Journal of Epidemiology and Global Health
Vol. **11**(**3**); September (2021), *pp.* 316–319
DOI: https://doi.org/10.2991/jegh.k.210521.001; ISSN 2210-6006; eISSN 2210-6014
https://www.atlantis-press.com/journals/jegh

Research Article

Clinical Features and Outcome of Low and High Corticosteroids in Admitted COVID-19 Patients

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ARTICLE INFO

Article History

Received 07 March 2021
Accepted 21 May 2021

Keywords

SARS-CoV-2
COVID-19
steroid
high-dose steroid

ABSTRACT

Introduction: There is no specific anti-viral therapies for 2019 Coronavirus Diseases (COVID-19) infection. Here, we compared patients receiving steroids at different dosages versus no steroids in severe and critical COVID-19 patients.

Methods: We retrospectively studied COVID-19 patients who received low-dose or high-dose corticosteroid therapy compared to no steroid.

Results: The study period, June–August 2020, included 169 patients with COVID-19 were included and there were 39.1% female and 60.9% male with an average age of 53.1 years. The distribution of cases was as follows: high-dose 39 (23.1%), low-dose 54 (32.0%), and no steroid 76 (45.5%). Of all the patients, Intensive Care Unit (ICU) admission was for 31 (18.3%), nine (5.3%) required intubation, and 52 (30.8%) had no comorbidities. There is no difference in the mean age between the different groups. However, those being treated with steroid were more likely to have a high sequential organ failure assessment (SOFA) score (0.37 ± 0.68, 0.36 ± 0.67 and 0.04 ± 0.34, for low-dose, high-dose steroid and no steroid groups, respectively ($p = 0.001$). Cox regression was not possible as the mortality rate was very low (3/169; 1.78%) and none of the multivariate methods would be possible. However, there was a significant difference in the hospital Length of stay (LOS) and the ICU LOS.

Conclusion: Cox regression was not possible as the mortality rate was very low (1.78%) and none of the multivariate methods would be possible as the model will not converge. However, in *t*-test only, intubation was associated risk of mortality.

1. INTRODUCTION

The emergence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) had resulted in a clinical spectrum of SARS-CoV-2 infection. Patients may present with symptoms ranging from mild to severe infection requiring intensive care unit admission. In addition, asymptomatic infections were also described [1–6]. The need for Intensive Care Unit (ICU) admission is estimated to be 5% with increased mortality compared to those who do not require ICU admission [7,8]. The physiologic description of the 2019 Coronavirus Diseases (COVID-19) consists of an initial viral replication phase and then the immune system reactions would lead to the development of inflammatory responses with a wide range of clinical findings [9,10]. The second phase of immune response may lead to a disproportionate and unregulated cytokine releasing storm resulting and subsequent emergence of acute respiratory distress syndrome, and death [11–13]. Based on the clinical presentation and the pathophysiology of COVID-19, the case fatality rates varies from 61.5% in those requiring intensive care admission in earlier studies [14] and may be lower as cited in more recent studies of a fatality rate of 25.8% [15].

Multiple studies across the world had included multiple interventions to cure SARS-CoV-2 infections. However, the main stay of therapy of such patients relies on supportive care [16]. It is also important to use immunomodulatory agents to treat cytokine releasing storm and this is being studies as well [16] as the use of corticosteroid therapy [10,16,17]. The landmark of steroid therapy in COVID-19 patients is the RECOVERY trial which utilized dexamethasone at a dose of 6 mg intravenous or oral once a day [18]. In the Kingdom of Saudi Arabia, studies had been conducted to describe the epidemiology and clinical features including those who required ICU admission and those who were cared for in quarantine facilities [4–6,8,19]. Here, we sought to further evaluate the utilization and effect of high- and low-dose of corticosteroids in comparison to no-steroid therapy in patients with severe and critical conditions of COVID-19.

2. MATERIALS AND METHODS

This is a retrospective study of COVID-19 patients who received systemic corticosteroids and those were compared to no steroid therapy. Initial patients did not receive steroid and subsequent patients were given corticosteroid based on the results from the RECOVERY trial (6 mg p.o./i.v. once per day) in June 2020. Then

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Data availability statement: Data available upon reasonable request.

in mid-July 2020, high-dose corticosteroid was used based on the hospital COVID-19 team consensus of slow clinical response in relation with low dexamethasone dosage.

High-dose weight-based dexamethasone dose was 0.1–0.2 mg/kg/day for moderate to severe illness and 0.2–0.4 mg/kg/day for critically ill. Methylprednisolone dose was 0.5–1 mg/kg/day for moderate to severe illness and 1–2 mg/kg/day for critically ill. Prednisone dose was 0.6–1.2 mg/kg/day for moderate to severe illness and 1.2–2.5 mg/kg/day. These doses were adjusted per use in connective tissue disease/autoimmune diseases. The indication for the use of steroid was per Infectious Diseases Society of America (IDSA) therapy recommendation in hospitalized with severe illness (O_2 saturation ≤94% on room air, the requirement of supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation).

We collected the demographic of the patients, reviewed medical history, laboratory findings, chest radiology, medication use and clinical outcomes during the administering of glucocorticoids. The study was approved by the Institutional Review Board (IRB) of the King Fahad Military Medical Complex (AFHER-IRB-2020-032).

2.1. Statistical Analysis

Descriptive analysis was used for qualitative and quantitative variables. Then further statistical analysis was performed using correlation between variables and patient outcomes. Cox regression model was used to calculate Hazard Ratio (HRs) and 95% Confidence Intervals (CIs).

The demographic characters were compared between three groups (low steroid, high steroid and no steroid) using statistical tests such as ANOVA (*F*-test) and Chi-square test, as appropriate. All statistical tests will be two-sided. A *p*-value of ≤0.05 was considered statistically significant.

3. RESULTS

During the study period from June to August 2020, 169 patients with COVID-19 were included and there were 39.1% female and 60.9% male (Table 1). The average age was 53.1 with standard deviation 16.7. The distribution of the patients was as follows: High-dose 39 (23.1%), low-dose 54 (32.0%), and no steroid 76 (45.5%). Of all the patients, 103 (60.9%) were male, ICU admission for 31 (18.3%), nine (5.3%) required intubation, and 52 (30.8%) had no comorbidities. The other patients (68.2%) had comorbidities as shown in Table 1.

The differences in the characteristics of the patients in the different groups are shown in Table 2. Those who received steroid were more

Table 1 | Socio-demographic characteristics of the cohort of the COVID-19 positive cases (*n* = 169)

Demographic characters	Frequency	Percentage
Male	103	60.9
Female	66	39.1
High-dose steroid	39	23.1
Low-dose steroid	54	32
No steroid	76	45
ICU admission	31	18.3
Intubated	9	5.3
Without intubation	160	94.7
With oxygen	92	54.4
Without oxygen	77	45.6
Bronchial asthma	6	3.6
Diabetes mellitus	21	12.4
Hypertension	73	43.2
Obesity	9	5.3
SCD	5	3
SLE	3	1.8
No comorbidities	52	30.8

SCD, Sickle cell disease; SLE, Systemic lupus erythematosus.

Table 2 | A comparison between the different groups (low-dose steroid, high-dose steroid and no steroid group)

Demographic characters	Low-dose steroid	High-dose steroid	No steroid group	*p*
Male	37 (68.5%)	28 (71.8%)	38 (50%)	0.03
Female	17 (31.5%)	11 (28.2%)	38 (50%)	
ICU admission	18 (33.3)	12 (30.8)	1 (1.3)	<0.0001
Intubation	7 (13)	2 (5.1)	0	0.005
Initial O_2 requirement	45 (83.3)	38 (97.4)	9 (11.8)	<0.0001
Comorbidity				
Bronchial asthma	1 (1.9)	3 (7.7)	2 (2.6)	<0.0001
Diabetes mellitus	9 (16.7)	2 (5.1)	10 (13.2)	
Hypertension	27 (50)	18 (46.2)	28 (36.8)	
Obesity	2 (3.7)	6 (15.4)	1 (1.3)	
Sickle cell disease	0	1 (2.6)	4 (5.2)	
Systemic lupus erythematosus	0	1 (2.6)	2 (2.6)	
No comorbidities	15 (27.8)	8 (20.5)	29 (38.2)	
Age mean (SD)	55.65 (16.95)	54.18 (15.67)	50.71 (16.97)	*F*-value 1.49 (*p* = 0.23)
SOFA score mean (SD)	0.37 (0.68)	0.36 (0.67)	0.04 (0.34)	0.001
Hospital LOS mean (SD)	10.30 (17.56)	5.95 (6.26)	2.97 (2.18)	0.001 (*F*-test)
ICU LOS mean (SD)	18 (58.1)	12 (38.7)	1 (3.2)	<0.0001
Initial oxygen requirement	45 (83.3)	38 (97.4)	9 (9.8)	<0.0001
Hydroxychloroquine	19 (35.2)	10 (25.6)	20 (26.3)	0.48
Azithromycin	49 (90.7)	36 (92.3)	57 (75)	0.02
Favipiravir	2 (3.7)	8 (20.5)	1 (1.3)	0.000
Triple therapy (PEGylated interferon, ribavirin, lopinavir/ritonavir)	16 (29.6)	1 (2.6)	0	<0.0001
Death	0	1 (33.3%)	2 (66.7%)	0.49

Table 3 | Risk of death in relation to multiple factors using Chi-square test

Parameters associated with status	Status		Chi-square (*p*-value)
	Alive	Dead	
Comorbidities			
Bronchial asthma	6 (100)	0	4.02 (0.67)
Diabetes mellitus	21 (100)	0	
Hypertension	70 (95.9)	3 (4.1)	
Obesity	9 (100)	0	
Sickle cell disease	5 (100)	0	
Systemic lupus erythematosus	3 (100)	0	
Age group			
≤52	87 (100)	0	3.24 (0.07)
>52	79 (96.3)	3 (3.7)	
O_2 requirement			
Yes	89 (96.7)	3 (3.3)	2.56 (0.11)
No	77 (100)	0	
Intubated			
Yes	8 (88.9)	1 (11.1)	4.75 (0.03)*
No	158 (98.8)	2 (1.3)	
ICU stay			
Yes	30 (96.8)	1 (3.2)	0.46 (0.50)
No	136 (98.6)	2 (1.4)	
Group			
Steroid	92 (98.9)	1 (1.1)	0.58 (0.45)
Non steroid	74 (97.4)	2 (2.6)	
High/Low			
High dose	38 (97.4)	1 (2.6)	1.44 (0.49)
Low dose	54 (100)	0	
No Steroid	74 (97.4)	2 (2.6)	
Favipiravir			
Yes	10 (90.9)	1 (9.1)	3.61 (0.06)
No	156 (98.7)	2 (1.3)	
Triple therapy			
Yes	17 (100)	0	0.34 (0.56)
No	149 (98)	3 (2)	
Hydroxychloroquine			
Yes	49 (100)	0	1.25 (0.26)
No	117 (97.5)	3 (2.5)	
Tocilizumab			
Yes	24 (100)	0	0.51 (0.48)
No	142 (97.9)	3 (2.1)	
Gender			
Male	102 (99)	1 (1)	0.98 (0.32)
Female	64 (97)	2 (3)	

* indicates significant *p* value.

likely to be in the ICU, require mechanical ventilation and have underlying comorbidities. There is no difference in the mean age between the different groups. However, those being treated with steroid were more likely to have a high Sequential Organ Failure Assessment (SOFA) score (0.37 ± 0.68, 0.36 ± 0.67 and 0.04 ± 0.34, for low-dose, high-dose steroid and no steroid groups, respectively ($p = 0.001$).

There was a significant difference in the hospital Length of stay (LOS) and the ICU LOS (Table 2). In addition, there is a significant difference in the use of azithromycin, favipiravir, and triple anti-viral therapy (PEGylated interferon, ribavirin, lopinavir/ritonavir). The low-dose steroid group was more likely to be on triple therapy than the high-dose steroid group (29.6% vs. 2.6%; $p < 0.0001$) and less likely to be on favipiravir (3.7% vs. 20.5%; $p < 0.0001$).

We tried to do multivariate analysis. However, Cox regression was not possible as the mortality rate was very low (3/169; 1.78%) and none of the multivariate methods would be possible as the model will not converge. However, a crosstabs and *t*-tests to show the differences are shown in Table 3. Only, intubation was associated risk of mortality.

4. DISCUSSION

The use of corticosteroid for the therapy of patients admitted with COVID-19 had been approved by the Saudi ministry of health on June 17, 2020. The protocol called for the use of steroid in adults with a respiratory rate ≥30/min, blood oxygen saturation equal to or less than 93%, a ration of the PaO_2/FiO_2 of less than 300, the presence of lung infiltration of 50% within 24–48 h [20]. In a recent study from Saudi Arabia, 40 patients with severe COVID-19 were treated with a combination of corticosteroid and tocilizumab and the mortality rate was 15% [13]. The patients in the high-dose steroid had a higher rate of the use of favipiravir than those in the low-dose steroid. The use of favipiravir was 38% in a study from Tokyo, Japan [21]. In a recent randomized controlled trial, the use of favipiravir was associated with shorter duration of illness in those with mild-moderate COVID-19 [22]. The mean days of ICU and hospital stay was 6 and 22 days in a study from Tokyo [21]. However, the mean (±SD) of ICU and hospital stay were 10.30 (±17.56) and 18 (5 ± 8.1) for low-dose steroid and were 12 (38.7) and 5.95 (6.26) for high-dose steroid, respectively.

The use of high-dose corticosteroid is not well studied in relation to COVID-19 cases. In a study from Tokyo, Japan, 16 (66.7%) of 24 patients received high-dose methylprednisolone (500–1000 mg) [21]. In a report of two cases, there was a suggestion that high-dose steroid might be of benefit in low resource countries [23]. In a retrospective study comparing high-dose versus conventional doses of corticosteroid, it was noted that high-dose group were more likely to have comorbid conditions [24]. The study showed that the risk of mortality and the need for mechanical ventilation was higher in the high-dose corticosteroid even after adjusting for baseline characteristics [24].

In our study, the ICU admitted patients were prescribed high-dose steroid and this can be explained by their illness severity, although most of them had required oxygen but were less to be mechanically intubated and had a shorter LOS. Moreover, underlying comorbidities was almost similar between the high versus the low steroid group except for hypertensive patients were more in low steroid group. In addition, the use of antiviral agents was more with low steroid group. However, our study is a retrospective study and thus no firm conclusions could be drawn and the role of high-dose steroid remains to be established if any. Cox regression was not possible as the mortality rate was very low (1.78%) and none of the multivariate methods would be possible as the model will not converge. However, in *t*-test only, intubation was associated risk of mortality.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

All authors contributed to the data gathering, analysis, or drafting the first draft. All authors approved the final draft.

FUNDING

No financial support was provided.

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