2)	0.314
Tocilizumab	7 (10)	13 (27)	0.017	5 (12)	12 (29)	0.057
Clinical characteristics within the first 48 hours after admission						
PaO_2/FiO_2 ratio < 200	28 (41)	20 (42)	0.906	18 (43)	17 (41)	0.825
Use of vasopressors	37 (54)	30 (63)	0.340	24 (57)	26 (62)	0.657

[a] Categorical variables are presented as number (percent), and continuous variable are presented as median (interquartile range).

Abbreviations: MP, methylprednisolone; BMI, body mass index; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen.

Table 2. Effectiveness and safety outcomes.

	Overall cohort (117)[a]			Propensity-matched cohort (84)[a]		
	Control (69)	**MP (48)**	***P***	**Control (42)**	**MP (42)**	***P***
Primary outcome						
28-day ventilator-free days[b]	2.46 (±6.55)	5.77 (±7.21)	0.058	3.14 (±6.22)	6.21 (±7.45)	0.044
Secondary outcomes						
28-day extubation	16 (23)	21 (44)	0.019	9 (21)	19 (45)	0.021
28-day death	20 (33)	10 (21)	0.139	15 (36)	8 (19)	0.087
28-day discharge	14 (20)	8 (17)	0.622	8 (19)	7 (17)	0.776
60-day extubation	36 (54)	31 (46)	0.182	23 (55)	27 (64)	0.374
60-day death	29 (42)	15 (31)	0.236	17 (41)	13 (31)	0.362
60-day discharge	26 (38)	23 (48)	0.270	15 (36)	19 (45)	0.374
Safety outcomes						
Positive cultures	32 (46)	26 (54)	0.407	19 (45)	22 (52)	0.513
Culture site			0.834			
- Pulmonary	25 (36)	21 (44)	--	15 (36)	17 (41)	--
- Urinary tract	5 (7)	4 (8)	--	2 (5)	4 (10)	--
- Intravascular	2 (2)	1 (1)	--	2 (5)	1 (1)	--
Days with blood glucose ≥ 180 mmol/L[b]	8 (3-14)	9 (3-16)	0.454	8 (2-14)	9 (3-17)	0.415

[a] Categorical variables are presented as number (percent), ventilator free days are presented as mean (standard deviation), and days with blood glucose ≥ 180 mmol/L are presented as median (interquartile range).

[b] Blood glucose values were evaluated through hospital day 21.

Abbreviations: MP, methylprednisolone.

Table 3. Multivariable linear regression analysis of characteristics associated with ventilator free days.

	Standardized β	Unstandardized β	95% confidence interval		*P*
			Lower	Upper	
Overall cohort					
Methylprednisolone	0.281	4.113	0.827	7.399	0.015
Age (years)	-0.179	-0.081	-0.168	0.006	0.067
Sequential organ failure assessment score	-0.155	-0.270	-0.723	0.184	0.241
White blood cell count[a] x10^3/µL	-0.101	-0.150	-0.426	0.126	0.283
Lactate dehydrogenase (U/L)[a]	0.037	0.001	-0.003	0.004	0.697
D-dimer ≥ 1 µg/mL[a]	-0.096	-1.620	-4.848	0.1608	0.322
Hydroxychloroquine	0.074	2.620	-4.342	9.581	0.457
Azithromycin	0.041	0.644	-2.653	3.941	0.699
Tocilizumab	-0.078	-1.491	-5.187	2.205	0.426
Propensity-matched cohort					
Methylprednisolone	0.262	3.782	0.085	7.480	0.045
Lactate dehydrogenase (U/L)[a]	0.086	0.002	-0.003	0.006	0.443
Hydroxychloroquine	0.083	2.792	-5.112	10.696	0.484
Azithromycin	-0.002	-0.030	-3.946	3.886	0.988
Tocilizumab	-0.067	-1.206	-5.301	2.889	0.559

[a]All laboratory values collected at admission.