Am J Transl Res 2022;14(2):1332-1338
www.ajtr.org /ISSN:1943-8141/AJTR0140117

Original Article

Treatment efficacy of Lianhua Qingwen capsules for eraly-stage COVID-19

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Received October 26, 2021; Accepted January 14, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Objective: To systematically determine the effect of Lianhua Qingwen Capsules on the early antiviral and anti-inflammatory action against COVID-19 (Coronavirus 2019) and its applicational value in the treatment of COVID-19. Methods: The clinical data of 66 early-mid-stage COVID-19 patients admitted to hospitals in Guangzhou between January 2020 and April 2020 were retrospectively analyzed. The patients receiving Lianhua Qingwen Capsule treatment were assigned to the observation group (n=33) and those given conventional therapy were included in the control group (n=33). The two groups were compared in terms of clinical effects and main symptom (fever, cough and fatigue) disappearance rate. Results: In comparison with the control group, 1) the total effective rate was significantly higher in the observation group (P<0.05); 2) the disappearance rates of fever, cough and fatigue were statistically higher in the observation group; 3) the treatment time was significantly shorter and patient recovery was significantly better in the observation group; 4) the laboratory index levels [white blood cell (WBC), interleukin-6 (IL-6), serum amyloid A (SAA)] were better in the observation group. Conclusion: Lianhua Qingwen Capsules can significantly improve the total effective rate for COVID-19 patients, as well as shorten the hospital stay and treatment time, which is worth of promotion in the clinic.

Keywords: Lianhua Qingwen, COVID-19, total effective rate, retrospective study, clinical symptoms, traditional Chinese medicine (TCM) treatment

Introduction

The 2019 novel coronavirus disease (COVID-19), caused by a novel viral pneumonia pathogen derived from SARS-CoV 2 first discovered in December 2019, was declared by the WHO in early March 2020 as a pandemic. This disease can be transmitted by droplets, aerosol-containing body fluids and faecal-oral routes, and its progression can lead to serious lung involvement and pulmonary failure [1, 2]. COVID-19 induces various symptoms such as fever, respiratory and gastrointestinal symptoms or it can be asymptomatic, and it has swept the globe [3, 4]. While with a lower fatality compared with SARS-CoV-1 and middle east respiratory syndrome coronavirus (MERS-CoV), the absolute death toll from COVID-19 is considerably high due to widespread viral infections [5]. Death from COVID-19 is due to cytokine storm syndrome induced hyperinflammation, and to address this, research is underway into the use of all kinds of therapeutic agents, including steroids, selective cytokine blockers, intravenous immunoglobulin, and JAK inhibitors [6]. The latest advances indicate that COVID-19 is a systemic disease targeting the lungs, blood vessels and immune system, involving severe lung inflammation and immune deficiency, including cytokine storm, neutrophil extracellular trap, and lymphocyte subset imbalance [7-9]. A cytokine storm is an excessive immune response to external stimuli such as viruses, which stimulates the body to secrete a large number of inflammatory factors, leading to a cascade of cytokines. The Chest X-ray findings showed diffuse patchy shadows in patients with COVID-19, often accompanied by lymphopenia [10]. In addition, coronavirus can activate monocytes and macrophages,

releasing massive inflammatory cytokines that accumulate in the lungs, which may be the main cause of local exudative lesions. Peripheral T lymphocyte subsets CD4 and CD8, on the other hand, were decreased in some patients, suggesting immunosuppression [11].

At present, human beings have no immunity to the novel coronavirus, and despite differences in age, gender, and race, susceptibility to the virus is the same depending on the chance of exposure [12]. Finding effective treatments for COVID-19 is therefore extremely important. The general clinical treatment for COVID-19 includes anti-infection, anti-inflammation, non-specific antiviral treatment and life support therapy [13, 14]. Traditional Chinese Medicine (TCM) plays an important role in the treatment of human diseases. Lianhua Qingwen is a classic Chinese medicinal preparation. Maxingshigan decoction, one of its components, has been used to treat plague for thousands of years, with antiviral and lung protective effects [15, 16]. It is shown that Lianhua Qingwen Capsules can block viral replication and change the virion morphology [17]. The treatment of COVID-19 is a global concern. At present, the treatment is still based on symptomatic treatment and TCM supportive therapy, and there is no specific antiviral treatment plan fully confirmed by clinical research. The clinical application of Lianhua Qingwen Capsules is still mainly empirical, and the observation indicators are limited to clinical symptoms. The effect of the drug on the negative outcomes of the nucleic acid detection (NAT) has not been reported, let alone the impact on the change of CT imaging. Available evidence suggests that integrated medicine, which means a combination of TCM and western medicine, may be more effective in treating COVID-19 than western medicine alone [18]. However, the sample size of these studies is too small to provide convincing evidence to demonstrate the hazards and advantages of integrated medicine for COVID-19. Lianhua Qingwen Capsule, extensively applied and highly recognized in the fight against SARS and influenza in China, has been confirmed by previous pharmacodynamic studies to significantly suppress the viability of SARS-CoV cultured *in vitro* [19]. Besides, it significantly inhibited COVID-19 viability, reduced viral content in the cytomembrane and cytoplasm, and suppressed cytokine over activation, as indicated by a recent study by the State Key Laboratory of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University [20]. On this basis, we used Lianhua Qingwen Capsules to treat COVID-19 and obtained encouraging results. The innovation of this study is the confirmation of the clinical significance of Lianhua Qingwen Capsules for the treatment of COVID-19 by systematically analyzing its effects on COVID-19 from the aspects of clinical indices, CT indices and laboratory indicators, which is of great significance for the prevention and treatment of COVID-19.

Data and methods

Clinical data

In this study, the clinical data of 66 patients with early-mid-stage COVID-19 admitted to hospitals in Guangzhou between January 2020 and April 2020 were retrospectively analyzed. The patients were assigned to an observation group (n=33) and a control group (n=33) based on different treatment methods. The male to female ratio in the observation group was 19:14, and the mean age was (42.35±0.23) years old. As for the control group, the male to female ratio was 17:16 and the average age was (42.53±0.12) years old. The general data, such as gender and age, was not significantly different between the two groups (all $P>0.05$). All subjects were informed about the significance of the study and voluntarily provided the signed informed consent. Ethical approval was obtained from the institutional committee of our hospital.

Inclusion and exclusion criteria

The diagnostic criteria for suspected and confirmed COVID-19 cases were based on the Diagnosis and Treatment Protocol for COVID-19 (Tentative 7th Edition) released by the National Health Commission of the People's Republic of China.

Inclusion criteria: 1) Confirmed diagnosis of COVID-19 in accordance with the diagnostic criteria. 2) Age: 18-60, regardless of sex. 3) High compliance and voluntary participation.

Exclusion criteria: 1) Age <18 or >60. 2) Presence of severe interstitial lung disease bronchiectasis and other underlying pulmonary

diseases confirmed by chest X-ray or CT. 3) Severe primary diseases, such as heart, kidney, lung, endocrine, blood, metabolism, or gastrointestinal tract diseases. 4) Malignant tumor(s) or mental diseases. 5) Pregnant or lactating women. 6) Uncompliant patients who were unwilling to sign informed consent forms.

Methods

All patients were treated in accordance with the "Protocol for Prevention and Control of COVID-19" promulgated by the General Office of the National Health Commission in February 2020. In the control group, patients were mainly treated with interferon (Xiamen Amoytop Biotech Co., Ltd.), arbidol (Jiangsu Wuzhong Pharmaceutical Group Corporation), Tonavir (AbbVie Deutschland GmbH & Co.KG), and other comprehensive treatments, including prevention and treatment of secondary bacterial infections, anti-inflammatory therapy (glucocorticoids), immune regulation, oxygen therapy, respiratory support (invasive and non-invasive mechanical ventilation), extracorporeal membrane oxygenation (ECMO), and symptomatic support. In the observation group, patients were additionally treated with Lianhua Qingwen Capsules (Beijing Yiling Pharmaceutical, State Drugs Administration License No. Z2004-0063), 1.4 g per time, twice a day.

Outcome measures and efficacy evaluation

Blood samples were collected from each participant for hematological investigations. A routine blood test [white blood cell (WBC)] was performed on the blood sample. Interleukin-6 (IL-6) was detected on a fully automated electro-chemiluminescence based immune-analyzer (Roche Diagnostics, Basel, CH), using the corresponding reagent. Serum amyloid A (SAA) was detected by immunoturbidimetry using Roche automatic biochemical analyzer (Roche Diagnostics, Basel, Switzerland). IL-6 is a pleiotropic cytokine producing either proinflammatory or anti-inflammatory effects [21]. SAA serves an important role in inflammation and is related to the severity of inflammation [22]. The corresponding reagents were purchased from Wuhan Fine Biotech Co., Ltd.

COVID-19 detection was made via real-time fluorescent quantitative polymerase chain reaction (RT-qPCR) following the reagent instructions. 2019-ncov NAT kits were purchased from Da'an Gene Co., Ltd. of Sun Yat-sen University. Positive test results were reviewed and confirmed by Baoji Center for Disease Control and Prevention.

Evaluation criteria of therapeutic effect: Markedly effective: disappearance of symptoms such as cough and expectoration. Effective: relieved cough and reduced expectoration. Ineffective: no significant improvement in or aggravation of symptoms such as cough and expectoration.

The patient records were sorted out, and the observational indicators used in this study were as follows: 1) Main symptom (fever, fatigue and cough) disappearance rate within 2 weeks (14 days) after treatment. During the observation time, if the symptom does not appear for more than 24 hours, it is defined as the disappearance of the symptom. 2) Time for body temperature to return to normal: the patients were given corresponding treatment upon admission, their body temperature was measured every day, and the time from admission to body temperature returned to normal was recorded (axillary temperature ≤37°C). 3) Time for Chest CT to show obvious inflammation absorption: the time of significant inflammation absorption on chest CT from admission to re-examination was recorded. 4) Time to 2 consecutive negative NATs for COVID-19: the time from admission to two consecutive negative NATs (with sampling intervals of at least 1 d) was recorded. Time from admission to the second negative NAT. 5) Length of hospital stay: the hospitalization time of patients was recorded.

The primary outcome measures were clinical symptom improvement and disappearance rates after treatment as well as clinical efficacy, and the secondary ones were the details of therapeutic indicators and laboratory indexes.

Statistical methods

In this study, SPSS 22.0 was used for data processing. The measurement data were expressed as $x\pm s$, and the difference between two groups was compared using the t test; the count data were represented by percentages and compared using the χ^2 test. The significance level was taken as $P<0.05$.

Table 1. Comparison of disappearance rate of main symptoms between the two groups [Number of symptom-free cases/Total number of cases (%)]

Group	Fever		Cough		Fatigue	
	Disappearance rate	Disappearance time (d)	Disappearance rate	Disappearance time (d)	Disappearance rate	Disappearance time (d)
Observation group (n=33)	28/32 (87.5)	7.03±0.76	23/31 (74.2)	8.76±0.34	25/30 (83.3)	8.39±0.63
Control group (n=33)	20/33 (60.6)	8.45±0.57	16/32 (50.0)	10.93±0.48	19/32 (59.4)	9.12±0.51
χ^2/t	5.3611	7.0506	3.9081	16.5541	4.3141	4.1239
P	0.0206	<0.0001	0.0481	<0.0001	0.0378	0.0001

Table 2. Details of the therapeutic efficiency

Group	Markedly effective	Effective	Ineffective	Total effective treatment rate
Observation group (n=33)	12	15	6	81.8% (27/33)
Control group (n=33)	7	11	15	54.5% (18/33)
χ^2				5.6571
P	/	/	/	0.0174

Table 3. Details of therapeutic indicators (x±s, d)

Group	Time for body temperature to return to normal	Time for chest CT to show obvious inflammation absorption	Time to 2 consecutive negative NATs for COVID-19	Length of stay
Observation group (n=33)	5.83±1.07	12.13±1.41	15.03±1.84	16.17±1.72
Control group (n=33)	7.04±1.39	14.87±1.27	17.11±1.42	18.09±1.56
t	3.9626	8.2946	5.1410	4.7499
P	0.0001	<0.0001	<0.0001	<0.0001

Results

Comparison of disappearance rate of main symptoms

The disappearance rates of fever, cough and fatigue in the observation group were significantly higher than those in the control group (P<0.05), see **Table 1**.

Comparation of clinical efficacy

The total effective rate was 81.8% (27/33) in the observation group and 54.5% (18/33) in the control group, with a significant difference between the two groups (P<0.05), see **Table 2**.

Comparison of therapeutic effect

Most of the patients underwent chest CT examination after symptom improvement, and NAT was performed after CT showed obvious inflammation absorption. The results showed that compared with the control group, the time for body temperature to return to normal, the time for chest CT to show obvious inflammation absorption and the time to 2 consecutive negative NATs for COVID-19 as well as the length of hospital stay were significantly shorter in the observation group (all P<0.05), see **Table 3**.

Chest X-ray analysis

Chest radiographs of normal people and early-mild-stage COVID-19 patients are displayed in **Figures 1** and **2**. The chest radiographs of normal people showed bilateral thorax symmetry without bone abnormality, and normal permeability of both lung fields with no abnormally increased density shadow (**Figure 1A**). While multiple small patchy shadows or qualitative changes can be seen in both lungs in patients with early-mid-stage COVID-19 (**Figure 1B**). After treatment, scar tissue and adhesions formed on the lungs were still present, but the shadows were less than before treatment (**Figure 2**).

CT analysis

CT images from patient Mr. Lin during different treatment periods are shown in **Figure 3**. The results showed multiple patchy ground glass opacities and higher density strip shadows in the posterior basal segments of the middle and lower lobes of the right lung at admission

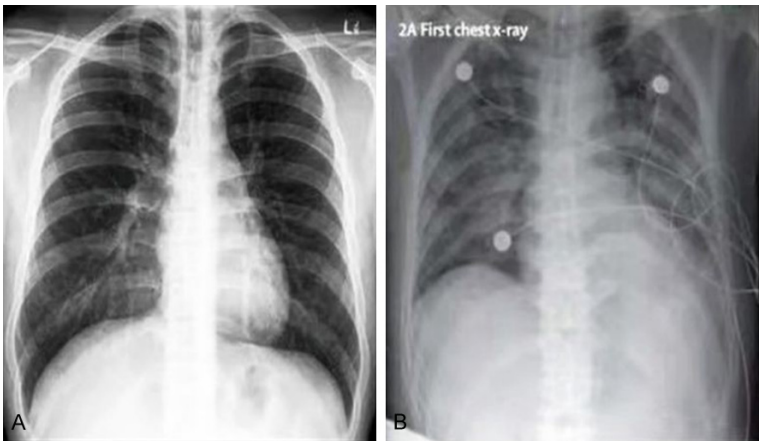

Figure 1. Chest radiographs. A: Chest radiograph of normal people; B: Chest radiograph of a patient with early-mid-stage COVID-19.

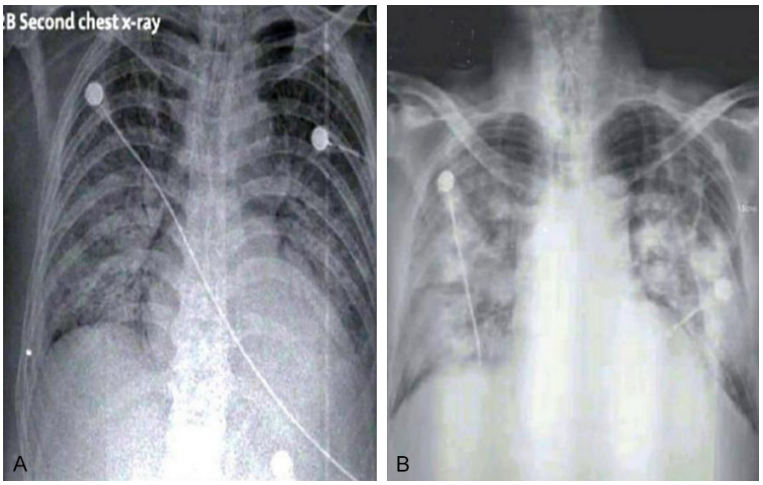

Figure 2. Chest radiographs of the patient. A: Before treatment; B: After treatment.

(**Figure 3A**). During the treatment, the focus area was obviously absorbed, and the density was lower than before treatment (**Figure 3B**, **3C**). CT re-examination after discharge showed a continuous decrease in the lesions of both lungs and multiple fibrosis lesions (**Figure 3D**).

Changes of laboratory indexes

The WBC count increased, and the ratio of SAA and IL-6 decreased in the observation group, versus the control group ($P<0.05$), see **Table 4**.

Discussion

The research results revealed that Lianhua Qingwen Capsules effectively improved the total effective rate of COVID-19 treatment, as it significantly ameliorated the symptoms of cough, fever and fatigue of patients, improved the disappearance rate of main symptoms, and shortened the duration of main symptoms on the basis of routine treatment. According to TCM, SARS-CoV-2 falls under the category of "pestilence", which refers to viral infection of the body and lungs [23]. It is characterized by toxin, heat, phlegm, and sputum stasis, obstructing the collaterals within the lungs. SARS-CoV-2 is an epidemic and acute infectious disease that is highly contagious, so it belongs to the miscellaneous "qi" between heaven and earth. According to the Inner Canon of Yellow Emperor, five kinds of pestilences can all spread from people to people, and the symptoms are the same for children as well as adults [24]. Analyzing the pathogenesis from the perspective of TCM, patients were infected in the transition from winter to spring, with exposure to the harm of heat and phlegm-stasis. As the harm of heat accelerates, it travels from the mouth and nose to inflict the lungs, resulting in the symptom of coughing. In addition, the warm-dryness hurts "qi and yin", so the symptoms can be dry cough without sputum. The stronger the heat-toxicity is, the more it travels to tubes and arteries, so the symptoms can be floating pulse, red tongue, and thin yellow coating on tongue, which are symptoms of intensive heat and "qi and yin" injury [25]. On the other hand, many studies on TCM therapies and modern pharmaceuticals have proven that Lianhua Qingwen Capsules can strengthen immunity and regulate immune function, with antiviral effects. Forsythia, honeysuckle, isatis root, and herbal houttuynia, the ingredients in Lianhua Qingwen Capsules, have the effects of heat-clearing and detoxicating, lung ventilation and heat dissipation, which has a very significant effect on influenza caused by the influenza A virus [26]. In addition, the results showed that on the basis

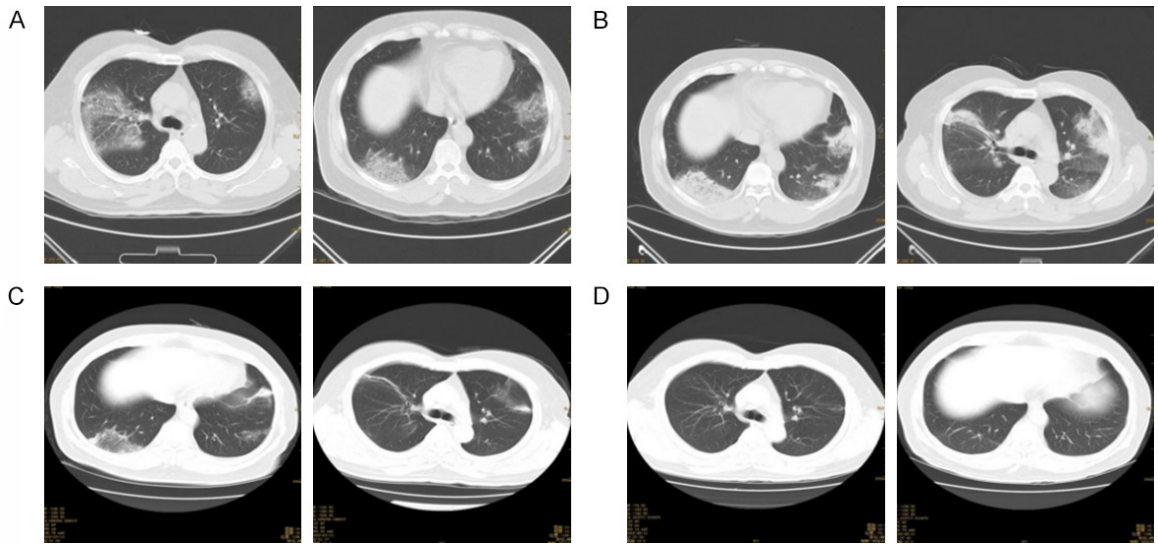

Figure 3. CT images of patient Mr. Lin (Male, Fifty-five years old) during different treatment periods. A: CT at admission (February 14, 2020); B: CT Reexamination after treatment (February 25, 2020); C: CT Reexamination after treatment (March 13, 2020); D: CT Reexamination after discharge (June 11, 2020).

Table 4. Changes of laboratory indexes

Group	WBC ($\times 10^9$/L)	IL-6 (pg/ml)	SAA (mg/L)
Observation group (n=33)	5.97±1.39	2.31±1.51	9.09±6.45
Control group (n=33)	3.92±1.31	12.39±7.41	109.27±63.45
t	6.1655	7.6571	9.0235
P	<0.0001	<0.0001	<0.0001

of conventional treatments such as anti-infection, anti-virus, and anti-inflammation, the nucleic acid negative conversion time of the observation group with additional Lianhua Qingwen Capsules was shorter than that of control group with routine treatment alone. This reveals that Lianhua Qingwen Capsules can significantly ameliorate the fever symptom of patients, improve the body's ability to remove virus, and prevent the deterioration of the condition.

In conclusion, Lianhua Qingwen Capsules are of great value in the treatment of COVID-19. However, there are still some deficiencies, mainly reflected in the limited number of samples, so relevant conclusions need to be further confirmed before major promotion. It is suggested to expand the sample size to provide a more solid foundation for the study of the clinical application potential of Lianhua Qingwen Capsules. On the other hand, COVID-19 is complicated. Although Lianhua Qingwen Capsule has been proven effective, it should be applied based on the actual situation of patients. Before starting any drug treatment, diagnosis and treatment should be considered comprehensively, so as to choose the most suitable treatment program for patients to avoid generalizing.

Disclosure of conflict of interest

None.

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