RESEARCH ARTICLE

Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients

Liu Zengli, Li Xiuhui, Gou Chunyan, Li Li, Luo Xiaolan, Zhang Chun, Zhang Yin, Zhang Jiaying, Jin Aihua, Li Hongyan, Zeng Yuan, Li Tongzeng, Wang Xiaojun

Liu Zengli, Li Xiuhui, Gou Chunyan, Li Li, Zhang Chun, Zhang Yin, Li Hongyan, Zeng Yuan, Luo Xiaolan, Integrated Traditional Chinese and Western Medicine Center, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China

Li Tongzeng, Zhang Jiaying, Jin Aihua, General Department of Infectious Diseases, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China

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Correspondence to: Wang Xiaojun, Integrated Traditional Chinese and Western Medicine Center, Beijing YouAn Hospital, Capital Medical University, Beijing 100069, China. w_xiaojun@126.com

Telephone: +86-10-83997206

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Abstract

OBJECTIVE: To evaluate the effectiveness and safety of Jinhua Qinggan granules in the treatment of patients with novel coronavirus pneumonia (COVID-19).

METHODS: Eighty cases of COVID-19 diagnosed from January 24 to February 17, 2020 in Beijing YouAn Hospital Affiliated to Capital Medical University were retrospectively analyzed. All 80 patients received symptomatic and supportive treatment. Among them, 44 patients took Jinhua Qinggan granules (treatment group) within 24 h of admission, and the remaining 36 patients either did not take Jinhua Qinggan granules or took the granules for less than 2 d (control group). In this study, we compared the duration of viral nucleic acid detection and of pneumonia absorption improvement between the two groups.

RESULTS: Among the 80 cases, 37 were male (46%) and 43 were female (54%) with age ranging from 15 to 86 years, with an average age of 51.19 years. The average duration of viral nucleic acid detection was (7 ± 4) d in the Jinhua Qinggan administration group and (10 ± 4) d for the control group (P = 0.010), following which, nucleic acid tests were negative. Of the two groups, 56.82% in the Jinhua Qinggan treatment group and 27.78% in the control group demonstrated negative nucleic acid tests within 7 d or less. The 7-day viral clearance rate was significantly higher in the Jinhua Qinggan group compared with the control group (P = 0.009). Furthermore, the pneumonia recovery time indicated by chest CT was (8 ± 4) d in the Jinhua Qinggan group, which was significantly shorter than the control group, at (10 ± 5) d (P = 0.021). No adverse reactions were found in the treatment group after taking this medicine.

CONCLUSION: In patients with COVID-19, Jinhua Qinggan granules can effectively shorten the duration of nucleic acid detection and promote the absorption of pneumonia inflammatory exudate without obvious adverse reactions.
INTRODUCTION

During December 2019, many unexplained pneumonia patients started to appear in Wuhan, Hubei Province, China. On December 31, this situation was reported to the WHO by the Health Commission of Hubei Province. 1 On January 7, 2020, relevant Chinese authorities confirmed that this was an infectious disease, termed novel coronavirus pneumonia (COVID-19), caused by a novel coronavirus named severe acute respiratory syndrome coronavirus (SARS-CoV)-2 by the World Health Organization (WHO). 1 The virus spread rapidly and widely, being highly infectious with a high incidence of susceptible populations. The epidemic quickly became the focus of global attention. Furthermore, there are currently no effective antiviral drugs for the treatment of COVID-19 pneumonia. Beijing YouAn Hospital Affiliated to Capital Medical University was one of the first designated hospitals for treatment of COVID-19 patients in Beijing since the outbreak. The hospital actively organized and explored treatment methods involving integration of Chinese and Western Medicines. Based on the clinical characteristics of COVID-19, this study aimed to evaluate the effectiveness and safety of Jinhua Qinggan granules in the treatment of patients with COVID-19.

METHODS

Inclusion criteria

The patients may have the following symptoms: (a) Fever, fatigue and dry cough are the main manifestations; (b) In the past 14 d, Novel coronavirus infection patients had been contacted or gathered; (c) The chest imaging manifestations: In the early stage, there were multiple small patch shadows and interstitial changes, with obvious extrapulmonary zone. Then it develops multiple ground glass shadows and infiltration shadows of the lungs, and in severe cases, lung consolidation may occur. At the same time, one of the following etiological evidences is available: (a) real-time fluorescence RT-PCR of respiratory specimens or blood specimens detected positive for new coronavirus nucleic acid; (b) viral gene sequencing of respiratory specimens or blood specimens, highly homologous to known novel coronavirus. The study included common and severe patients diagnosed with new coronavirus pneumonia. The common type can only show fever, respiratory tract and other symptoms, and the above-mentioned manifestations of pneumonia can be seen in imaging. Those who meet any of the following are severe patients, (a) respiratory distress, RR ≥ 30 times / min; (b) at rest, the oxygen saturation is ≤ 93%; (c) arterial blood oxygen partial pressure ([PaO2]/ oxygen absorption concentration (FiO2) ≤ 300 mm Hg (1 mm Hg = 0.133 kPa).

Exclusion criteria

Exclusion criteria were as follows: 2 (a) patients with critical COVID-19: such as respiratory failure occurs and requires mechanical ventilation, or shock, or combined with other organ failure requires ICU monitoring treatment; (b) patients with any other chronic respiratory disease, respiratory bacterial infections, or other respiratory diseases affecting clinical trial evaluation; and (c) patients with underlying diseases such as severe primary immunodeficiency, acquired immunodeficiency syndrome, congenital respiratory malformation, congenital heart disease, pulmonary dysplasia.

From January 24 to February 17, 2020, 95 patients diagnosed with COVID-19 were admitted to Beijing YouAn Hospital, Capital Medical University and 80 patients were included in this study. Among those 80 cases, 37 were male (46%) and 43 were female (54%). Their ages ranged from 15 to 86 years, with an average age of 51.19 years. The patients were randomly divided into a treatment group of 44 cases and a control group of 36 cases. All patients gave informed consent and the trial was approved by the Ethics Committee of Beijing YouAn Hospital, Capital Medical University.

Treatments

Eighty patients were diagnosed with common or severe COVID-19 and admitted to Beijing YouAn Hospital, Capital Medical University. These patients were divided into Jinhua Qinggan treatment and control groups. Forty-four patients in the treatment group received Jinhua Qinggan granules within 24 h after admission and continued treatment for 7 d, while the 36 patients in the control group did not take Jinhua Qinggan granules, or took them for less than 2 d. Following this, patients’ clinical information was retrospectively analyzed. Upon admission, all patients in both groups were given oxygen inhalation, and symptomatic and supportive treatment (Table 1). The patients randomized to the treatment group began to take Jinhua Qinggan granules [Juxiechang (Beijing) Pharmaceutical Co., Ltd., National Medicine Permission No. Z20160001] within 24 h after admission, at a dose of 1 bag(6 g) twice a day for adult, morning and evening, for 7 consecutive days.

Measurements

SARS-CoV-2 nucleic acid in respiratory specimens was detected by Reverse transcription fluorescence PCR and the time to viral clearance/negative nucleic acid test was recorded and compared between treatment
and control groups after 7 d of treatment. The test was started on the second day after admission, and the test was conducted once every other day until the test result was negative for two consecutive times. Detection of SARS-CoV-2 nucleic acid in respiratory specimens was based on the most recent test result. If the results of two consecutive tests were negative, then the time taken as time of viral clearance was that of the first negative test. Pneumonia recovery time, defined as the time from admission to obvious improvement of pulmonary inflammation exudation and absorption detected by chest computed tomography (CT), was also observed. Baseline values and any changes in white blood cell and lymphocyte counts after 7 d of treatment were also compared between the two groups. Finally, the two groups were compared after treatment to evaluate the clinical efficacy of Jinhua Qinggan granules, including observation of any adverse reactions to assess the safety of the treatment.

Statistical analyses
SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA) was used for data processing. Normally distributed data were compared between the two groups by one-way analysis of variance and expressed as mean ± standard deviation ( \( \bar{x} \pm s \)). The rank sum test was used to compare the means of the two groups where data were not normally distributed, expressed as number of cases (percentage). The \( \chi^2 \) test was used to compare the two groups. \( P < 0.05 \) was considered to be statistically significant.

RESULTS

Clinical characteristics of study participants
There are no differences in age, sex, medical history, epidemiological history, Clinical classification and leucocyte or lymphocyte counts (\( P > 0.05 \)). The main symptoms of patients in the two groups included fever, cough, fatigue, and sputum, muscle soreness, headache, chest tightness, among which, fever, cough, and fatigue were the most common. After comparison, there were no significant differences in the numbers of major symptoms (Table 2, \( P > 0.05 \)), and also no significant differences in the average body temperature between the two groups of patients (Table 2, \( P = 0.189 \)). The baseline data of the two groups were comparable.

Time to viral clearance
The average time taken for virus to be cleared and nucleic acid detection to become negative was \((7 \pm 4)\) d in the Jinhua Qinggan-administered group and \((10 \pm 4)\) d for the control group (\( P = 0.010 \)). Twenty-five (56.82%) patients in the Jinhua Qinggan treatment group and ten (27.78%) in the control group demonstrated negative nucleic acid results in 7 d or less. The 7-day positive-to-negative conversion rate was significantly higher in the Jinhua Qinggan group compared with the control group (\( P = 0.009 \) (Figure 1). Treatment group: received Jinhua Qinggan granules treatment for 7 d; control group: did not take Jinhua Qinggan granules, or less than 2 d. SARS-CoV: severe acute respiratory syndrome coronavirus.

Pneumonia recovery time
The pneumonia recovery time indicated by chest CT was \((8 \pm 4)\) d in the Jinhua Qinggan-treated group. This was dramatically shorter by approximately 2.3 d, compared with the control group at \((10 \pm 5)\) d (\( P = 0.021 \)). The 7-day pneumonia recovery rate in the treatment group reached 45.45%, but there was no significant difference compared with the control group (27.78%) (\( P = 0.104 \)), which may be related to the low number of patients in this clinical study. Figure 2 shows that the pneumonia recovery rate in the treatment group was higher than that of the control group at each time point \((7, 10, 15)\) d.

Leukocyte and granulocyte changes
Blood cell counts of the treatment group were compared between baseline and after 7 d of treatment with Jinhua Qinggan granules. Regardless of the absolute white blood cell or lymphocyte values, the treatment group showed a significant increase from baseline (Table 3, \( P < 0.05 \)), while the leukocyte and lymphocyte counts of the control group were not significantly changed from baseline after 7 d of hospitalization (Table 3, \( P > 0.05 \)). Furthermore, when comparing the two groups at 7 d after hospitalization, leukocyte and lymphocyte counts in the treatment group were significantly higher than those in the control group (Table 3, \( 5.7 \pm 1.3 vs 4.9 \pm 1.7, P = 0.021; 1.4 \pm 0.6 vs 1.1 \pm 0.5, P = 0.011, \) leukocytes and lymphocytes, respectively).

Table 1 Western Medicine treatments received by patients in the treatment and control groups (n)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>( \alpha ) interferon atomization</th>
<th>Antibiotic</th>
<th>Antiviral drugs</th>
<th>Hormone</th>
<th>Hepatoprotective agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>44</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Control</td>
<td>36</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>17</td>
</tr>
</tbody>
</table>

Notes: treatment group: received Jinhua Qinggan granules treatment for 7 d; control group: did not take Jinhua Qinggan granules, or less than 2 d.
The novel SARS-CoV-2 coronavirus, a new type of coronavirus, is the seventh coronavirus to emerge and cause infection in humans, leading to global outbreaks of severe acute respiratory disease. Other emergent coronaviruses to cause similar, although less widespread, disease include SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). According to research, the estimated mean R0 of SARS-CoV-2 ranges from 2.24 to 3.58, and the population is generally susceptible, which suggests that SARS-CoV-2 has a strong transmission ability and a very large susceptible population.

**DISCUSSION**

The novel SARS-CoV-2 coronavirus, a new type of coronavirus, is the seventh coronavirus to emerge and cause infection in humans, leading to global outbreaks of severe acute respiratory disease. Other emergent coronaviruses to cause similar, although less widespread, disease include SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). According to research, the estimated mean R0 of SARS-CoV-2 ranges from 2.24 to 3.58, and the population is generally susceptible, which suggests that SARS-CoV-2 has a strong transmission ability and a very large susceptible population.

**Table 2 Baseline characteristics of patients (x ± s)**

<table>
<thead>
<tr>
<th>Project</th>
<th>Treatment group (n = 44)</th>
<th>Control group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [n (%)]</td>
<td>Male 21 (47.73)</td>
<td>16 (44.44)</td>
</tr>
<tr>
<td></td>
<td>Female 23 (52.27)</td>
<td>20 (55.56)</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>50.73</td>
<td>51.75</td>
</tr>
<tr>
<td>Medical history [n (%)]</td>
<td>Diabetes 2 (4.55)</td>
<td>2 (5.56)</td>
</tr>
<tr>
<td></td>
<td>Hypertension 6 (13.64)</td>
<td>5 (13.89)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease 2 (4.55)</td>
<td>2 (5.56)</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis 1 (2.27)</td>
<td>2 (5.56)</td>
</tr>
<tr>
<td>Epidemiological history [n (%)]</td>
<td>Tourism and residence history in Wuhan/close contact history 28 (63.64)</td>
<td>25 (69.44)</td>
</tr>
<tr>
<td></td>
<td>Cluster disease 16 (36.36)</td>
<td>10 (27.78)</td>
</tr>
<tr>
<td></td>
<td>Non-contact history 0 (0.00)</td>
<td>1 (2.78)</td>
</tr>
<tr>
<td>Main symptoms (top three) [n (%)]</td>
<td>Fever 30 (68.18)</td>
<td>26 (72.22)</td>
</tr>
<tr>
<td></td>
<td>Cough 18 (40.91)</td>
<td>22 (61.11)</td>
</tr>
<tr>
<td></td>
<td>Fatigue 13 (29.55)</td>
<td>14 (38.89)</td>
</tr>
<tr>
<td>Body temperature (℃)</td>
<td>37.8±0.9</td>
<td>38.1±0.8</td>
</tr>
<tr>
<td>Clinical classification [n (%)]</td>
<td>Common 37 (84.09)</td>
<td>28 (77.78)</td>
</tr>
<tr>
<td></td>
<td>Severe 7 (15.91)</td>
<td>8 (22.22)</td>
</tr>
<tr>
<td>White blood cell count (× 10^9/L)</td>
<td>4.5±1.5</td>
<td>4.2±1.6</td>
</tr>
<tr>
<td>Neutrophil count (× 10^9/L)</td>
<td>3.0±1.6</td>
<td>2.7±1.6</td>
</tr>
<tr>
<td>Lymphocyte count (× 10^9/L)</td>
<td>1.1±0.5</td>
<td>1.1±0.5</td>
</tr>
</tbody>
</table>

Notes: treatment group: received Jinhua Qinggan granules treatment for 7 d; control group: did not take Jinhua Qinggan granules, or less than 2 d.

**Figure 1 Conversion rate from positive to negative SARS-CoV-2 nucleic acid detection in respiratory specimens during hospitalization in treatment and control groups**

**SARS-CoV-2: severe acute respiratory syndrome coronavirus.**

**Safety evaluation**

During the application of Jinhua Qinggan granules in combination with conventional treatment, laboratory tests such as routine blood workup, and liver and kidney function tests did not show significant adverse reactions. Compared with baseline, no patient demonstrated any other symptoms or signs of adverse events. However, all patients showed improvements of the original respiratory and digestive tract symptoms.

**DISCUSSION**

The novel SARS-CoV-2 coronavirus, a new type of coronavirus, is the seventh coronavirus to emerge and cause infection in humans, leading to global outbreaks of severe acute respiratory disease. Other emergent coronaviruses to cause similar, although less widespread, disease include SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). According to research, the estimated mean R0 of SARS-CoV-2 ranges from 2.24 to 3.58, and the population is generally susceptible, which suggests that SARS-CoV-2 has a strong transmission ability and a very large susceptible population.
From the perspective of onset and clinical symptoms, COVID-19 belongs to the "plague" category of Traditional Chinese Medicine (TCM).6 Jinhua Qinggan granules are an effective treatment prescription selected by Chinese and Western medical experts organized by Beijing Administration of Traditional Chinese Medicine after more than six months’ efforts, referring to more than 100 ancient prescriptions in TCM classics such as Treatise on Febrile Diseases, Wenyi Lun and Wending Taobian, drawing on the achievements of clinical experts and repeated screening. This prescription consists of the combination of Maxingshigan decoction and Yinqiao San, which is composed of Jinyinhu (Flores Lonicerae), Zhihu (Glycyrrhizae Radix et Rhizoma), Shigao (Gypsum Fibrosum), Dahuang (Rheum palmatum), Jinyinhua (Flos Lonicerae), and other medicinal herbs. It has the effect of dispersing wind and promoting pharynx and relieving cough. The fever, cough, headache, muscle soreness and other symptoms caused by the flu can also be improved rapidly. At present, there are no effective drugs for treatment of COVID-19, the disease caused by SARS-CoV-2 infection. However, previous studies have shown that Jinhua Qinggan granules can significantly reduce the level of several cytokines in patients with influenza and enhance immune function. The National Health Commission explicitly emphasized the recommendation to use Jinhua Qinggan granules for patients during the medical observation period in the "Diagnosis and Treatment Program for COVID-19 (trial version 4th)".7 Their use has also been recommended in subsequent diagnosis and treatment plans.6,11

Jinhua Qinggan granules have significant effects in reducing fever, alleviating other cold symptoms, improving symptoms in Traditional Chinese Medicine symptom patterns.8 It is known as "Oseltmivir of Traditional Chinese Medicine", indicating that Jinhua Qinggan granules have a more comprehensive mechanism in treating influenza, which is in line with the "multi-target" mechanism of Chinese medicine. Investigators found that maxingshigan had inhibitory effects on influenza virus A by directly killing the virus, interfering with virus adsorption, inhibiting virus proliferation, and protecting the cells from being infected with virus.9,10 Reports have shown that the majority of patients with COVID-19 demonstrate common or mild disease. There were 80 patients with common and severe COVID-19 included in this study, with the proportion of common-type patients being 81.25%, which is consistent with the data presented in the joint investigation report of China-WHO.11 According to our statistical results, the time taken for nucleic acid testing to become negative in respiratory tract specimens of the patients in the treatment group, who were given Jinhua Qinggan granules within 24 h of admission, was on average approximately 2.5 d earlier than the control group. Furthermore, the rate of viral clearance, as indicated by two consecutive negative RNA tests, was more than 50% within 7 d in the treatment group, while only 28% of patients in the control group cleared virus in respiratory tract samples within 7 d. This shows that Jinhua Qinggan granules have significant antiviral effect on patients with common and severe COVID-19. Similarly, when measuring improvement of the observed pneumonia in the two groups, the pneumonia recovery time in the treatment group averaged 8.0 d while the control group averaged 10.3 d. The recovery time of pneumonia exudation and absorption in the Jinhua Qinggan granule-treated group was faster than that of the control group by approximately 2.3 d. This result clearly shows that Jinhua Qinggan granules can promote early absorption of pulmonary inflammation in patients with COVID-19, thereby rapidly improving clinical symptoms. Jinhua Qinggan granule treatment also has a significant effect on leukocyte and lymphocyte counts. Comparison between admission and 7-day counts in the two groups showed that the white blood cell counts of the patients in the treatment group increased significantly following 7 d of treatment compared with baseline, and the lymphocyte counts were also increased significantly compared with those at time of admission. Lymphocytes are the "guards" of the human immune system against external infections. Clinical studies have found that peripheral blood lymphocyte values in patients with common COVID-19 are significantly higher than those in severe and critically ill patients, which

Table 3 Changes in leukocyte and lymphocyte counts before and after treatment in treatment and control groups (×10^9/L, ± ± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>WBC</th>
<th>LYM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>44</td>
<td>Baseline</td>
<td>4.6±1.6</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after treatment</td>
<td>5.7±1.3</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Control</td>
<td>36</td>
<td>Baseline</td>
<td>4.2±1.6</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after treatment</td>
<td>4.9±1.7</td>
<td>1.1±0.5</td>
</tr>
</tbody>
</table>

Notes: treatment group: received Jinhua Qinggan granules treatment for 7 d; control group: did not take Jinhua Qinggan granules, or less than 2 d. WBC: white blood cell count; LYM, lymphocyte count."P < 0.05, treatment group baseline counts were compared with those at 7 d after treatment; 'comparison of leukocyte counts between treatment and control groups after 7 d of treatment, P = 0.021; 'comparison of lymphocyte counts between treatment and control groups after 7 d of treatment, P = 0.011.
indicates the pathogenesis of COVID-19 is similar to that of pneumonia caused by SARS and MERS coronaviruses, and there may be a process of cellular immune damage. In the treatment group in this study, peripheral blood lymphocytes increased from baseline after treatment with Jinhua Qinggan granules, which also shows that this treatment can effectively promote the recovery of the immune system in patients with COVID-19. From this point, we boldly speculate that the application of Jinhua Qinggan granules may reduce the probability of further exacerbation in common and severe patients, thereby reducing mortality. Unfortunately, in this study, two cases in each group progressed to critical disease, but this was not statistically significant due to the limited sample size. An achievement of reduced pulmonary inflammation and negative nucleic acid tests for SARS-CoV-2 are important criteria for judging propriety of patient discharge. Therefore, administering Jinhua Qinggan granules as early as possible after admission can reduce the time taken to clear the virus and obtain negative nucleic acid test results in respiratory samples, and promote the absorption of pneumonia, which can reduce the length of hospital stay for patients. Crucially, this will also reduce the pressure of hospital admissions and treatment, freeing up valuable medical resources to treat critical patients. This is of great significance in reducing the social and economic expenditure involved in fighting this ongoing pandemic.

In conclusion, Jinhua Qinggan granules can effectively shorten the time taken to clear SARS-CoV-2 and promote the absorption of pneumonia inflammatory exudate without significant adverse reactions. Because there are some limitations in this study, such as the small sample size of the two groups and the absence of CD4 lymphocytes in the monitoring of patient immune function, additional well-designed clinical studies are needed in the future to further confirm our findings.

REFERENCES


