Clinical Effect of Yinhuang Qingfei Capsules in Treatment of Asymptomatic and Mild/Common Severe Acute Respiratory Syndrome Coronavirus 2 Infection: An Analysis of 242 Cases

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Abstract [**Objectives**] To investigate the clinical effect of Yinhuang Qingfei capsules in the treatment of asymptomatic and mild/common severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. [**Methods**] A total of 362 patients with SARS-CoV-2 infection were divided into the treatment group with 242 patients and control group with 120 patients according to their treatment regimen. The patients in the control group were given standard treatment regimen and those in the treatment group were given Yinhuang Qingfei capsules in addition to the treatment in the control group. The two groups were observed in terms of average length of hospital stay, mean time for nucleic acid clearance, TCM syndrome score, and progression to severe/critical illness, and clinical outcome was compared between the two groups. [**Results**] There was a significant difference in the overall response rate between the treatment group and the control group [97.52% (236/242) vs 95.00% (114/120), $P<0.05$]. Compared with the control group, the treatment group had significantly shorter length of hospital stay and time for nucleic acid clearance ($P<0.05$). After 7 days of treatment, both groups had a significant change in TCM syndrome score, and there was a significant difference in TCM syndrome score between the two groups ($P<0.05$); after 15 days of treatment, both groups had a TCM syndrome score of 0. Progression to severe/critical illness was not observed in either group. [**Conclusions**] Compared with the standard treatment regimen alone, standard treatment regimen combined with Yinhuang Qingfei capsules can effectively shorten the length of hospital stay and time for nucleic acid clearance and improve TCM symptoms in patients with asymptomatic and mild/common SARS-CoV-2 infection.

Key words Severe acute respiratory syndrome coronavirus 2 infection, Asymptomatic, Mild/common, Yinhuang Qingfei capsules

1 Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has occurred in various parts of the world, posing a serious threat to human health. At present, among the five "variants of concern" (VOC) proposed by the World Health Organization (WHO), Omicron strain has become the main epidemic strain, with characteristics of strong transmission power, fast transmission speed, strong stealth and so on. Currently, those who had been vaccinated and newly infected with Omicron strain were mostly asymptomatic and mild.

Yinhuang Qingfei capsules are recommended in the *TCM Diagnosis and Treatment Plan for COVID-19 Prevention and Control in Hunan Province* (2nd edition in 2021). The Chinese patent drug consists of 14 kinds of traditional Chinese medicine, such as Descurainiae Semen Lepidii Semen, Ephedrae Herba, Armeniacae Semen Amarum, Fritillariae Thunbergii Bulbus, Eriobotryae Folium, Ginkgo Folium, Folium Isatidis, Acori Tatarinowii Rhizoma, Dioscoreae Nipponicae Rhizoma, *Artemisia rupestris* L., Schisandrae Chinensis Fructus, Aurantii Fructus Immaturus, Raw Gypsum, Glycyrrhizae Radix Et Rhizoma, and has the effect of clearing the lungs and eliminating phlegm, relieving cough and asthma. The drug is often used for phlegm-heat blocking lung syndrome of acute attack of chronic bronchitis, and the symptoms include cough and phlegm, yellow and sticky sputum, chest tightness, wheezing, fever and thirst, dry stool and yellow urine, red tongue, yellow and sticky fur, *etc.* In this paper, to objectively evaluate the clinical efficacy of Yinhuang Qingfei capsules in the treatment of SARS-CoV-2 infection, a clinical study was conducted in three designated temporary hospitals for the treatment of SARS-CoV-2 infection in Pudong District of Shanghai.

2 Data and methods

2.1 Clinical data

2.1.1 General information. A total of 362 patients with SARS-CoV-2 infection who received treatment from Shanghai Pudong New Area Pulmonary Hospital, Nanhua Hospital of Shanghai Pudong New Area, and Heqing Hospital of Shanghai Pudong Hospital from March to May in 2022 were randomly divided into two groups: treatment group (242 cases) and control group (120 cases). In the treatment group, there were 120 males and 122 females; their average height was (166.12 ± 9.33) cm; their average body mass was (63.00 ± 10.25) kg. In the control group, there were 46 males and 74 females; their average height was (164.40 ± 9.73) cm; their average body mass is (62.72 ± 10.11) kg. There was no significant difference between the two groups in gender, height and body mass ($P>0.05$), so they were comparable.

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2.1.2 Diagnostic criteria. The diagnostic criteria in the *Scheme for the Diagnosis and Treatment of Corona Virus Disease* 2019 (*Trial Ninth Edition*)[2] were adopted. (i) Suspected cases. ① Epidemiological histories: there was a travel history or residence history in the community where cases were reported within 14 d before the onset of the disease; there was a history of contact with a person infected with SARS-CoV-2 within 14 d before the onset of the disease; there was a history of contact with patients who had fever or respiratory symptoms and were from in the community with reported cases within 14 d before the onset of the disease; 2 or more cases with fever and/or respiratory symptoms appeared in a small area such as home, office, school class, *etc.* within 14 d. ② Clinical manifestations: there was fever and/or respiratory symptoms and other clinical manifestations related to COVID-19; patients had the above imaging features of COVID-19; in the early stage of the disease, the total number of white blood cells was normal or decreased, and the number of lymphocytes was normal or reduced. Suspected cases can be determined according to the following conditions: there was any 1 of the above epidemiological histories and any 2 of the clinical manifestations; there was no clear epidemiological history, and there were all 3 of the clinical manifestations; there were any 2 of the clinical manifestations, and the specific IgM antibody of SARS-CoV-2 was positive (except patients who were recently inoculated against SARS-CoV-2 vaccine). (ii) Confirmed cases. Suspected cases who had one of the following etiological or serological evidences: ① the nucleic acid test of SARS-CoV-2 was positive; ② patients who were not inoculated against SARS-CoV-2 vaccine had positive specific IgM and IgG antibodies of SARS-CoV-2.

2.1.3 Clinical classification criteria. The clinical classification criteria in the *Scheme for the Diagnosis and Treatment of Corona Virus Disease* 2019 (*Trial Ninth Edition*)[2] were adopted. (i) Mild type. The clinical symptoms were mild, and there were no signs of pneumonia on imaging. (ii) Common type. Patients had the above clinical manifestations, and pneumonia could be found by iconography. (iii) Severe type. Adults met any of the following criteria: they had shortness of breath, and respiratory rate was $\geqslant$ 30 times/min; at rest, arterial oxygen saturation was $\leqslant$93% when inhaling air; arterial partial oxygen pressure (PaO_2)/oxygen absorption concentration (FiO_2) was $\leqslant$300 mmHg (1 mmHg$\approx$0.133 kPa); at high altitudes (above 1 000 m), PaO_2/FiO_2 should be corrected according to the following formula: $PaO_2/FiO_2 \times 760$/atmospheric pressure (mmHg). The clinical symptoms worsened progressively, and lung imaging showed that the progress of lesions was >50% within 24 – 48 h. (iv) Critical type. One of the following conditions can be met: there was respiratory failure, and mechanical ventilation was needed; patients went into shock; there was failure of other organs, and intensive care unit was required.

2.1.4 Inclusion criteria. (i) The above diagnostic criteria were met, and the nucleic acid test of SARS-CoV-2 was positive. (ii) The clinical type was mild or ordinary. (iii) The nucleic acid test of influenza virus was negative. (iv) The patients were asymptomatic, and their nucleic acid test of SARS-CoV-2 was positive. (v) They voluntarily participated in the study and signed the informed consent.

2.1.5 Exclusion criteria. (i) They were pregnant women, or their urine pregnancy test was positive. (ii) They also suffered from serious basic respiratory diseases, malignant tumors, mental diseases, *etc.* (iii) They could not cooperate with this study. (iv) They were allergic or intolerant to the drugs used in the study.

2.2 Treatment method

2.2.1 Control group. The relevant diagnosis and treatment scheme in the *Scheme for the Diagnosis and Treatment of Corona Virus Disease* 2019 (*Trial Ninth Edition*)[2] was adopted. (i) Patients rested in bed, and supportive treatment was strengthened to ensure adequate energy and nutrition intake. (ii) Effective oxygen therapy measures were taken, that is, oxygen was administered through a nasal catheter and mask, and high-flow nasal cannula oxygen therapy was adopted. (iii) Standard prone position treatment was adopted, and the treatment time was not less than 12 h per day. (iv) Psychological counseling was strengthened.

2.2.2 Treatment group. On the basis of the treatment in the control group, patients in the treatment group were treated with Yinhuang Qingfei capsules. Yinhuang Qingfei capsules (Hu'nan Anbang Pharmaceutical Co., Ltd., approval number: SFDA approval number Z20020075, specification: 0.15 g/capsule) were taken orally (0.45 g/time, 3 times/d). Patients in the both groups were treated for 15 d.

2.3 Observation of curative effect

2.3.1 Observation indicators. Observation indicators included average length of hospital stay, mean time for nucleic acid clearance, average TCM syndrome score, and progression to severe/critical illness. Among them, average TCM syndrome score was determined according to the scoring standard of TCM syndromes of cold in the *Guiding Principles for Clinical Research of New Chinese Medicine Drugs*[3]. The symptoms of cough during the day, cough at night, sputum, asthma, chest tightness, shortness of breath, dry stool, yellow urine, fatigue, dry throat and thirst were observed, and the scores of no, light, medium and severe symptoms were 0, 2, 4, and 6. In addition, the score of body temperature <37.3 ℃ was 0, and that of body temperature $\geqslant$ 37.3 ℃ was 2. The score of negative nucleic acid test was 0, and that of positive nucleic acid test was 2. Finally, the total score was counted to obtain the average.

2.3.2 Criteria of curative effect. It was formulated according to the relevant standards in the *Guiding Principles for Clinical Research of New Chinese Medicine Drugs*[3]. Recovery: clinical symptoms and signs disappeared or basically disappeared, and the reduction rate of TCM syndrome score was $\geqslant$95%. Obvious effect: clinical symptoms and signs were significantly improved, and the reduction rate of TCM syndrome score was $\geqslant$70% but <95%. Effective: clinical symptoms and signs were improved, and the reduction rate of TCM syndrome score was $\geqslant$30% but

<70%. Ineffective: clinical symptoms and signs were not significantly improved or even aggravated, and the reduction rate of TCM syndrome score was <30%. Reduction rate of TCM syndrome score = (TCM syndrome score before treatment − TCM syndrome score after treatment)/TCM syndrome score before treatment × 100%.

2.3.3 Statistical methods. SAS statistical software was used to analyze the data. The measurement data were described as mean ± standard deviation ($\bar{x} \pm s$), median, lower quartile (q1), upper quartile (q3), minimum (min) and maximum (max). Paired *t*-test was used for intra-group comparison. The statistical data were expressed as rate (%), and χ^2 test was used. Rank sum test was used for rank data. $P<0.05$ meant the difference was statistically significant.

3 Results and analysis

3.1 Comprehensive efficacy The overall response rate of the two groups was 97.52% (treatment group) and 95.00% (control group), respectively, and the difference between the two groups was statistically significant ($P<0.05$) (Table 1).

Table 1 Comparison of comprehensive efficacy between the two groups (cases, %)

Group	Number of cases	Recovery	Obvious effect	Effective	Ineffective	Overall response rate
Treatment	242	128 (52.89)	11 (4.55)	97 (40.08)	6 (2.48)	236 (97.52)[a]
Control	120	50 (41.67)	17 (14.17)	47 (39.16)	6 (5.00)	114 (95.00)

NOTE Compared with the control group, [a]$P<0.05$. The same in Table 2 and Table 3.

3.2 Average length of hospital stay The difference between the two groups in the average length of hospital stay was statistically significant ($P<0.05$) (Table 2).

Table 2 Comparison of the average length of hospital stay between the two groups ($\bar{x} \pm s$, d)

Group	Number of cases	Average length of hospital stay	Median (q1,q3)	min-max
Treatment	242	7.49 ± 3.93[a]	7.00 (5.00,9.00)	2.00 − 39.00
Control	120	9.28 ± 3.34	9.50 (6.00,13.00)	3.00 − 14.00

3.3 Mean time for nucleic acid clearance There was a significant difference between the treatment group and the control group in the mean time for nucleic acid clearance ($P<0.05$) (Table 3).

Table 3 Comparison of mean time for nucleic acid clearance between the two groups ($\bar{x} \pm s$, d)

Group	Number of cases	Mean time for nucleic acid clearance	Median (q1,q3)	min-max
Treatment	242	6.04 ± 2.71[a]	6.00 (4.00,8.00)	1.00 − 13.00
Control	120	8.31 ± 2.98	8.00 (6.00,10.00)	3.00 − 13.00

3.4 Average TCM syndrome score After 7 d of treatment, the TCM syndrome scores of the two groups were lower than that before treatment. That of the treatment group was lower than the control group, and the difference was statistically significant ($P<0.05$). After 15 d of treatment, the TCM syndrome scores of the two groups were 0 (Table 4).

Table 4 Comparison of average TCM syndrome score between the two groups ($\bar{x} \pm s$, points)

Group	Number of cases	Before treatment	After 7 days of treatment	After 15 days of treatment
Treatment	242	11.50 ± 7.05	2.10 ± 3.21[ab]	0[a]
Control	120	11.65 ± 8.40	3.93 ± 3.83[a]	0[a]

NOTE Compared with the group before treatment, [a]$P<0.05$. Compared with the control group after treatment, [a]$P<0.05$.

3.5 Progression to severe/critical illness There was no progression to severe/critical illness in both of the groups.

4 Discussion

SARS-CoV-2 infection falls into the category of "epidemic disease" in traditional Chinese medicine. Pestilence is related to pestilential pathogen and foul secretion. At the same time, due to the differences in regions, climate, environment and living habits, there will be different syndromic characteristics such as cold, heat, blood stasis and dryness[4]. The pathogenesis of pestilence is characterized by cold, dampness, heat, toxicity, stasis and deficiency, so it is treated by promoting the lungs, clearing the lungs, removing dampness, and detoxification.

Yinhuang Qingfei capsules are made from Maxing Shigan Decoction and Tingli Dazao Xiefei Decoction in Zhang Zhongjing's *Treatise on Febrile Diseases* by addition and subtraction. Maxing Shigan Decoction has the functions of clearing the lungs and eliminating phlegm, lowering the lungs, relieving cough and asthmatic asthma, detoxifying and promoting blood circulation, and it is the core prescription for the treatment of pulmonary infectious diseases. Tingli Dazao Xiefei Decoction has the effects of purging the lungs of pathogenic fire and protecting the spleen. Studies have shown that Yinhuang Qingfei capsules can improve the symptoms of pulmonary infectious diseases, reduce C-reactive protein and procalcitonin, shorten the time for clinical symptoms to resolve, improve lung function, and promote the rehabilitation of patients[5]. In the formula, honey ephedra is pungent and warm, and has the effects of freeing the lungs and relieving asthma, dispelling outward appearance and dispelling evil. Raw gypsum is pungent, sweet and very cold, and can clear lung heat to produce fluid. The compatibility of the two drugs as sovereign drugs can not only disperse lung stroke heat but also clear lung stasis heat. Fritillariae Thunbergii Bulbus is sweet and slightly cold, mainly affects the lungs, and can dissipate phlegm, eliminate stagnation and clear heat. Acori Tatarinowii Rhizoma has the effect of clearing phlegm, dispelling dampness and appetizing appetite. Aurantii Fructus Immaturus is bitter, pungent and mildly cold, and can reduce phlegm

and relieve stagnant qi. The combination of the two drugs can not only clear heat, reduce phlegm, and eliminate stagnation, but also strengthen the effect of the sovereign drugs to clear lung heat. The three are minister drugs. Armeniacae Semen Amarum is bitter and warm, and can disperse the lungs and expel wind to relieve asthma and cough. It can be compatible with honey ephedra or raw gypsum. Descurainiae Semen Lepidii Semen. is bitter and warm, and can purge the lungs and relieve asthma. Armeniacae Semen Amarum has the main effect of diffusing the lungs and relieving asthma, while the main effect of Descurainiae Semen Lepidii Semen. is purging the lungs and relieving asthma, so their compatibility can diffuse and purge the lungs and relieve asthma. Eriobotryae Folium can reduce and relieve lung qi, and relieve cough and asthma. The combination of the three drugs has the effect of purging the lungs and relieving cough and asthma. Phlegm and dampness are easy to block qi into stasis. Dioscoreae Nipponicae Rhizoma and *Artemisia rupestris* L. can be used to promote blood circulation and remove blood stasis. Folium Isatidis can help gypsum clear heat and remove toxicity. Fructus Schisandrae Chinensis as corrigent is astringent, and has the effect of supplementing qi and promoting the production of body fluid. Ginkgo leaves can constrain the lungs and relieve asthma, and astringe lung qi. Licorice is used to blend the various drugs and is as conductant drug. Yinhuang Qingfei capsules have the effects of diffusing the lungs, clearing heat, detoxification, reducing phlegm, and relieving asthma, which is consistent with the treatment of the disease, corresponding with its pathogenesis, so the curative effect was good.

According to the report of Academician Zhong Nanshan's team, among the patients infected with SARS-CoV-2, the proportion of mild cases is 83.25%. Therefore, strengthening the treatment of mild/ordinary cases and preventing further transmission of the disease are of great significance for preventing the spread of the epidemic[6]. The results of this study show that the overall response rate in the treatment group was 97.52%, higher than 95.00% in the control group ($P<0.05$); the average length of hospital stay and mean time for nucleic acid clearance in the treatment group were shorter than those in the control group ($P<0.05$). The average TCM syndrome score after 7 d of treatment was lower than that in the control group ($P<0.05$). It shows that compared with the single use of the standard treatment plan, the use of Yinhuang Qingfei capsules could more effectively shorten the length of hospital stay and the time for nucleic acid clearance of asymptomatic and mild/ordinary patients with SARS-CoV-2 infection, and improve the symptoms of traditional Chinese medicine, with certain advantages and good safety.

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