Original Article

Efficacy and safety of glucocorticoids in treatment of COVID-19: a retrospective study

Lingling Fei[1#], Xixi Gao[2#], Qi Zhang[2#], Xiaoli Tan[2#], Fang Xu[3], Qianli Pan[2], Wenyu Chen[2]

[1]Department of Hepatobiliary Surgery, Affiliated Hospital of Jiaxing University/The First Hospital of Jiaxing, Jiaxing, China; [2]Department of Respiration, Affiliated Hospital of Jiaxing University/The First Hospital of Jiaxing, Jiaxing, China; [3]Department of Mental Health, Xiuzhou Kang'an Hospital of Jiaxing, Jiaxing, China

Contributions: (I) Conception and design: L Fei, F Xu, W Chen; (II) Administrative support: L Fei, X Gao; (III) Provision of study materials or patients: Q Zhang, W Chen; (IV) Collection and assembly of data: Q Pan; (V) Data analysis and interpretation: X Tan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qianli Pan; Wenyu Chen. Department of Respiration, Affiliated Hospital of Jiaxing University/The First Hospital of Jiaxing, No.1882, South Zhonghuan Road, Jiaxing 314000, China. Email: baisun1589@163.com; 49530190@qq.com.

Background: Novel coronavirus pneumonia is a novel kind of highly contagious disease without any specific drugs. Considering the successful experience of antiviral therapy combined with glucocorticoids (GCs) in severe acute respiratory syndrome, this study was designed to evaluate the clinical efficacy of GCs in treating patients with coronavirus disease 2019 (COVID-19).

Methods: A cohort of 42 patients with COVID-19 admitted to The First Hospital of Jiaxing from January 4, 2020, to February 16, 2020, were included and grouped into a test group (n=20) and control group (n=22) based on their therapeutic regimens. There were no significant differences in baseline characteristics between patients in the two groups. Conventional treatment (antiviral therapy) was given to patients in both groups, while an additional hormone drug (GCs) was used in patients in the test group. Indices including body temperature, blood routine indices [white blood cell (WBC), lymphocyte, monocyte, and C-reactive protein (CRP)], blood biochemical indices [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], and complications were recorded during the treatment. Time to achieve negative virus nucleic acid (nCoV-RNA) testing, and hospital stays were also observed and compared between the two groups.

Results: All included patients completed the trial. After treatment, superior therapeutic efficacy was achieved in patients in the test group, with body temperature dropping more significantly with a much shorter recovery time compared to the control group (P=0.0412). Simultaneously, the percentage of patients with abnormal blood routine indices (WBC), monocyte, and (CRP) in the test group was reduced more sharply, while no noticeable difference was observed in the number of patients who developed abnormal blood biochemical indices during treatment between the two groups. Additionally, a shorter duration of hospital stays was found in the test group relative to the control group (14.84±8.76 *vs.* 18.25±7.42 days, P>0.05). Patients who received GCs had a shorter recovery time for body temperature and inflammation.

Conclusions: Hormonotherapy with GCs can accelerate the recovery time for body temperature as well as inflammation in patients with COVID-19. It deserves promotion and application in the clinical treatment of coronavirus disease as a form of adjuvant medicine. The ongoing focus of research is on long-term adverse events in GCs.

Keywords: Glucocorticoids (GCs); coronavirus disease 2019 (COVID-19); novel coronavirus; treatment

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Introduction

Coronavirus disease 2019 (COVID-19) is a novel, highly infectious disease not currently well contained and has led to a large-scale pandemic affecting many worldwide (1). The main routes of transmission are droplet and human-to-human, and less so fecal and oral (2,3). By March 13, 2020, a total of 134,064 confirmed cases of COVID-19 had been reported worldwide and there were 4,968 deaths. At present, no specific medicine has been developed, and the predominant management now relies on antiviral and symptomatic treatments (4). Here, we used glucocorticoids (GCs) to evaluate their possible therapeutic efficacy in treating the patients with COVID-19.

GCs are synthesized under the stimulus of adrenocorticotrophic hormone (ACTH) in the adrenal gland and are activated with pronounced circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis. ACTH and arginine vasopressin are released from parvocellular neurons of the paraventricular nucleus, and upon reaching the anterior pituitary, corticotropin releasing hormone (CRH) is in turn released. GCs are involved in various physiological processes, such as metabolism, cardiovascular regulation, reproduction, emotion, cognition, and the immune response. In addition, they can regulate self-production via the negative feedback of ACTH and CRH (5), and have been widely applied in the treatment of inflammation and autoimmune disease due to their role in the immune system (6). Based on previous treatment experience against the severe acute respiratory syndrome (SARS, another coronavirus disease), it is clear that conventional antiviral treatment with additional hormonotherapy with GCs can protect the immune system from injury and be effectively used in clinical treatment (7). More specifically, GCs contribute to inhibition of the systemic inflammatory response, prevention of alveolar exudation and damage, and pulmonary fibrosis (8). In a large randomized clinical trial exploring potential treatments for COVID-19 (RECOVERY), scientists concluded that dexamethasone reduces the risk of death by 35% in COVID-19 patients receiving mechanical ventilation, and compared to standard care, oxygen supplementation is reduced by 20% in the study group, however, dexamethasone does not have a beneficial effect on hospitalized patients with COVID-19 not receiving respiratory support (9). Whilst the trial had some methodological deficiencies, for example, it failed to measure immune system activation or assess side effects, it clearly defined a precise target population who could benefit from glucocorticoid therapy. Other clinical studies of glucocorticoid use in COVID-19 patients also have limitations, including insufficient test power, lack of clear indicators of clinical progression, or insufficient investigation of potential side effects (10-12). Thus, studies on the efficacy and safety of GCs in patients with COVID-19 are warranted.

We used GCs in the treatment of patients with COVID-19, with conventional antiviral treatment as the basic treatment to explore whether this combination could produce as good a therapeutic efficacy in COVID-19 as SARS, and whether it was safe to use in clinical practice. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-659/rc).

Methods

Subject enrollment

This is a retrospective, non-randomized study. A total of 42 patients admitted to The First Hospital of Jiaxing from January 4, 2020, to February 16, 2020, were recruited, including 24 males and 18 females aged from 16 to 72 years old. All patients were confirmed as COVID-19 by means of pathological and imaging diagnosis, and their viral nucleic acid test (nCoV-RNA) was positive. According to the therapeutic regimen, patients undergoing conventional treatment were grouped into a control group (n=22), while the remaining patients who received conventional treatment combined with hormonotherapy were classified into a test group (n=20). The general clinical information of all patients is detailed in *Table 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of The First Hospital of Jiaxing (No. LS2020-010). Informed consent was taken from all the patients or their legal guardians.

Treatment regimen

The conventional treatment regimens for the test and control groups were designed as follows:

(I) Oseltamivir (Oseltamivir Phosphate Capsule; Yichang HEC Changjiang Pharmaceutical Co., Ltd., Yichang, China) one capsule (75 mg) two times daily, applied to teenagers over 13 years old and adults, for consecutive 5 days;

Table 1 General clinical information of patients in the two groups

Item	Test group (n=20)	Control group (n=22)	P value
Age (years)	30–72	16–70	
Gender			0.72
Male	12	12	
Female	8	10	
History			0.12
Yes	8	4	
No	12	18	
Cough			0.17
Yes	15	12	
No	5	10	
Fever			0.33
Yes	17	16	
No	3	6	
Hemoptysis			0.49
Yes	2	1	
No	18	21	
Chest distress			0.72
Yes	2	3	
No	18	19	

(II) Moxifloxacin (Moxifloxacin Hydrochloride Tablets; Bayer HealthCare, Leverkusen, Germany) one tablet (0.4 g) every 2–4 h, orally;
(III) KALETRA (Lopinavir/Ritonavir Oral Solution, 80 mg/20 mg per mL; AbbVie Ltd., USA), 5 mL (400/100 mg) two times daily or 10 mL (800/200 mg) once daily, applied to adults, with a meal;
(IV) Manuosu (Arbidol Tablets; Suzhou Pharmaceutical Factory, Jiangsu Wuzhong Pharmaceutical Group Corporation, Suzhou, China), two tablets (0.2 g) three times daily, applied to adults, orally;
(V) Prezcobix (Darunavir and Cobicistat Tablets; Janssen Ortho, LLC, USA), one tablet (867.28 mg/150 mg) once daily, with a meal;
(VI) Jaferon (Recombinant Human Interferon α2b Spray; Tianjin Sinobioway Biomedicine Co., Ltd., Tianjin, China), sprayed on affected body parts three times daily.

For patients in the test group, hormonotherapy was additionally performed, with Milesong (methylprednisolone sodium succinate for injection; Shanghai Shyndec Pharmaceutical Co. Ltd., Shanghai, China) given by intravenous injection at 20–60 mg/day (the dosage could be adjusted following the specific condition of each subject).

Evaluation index

The efficacy of GCs was measured by the following criteria:

(I) Proportion of patients with abnormal blood indices [white blood cell (WBC, 10^9/L), lymphocyte (10^9/L), monocyte (10^9/L), and C-reactive protein (CRP, mg/L)];
(II) Body temperature, time to achieve negative nCoV-RNA, and hospital stay.

The safety of GCs was measured by the following criteria:

(I) Incidence of toxic and side effects during the process of treatment;
(II) Proportion of patients with abnormal blood biochemical indices [alanine aminotransferase (ALT, U/L) and aspartate aminotransferase (AST, U/L)].

Statistical analysis

All data were processed using SPSS 22.0. The chi-square test was used to compare the baseline characteristics of the two groups. Measurement data were exhibited as $\bar{x}$±s, with *t*-test performed for validation of comparisons between the two groups. Part of the enumeration data are presented in the form of percentage (%), accompanied by chi-square test conducted for verification. All tests were two-sided. P<0.05 was defined as the threshold for statistical significance.

Results

Comparative analysis of body temperature in the two groups

As most subjects had developed fever when admitted to hospital, we made a track record of daily temperature for 10 days in total. As revealed in *Figure 1A*, the body temperature of patients in the test group dropped significantly compared with the control group. Additionally, temperature recovery time was calculated and compared between the two groups and showed the temperature of patients in the test group returned to normal in a shorter time (*Figure 1B*, P=0.0412). These results demonstrated

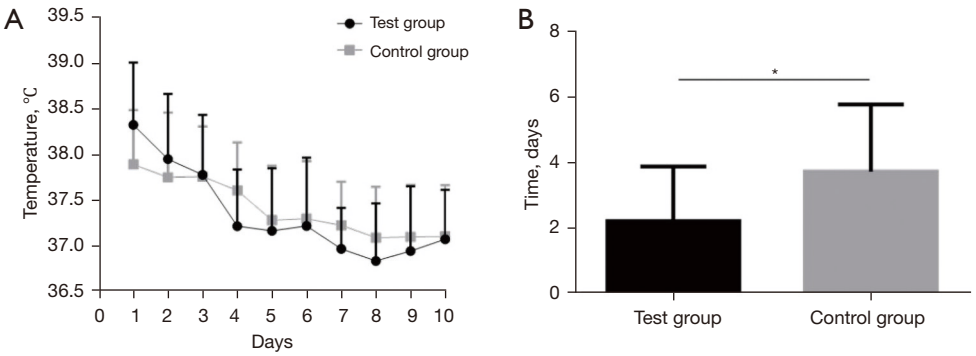

Figure 1 Comparative analysis of changes of body temperature and temperature recovery time between the two groups. (A) Changes of body temperature within 10 days; (B) temperature recovery time of patients in the two groups. *, P<0.05.

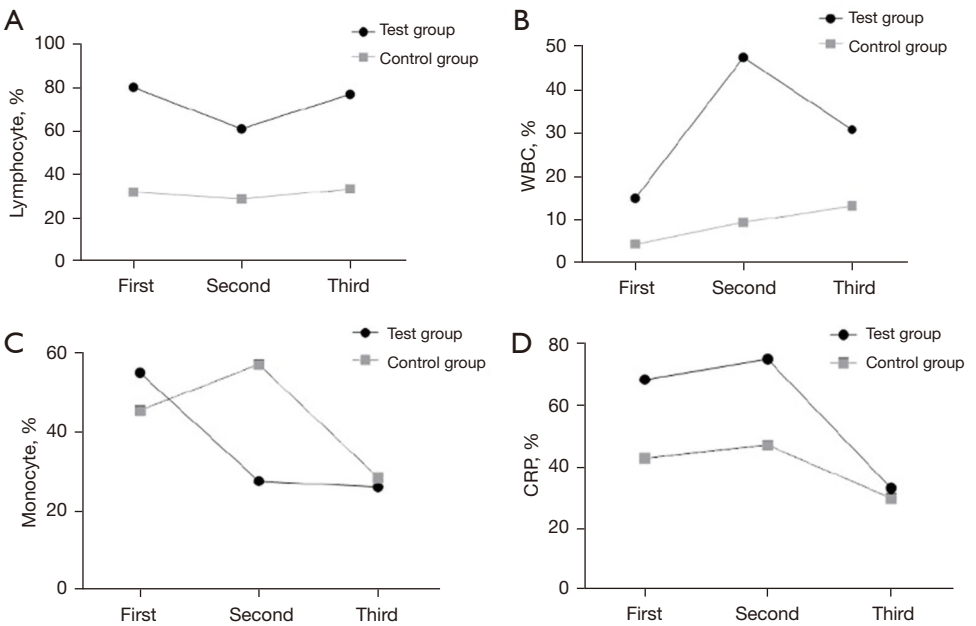

Figure 2 Proportion of patients with abnormal blood indices in the two groups. Comparative analysis of the proportion of patients with abnormal (A) lymphocytes, (B) WBC, (C) monocytes and (D) CRP between the test group and the control group. The content within the following ranges was considered abnormal: lymphocyte, (1.1–3.2)×10^9/L; WBC, (3.5–9.5)×10^9/L; monocyte, (0.1–0.6)×10^9/L; CRP, 0–5 mg/L. WBC, white blood cell; CRP, C-reactive protein.

hormonotherapy combined with conventional treatment contributed to a shorter temperature recovery time.

Comparative analysis of blood routine between the two groups

Blood indices including WBC, lymphocyte, monocyte, and CRP levels were evaluated from the commencement of treatment and recorded three times. The results showed patients with WBC counts at the first test accounted for a larger proportion in the test group than those in the control group. Similarly, lymphocyte, monocyte, and CRP levels were abnormal in patients with a larger proportion in the test group. After three tests, the proportion of patients with abnormal lymphocytes in the test group remained high (*Figure 2A*), while an accelerated decrease in the proportion of patients in the test group in abnormal WBC, monocyte, and CRP levels relative to the control group was seen

(*Figure 2B-2D*), with no statistical significance (P>0.05).

Comparative analysis of adverse reactions in the two groups

Various complications developed in patients in both groups, including nausea, vomit, diarrhea, night sweats, spontaneous perspiration, and skin rashes. Statistically, we found skin rashes were less likely to appear in patients undergoing hormonotherapy (5% in test *vs.* 13.6% in control), while night sweats and spontaneous perspiration occurred more in patients in the test group (10% *vs.* 0%). Detailed information is listed in *Table 2*.

Comparative analysis of blood biochemical indices in the two groups

To determine whether hormonotherapy was safe in the treatment of patients with COVID-19, blood biochemical tests were performed three times during treatment, and indices including ALT and AST were recorded. As seen in *Figure 3A,3B*, the proportion of patients in the test group who developed abnormal ALT or AST exhibited was not significantly different from that in the control group (P>0.05). Hence, it could be seen hormonotherapy did not produce severe toxicity and side effects and could be safely applied.

Table 2 Complications in the two groups during treatment

Complication	Test group (n=20), n (%)	Control group (n=22), n (%)
Nausea/vomiting	2 (10.0)	3 (13.6)
Diarrhea	4 (20.0)	4 (18.2)
Night sweat/spontaneous perspiration	2 (10.0)	0
Skin rash	1 (5.0)	3 (13.6)

Comparative analysis of the time to achieve negative nCoV-RNA and hospital stays

The time to achieve negative nCoV-RNA testing was examined three times, and the results showed no noticeable difference between the two groups (*Figure 4A*, P>0.05). Additionally, the duration of hospital stay of patients in the test group was reduced relative to that in the control group (14.84±8.76 days *vs.* 18.25±7.42 days), yet this was not statistically significant (*Figure 4B*, P>0.05).

Discussion

This study focused on COVID-19 treatment and the use of hormonal GCs to clarify their possible therapeutic efficacy. The results showed patients receiving GCs had a shorter temperature recovery time than those not, and the proportion of patients in the test group who developed abnormal inflammatory indices was reduced more sharply after treatment. Additionally, although there was no significant difference observed between the two groups, patients in the test group had a shorter duration of hospital stay, with the time for the two groups as (14.84±8.76) and (18.25±7.42) days, respectively. Overall, the therapeutic regimen used in the test group produced superior efficacy compared to the conventional treatment applied in the control group.

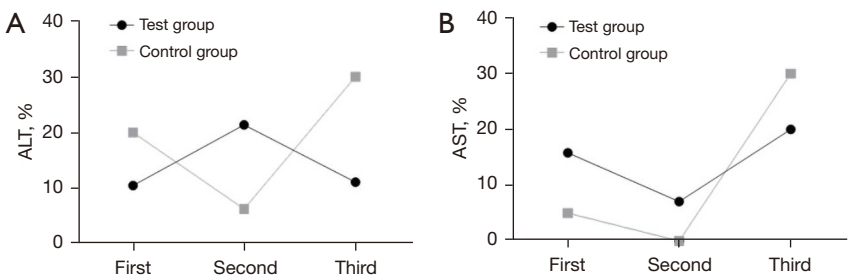

Figure 3 Proportion of patients with abnormal blood biochemical indices in the two groups. The proportion of patients who developed abnormal (A) ALT or (B) AST in the test group and the control group was statistically analyzed. The value within the following ranges was considered abnormal: ALT, [9–50] U/L for males and [7–40] U/L for females; AST, [15–40] U/L for males and [13–35] U/L for females. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

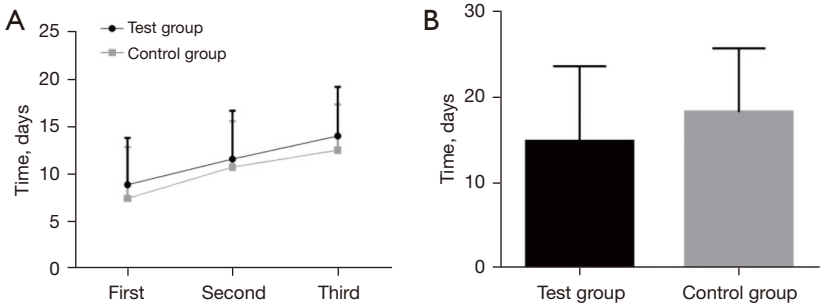

Figure 4 Comparative analysis of the time to achieve negative nCoV-RNA and hospital stay. Comparative analysis of the time (A) to achieve negative nCoV-RNA (novel coronavirus-RNA) and (B) hospital stay between the two groups.

GCs, like methylprednisolone, are powerful immunosuppressive agents used in the treatment of autoimmune diseases. Their functional mechanism can be specifically described as: (I) blocking macrophage phagocytosis, coping with antigens, and producing interleukin-1; (II) accelerating the process of lymphocyte destruction and disintegration in susceptible animals to sharply decrease the cell population of lymphocytes in blood circulation; (III) inhibiting the cellular immune response in low dosages; (IV) suppressing the humoral immune response in high dosage and inhibiting the conversion of B lymphocytes to plasma cells; (V) anti-inflammatory reaction (13). A previous study reported the autoimmune mechanism plays an invaluable role during the pathogenic and damage processes caused by the SARS virus. Specifically, infection with the SARS virus can lead to a weakness of the immune tolerance to some antigens in lung tissue and the production of autoantibodies, resulting in severe lung tissue damage (14). Additionally, there is evidence hormonotherapy applied in SARS treatment not only contributes to the enhancement of autoimmune tolerance of patients, but also leads to a shorter duration of hospital stay (15). In the present study, a similar effect was found in that the length of stay in hospital of patients with COVID-19 who underwent hormonotherapy was reduced. Fever generally appears to be the first clinical manifestation of COVID-19 (16), which means the change in body temperature can be used as an indicator for the improvement of therapeutic outcomes. Thus, our study recorded the temperature recovery time of patients in the two groups and found this was much shorter in patients undergoing hormonotherapy. Moreover, inflammation-related indices including WBC, lymphocyte, monocyte, and CRP levels were examined and seen to be abnormal in most patients in the test group before treatment. After treatment, the percentage of patients with abnormal lymphocyte counts in the test group was still high, yet in terms of other indices, the percentage was decreased with a higher speed relative to the control group. This elucidated hormonotherapy was effective in treating inflammation. We also discovered that skin rashes appeared less in patients undergoing hormonotherapy, and the hospitalization time was much shorter, with no significant difference observed in the test and control groups.

In conclusion, hormonotherapy combined with conventional treatment can significantly accelerate the recovery time for body temperature as well as inflammation in patients with COVID-19 and can shorten the duration of hospital stays. These results suggest hormonotherapy with GCs deserves promotion and application in the clinical setting.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-659/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-659/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-659/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of The First Hospital of Jiaxing (No. LS2020-010). Informed consent was taken from all the patients or their legal guardians.

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