Pharmaceutical Sciences Asia

Pharm Sci Asia 2020; 47(3), 221-225
DOI:10.29090/psa.2020.03.019.0076

Mini Review

The role of corticosteroid for the treatment of Coronavirus Disease-2019 (COVID-19): A narrative review

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KEYWORDS:
COVID-19, ARDS, Corticosteroids, Cytokine Storms.

ABSTRACT

Acute respiratory distress syndrome (ARDS) is a most common complication in patients with severe COVID-19 with high rate of mortality. Corticosteroids have been used in the management of SARS-CoV and MERS-CoV several years ago. Data about the effectiveness of corticosteroids in the management of COVID-19 is lacking. It has been proposed that the corticosteroids have a modulatory effect by suppressing cytokine storms in severe COVID-19. The aimed of this study is to review literature that discussed the use of corticosteroids in patients with COVID-19 related ARDS. Pubmed database was used to select the article in this review with the keywords SARS-CoV-2, COVID-19, corticosteroid, pneumonia, and ARDS. Elderly and patients with underlying disease are more likely to develop severe COVID-19 and lead to ARDS. Because of the immunosuppressive activity, corticosteroid could modulate the cytokine storms in COVID-19 patients with ARDS. The use of corticosteroids may offer the benefit in COVID-19 with ARDS, by reduce the mortality rate and duration of treatment. The administration of corticosteroids should be considered in COVID-19 patients with signs of ARDS and refractory shock. The low until moderate dose and short treatment of corticosteroids are recommended to minimize the adverse effects.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause Corona Virus Disease-2019 or well known as COVID-19 [1]. In many cases, the symptoms of the disease such as cough, flu, and fever. However, it also cause severe respiratory infections, such as pneumonia and acute respiratory distress syndromes (ARDS), especially in elderly and patients with chronic underlying disease such as diabetes mellitus, cancer, and hypertension [2,3]. Generally, patients admitted to the ICU because of ARDS and or sepsis related to pneumonia [4].

Corticosteroids have been used in SARS-CoV and MERS-CoV patients with severe respiratory disease. However, the use of corticosteroids in COVID-19 patients was still controversial. Since World Health Organization stated that corticosteroids should not routinely used in COVID-19 unless any indications are needed[5]. Several studies have reported the findings of corticosteroids administration in COVID-19 patients, but these findings remains

controversial. In this review, we discussed the role of corticosteroids in COVID-19 patients.

2. METHOD

PubMed database was used to select the article to be reviewed in this study. The keywords to select the article were SARS-CoV2, COVID-19, corticosteroids, pneumonia, and ARDS. The inclusion criteria were the article to this review focused on the use of corticosteroids in COVID-19 with or without pneumonia and or ADRS. The exclusion criteria were the articles which not reported the clinical outcomes or laboratory findings of using corticosteroids in COVID-19 patients with or without pneumonia and or ARDS.

3. DISCUSSION

Prevalance and Criteria COVID-19 Related ARDS

Acute Respiratory Distress Syndrome (ARDS) is an emergency situation of the lungs due to the accumulation of fluid in the alveoli which causes disruption of gas exchange and reduce the distribution of oxygen to the tissues [6.] Approximately 15% of COVID-19 infection leads to severe cases and develops into multi organ dysfunctions syndrome (MODS), primarily respiratory failure, considering to ICU admission. The respiratory system is a most affected by COVID-19 with a small percentage damage to other organs. Several studies reported that incidence of acute myocardial injury was 7.2–17% and incidence of acute renal injury was 2.9–15% in severe case of COVID-19 patients. The incidence of ARDS in COVID-19 patients was 15.6–31% and the highest incidence of organ injuries. Dry cough was the most common symptom of COVID-19 and the production of sputum was less [7, 8–11].

The criteria for COVID-19 related to ARDS as follows [5] :

a. Initial: within 1 week of the onset or worsening of respiratory symptoms.
b. Chest imaging (radiography, CT scan, or ultrasonography): bilateral opacity, which cannot be distinguished whether due to excess fluid (volume overload), lobe collapse or lung collapse, or nodules.
c. Origin of pulmonary infiltration: respiratory failure that cannot be distinguished whether due to heart failure or excess fluid. Objective assessment (eg, echocardiography) is needed to ensure there is no hydrostatic cause of infiltration / edema if there are no risk factors.
d. Weakened oxygenation in adult patients:
    i. Mild ARDS: 200 mmHg <PaO2 / FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O, or not ventilated)
    ii. Moderate ARDS: 100 mmHg <PaO2 / FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O, or not ventilated)
    iii. Severe ARDS: PaO2 / FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O, or not ventilated)
    iv. If PaO2 is not available, SpO2 / FiO2 ≤ 315 indicates the occurrence of ARDS (including in patients who are not ventilated).

The ARDS WHO criteria defined that to diagnose as ARDS patient, the onset must be within one week of a known clinical insult or new or worsening respiratory symptoms . In some studies found that the onset of ARDS in COVID-19 patients was 8-14 days. It indicated that the one week onset limit defined by ARDS WHO criteria didn't apply to COVID-19 related ARDS [7,9,11] .

Immunology Reponses of COVID-19 Related ARDS

ARDS is a leading cause of death in COVID-19 patients. The incubation period of COVID-19 was begun about 3-14 days (median 5 days). In this period, leukocytes and lymphocytes is still normal or small decreased and the patient is asymptomatic. In the next phase (initial symptoms), the virus spreads through the bloodstream, especially in tissues that express ACE2 like lungs, digestive tract and heart. Symptoms in this phase is generally mild. The second attack occurred four to seven days after the initial symptoms. At this time patient still have fever and dyspnea, lesions in the lungs worsen, and decreased of lymphocytes count. Inflammatory markers start to increase and hypercoagulation occur. If not resolved, the inflammation process cause cytokines storm that lead to ARDS, sepsis, and other complications [12,13] .

Immune responses in patients with mild manifestations of COVID-19, an increase of activated T cells was observed, especially CD8 T

cells on day seven until nine. In addition, there was an increase in antibody secreting cells (ASCs) and follicular helper T cells in the blood on the 7th day, three days before symptom resolution. A progressive increase in SARS-CoV-2 IgM or IgG was also found from day 7 to day 20. These immunological changes last up to 7 days after the symptoms resolve. It also found a decrease in CD16+, CD14 + monocytes compared to healthy controls. Natural killer (NK) cells and monocyte chemo attractant protein-1 (MCP-1; CCL2) were also found to be decreased, but the levels were similar to healthy controls. It showed that in patients with non-severe manifestations of COVID-19 there was no increase in pro-inflammatory chemokines and cytokines, even when symptomatic [14] .

A lower lymphocyte count, leukocytes and a higher neutrophil-lymphocyte ratio, and a lower percentage of monocytes, eosinophils and basophils in severe cases of COVID-19 related ARDS. Pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8 and infection biomarkers such as procalcitonin (PCT), ferritin and C-reactive protein are also higher in severe clinical cases of COVID-19. Helper T cells, suppressor T cells, and regulator T cells were found to be decreased in with lower T helper and regulator T levels [15]. COVID-19 patients with ARDS also showed a decrease in CD4 and CD8 T lymphocytes. This excessive immune response cause lung damage and fibrosis resulting in functional disability [16].

The Rationale Use of Corticosteroids in COVID-19 Related ARDS

Corticosteroids are widely used for modulation of a variety of inflammatory conditions. They can be used in a daily dose regimen or a pulse therapy in autoimmune disease. However, the use of corticosteroids must be careful because of potential serious adverse effects. Corticosteroids modulate the process of hyper-inflammation and inhibit immune responses to protect a human body against the virus [17]. The use of steroid has been thought to be useful in the late phase of ARDS or well known as the fibroproliferative phase. The high level of plasma cytokine persistently leads to worsen ARDS survival rates. Late phase of ARDS with more than 7 days after onset is characterized by persistent inflammation that may respond to steroids [18]. Corticosteroids are considered for the treatment of ARDS. It because corticosteroids do not directly inhibit virus entry or virus replication, but their mechanism is anti-inflammatory and suppress immune response. Although the administration of corticosteroids to treat ARDS patients remains unclear, therapy with corticosteroids is proposed to reduce morbidity and mortality. In the early onset of inflammation, steroids reduce the dilation of capillary, leukocyte infiltration, inflammatory cell exudation, and phagocytosis. In the late onset, steroids inhibit over activity of capillary proliferation and reduce the activity of fibroblasts. Furthermore, by binding to their receptors, steroids inhibit the signaling of nuclear transcription factor-κB (NF-κB) and further inhibit the transcription and translation of inflammatory factors [19]. These was the reason why the administration of steroids therapy might be needed in severely ill patients with coronavirus infection.

In 2003, when SARS-CoV became an epidemic in some countries, corticosteroids were used as a part of therapy in SARS-CoV patients with severe respiratory disease. In a meta-analysis reported that the use of corticosteroid in SARS, only four studies indicated conclusive data and corticosteroid induced a higher mortality rate [20] . But this study was only reported on the similar coronavirus, SARS-CoV and MERS-CoV, not in SARS-CoV-2. Study has reported that the administration of corticosteroids increased the rates of infection, mortality and other complications in survivors of influenza pneumonitis. Moreover, corticosteroids when used in patients with SARS and MERS infection delayed the viral clearance [17]. In a RCT study included non-critically SARS patients, the early onset, or less than seven days of the disease, the use of hydrocortisone in early, less than 7 days of illness was associated with high level of plasma viral load [21] .

Based on the pathophysiology of inflammation in ARDS, there have been many studies on high-dose corticosteroids. In some studies, the aim was to prevent ARDS in patients with high risk, such as septic shock, whereas in other studies steroids are given in cases of ARDS that have manifested. Methylprednisolone was commonly used with a dose 30mg/kg BW every 6 hours for 1-2 days, but none of these studies showed the benefits of steroids, and one study mentioned a higher incidence of infections in patients receiving steroid therapy [8].

Shang, *et al*, considered the administration of corticosteroid in COVID-19 with pneumonia [22] . It is based on the study by Chen, *et al*, reported

that corticosteroids reduce mortality and duration of treatment in critical SARS. The corticosteroids dose is a low to moderate dose (≤0.5-1 mg /kg of methylprednisolone or equivalent) for less than seven days. This dosage is based on expert consensus in China[23] . Australia reported an observational study of corticosteroid therapy in 11 of 31 patients originating from China. There were no correlation between corticosteroids with the time of virus clearance, duration of treatment and duration of symptoms [24] . Guidelines in Italy recommended the use with a dose of dexamethasone 20 mg / day for 5 days followed by 10 mg / day for 5 days in the case of COVID-19 patients with ARDS [25] . Society of Critical Care Medicine stated that the use of hydrocortisone 200 mg / day can be considered in critical cases of COVID-19 [26] .

A current study by Wu *et al*, 84 of 201 patients with COVID-19 pneumonia were ARDS. Patients with ARDS, significantly less likely to be treated with antiviral therapy and more likely to be treated with methylprednisolone. Older age, fever, underlying disease, low count of neutrophil and lymphocyte, high level of hs-CRP were significantly associated with high risk to develop ARDS. Patients who received methylprednisolone had a higher grade on the Pneumonia Severity Index (PSI) than that of did not receive methylprednisolone. Patients with ARDS who died, IL-6 was statistically significant associated with death. The administration of methylprednisolone significantly reduced the risk of deaths in COVID-19 patients pneumonia with ARDS. The limitation of a study by Wu *et al*, was small sample size and the dose and duration of methylprednisolone was not clearly stated [27] .

The study by Wang *et al*, reported that in patient who received methylprednisolone with a dose 1-2mg/kg daily for 5-7 days, improvement of clinical outcomes (fever and oxygen saturation) as well as lung lesions was faster compared with patients who did not receive methylprednisolone. The mortality rate was higher in patients who did not receive methylprednisolone (10%) compared with patients who receive methylprednisolone (3,8%). Furthermore, there were no differences in inflammatory markers between two groups six days after treatment [28] .

Several studies have also reported the use of corticosteroids in COVID-19 pneumonia. The study by Wang *et al*, showed that treatment with glucocorticoid was significantly associated with higher risk of ICU admission [9] . A study by Ling *et al*, reported that the administration of corticosteroids was significantly longer the duration of viral DNA detection on throat swabs and feces [29] . Another study by Liu *et al*, also reported that the use of methylprednisolone IV with dose 30-80 mg daily, did not show any beneficial effects [30] . Overall, these studies have many limitations. First, the percentage of patients who received corticosteroids was less than fifty percent. It showed that the number of patients who did not receive corticosteroids was much more higher compared with patients who received corticosteroids. Second, the type, dosage, and duration of corticosteroids varied among studies. Third, small number of patients and in a single center with heterogeneous data based on only on retrospective data.

The use of steroids in critically corona virus was significantly associated with high rate of mortality, longer the duration of hospitalization, higher rate infection of bacteria, and hypokalemia. The critical patients were significantly more likely require the administration of steroids. It is reported in patients with ARDS caused by other factors, not in COVID-19, that the administration of high-dose corticosteroids for a prolonged time help to accelerate the improvement of ARDS. Moreover, methylprednisolone reduced the periods of need for invasive mechanical ventilation and lowered mortality in ARDS patients [31] .

4. CONCLUSION

Hyper-inflammatory immune response with features of cytokine storm cause severe disease of COVID-19 and lead to ARDS. Overall, the use of corticosteroids should be considered in COVID-19 patients related ARDS and refractory or septic shock. Some findings indicate that corticosteroids reduce the mortality rate in COVID-19 patients pneumonia and ARDS. The high dose and prolonged treatment of corticosteroids should be avoided to maximize the beneficial effects to reduce the cytokine storms, improve the clinical outcome and to minimize the adverse effects. The randomized controlled trial was called to evaluate the benefit of the use of corticosteroids in COVID-19.

Conflict of interest (If any)

The authors declare no conflict of interest in this study.

Funding

The authors declare no supporting funding in this study

Article info:
Received August 23, 2019
Received in revised form October 28, 2019
Accepted November 2, 2019

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