Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-1

Xiaowei Fang , Qing Mei , Tianjun Yang , Lei Li , Yinzhong Wang , Fei Tong , Shike Geng , Aijun Pan

PII: S0163-4453(20)30168-7
DOI: https://doi.org/10.1016/j.jinf.2020.03.039
Reference: YJINF 4513

To appear in: *Journal of Infection*

Accepted date: 24 March 2020

Please cite this article as: Xiaowei Fang , Qing Mei , Tianjun Yang , Lei Li , Yinzhong Wang , Fei Tong , Shike Geng , Aijun Pan , Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-1, *Journal of Infection* (2020), doi: https://doi.org/10.1016/j.jinf.2020.03.039

Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-1

Keywords: COVID-19; SARS-CoV-2; corticosteroid; viral clearance;

Dear Editor,

Since December 2019, Corona Virus Disease 2019 (COVID-19) cases have occurred in Wuhan, Hubei (1). The epidemic spread rapidly to other regions outside of China and had a great impact on public health and the economy. To the best of our knowledge, no specific antiviral treatment for COVID-19 has been confirmed so far. A recent study demonstrated that cytokine storm syndrome is associated with the severity of COVID-19 (2). Due to their anti-inflammatory and immunoregulatory properties, corticosteroids have been widely used in China for the treatment of patients with COVID-19, especially in cases with secondary acute respiratory distress syndrome (ARDS). Furthermore, China's National Health Commission has released a Diagnosis and Treatment Scheme for Pneumonitis with COVID-19 Infection (3). According to this, systemic corticosteroid therapy (methylprednisolone, <1-2 mg per kg of body weight, 3-5 days) is recommended as adjuvant therapy (3). The release of this guideline immediately caused controversy regarding whether patients with COVID-19 could benefit from corticosteroid therapy, since this has been associated with a delay in viral clearance. The present study investigated the effect of low-dose corticosteroid therapy on SARS-CoV-2 clearance time.

The present study collected clinical data of 78 patients with confirmed COVID-19 who were admitted to the Infectious Diseases Branch of Anhui Provincial Hospital between January 22, 2020 and March 1, 2020. A total of 55 and 23 cases were diagnosed with general and severe COVID-19, respectively. All patients received standard treatment, including antiviral therapy, oxygen therapy, antibacterial

drugs and symptomatic therapies. Furthermore, patients in the severe group received the necessary supportive treatment. Corticosteroids were administrated to a subset of patients according to severity and the individual opinion of clinicians. More severe patients were treated with corticosteroids, leading to inconsistent baseline data (i.e., age, comorbidities and laboratory findings) between patients receiving corticosteroids and those who did not. Therefore, the 78 patients were divided into a general and a severe group, and separate data analysis was conducted for each group. Table 1 shows the demographic characteristics, comorbidities, laboratory test results and antiviral treatment of patients with or without corticosteroid treatment in the general and severe groups. In total, there were 25 patients who received corticosteroids, while the remaining patients did not receive corticosteroids (Table 1). Oral methylprednisolone [median hydrocortisone-equivalent dose, 237.5 mg/day (IQR, 206.3-300.0 mg/day)] was administered to 9 patients in the general group for a median duration of 7 days (IQR, 5.5-8.0 days), while intravenous methylprednisolone [median hydrocortisone-equivalent dose, 250.0 mg/day (IQR, 250.0-250.0 mg/day)] was administered to 16 patients in the severe group for a median duration of 4.5 days (IQR, 3.5-5.8 days). The 9 patients in the general group received a higher total dose of corticosteroids and had a longer duration of corticosteroids treatment, since all of them were hospitalized at the early stage of the epidemic and treated by the same medical team. Starting at 3 days after admission, ~2-3 throat swabs or sputum samples were routinely collected once per week from all patients for reverse transcription-polymerase chain reaction (RT-PCR) testing to assess viral clearance. If the RT-PCR test result was negative, the test was repeated the next day to avoid false-negative results. Briefly, an independent sample t-test was conducted to compare virus clearance time between the corticosteroid group and the non-corticosteroid group, and there was no significant difference identified in both patients in the general group (17.6±4.9 vs. 18.7±7.7 days; P=0.667) and patients in the severe group (18.8±5.3 vs. 18.3±4.2 days; P=0.84).

There has been controversy regarding whether corticosteroid use may delay viral

clearance in patients with viral pneumonia for a long time. Initially, this phenomenon was observed in studies investigating severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus (MERS) (4, 5). However, the dose of corticosteroids may have a significant impact on the results. An observational study by Cao on influenza A (H7N9) viral pneumonia has demonstrated that high doses of corticosteroids (>150 mg/d methylprednisolone) are associated with increased risks of mortality and delayed viral clearance, while there was no difference between patients in the low-dose group (25-150 mg/d methylprednisolone) and controls (6). In the present study, all 25 patients were treated with low-dose corticosteroids, and the conclusions were similar to those of Cao.

In another retrospective observational study reporting on patients with MERS who were critically-ill, nearly half of the enrolled patients received low-dose corticosteroids [median hydrocortisone-equivalent dose, 300.0 mg/day (IQR, 200.0-400.0 mg/day)] (5). When compared with the cases who were not treated with corticosteroids, the authors concluded that the administration of corticosteroids was associated with delayed viral clearance. Unlike in the study reporting on MERS, the patients enrolled in the present study exhibited an improved health status. Even in patients in the severe group, the SOFA score on the first day of admission was much lower than that of patients with MERS [2.0 (IQR, 0-2.8) vs. 9.0 (IQR, 6.0-12.0)] (5). Therefore, these two studies involved patients with different severities of illness; however, whether corticosteroids exerted greater effects in critically-ill patients requires further investigation. Furthermore, the study reporting on patients with MERS included RT-PCR data from 14 intensive care units, and the nucleic acid test results were not protocolized and varied among centers (5). In the present study, all patients were from a single center, and all swab samples were tested using a unified approach at the Chinese Center for Disease Control to avoid measurement bias.

In fact, a similar study analyzing data from 72 patients with COVID-19 was conducted at the First Affiliated Hospital of Zhejiang University, and the conclusions were consistent with the results of the present study (7). However, these two

retrospective studies have unavoidable limitations, such as small sample size, poor controllability of the data and bias in the process of data collection. In conclusion, low-dose corticosteroid therapy may not delay viral clearance in patients with COVID-19; however, this still needs to be confirmed by well-designed and large-scale RCTs with a longer follow-up duration.

Ethics approval and consent to participate

Ethics approval was obtained from Anhui Provincial Hospital Institutional Review Board (ethical approval no. 2020-P-008).

Declarations of interests

The authors declare that they have no competing interests.

Consent for publication

All the authors agree to publish.

Acknowledgments

We thank all medical staff working in the Infectious Diseases Branch of Anhui Provincial Hospital for their essential assistance with case collection. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Chen J, Qi TK, Liu L, Ling Y, Qian ZP, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020 Mar 11. PMID: 32171869.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet.2020 Feb 15; 395(10223): 497-506. PMID: 31986264.

3. National Health Commission of the People's Republic of China. The 5th trial version of Diagnosis and Treatment Scheme for Pneumonitis with 2019-nCoV Infection (In Chinese). [cited 2020 Mar 20]. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml (2020).

4. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. 2004 Dec;31(4):304-9. PMID: 15494274.

5. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Al Mekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with the Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018 Mar 15;197(6):757-767. PMID: 29161116.

6. Cao B, Gao H, Zhou B, Deng X, Hu C, Deng C, et al. Adjuvant Corticosteroid Treatment in Adults With Influenza A (H7N9) Viral Pneumonia. Crit Care Med. 2016 Jun;44(6):e318-28. PMID: 26934144.

7. Ni Q, Ding C, Li YT, Zhao H, Liu J, Zhang X, et al. Retrospective study of low-to-moderate dose glucocorticoids on viral clearance in patients with novel coronavirus pneumonia. Chin J Clin Infect Dis. 2020,13 (2020-02-28). [cited 2020 Mar 20]. Available from: http://rs.yiigle.com/yufabiao/1182773.htm.

Table 1. Demographics and baseline characteristics of patients infected with COVID-19 according to illness severity and corticosteroid use.

Variable	General group (n=55)			Severe group (n=23)		
	Corticosteroids (n=9)	No Corticosteroids (n=46)	P-value	Corticosteroids (n=16)	No Corticosteroids (n=7)	P-value
Age (years), mean ± SD	40.2±12.6	39.9±15.5	0.959	60.6±13.6	54.3±15.4	0.33
Male sex, n (%)	5 (55.6)	22 (47.8)	0.952	12 (75)	5 (71.4)	>0.99
Days from onset of symptoms to hospitalization, median (Q1, Q3)	7 (4, 7.5)	5 (3, 7)	0.305	6.39±3.9	8.3±3.6	0.429
SOFA score, median (Q1, Q3)	/	/	/	2.0 (0, 2.8)	2.0 (1.0, 3.0)	0.702
ARDS, n (%)	0	0	/	8 (50)	1 (14.3)	0.176
Comorbidities						
Hypertension, n (%)	1 (11.1)	4 (8.7)	>0.99	8 (50)	2 (28.6)	0.405
Diabetes, n (%)	1 (11.1)	3 (6.5)	0.522	4 (25)	0	0.273
Coronary heart disease, n (%)	0	1 (2.2)	>0.99	2 (12.5)	0	>0.99
Cerebrovascular disease, n (%)	0	0	/	2 (12.5)	1 (14.3)	>0.99
Chronic kidney disease, n (%)	0	2 (4.3)	>0.99	1 (6.3)	0	>0.99
Chronic liver disease, n (%)	2 (22.2)	1 (2.2)	0.066	0	0	/
Malignant tumor, n (%)	0	1 (2.2)	>0.9	0	0	/

			9			
Immunosuppressive, n (%)	0	1 (2.2)	>0.99	0	0	/
WBC count ($x10^9$/L), median (Q1, Q3)	4.6 (4.0, 5.5)	4.9 (3.9, 6.0)		6.5 (5.5, 10.6)	5.4 (4.8, 11.9)	0.789
Lymphocyte count ($x10^9$/L), median (Q1, Q3)	0.89 (0.84, 1.38)	1.33 (1.16, 1.79)	0.062	0.62 (0.37, 0.98)	1.14 (0.73, 1.36)	0.082
CRP (mg·/L), median (Q1, Q3)	22.1 (8.9, 36.4)	4.2 (0.7, 16.6)	0.091	47.8 (30.0, 102.3)	23.5 (8.5, 72.0)	0.124
PCT <0.5 ng/mL, n (%)	9 (100)	46 (100)	/	15 (93.8)	7 (100)	>0.99
PT (s), median (Q1, Q3)	14 (13.6, 15.3)	14.4 (13.4, 16.2)	0.793	14.3 (13.0, 15.0)	14.1 (13.7, 14.6)	0.894
APTT (s), median (Q1, Q3)	38.7 (35.3, 42.0)	37.1 (34.6, 42.9)	0.649	35 (30.2, 39.5)	36.7 (27.4, 38.8)	0.462
D-Dimer (μg/ml), median (Q1, Q3)	0.25 (0.2, 0.29)	0.18 (0.08, 0.25)	0.09	0.45 (0.25, 0.62)	0.22 (0.19, 0.63)	0.452
Troponin I (μg/L), median (Q1, Q3)	0.08 (0.07, 0.11)	0.08 (0.06, 0.19)	0.90	0.31 (0.09, 0.56)	0.12 (0.1, 0.44)	0.72
Total bilirubin (μmol/L), median (Q1, Q3)	14.5 (12.6, 23.3)	14.9 (11.3, 19.3)	0.838	17.1 (15.3, 21.4)	17.1 (11.1, 19.4)	0.452
Albumin (g/L), median (Q1, Q3)	44.2 (41.0, 45.0)	44.9 (41.3, 47.7)	0.847	35.2 (32.9, 37.4)	39.3 (36.8, 42.2)	0.022
Creatinine (μmol/L), median (Q1, Q3)	66 (58, 71)	71 (60, 81)	0.052	74.0 (54.0, 82.0)	68 (59, 76)	0.82
Antiviral therapy						
Lopinavir/Ritonavir only, n (%)	7 (77.8)	37 (80.4)	0.785	4 (25.0)	3 (42.9)	0.626
Lopinavir/Ritonavir+IFN-α inhalation, n (%)	2 (22.2)	9 (19.6)		12 (75.0)	4 (57.1)	
TCM, n (%)	3 (33.3)	19 (41.3)	0.941	16 (100)	6 (85.7)	0.304

Methylprednisolone						
Oral, n (%)	9 (100)	/	/	0	/	/
Intravenous, n (%)	0	/	/	16 (100)	/	/
Duration of corticosteroid treatment (days), median (Q1, Q3)	7 (5.5, 8.0)	/	/	4.5 (3.0, 5.8)	/	/
Total dose of methylprednisolone (mg), median (Q1, Q3)	280 (220, 360)	/	/	160 (120, 240)	/	/
Dose of methylprednisolone per day (mg), median (Q1, Q3)	38 (33, 48)	/	/	40 (40, 40)	/	/
Time to SARS-CoV-2 RNA clearance (days), mean ± SD	17.6±4.9	18.7±7.7	0.667	18.8±5.3	18.3±4.2	0.84

WBC white blood cell, CRP C-reaction protein, PCT Procalcitonin, TCM Traditional Chinese Medicine, PT prothrombin time, APTT Activated partial thromboplastin time