Clinical efficacy of corticosteroids in the early stage of worsening of COVID-19 pneumonia

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Case Report

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Abstract

Background: The World Health Organization (WHO) recommends using corticosteroids in patients with severe coronavirus disease 2019 (COVID-19) and acute respiratory distress syndrome (ARDS), and a large randomized controlled clinical trial in the UK found that dexamethasone was effective in reducing the number of deaths in patients with severe COVID-19.

Case presentation: Herein, we described a case of COVID-19 with the clinical characteristics of the mild-symptomatic stage deteriorating to a critically ill state, who showed dramatic improvement with corticosteroids in the early stage of worsening of COVID-19 pneumonia.

Discussion: This article further discusses the most suitable timing and dosage of corticosteroid to maximize its effect during the worsening of COVID-19 pneumonia.

Learning points:

• One of the main pathophysiological hypotheses for severe COVID-19 pneumonia is related to cytokine storm and viral load.

• The clinical factors should be considered as the initial sign of a cytokine storm, and corticosteroid therapy may be useful in these patients.

Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered coronavirus, namely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. To date, there is no licensed treatment or approved vaccine to combat COVID-19. COVID-19 is highly infectious and can lead to fatal comorbidities, especially acute respiratory distress syndrome (ARDS). Various pro-inflammatory cytokines were found to be elevated in patients infected with SARS-CoV-2, suggesting the possible existence of a cytokine storm [2] in some patients. Furthermore, patients that require intensive care unit (ICU) admission showed higher concentration of particular cytokines compared with those not requiring ICU admission, suggesting that the levels of pro-inflammatory cytokines were associated with disease severity [3,4]. Therefore, it is essential to develop an effective treatment strategy to control the spread of the virus and prevent the formation of cytokine storm. Corticosteroids have been used in some patients to suppress the cytokine storm [5-8]. However, evidence from patients with Middle East Respiratory Syndrome (MERS) and ARDS indicated that corticosteroids did not provide a survival benefit [9], but delayed the clearance of the virus. Therefore, the systemic use of corticosteroids is not recommended by the World Health Organization (WHO). In another study, low but not high-dosage corticosteroids reduced mortality in people with ARDS [10], suggesting that dosage may be an important co-variate in data analyses. Hence, we discussed questions related to the timing and dosage of corticosteroid administration.

Case Presentation

On February 9, 2020, a 52-year-old Chinese woman from Hebei was admitted to the Petroleum Clinical Medical College of Hebei Medical University, with cough and fever that lasted three days and two days, respectively. The patient's medical history included hypertension and coronary heart disease for eight years. The patient's medications included one tablet each of Nifedipine extended-release (30 mg) and Bayaspirin (100 mg) orally taken daily. The patient denied a history of recent travel, however, she was in close contact with her son who had tested positive for COVID-19 five days ago. She was immediately isolated in an airborne infection isolation room (AIIR) because her throat swab tested positive for SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR).

The patient's body temperature was 38.6^{o}C, with oxygen saturation of 91% on room air and respiratory rate of 20 breaths/min. On examination, her lungs were clear to auscultation. Laboratory investigations revealed 5.3×10^{9}/L white blood cell (WBC) count, 1.12×10^{9}/L lymphocyte count, 12.6 g/dL hemoglobin and 153×10^{9}/L platelet count. C-reactive protein (CRP) was elevated at 75.6 mg/L (≤7.5 mg/L), and procalcitonin was <0.1 ng/ml (normal ≤0.5 ng/ml).

At admission, her blood glucose was 11.28 mmol/L, with glycosuria+++, and ketone bodies±. Her liver and renal function tests, and serum lactate were normal. However, chest CT showed subtle ground-glass opacities or consolidation in both lungs, affecting 20-30% of the total pulmonary parenchyma, without pleural effusion (Fig. 1). She was treated with lopinavir/ritonavir tablets (two tablets twice daily), Arbidol capsule (two capsules three times daily), α-interferon atomization inhalation (5 million units, twice daily) and traditional Chinese medicine (Lianhua Qingwen capsule, four tablets twice daily).

Within two days of admission, the patient presented with persistent fever, severe dry cough and shortness of breath. She was tachypneic at 34 breaths/minute. Her oxygen saturation was 86% by mask oxygen inhalation at 5 L/min.

Repeat chest CT showed rapid development of bilateral diffuse ground-glass opacities affecting 25-50% of the total pulmonary parenchyma, associated with alveolar condensations and bronchial signs. Bedside ultrasonography revealed left ventricular ejection fraction (LVEF) 50%, ventricular wall motion normality, and Kerley's B line on bilateral dorsal lungs.

She received high-flow-oxygen therapy (flow rate of 60 L/min, oxygen concentration of 65%) and maintained at 88% oxygen saturation (SaO_2). Treatment with intravenous methylprednisolone (40 mg/day, five days) and furosemide (20 mg immediately) was initiated. Meanwhile, the amount of exercise by the patient was reduced and low molecular weight heparin (LMWH, 0.3 ml once every 24 hours) was subcutaneously injected.

After three days of administration, the patient's body temperature was 36.8^{o}C, while the blood pressure was 78/50 mmHg, with depressed spirit and profuse sweating. Laboratory examinations showed normal WBC count, liver function, kidney function, troponin, amino-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimer level and electrocardiogram. However, lymphocyte count (0.59×10^{9}/L) was significantly lower than previous test, and Fasting blood glucose

was 20.19 mmol/L. Thereafter, 0.9% saline (250 ml) was rapidly infused (10 min), but no significant improvement was observed. Based on blood pressure and blood glucose levels, vasoactive drugs dopamine and insulin were administered. The blood pressure was maintained at 90-100/60-70 mmHg and blood glucose at 13-15 mmol/L. The patient was intubated and initiated on mechanical ventilation because her oxygenation index was low (122 mmHg) and her condition did not show obvious improvement in a few hours, with an increase in oxygen requirements.

Despite the deep sedation, significant ventilator dyssynchrony was initiated to maintain the lungs' protective ventilation. The patient was supported with a volume-controlled ventilation: tidal volume 350 ml, FiO_2 0.8, PEEP 10 cmH_2O and respiratory rate 20 breaths/min, with a platform pressure of 20 cmH_2O. Repeat arterial blood gas showed that pH was 7.43, partial pressure of carbon dioxide ($PaCO_2$) was 38.8 mmHg and PaO_2 was 158 mmHg. After adjusting FiO_2 to 0.55, the patient did not require prone ventilation.

After five days of mechanical ventilation, normothermia and oxygenation were achieved, ground glass opacities on chest X-ray improved and all bacterial cultures returned negative. Thereafter, she was successfully extubated.

On day 15 post-admission, the patient's pharyngeal swab tested negative for COVID-19 (Table 1).

During the post-discharge follow-ups, the patient reported no special discomfort, with chest CT improvement at 1, 3 and 6 months (Figure 1).

Discussion And Conclusion

According to the WHO data, China had about 17,000 patients when COVID-19 was first reported. Among those patients, 82% were mildly infected cases; 15% were severely infected cases; 3% were critically ill cases. Overall, China had a mortality rate of 2%. However, 50% of the mortality was associated with critically ill patients [1,5,8]. Thus, it was recommended to closely monitor the characteristics and intervention of patients during the transition from mild to severe stage. Herein, we described the clinical course of COVID-19 infection in a patient who rapidly developed ARDS, requiring intubation. This case highlighted the need to identify risk factors associated with critical illness so that at-risk patients can be promptly identified and closely monitored.

1. *Risk factors for the worsening of COVID-19*

Studies have shown that elderly and people with underlying comorbidities are at increased risk during the treatment of COVID-19 infection because they are susceptible to more severe disease. Among the death cases due to COVID-19, 60.9% of patients had hypertension; 47.8% had diabetes; 17.4% had cardiovascular diseases. Among the critically ill patients, the proportions of patients with hypertension, diabetes, and cardiovascular diseases were as high as 58.3%, 22.2%, and 25%, respectively [1,5,6,11-14]. In addition, the use of drugs for patients who have underlying diseases will worsen the SARS-CoV-2 infection. Previous studies have confirmed that SARS-CoV-2 uses angiotensin-converting enzyme II (ACE2) as the receptor to enter human cells [15]. ACE2 is an isoenzyme of ACE, however, they have different effects. ACE2 facilitates vasodilation, which causes the lowering of blood pressure. ACEI antihypertensive drugs can inhibit the function of ACE while increasing the reflectivity of ACE2. In Ferrario's study, the use of ACEI antihypertensive drugs in mice caused the level of ACE2 to increase by 4.7 times [16]. Thus, COVID-19 patients with associated complications, such as hypertension in the present case, will increase the rate of replication of the virus and the severity of the disease if ACEI drugs are used. Moreover, the viral infection itself also worsens the underlying diseases. For example, ACE2 is expressed in the pancreas. During SARS-CoV-2 infection, the islets of Langerhans can be damaged by insulin receptors, which worsens diabetes. Long-term hyperglycemia in diabetes patients will inhibit the phagocytosis ability of WBCs. The damage of WBCs is often accompanied by immune abnormalities.

2. *Theories of "viral load", "cytokine storm" and clinical manifestations*

According to the Lancet, SARS can lead to the infection of the lower respiratory tract, and SARS-CoV-2 receptor is highly expressed in both upper and lower respiratory tracts [7]. Immune response and inflammation are the main methods by which viruses are "killed". Cytokine storm is induced when immune response and high viral load occur at the same time. The inflammation response leads to a vicious cycle that continues to cascade and expand, producing numerous inflammatory mediators and cytokines. This process leads to the damage of vascular endothelial cells, alveolar epithelial cells, and interstitial components; ultimately resulting in pulmonary edema, respiratory failure, and death.

The clinical difference between SARS and SARS-CoV-2 is that SARS-CoV-2 patients experience a milder symptom of dyspnea as observed by comparing lung CT images. However, hypoxemia appears more consistent with the CT scan. Findings from many published clinical cases demonstrated that during the worsening of SARS-CoV-2, clinicians should closely monitor the following factors: a persistent fever, progressive dyspnea, continuously declining oxygenation, progressively declining lymphocyte count, and rapid expansion in lung lesions shown by CT images. Most importantly, the increase in ground-glass opacities (50% increase in 48 hours) and alveolar consolidation should be carefully observed [17]. Many scholars also monitored the ratio of neutrophils and lymphocytes, the continuous decline in CD4+ and CD8+ T cells, and the progressive increase in IL-6 and CRP. The symptoms described above, or abnormal laboratory and lung CT findings suggest worsening of the disease, and intervention treatments should be administered at the earliest.

3. *Complications of SARS-CoV-2 infection*

High-flow-oxygen inhalation and invasive ventilation were necessary for our patient with severe acute respiratory infection and respiratory distress on day 3 of admission. After nearly five days of invasive ventilator-assisted respiration and drug therapy, the patient's arterial partial pressure of oxygen, oxygenation index, and oxygen saturation had significantly improved. One of the factors that lead to the worsening of COVID-19 is the complication of ARDS.

ARDS is the most common complication of COVID-19. The incidence of ARDS in critically ill patients is as high as 67%, and the mortality rate after ARDS is nearly 50%. The factors that typically trigger ARDS exist in the respiratory tract, lung interstitium, and blood circulation. SARS-CoV-2 infection damages the

pulmonary vascular endothelium, increasing vascular permeability, causing massive fluid and proteins to enter the interstitium of the lungs. Furthermore, the alveolar epithelial damage increases the difficulty in clearing alveolar fluids and proteins. Extensive accumulation of proteins is observed in the alveolar cavity, and the exuded fibrinogen aggregates into cellulose, forming a transparent membrane with the epithelial debris of necrotic alveoli. Pulmonary edema and the formation of the transparent membrane reduce the surface area of the alveoli, increasing the thickness of the alveolar diffusing membrane, ultimately leading to an insufficient supply of oxygen.

SARS-CoV-2 can infect the lungs for the second time through the ACE2 receptor on the pulmonary capillaries. Next, the virus combines with the ACE2 receptor on the systemic capillaries to enter tissues and organs, tagging the vascular endothelial cells. Thus, the immune system can attack the vascular endothelial cells. The simultaneous occurrence of immune response and high viral load can induce a cytokine storm, which produces numerous inflammatory mediators and cytokines, leading to partial or full damage of body organs, mainly represented by the collapse in the lungs.

According to Medrxiv's research, ACE2 expression is higher in human kidneys (100 times higher than in lungs). Among 59 cases of COVID-19, 63% of the patients had proteinuria; 19% and 27% of the patients had increased creatine and urea nitrogen, respectively. Additionally, all the patients had kidney abnormalities, indicating that COVID-19 can cause damage to the kidneys.

4. *Corticosteroids and COVID-19*

Various protocols recommend complementary treatments for managing complex severely ill COVID-19 patients. For example, antivirals, inhaled aerosolized recombinant human interferon and low-molecular-weight heparin [18] have been developed in various countries.

Corticosteroid is considered as a potential treatment for ARDS due to its role in reducing inflammation and fibrosis. It has been reported that treatment with methylprednisolone needs further evaluation. Specifically, corticosteroids may affect virus clearance in COVID-19 patients, but may be beneficial in severe progressive patients [19,20].

Kang [21] reported a comparison of corticosteroid use between severe and non-severe COVID-19 patients. Their definition of severe COVID-19 pneumonia was the same as that of the WHO: fever or suspected respiratory infection, along with one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or arterial oxygen saturation measured by pulse oximeter (SpO_2) ≤93% on room air. The WHO definition of "severe" includes patients admitted to the hospital with pneumonia who can be managed in medical wards and are not critically ill. The best evidence suggests that about 85% of such patients will never progress to critical illness such as ARDS [5]. They suggest using corticosteroids in patients with severe COVID-19 and ARDS (weak recommendation). Every country or region has its guidelines on the usage of corticosteroids for COVID-19 pneumonia (Attached Table 1).

In clinical practice, known antivirals are ineffective in severe COVID-19, wherein the cause of uncontrolled disease may be a cytokine storm. To halt the progression of the disease, corticosteroids may play a role in controlling the cytokine storm. However, several questions remain. When is the most effective time for corticosteroid therapy? Which dosages or durations are appropriate?

Studies have shown that less than half of the COVID-19 patients were given systemic corticosteroids, mostly in severely ill patients with ARDS [1,5,22]. Methylprednisolone shortened the duration of invasive mechanical ventilation and lowered the mortality in ARDS patients [18,22,23].

5. *Appropriate timing for the usage of glucocorticoids in COVID-19 patients*

The pathological manifestations of COVID-19 are mostly diffuse alveolar damage and fibrous mucus exudation with severe inflammatory lesions. Thus, many experts believe that glucocorticoids are an effective treatment for COVID-19, but not for mild infections. To reduce or prevent the occurrence of ARDS, specialists suggest that glucocorticoid treatment is necessary for critically ill patients.

Clinically, some doctors administered a low-to-moderate dosage of glucocorticoids. The dosage used depends on the rapid increase of imaging sites and the scope of expansion of consolidation, as well as the severity of the oxygenation index [23]. In addition to the vital signs determined by the clinicians, lung CT is another useful tool for determining whether COVID-19 pneumonia has worsened. Typical CT features are described as bilateral multiple lobular and sub-segmental areas of consolidation in patients admitted in the intensive care unit (ICU), and bilateral ground-glass opacity and sub-segmental areas of consolidation in non-ICU patients [1]. The abnormalities are typically in peripheral and lower-lobe distributions. Another study indicated that the findings could be unilateral in up to 25% of the cases [11]. In resolving cases with less severity, chest CT images showed bilateral ground-glass opacities, whereas the consolidation had resolved [24].

The timing of the glucocorticoid usage in treating COVID-19 pneumonia should be based on the following factors: continuous fever; respiratory rate >30 breaths/min; severe respiratory distress; arterial oxygen saturation measured by pulse oximeter (SpO_2) ≤93% on room air; progressive decline in lymphocyte count; rapid expansion of lung lesions on CT image, especially the increase in ground-glass opacities (50% increase in 48 hours) or more consolidation. Any changes in the factors described above should be considered as the initial sign of a cytokine storm, and the early stage of glucocorticoids should be used for intervention.

6. *Clinical dosage of glucocorticoids used in patients with COVID-19 pneumonia*

Methylprednisolone use is controversial for SARS infection. In multiple cases, dose-related toxicity was observed. A lower dose of methylprednisolone (250–500 mg/day) demonstrated some improvements in a subset of critical SARS patients. However, prolonged usage in the absence of any specific antimicrobial agent predisposed the patients to disseminated fungal infection [19,20]. It was recommended that corticosteroids should only be used as a 'rescue therapy' and not as a treatment because it might impair the host viral clearance.

Several studies supported the use of corticosteroids at low-to-moderate doses in patients with virus infection. Reports showed that low-to-moderate doses of corticosteroids were also associated with reduced mortality in patients with viral pneumonia when the oxygenation index was <300 mmHg [25]. Recently, Song et al. reported that methylprednisolone treatment might be beneficial for patients with COVID-19 who developed ARDS [8].

Lei suggested improvement in clinical signs of patients using 40 mg methylprednisolone once or twice a day. Based on our clinical experience, continuous administration of 0.75 mg/kg of methylprednisolone once or twice a day for five days may improve patients' symptoms, especially difficulty in breathing. The use of corticosteroids is essential in the early stage of worsening of COVID-19 because it regulates immune response, which causes less damage to lung tissues.

7. Other treatments are also necessary for severe COVID-19 patients, such as humidified oxygen with high-flow rate and volume in the early stage of the disease, ventilation in supine position, moderate fluid restriction, plasma of anti-COVID-19 antibodies in the recovery period [26], subsequent mechanical ventilation, ECOM, etc.

In conclusion, Corticosteroid treatment for COVID-19 remains controversial as the evidence is inconclusive, and the general recommendation is not advisable. However, many experts recommend to use corticosteroids for severe COVID-19 patients who have not yet developed ARDS. We recommend that a low-to-moderate dose of corticosteroids (0.75 mg/day) should be used for a short period (five days), with caution. The decision of the initial corticosteroid treatment should be based on the judgment of the clinical course, such as continuous fever, lower blood oxygen, progressive decline in lymphocytes, rapid progression in lung CT, etc. Lastly, it is necessary to detect the associated complications and assess the treatment responses to corticosteroids.

List Of Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; AIIR: airborne infection isolation room; RT-PCR: reverse transcriptase-polymerase chain reaction; LVEF: left ventricular ejection fraction; LVEF: left ventricular ejection fraction; ACE2: angiotensin-converting enzyme II;

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committees of the Petroleum Clinical Medical College of Hebei Medical University [KYLL-2020-06], and all participants provided written informed consent.

Consent for publication

All participants provided written informed consent for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to Hebei law but are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

ZL and D-FZ took care of the patient, carried out the studies, participated in collecting data, and drafted the manuscript. HW and J-QL performed critically for important intellectual content. QW, JL, C-JJ, C-LG and J-ML took care of the patient and participated in acquisition, analysis, or interpretation of data and drafted the manuscript. All authors read and approved the manuscript.

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Table

Table 1. Clinical course of the patient after admission

Day of illness	3	4	5	6	7	8	9	10	11	12
Day of hospitalization	1	2	3	4	5	6	7	8	9	10
Temperature(°C)	37	38.6	39	36.8	37	36.8	37	36.5	36	36.4
Neutrophil count(10^9/L)	3.96		6.4	5.74	6.48	4.74	5.74		12	8.35
Lymphocyte count(10^9/L)	1.12		0.59	0.71	0.48	0.59	0.94		1.13	0.55
Glutamic oxalacetic transaminase(U/L)	21		29		22		36		38	42
Albumin(g/L)	40.7		35		33.1		35.9		34.4	32.7
Fasting plasma glucose(mmol/L)	11.28		20.19		15.46		8.45		9.8	14.2
C-reactive protein（mg/L）	75.6				25.1				5	6.4
Creatinine(μmol/L)	41.6		60.3		63.3		38		36.9	32.2
Procalcitonin(μg/L)	0.1		0.16		0.19		0.15		0.1	0.1
Lactate dehydrogenase(U/L)	357		410		408		364		363	337
NT-proBNP (pg/ml)			303.4		218.8					122.9
D-dinner(ng/ml)					0.3		10		10	4.2
Oxygen supplementation	2L	5L	65%	80%	100%	60%	50%	45%	40%	40%
Mode of ventilation			High flow (60L/min)	High flow (60L/min)	Volume Control	Volume Control	Pressure support	Pressure support	Pressure support	High flow (45L/min)
Tide volume (ml)					450	450				
Pressure support (cmH2O)							20	15	12	
Plateau pressure (cmH2O)					23	20				
PEEP (cmH2O)					10	10	10	8	5	
Pao2/Fio2 ratio	189	143	132	96	104	208	254	337	462	252
Propofol（mg/hour）					30	30	30	40	10	
Midazuolun（ml/h）					4	3	3	6	3	
Morphine（mg/h）					3	2	1			
Fentanyl（ug/kg/h）								0.32	0.24	
Glasgow Coma Scale					Paralyzed	E2VT-M4	E2VT-M4	E2VT-M4	E4VT-M6	E4VT-M6
S-CoV-2 RT-PCR(throat swab)	Positive	Positive								
Antimicrobial therapy	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	Arbidol	Arbidol	Arbidol	Arbidol	Arbidol	Arbidol

Methylprednisolone (mg/d)			40	40	40	40	40			
24 hours fluid balance (ml) (Total input-total output)	620	200	-1350	-1060	1030	-182	50	-309	-880	-325

COVID-19: Coronavirus disease 2019; CT: Computed tomography; FiO2: Fraction of inspired oxygen; PaO2: Partial pressure of oxygen; PEEP: Positive end–expiratory pressure; RT-PCR: Reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2;E2VTM4:Eyes open and moto withdrawal in response to painful stimulation;E4VTM6: Eyes open spontaneously obeys commands for movement;E4V5M6: Eyes open spontaneously Oriented and obeys commands for movement