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Treatment of Critical, Severe and Non-Severe COVID-19 by Corticosteroids

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Abstract

Glucocorticoids or corticosteroids have main anti-inflammatory effects to inhibit a vast number of pro-inflammatory genes that involve encoding of cell adhesion molecules, chemokines, cytokines, inflammatory receptors and enzymes to restore homeostasis and address the inflammatory process. A previous systematic review and meta-analysis revealed that severe COVID-19 patients were more likely to require corticosteroids treatment (RR = 1.56, 95 % CI = 1.28-1.90, p < 0.001). The length of stay (LOS) was longer in the corticosteroid group (WMD = 6.31, 95 % CI = 5.26-7.37, p < 0.001, I2 = 1.8 %, p = 0.361 as well as the same results in the subgroup analysis of SARS-CoV-infected patients (WMD = 6.34, 95 % CI = 5.24-7.44, p < 0.001, I2 = 50.3 %, p = 0.156). X et al demonstrated that COVID-19 patients treated with corticosteroids were more likely to be associated with harm, whereas Russell et al. concluded that either inhaled or systemic corticosteroid was distinguished. The WHO recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of critical and severe COVID-19 patients (strong recommendation, based on moderate certainty evidence). Even the WHO's strong recommendations, these recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician. These recommendations are applied to critical and severe COVID-19 patients regardless of hospitalization status. The WHO suggests not using corticosteroids in treating non-severe COVID-19 patients (conditional recommendation, based on low certainty evidence). In conclusion, urge caution before using corticosteroids for ARDS-associated COVID-19. Corticosteroids are not recommended for mild COVID-19 patients. Moderate corticosteroids can be used in critical and severe COVID-19 patients. Currently, there has been no enough clinical trials or observational studies to examine the use of ICS in COVID-19. A rigorous blinded randomized multicentric clinical trials are urgently needed to further conclusion verification for the harm or benefit of corticosteroid treatment with confidence.

Keywords: Corticosteroids; COVID-19; Critical; SARS-CoV-2; Severe; Non-Severe

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; CI: Confidential Interval, COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; 2019-nCoV: Novel Coronavirus 2019; I^2: A statistically identifying and measuring method for the heterogeneity in meta-analysis or variation in study outcomes between studies (I^2 = (Q-df) X 100/Q (Q: Chi-Squared Statistic; df: Degree Of Freedom)); ICS: Inhaled Corticosteroids; MERS-CoV: Middle-East-Respiratory-Syndrome Coronavirus; NF-kB: Nuclear Transcription

Factor-kB; P: Probability, RCT: Randomized Control Trial; RR: Relative Risk; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2, WMD: Weighted Mean Difference; WHO: World Health Organization.

Introduction

Glucocorticoids or corticosteroids have main anti-inflammatory effects to inhibit a vast number of pro-inflammatory genes that involve encoding of cell adhesion molecules, chemokines, cytokines, inflammatory receptors and enzymes to restore homeostasis and address the inflammatory process [1]. A previous systematic review and meta-analysis revealed that severe COVID-19 patients were more likely to require corticosteroids treatment (RR = 1.56, 95 % CI = 1.28-1.90, $p < 0.001$) [2]. The length of stay (LOS) was longer in the corticosteroid group (WMD = 6.31, 95 % CI = 5.26-7.37, $p < 0.001$, $I^2 = 1.8$ %, $p = 0.361$ as well as the same results in the subgroup analysis of SARS-CoV-infected patients (WMD = 6.34, 95 % CI = 5.24-7.44, $p < 0.001$, $I^2 = 50.3$ %, $p = 0.156$) [2]. Nine studies in this systematic review and meta-analysis by pooled relative risk demonstrated higher mortality in COVID-19 patients receiving corticosteroid treatment (RR = 2.11, 95 % = 1.13-3.94, $p = 0.019$, $I^2 = 80.9$ %, $p < 0.001$), whereas mortality of neither SARS-CoV (RR = 2.56, 95 % CI = 0.99-6.63, $p = 0.053$, $I^2 = 77.4$ %, $p < 0.001$) nor MERS-CoV (RR = 2.06, 95 % CI = 0.66-6.44, $p = 0.213$, $I^2 = 89.4$ %, $p = 0.002$) [2].

Corticosteroid-treated COVID-19 patients were more likely to develop adverse reactions, such as hypokalemia (RR = 2.21, 95 % CI = 1.07-4.55, $p = 0.032$, $I^2 = 53.1$ %, $p = 0.104$) and bacterial infection (RR = 2.08, 95 % CI = 1.54-2.81, $p < 0.001$, $I^2 = 0.0$ %, $p = 0.926$) [2]. The study revealed no association between corticosteroid treatment and the development of hypocalcemia (RR = 1.35, 95 % CI = 0.77-2.37, $p = 0.302$, $I^2 = 80.4$ %, $p = 0.024$) and or hyperglycemia (RR = 1.37, 95 % CI = 0.68-2.76, $p = 0.376$, $I^2 = 74.2$ %, $p = 0.049$) [2]. Nevertheless, funnel plots in this study demonstrated no publication bias on the corticosteroid usage in critical and non-critical COVID-19 patients, whereas mortality might be included in the publication bias [2]. Different previous studies have demonstrated corticosteroid effects varying from harmful to beneficial [3]. Wu *et al* concluded that use of steroids was not statistically different between COVID-19-related-acute-respiratory- distress-syndrome (ARDS) survivors and COVID-19-related-ARDS non-survivors [4].

Inhaled Corticosteroids for Treatment or Prevention of COVID-19

X et al. demonstrated that COVID-19 patients treated with corticosteroids were more likely to be associated with harm, whereas Russell, et al. concluded that either inhaled or systemic corticosteroids were distinguished [5,6]. In a previous *in vitro* study, inhaled corticosteroids (ICS) can inhibit SARS-CoV-2 (COVID-19) replication in infected epithelial cells [7]. COVID-19 patients with ICS treatment has been demonstrated reduction of inflammatory biomarkers and improvement of pulmonary physiology [8,9]. Patients with stable asthma and stable chronic obstructive pulmonary disease (COPD) while using ICS should continue ICS treatment. At the onset of an exacerbation of asthma, there is no evidence to suggest increasing the dose of ICS. Ciclesonide, a proposed candidate ICS has been demonstrated suppression of SARS-CoV-2 (COVID-19) replication in cultured cells and suggested direct inhibition of acting anti-viral activity [10].

The World Health Organization's Recommendation in Corticosteroids for COVID-19 Treatment

Eight randomized control trials (RCTs) (7,184 COVID-19 Patients) were reviewed by the World Health Organization's panel on July 17, 2020 [11]. The largest of the seven trials, " RECOVERY " reported the mortality among subgroup of 6,425 hospitalized patients with severe and non-severe COVID-19 (2,104 were randomized to dexamethasone and 4,321 were randomized to usual care) in the United Kingdom by evaluating the effects of oral or intravenous dexamethasone 6 mg prescribed once daily for up to 10 days. Sixteen percent of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60 % of patients were receiving oxygen only (with or without non-invasive ventilation), and 24 % were receiving neither at the time of randomization [12]. The seven other smaller trials included approximately 700 critically ill patients (critically illness definition varied across the studies, enrollment was up to June 9, 2020) and 63 non-critically ill patients [11]. Approximately four-fifths were invasively mechanically ventilated, approximately 50 % of patients were randomized to receive corticosteroid treatment, and approximately 50 % were randomized to no corticosteroid treatment [11]. All trials reported the mortality at 28 day after randomization, whereas one trial reported at 21 days and the other reported at 30 days [11].

The corticosteroid regimens in the trials included methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID trial), dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (DEXA-COVID and CoDEX trials) [13,14], hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (CAPE-COVID trial), hydrocortisone 200 mg daily for 7 days (REMAP-CAP), methylprednisolone 40 mg every 12 hours for 5 days (Steroids-SARI) [15-18]. Seven of these studies were conducted in Brazil, China, Denmark, France, and

Spain, whereas REMAP-CAP was recruited in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia, and the United Kingdom [11]. The WHO's panel reviewed the data from the GLUCOCOVID (n = 63) trial only the data involving the outcome of mechanical ventilation due to the mortality data being not reported by subgroup [13]. The WHO recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of critical and severe COVID-19 patients (strong recommendation, based on moderate certainty evidence) [11]. Even the WHO's strong recommendations, these recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician. These recommendations are applied to critical and severe COVID-19 patients regardless of hospitalization status [11]. The WHO suggests not to use corticosteroids in treating non-severe COVID-19 patients (conditional recommendation, based on low certainty evidence) [11].

The WHO defines the exclusive categories of the COVID-19 illness severity as the following [11]:

1. Critical COVID-19 is defined by the criteria for ARDS, sepsis, septic shock or other conditions that normally would require the life-sustaining therapy provision, such as vasopressin therapy or mechanical ventilation (invasive or non-invasive)
2. Severe COVID-19 is defined by any of:

- Signs of severe respiratory distress (for examples; inability to complete full sentences, accessory muscle use; and in children, grunting, central cyanosis, severe chest wall in drawing, or presence of any other general danger signs).
- Respiratory rate > 30 breaths per minute in adults and children > 5 years old; at least 60 breaths per minute in children less than 2 months; at least 50 breaths per minute in children 2-11 months; and at least 40 breaths per minute in children 1-5 years old.
- Oxygen saturation < 90 % on room air.

3. Non-severe COVID-19 is defined by absence of any signs sever or critical COVID-19.

Discussion

Clinically, corticosteroids are widely used in severe pneumonia. Russell et al. suggested that corticosteroids should not be administered in COVID-19-induced shock or lung injury outside of a clinical trial [6]. Nevertheless, Chinese investigators suggested short course of low-to-moderate doses of corticosteroids for critical COVID-19-pneumonia patients [19]. Results from systematic reviews and meta-analyses indicated that severe COVID-19 patients were more likely to require corticosteroid treatment. In the early stage of inflammation, glucocorticoids reduce phagocytosis, leukocyte infiltration, inflammatory cell exudation, and capillary dilatation, whereas in the late stage of inflammation, glucocorticoids inhibit the excessive proliferation of fibroblasts and capillaries [1]. Additionally, glucocorticoids can inhibit nuclear transcription factor-kB (NF-kB) signaling and further inhibit the transcription and translation of inflammatory factors [1]. These can explain why corticosteroid treatment is more needed in critically and severely ill patients with COVID-19 infection. Nevertheless, there are number of limitations as the following: 1) Most of systematic reviews and meta-analyses are retrospective cohort studies, historical control studies, etc. that lack of randomized controlled trials with suitable design. 2) There is no uniform standard for the dosage and time of corticosteroids used in the studies, and 3) other therapeutic options may influence the corticosteroid effects. Finally, the publication bias of corticosteroid treatment in COVID-19 patients may be due to other currently non-reported developments [2].

Conclusion

ICS could reduce the inflammatory ARDS-like response affecting a minority of COVID-19 patients and may directly inhibit viral replication. Urge caution before using corticosteroids for ARDS-associated COVID-19. Corticosteroids are not recommended for mild COVID-19 patients. Moderate corticosteroids can be used in critical and severe COVID-19 patients. Currently, there have been no enough clinical trials or observational studies to examine the use of ICS in COVID-19. Rigorous blinded randomized multicentric clinical trials are urgently needed to further conclusion verification for the harm or benefit of corticosteroid treatment with confidence.

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