Corticosteroid Treatment in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

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Research Article

Keywords: SARS-CoV-2, COVID-19, Corticosteroid, mortality, hospitalization stay, viral shedding

Posted Date: May 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27386/v1

Abstract

Objectives: The role of corticosteroids in the treatment of COVID-19 is controversial. In this paper, we intend to study the application value of corticosteroid in critically ill patients with COVID-19.

Methods: We collected data from 120 patients who were diagnosed with COVID-19 in the Wuhan Union Hospital. In the first part of this study, the outcome of patients given corticosteroids was compared with that of patients not given corticosteroids. The second part of the study was a matched (1:1) case–control study. After matching the baseline characteristics between the two groups, the effect of corticosteroid use on the outcome was analyzed again.

Results: Analysis of data without adjusting differences in baseline characteristics indicated that the proportion of mechanical ventilation and the mortality was higher in the corticosteroid treatment group in severely ill patients. The length of hospitalization and viral shedding have no significant difference between the two groups. After adjusting the difference between the corticosteroid and non-corticosteroid treatment group, analysis revealed that the use of corticosteroids had no effect on the outcome.

Conclusions: Among the critically ill patients, the use of corticosteroids has no effect on length of hospitalization, viral shedding or mortality rates.

Introduction

In December, 2019, a series of pneumonia cases of SARS-CoV-2 emerged in Wuhan, Hubei, China, which spreads rapidly and the clinical symptoms are diverse. Fever, dry cough and anorexia are the main symptoms. Mild patients may only show low fever and fatigue, and severe patients may have acute respiratory distress syndrome, septic shock, multiple organ failure or even death in a short duration of time. From SARS, H1NI to MERS, the application of corticosteroids in viral pneumonia has long been controversial. Among them, Clark D Russal and colleagues believe that corticosteroids are not suitable for 2019n-Cov lung injury based on existing clinical evidence[1]. Professor Shang raised the opposite view that corticosteroids can be used in the treatment of this disease, considering the influence of limited research methods and uncertainty of various research results. The application should be cautious, especially the indications and dosage[2].

In the treatment of this disease, corticosteroids was usually empirically applicated to critically ill patients, which was based on the situation of patient, besides the basically routine treatment. However, few study have been done on the treatment effect of corticosteroids on patients with COVID-19. Therefore, the aim of this study is to propose some valuable suggestions for the application of corticosteroids in clinical work.

Materials And Methods

Study population

This single-center, retrospective study includes 120 patients who were confirmed with COVID-19 in the Wuhan Union Hospital after January 8, 2020 and were discharged or had died before April 10, 2020. The diagnostic criteria and clinical classification criteria of COVID-19 refer to the provisional WHO guidelines. This study was approved by the institutional review board of Wuhan Union Hospital. All patients included in this study were treated with standard drugs in the isolation ward of Wuhan Union Hospital. Methylprednisolone succinate is the most common used corticosteroid. The dosage and duration of the hormone vary from person to person. All patients were given antiviral treatment, regularly monitored the patient's vital signs, laboratory and imaging changes during hospitalization, and varied degrees of oxygen therapy support according to the patient's severity.

Data collection

The following information was collected from the electronic case for included patients: epidemiology, demographic characteristics, clinical, impactology (including lung CT or chest radiography results), laboratory (blood routine, biochemistry, coagulation function, myocardial enzymes, inflammation indicators), medication and other interventions, prognostic indicator.

The main outcome event was the mortality during hospitalization. The secondary outcome event is the length of virus shedding which is defined as the event from the onset to two consecutive tests that turn negative and no more positive tests occur, and the length of hospitalization of surviving patients.

Statistic analysis

Results were analyzed with SAS software version 9.4. Categorical variables were compared by Fisher exact test or chi-square test, and continuous variables were compared by Mann-Whitney U test. All tests were tow-tailed and $P < 0.05$ is considered statistically significant.

To reduce the effect of potential confounding in this study, we performed rigorous adjustment for differences in baseline characteristics by propensity score analysis, and then compared the outcomes between corticosteroid treatment group and non-corticosteroid treatment group.

Results

In this study, 71 patients used corticosteroids and 49 patients did not among the 120 critically ill patients. Among them, the levels of lactate dehydrogenase and C-reactive protein were higher in the corticosteroid treatment group, while the lymphocyte count was lower. Furthermore, the proportion of mechanical ventilation and mortality in the corticosteroid treatment group were higher. There were no significant differences between the two groups among age, gender, symptoms, length of hospitalization and viral shedding. (Table 1)

Table 1 shows that the mortality rate in the corticosteroid treatment group was significantly higher than that in the non-corticosteroid treatment group, and it was statistically significant. However, this does not necessarily mean that adjuvant corticosteroid therapy will increase the mortality rate of patients, and this phenomenon may be partially attributed to our clinical medication “habit” of corticosteroids to critically ill patients. As can be seen in the table, the baseline characteristics of the two groups of patients were obviously unevenly distributed. Therefore, we matched the baseline characteristics between the two groups and analyzed the effects of corticosteroid on mortality, length of hospitalization and viral shedding.

There were 66 patients in 33 pairs with and without steroid treatment who were successfully matched for propensity for steroid treatment. Table 2 shows the general characteristics and outcomes of the corticosteroid treatment group and the non-corticosteroid treatment group after matching the baseline characteristics. The mortality rates during hospitalization of the corticosteroid treatment group was 6.1%, the non-corticosteroid treatment group was 9.1%. The hospitalization stay and viral shedding of the corticosteroid treatment group were longer, while none of the above-mentioned outcome events reached statistical differences. These results indicated that corticosteroid treatment did not have affect on the hospitalization stay, SARS-CoV-2 viral shedding or mortality rates of critically ill patients.

Discussion

Corticosteroids are widely utilized in the treatment of severe pneumonia, including the Middle East respiratory syndrome and severe acute respiratory syndrome. However, this therapy has been controversial so far. This study revealed that the use of corticosteroids has no effect on the hospitalization stay, SARS-CoV-2 viral shedding or mortality rates of critically ill patients.

At present, there is no specific drug for COVID-19. Critically ill patients often die from the rapid progress of the disease in a short duration of time. The pathogenesis of COVID-19 has not yet been elucidated, but excessive inflammatory response may be one of the reasons for the increased mortality of critically ill patients. Corticosteroids contributes to the patient's outcome through reducing inflammatory factors and relieving the inflammatory response. Our results of study seems not be in line with this view. Considering the limitations of data sample size and possible selection bias, these data and results deserve further integrated analysis.

Some early studies on SARS and MERS have illustrated that proinflammatory factors in serum increased significantly during viral infection, and after 5-8 days corticosteroid treatment of SARS the levels of plasma chemokines (IL-8, IP -10, MCP-1) reduced significantly, thereby relieving chemokine-related lung inflammation of SARS patients[4-5]. At the same time, the article of Craddock about "Hypercortisol" in severe acute diseases demonstrated that the immune response of self-antigens caused by disease or trauma exposure might be suppressed by corticosteroids to offset the possibility of autoimmune attacks [6]. This may explain why corticosteroids can be used in critically ill patients to relieve disease. The results of a retrospective study of Rong-chang Chen on SARS patients also confirmed this view that

appropriate administration of corticosteroid therapy in critically ill patients can reduce mortality and shorten hospitalization stay[7]. Although the study of Antoni Torres, MD, PhD and colleagues did not find the effect of the use of corticosteroid on mortality, the corticosteroid group significantly reduced the risk of treatment failure and relieved the inflammatory response[8]. Hilde H.F. Remmelts[9] and Garcia-Vidal [10]also confirmed the positive side of glucocorticoids. However, corticosteroids are a double-edged sword, which exerts anti-inflammatory and immunosuppressive effects. Prolonged viral shedding, double infection and increased mortality are the most reported adverse events in the literature[11-14]. A small prospective, randomized, double-blind, placebo-controlled trial conducted by Nelson Lee et al also confirmed that patients who received hydrocortisone early had significantly higher concentrations of SARS-Cov RNA in the second and third weeks compared with the control group. It is considered that the virus removal mainly depends on the body's self-immunity. The early use of corticosteroids may coincide with the period of virus replication, which inhibits the body's self-immunity function, resulting in delay in virus removal[15]. No effect of corticosteroid use on length of viral shedding was found in this study, which was considered to be related to the late prevalence of corticosteroid treatment in patients (median time from onset to corticosteroid treatment was 14 days) and effective antiviral treatment. Although the use of corticosteroid therapy in critically ill patients did not increase mortality and lengthen hospitalization stay, this study did not further explore the adverse reactions that may be caused by glucocorticoids such as superinfection and gastrointestinal bleeding. The clinical application still needs to be cautious.

Numerous studies on the application of corticosteroids in pneumonia have described different results. This may be mainly due to the population included in different studies, thedifferent use time and dosage of corticosteroids. In addition, most of the studies are retrospective and observational studies, and there are selection differences and confounding biases. In the future, rigorous, multi-center, and large-scale prospective studies are needed to verify the clinical efficacy of corticosteroids.

Our study also has the following limitations: ① This experiment is a retrospective study, and due to the limitation of sample size and the partial lack of patient data, it is impossible for us to match all baseline characteristics between groups; ②The time for patient nucleic acid testing is determined by the doctor-in-charge, therefore, the length of virus shedding may be limited by the frequency of specimen collection, and at the same time is also limited by the low positive rate of the detection method; ③ Our study only focused on the patients' short-term partial outcomes, superinfections, complications, and long-term side effects of corticosteroids may require further research to ensure the safety of patients receiving corticosteroid therapy.

The current application of corticosteroids in critically ill patients with COVID-19 is inconclusive. In conclusion, our analysis of 120 critically ill patients with COVID-19 in Wuhan Union Hospital showed that among the critically ill patients, the use of corticosteroids has no effect on length of hospitalization, SARS-CoV-2 viral shedding or mortality rates.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Wuhan Union Hospital [0124-1] and the patients consented to publication. This study does not contain any personal information that could lead to the identification of the patients.

Competing interests

The authors declare no competing interests.

Acknowledgements

We thanks all members of Wuhan Union Hospital for data collection and our health care workers for their dedication to the care for 2019n-Cov pneumonia patients in Wu Han.

Funding

This work was supported by the Fundamental Research Funds for the Central Universities [grant number 2020kfyXGYJ009].

Ethical approval

This study was approved by the institutional review board of Wuhan Union Hospital [0124-1].

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Tables

Table 1 General characteristics of the patients between corticosteroid treatment and no corticosteroid treatment groups in 120 critically ill patients

	Total（n＝120）	Corticosteroid treatment （n＝71）	No corticosteroid treatment（n＝49）	P value
Age（year	61.5(47-70)	64(47-71)	58(47-67)	0.546
Male	68(56.7)	43(60.6)	25(51.0)	0.300
Cough	78(65.0)	46(64.8)	32(65.3)	0.953
Sputum	44(36.7)	29(40.9)	15(30.6)	0.253
Dyspnoea	52(43.3)	33(46.5)	19(38.8)	0.403
Fatigue	80(66.7)	51(71.8)	29(59.2)	0.149
Fever	103(85.8)	63(88.7)	40(81.6)	0.273
Highest temperature,℃	38.5(38-39.2)	38.5(38-39.2)	38.9(37.5-39.3)	0.949
Duration of fever,d	10(5-14)	10(7-14)	10(2-14)	0.312
Neutrophils, G/L	4.59(2.96-7.07)	5.07(3.1-7.02)	4.35(2.62-7.43)	0.687
Leucocytes, G/L	0.73(0.47-1.06)	0.67(0.41-0.99)	0.85(0.59-1.15)	0.022
Lactate dehydrogenase,U/L	331.5(231-475)	379(258-519)	264(194-379)	0.004
Alanine aminotransferase,U/L	34.5(20-59.5)	35(20-60)	34(20-55)	0.619
Serum creatinine,umol/l	70.5(58.45-87.4)	73.4(58.4-88.1)	66.4(58.5-80.4)	0.318
C-reactive protein ,mg/L	43.85(11.38-93.68)	65.35(17.93-99.59)	28.32(7.32-66.28)	0.033
D-dimer≥1（ug/ml	55(45.83)	34(47.89)	21(42.86)	0.587
troponin I	7.25(2.55-19.56)	7(2.9-24.9)	7.3(2.3-16.4)	0.518
Hypertension	41(34.2)	28(39.5)	13(26.5)	0.143
Diabetes	15(12.5)	8(11.3)	7(14.3)	0.623
Coronary heart disease	14(11.7)	8(11.3)	6(12.2)	0.870
Chronic kidney disease	3(2.5)	3(4.2)	0(0)	0.269
Chronic pulmonary	3(2.5)	3(4.2)	0(0)	0.269

disease				
Other comorbidities	18(15)	8(11.3)	10(20.4)	0.168
Antibiotic treatment	119(99.2)	71(100)	48(98.0)	0.408
Mechanical ventilation	38(31.7)	33(46.5)	5(10.2)	0.000
Died	23(19.2)	20(28.2)	3(6.1)	0.003
the length of hospitalization,d	25(11-40)	21(12-39)	25.5(11-40)	0.715
the length of viral shedding□d	18(13-24)	18.5(12-29)	17.5(13-22)	0.668

Data reported as n (%) or median

The P value of the data comparison between the corticosteroid treatment group and the no corticosteroid treatment group comes from the chi-square test□Fisher exact test and the Mann-Whitney U test

All the above patients' lung imaging is bilateral infiltration, and all are given antiviral treatment

Table 2 General characteristics of the patients between corticosteroid treatment and no corticosteroid treatment groups in 66 critically ill patients□propensity-matched case–control study

	Total（n＝66）	Corticosteroid treatment（n＝33）	No corticosteroid treatment（n＝33）	PValue
Age，year	63.5(47-71)	64(51-71)	58(47-69)	0.366
Male	35(53.0)	18(54.6)	17(51.5)	0.805
Cough	43(65.2)	21(63.6)	22(66.7)	0.796
Sputum	21(31.8)	11(33.3)	10(30.3)	0.792
Dyspnoea	30(45.5)	17(51.5)	13(39.4)	0.323
Fatigue	50(75.8)	24(72.7)	26(78.8)	0.566
Fever	56(84.9)	30(90.9)	26(78.8)	0.170
Highest temperature, ℃	38.4(38-39)	38.4(38-38.5)	38.4(37.5-39)	0.913
Duration of fever,d	10(5-14)	12(9-15)	10(1.5-13)	0.055
Neutrophils, G/L	4.75(2.72-7.43)	3.84(2.81-6.2)	5.41(2.62-8.71)	0.555
Leucocytes, G/L	0.81(0.53-1.14)	0.81(0.52-1.06)	0.84(0.64-1.14)	0.635
Lactate dehydrogenase,U/L	295(194-396)	298(218-396)	264(194-393)	0.434
Alanine aminotransferase,U/L	30(17-46)	32(17-46)	26(17-44)	0.842
Serum creatinine,umol/l	71.15(58.2-83.2)	77.4(58.2-87.9)	66.1(58.5-77.8)	0.336
C-reactive protein ,mg/L	36.99(6.4-85.06)	39.75(8.8-75.85)	34.29(6.4-91.57)	0.798
D-dimer≥1，ug/ml	30(45.45)	16(48.48)	14(42.42)	0.621
troponin I	5.95(2.3-11.7)	4.3(2.5-11.4)	7.3(2.3-15.6)	0.560
Hypertension	22(33.3)	11(33.3)	11(33.3)	1.000
Diabetes	11(16.7)	6(18.2)	5(15.2)	0.741
Coronary heart disease	5(7.6)	2(6.1)	3(9.1)	1.000
Chronic kidney disease	1(1.5)	1(3.0)	0(0)	1.000
Chronic pulmonary disease	2(3.0)	2(6.1)	0(0)	0.492

Other comorbidities	10(15.2)	3(9.1)	7(21.2)	0.170
Antibiotic treatment	66(100)	33(100)	33(100)	0.170
Mechanical ventilation	9(13.6)	4(12.1)	5(15.2)	1.000
Died	5(7.6)	2(6.1)	3(9.1)	1.000
the length of hospitalization,d	23(12-38)	29(14-39)	21.5(8-35)	0.112
the length of viral shedding□d	18(13-23)	19(14-29)	18(13-21)	0.473

Data reported as n (%) or median

The P value of the data comparison between the corticosteroid treatment group and the no corticosteroid treatment group comes from the chi-square test□Fisher exact test and the Mann-Whitney U test

All the above patients' lung imaging is bilateral infiltration, and all are given antiviral treatment