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Clinical efficacy of low-dose emetine for patients with COVID-19: a real-world study

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Abstract

Objective: Emetine, an isoquinoline alkaloid that is enriched at high concentrations in the lung, has shown potent in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The aim of this study was to better understand the effectiveness of low-dose emetine for patients with coronavirus disease 2019 (COVID-19).

Methods: In this real-world study, 63 patients with mild or common COVID-19 were recruited from Wuhan Fangcang Shelter Hospital and five COVID-19-designated hospitals in Anhui Province, China from February to March 2020. Thirty-nine patients from Wuhan Fangcang Shelter Hospital were assigned to a pragmatic randomized controlled clinical trial, and 24 patients from the 5 COVID-19-designated hospitals in Anhui Province underwent a real-world study. The medication course of emetine was less than 10 days. The main symptoms and adverse reactions of all patients were observed and recorded. The primary outcome measure was the time required for a negative SARS-CoV-2 RNA result or the negative result rate on day 10. Secondary outcomes included axillary temperature, transcutaneous oxygen saturation, and respiratory frequency recovery. The study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University on February 20, 2019 (approval No. PJ2020-03-19) and was registered with the Chinese Clinical Trial Registry on February 20, 2019 (registration number: ChiCTR2000030022).

Results: The oxygen saturation values were higher in the treatment group than in the control group on the first day after enrollment for patients treated at Fangcang Shelter Hospital. The axillary body temperature, respiratory rate, and oxygen saturation among patients in Fangcang Shelter Hospital were related to the time effect but not to the intervention measures. The respiratory rate and oxygen saturation of patients in the Anhui designated hospitals were related to the intervention measures but not to the time effect. The axillary body temperature of patients in Anhui designated hospitals was related to the time effect but not to the intervention measures.

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Conclusion: Our preliminary study shows that low-dose emetine combined with basic conventional antiviral drugs improves clinical symptoms in patients with mild and common COVID-19 without apparent adverse effects, suggesting that moderately increased doses of emetine may have good potential for treatment and prevention of COVID-19.

Keywords: arbidol, COVID-19, emetine, randomized controlled clinical trial, real-world study

Introduction

The main infection route of coronavirus disease 2019 (COVID-19) is via invasion of the human respiratory tract epithelial cells, and the disease can be spread through respiratory tract droplets, aerosols, and virus-containing secretions.[1,2] According to the Chinese COVID-19 Diagnosis and Treatment Guideline (Trial version 7), COVID-19 can be divided into 4 types: mild, common, moderate, and severe. The early manifestations of COVID-19 infection are pulmonary edema, protein exudation, pulmonary interstitial thickening, and multinucleated giant cell and macrophage infiltration in the alveolar cavity.[3] Therefore, the symptoms of most patients mainly involve the respiratory tract, including cough and sputum, while common clinical symptoms also include fever, limb weakness, and headache.[4,5] Some patients, especially children and neonates, may only show diarrhea, low fever, mild fatigue, and drowsiness, without pneumonia, and a small number of patients may not have any clinical manifestations.[4,6]

Vaccination is an effective means to prevent infections without obvious variant viruses. Although the development of a vaccine against COVID-19 has entered the clinical trial stage, time will be required for it to be officially put into use. Therefore, the rapid development of effective clinical treatment drugs and efforts to improve the cure rate and reduce the mortality rate are still the top priority of COVID-19 treatment. Although many institutions domestically and abroad have successfully verified the efficacy of at least 50 different drugs for COVID-19 in hundreds of clinical trials, currently, no specifically effective drugs with high safety profiles have been found.[7] Seeking potential therapeutic drugs from existing antiviral drugs is the most efficient strategy. Emetine is an isoquinoline type alkaloid that has potent broad-spectrum inhibitory activities against a variety of DNA and RNA viruses. It can prevent viruses from entering cells, thus inhibiting viral replication enzyme activity and intracellular transport, and can also inhibit the translation of viral proteins.[8] A team at the University of Frankfurt Medical Virology Institute and the Goethe University School of Medicine used proteomic methods to predict that inhibition of protein translation may be effective in preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication.[9] Our previous research demonstrated that pretreatment of Vero cells with emetine could effectively block virus invasion with an EC50 of 0.019 μM. Meanwhile, emetine can effectively inhibit SARS-CoV-2 replication in Vero cells with an EC50 of approximately 0.007 μM. In vivo animal experiments have shown that emetine can be enriched in lung tissue for more than 12 hours. With a single oral administration of 1 mg/kg, the effective lung concentration can reach 1.8 M at 12 hours, far exceeding the in vitro EC50. Given the effective inhibition of COVID-19 invasion and replication and its good lung aggregation characteristics, emetine shows potential value in the treatment of COVID-19.

The purpose of this study was to evaluate the feasibility and clinical efficacy of emetine in the treatment of COVID-19 patients. Because of local skin necrosis, cardiotoxicity, and other toxic side effects, amoebic dysentery is treated by intravenous injection of emetine.[10] Emetine containing Xiaoer Huatan Zhike Granules as the main ingredient was chosen as the treatment modality based on comprehensive consideration of the effectiveness, safety, comfort, drug accessibility, and economic cost.

Subjects and methods

Patients

This real-world study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University on February 20, 2019 (approval No. PJ2020-03-19) and was registered with the Chinese Clinical Trial Registry on February 20, 2019 (registration number: ChiCTR2000030022). The study was conducted from February 20, 2020 to April 5, 2020 in Wuhan and Anhui. This study adopted the conventional treatment protocols for patients with mild and common COVID-19 recommended in the "COVID-19 Diagnosis and Treatment Guideline (Trial Version 6)" and only performed clinical trials for antiviral therapy. Because of the emergency nature of the trial, no placebo was prepared. This study was conducted according to the principles of the *Declaration of Helsinki* and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. Mild and common COVID-19 patients aged between 18 and 80 years old were included in this study.

Inclusion criteria

(1) Patients ranging in age from 18 to 80 years (including boundary values) with no gender limitation.
(2) Positive SARS-CoV-2 RNA detection from respiratory droplets by real-time polymerase chain reaction (RT-PCR).
(3) Mild or common COVID-19 (with symptoms such as fever, respiratory tract symptoms, and pneumonia confirmed by imaging).
(4) Hospitalized for the following reasons: fever (axillary temperature greater than or equal to 36.7°C) and respiratory rate more than 24 per minute or cough (at least one item for shortness of breath and cough).
(5) Signed informed consent form.

Exclusion criteria

(1) Known or suspected to be allergic to the components of the test drug.
(2) Patients with confirmed hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), or other viral infections.
(3) Patients classified as severe or critical types with complications such as respiratory failure and acute respiratory distress syndrome.
(4) Patients who had participated in other clinical trials or had used experimental drugs within 12 weeks before enrollment.
(5) Women of childbearing age with positive pregnancy tests.

(6) Patients who were using other drugs with immunomodulatory functions for prevention or treatment.
(7) Patients who may be transferred to non-participating hospitals within 72 hours.
(8) Patients with other factors not suitable for participating in this trial.

Treatment method

A single-center pragmatic randomized controlled clinical trial was conducted; participants were randomly assigned by the envelope method and received the prepared drug with the corresponding number.

Treatment group: Emetine (Chongqing Taiji Industry (Group) Co., Ltd., Chongqing, China) 3.6 mg per os, 3 times per day for 10 days + routine antiviral therapy (Arbidol, 200 mg per os, 3 times per day for 10 days, CSPC Pharmaceutical Group Ltd., Shijiazhuang, China).

Control group: Arbidol, 200 mg, per os, 3 times per day for 10 days.

Multicenter real-world study:

Treatment group: Emetine 3.6 mg per os, 3 times per day for 10 days + routine antiviral therapy.
Control group: routine antiviral therapy.

Observation index

Training nurses assessed patients once a day according to diary cards containing the target information. The clinical data of the two groups were analyzed, including the disappearance rate and number of days of the cardinal symptoms (fever, fatigue, and cough), the disappearance rate of other symptoms and signs, the severity of cardinal symptoms, and the rate of clinical worsening.

Outcome evaluation

Primary efficacy index: The time required for a negative SARS-CoV-2 RNA result or the rate of negative results on day 10.

Secondary efficacy index: The improvement rate and time of cardinal symptoms (axillary temperature, transcutaneous oxygen saturation, and respiratory frequency recovery).

Statistical analysis

SAS 9.4 software for Windows (SAS, Cary, NC) was used for the statistical analysis. All statistical tests were two-sided. Numbers and composition ratios were used to represent count data, while the mean values and standard deviations were calculated for continuous data. Independent two-sample *t*-tests or the Wilcoxon rank sum test were used to compare continuous data between groups, and the chi-square test or Fisher exact probability test was used to compare count data. Repeated measures analysis of variance (repeated measures ANOVA) was performed to explore the effect of time and treatment on efficacy parameters. A value of $P < 0.05$ was defined as statistically significant.

Results

Study population

The patient flow diagram is shown in Figure 1. A total of 64 subjects from 6 centers (Wuhan Fangcang Shelter Hospital, the First Affiliated Hospital of Anhui Medical University, The Third Affiliated Hospital of Anhui Medical University, Anhui Feidong County People's Hospital, The Second People's Hospital of Hefei, and Anhui Suzhou Hospital) were enrolled in this study, including 1 subject who was rejected for violation of the inclusion criteria and 2 subjects who dropped out without completing the observation (the 2 subjects who dropped out were included in the analysis because they took the drug at least one time, which did not affect efficacy analysis). A randomized, controlled study was performed on the 39 patients from Wuhan Fangcang Shelter Hospital, while a real-world study was conducted for the 24 patients who were enrolled from the designated COVID-19 hospitals in Anhui Province, China. The items observed in this study included vital signs, axillary temperature, oxygen saturation, and RT-PCR results of blood or respiratory secretion samples.

The recent outbreak of pneumonia caused by SARS-CoV-2 resulted in a public health emergency. Given this urgent situation and the limited availability of population samples, potential samples in compliance with the inclusion criteria were selected. Finally, 39 and 24 patients were enrolled from Wuhan Fangcang Shelter Hospital and the designated COVID-19 hospitals in Anhui Province, China.

Comparison of the general clinical situation of enrolled patients

No significant differences were found in the baseline data at the time of enrollment between the treatment and the control group in Wuhan Fangcang Shelter Hospital and the Anhui designated hospitals, except for the age and pulse of the treatment group and control group in the Anhui designated hospitals (the age was younger in the treatment group than in the control group, and the pulse was higher in the treatment group than in the control group) (Table 1).

Comparison of efficacy indicators

The low-dose emetine intervention had no significant effect on the viral nucleic acid conversion of patients in the treatment group and the control group in Fangcang Shelter Hospital and Anhui designated hospitals ($P > 0.05$). There was no significant difference in the axillary body temperature, respiratory rate, and oxygen saturation between the treatment and control groups, except that the oxygen saturation was higher in the treatment group than in the control group on the first day after enrollment for treatment. The respiratory rate was higher in the treatment group than in the control group at enrollment in the designated hospitals in Anhui Province (Table 2). The axillary body temperature, respiratory rate, and oxygen saturation among patients in Fangcang Shelter Hospital were related to the time effect but not to the intervention measures (Table 3). The respiratory rate and oxygen saturation of patients in the Anhui designated hospitals (repeated measurements on days 7 and 10 were excluded because of missing data) were related to the intervention measures but not to the time effect. The axillary body temperature of patients in the Anhui designated hospitals was related to the time effect but not to the intervention measures (Table 3). However, the data analysis results for patients treated in Anhui fixed-point hospitals need to be cautiously interpreted because two timepoints were excluded from repeated measures ANOVA for these patients, and the data at some points were not comparable (Table 2), which may cause deviation in the analysis and discussion of the true efficacy of low-dose emetine.

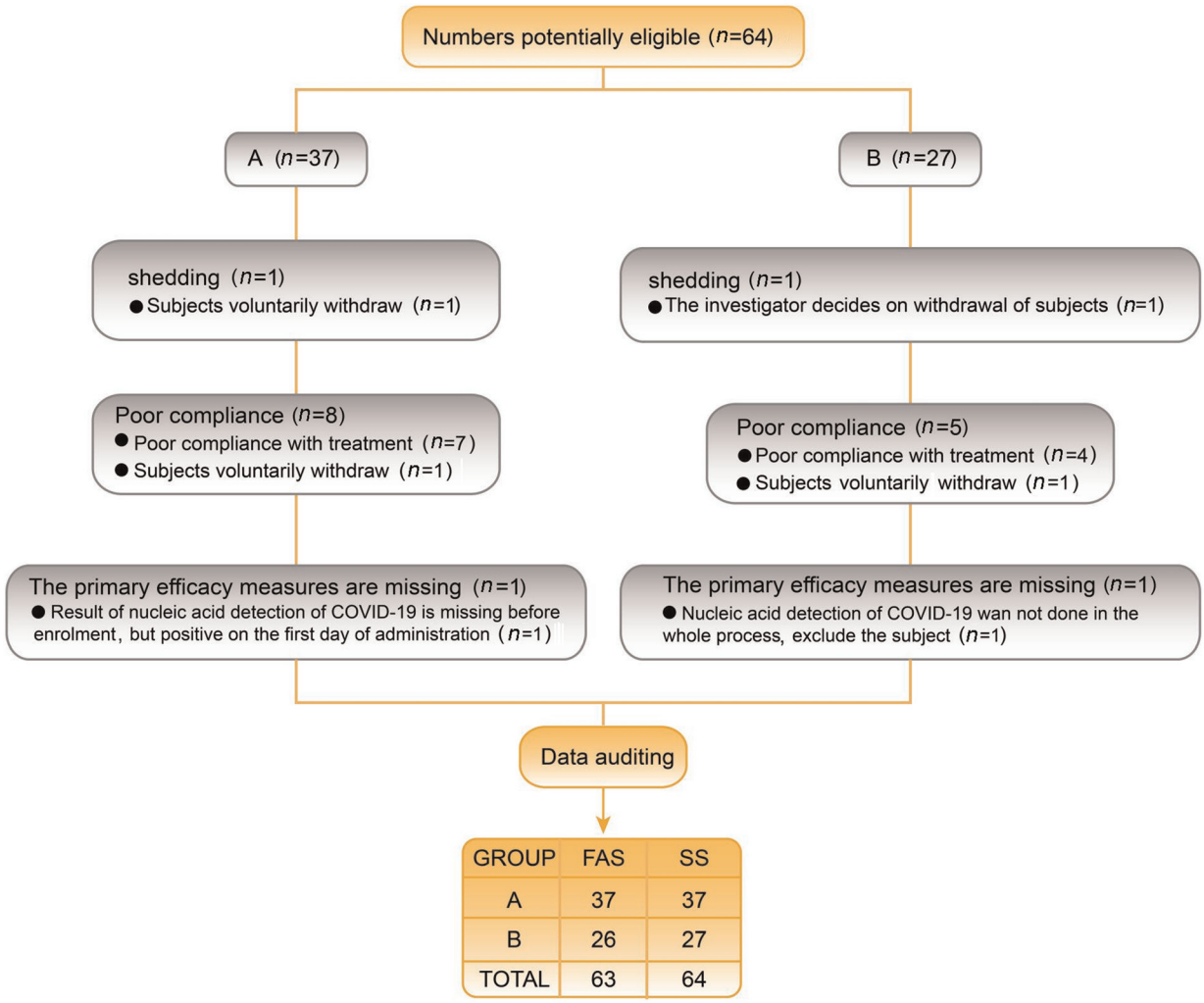

Figure 1. Flow diagram of the study. COVID-19 = coronavirus disease 2019, FAS = full analysis set, SS = safety set.

Discussion

The rapid spread of COVID-19 worldwide poses a serious threat to global public health. Most of the current drug choices for treatment of COVID-19 are based on previous treatment experience of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) or influenza virus. To date, there is no specifically effective drug for COVID-19 with a high safety profile. Research teams from China, France, and other countries have found that chloroquine and hydroxychloroquine can improve the radiological examination results of patients, facilitate virus clearance, and alleviate disease progression. In a few cases, hydroxychloroquine combined with azithromycin was found to increase the virus clearance rate,[11] but its reliability still requires further investigation. There have been some recommendations against large-scale clinical use of these two drugs because rare and serious adverse reactions (<10%), including QTc prolongation, hypoglycemia, neuropsychiatric symptoms, and retinopathy, have been observed.[12]

Among traditional antiviral drugs, ribavirin and oseltamivir are ineffective in treating SARS-CoV-2 infections. In addition, they may cause additional complications.[13,14] Lopinavir-ritonavir is a protease inhibitor that has been widely used to treat AIDS. Wang et al[14] randomized and validated its efficacy in 199 patients diagnosed with SARS-CoV-2 infection. The results showed that the treatment time until clinical improvement of lopinavir-ritonavir was not significantly distinct from that of the standard treatment. Gastrointestinal adverse events were more common in the lopinavir-ritonavir group, with early discontinuation of 13 patients (13.8%). Therefore, the researchers suggested that for severe adult COVID-19 patients, lopinavir-ritonavir does not provide any benefits beyond the standard treatment.[15] Radecivir has shown a significant inhibitory effect on SARS-CoV-2 during in vitro experiments. Additionally, a clinical controlled study found that some patients with mild to moderate COVID-19 showed improvement after receiving Radecivir, but its exact efficacy needs to be further evaluated.[16] Many studies have shown that Arbidol exerts a good treatment effect on COVID-19, reducing the mortality of patients to a certain extent and producing less toxicity and fewer side effects.[17–19] Therefore, in this study, based on the results of clinical trials of antiviral drugs and the current general consensus on combination therapy, Arbidol was selected as the basic antiviral drug.

Emetine has an antiparasitic effect and a broad spectrum of antiviral activities. Khandelwal's study found that emetine can reduce the titers of various DNA and RNA viruses, significantly delay the death of chicken embryos caused by bovine herpes virus, decrease the damage to the chorioallantoic membrane induced by the small ruminant virus, and reduce the mortality of chicken embryos.[20] Chaves et al[21] found that emetine can

Table 1

Comparison of sociodemographic characteristics, vital signs before enrollment, and medical history between the two groups of patients at Wuhan Fangcang Shelter Hospital and five designated hospitals in Anhui Province

	Wuhan Fangcang Shelter Hospital				Five designated hospitals in Anhui province			
Variables	Treatment group (n=27)	Control group (n=12)	t/Z	P	Treatment group (n=10)	Control group (n=14)	t/Z	P
Sociodemographic characteristics								
Gender [n (%)]			NA	0.488			NA	1.000
Male	11 (40.7)	7 (58.3)			4 (40.0)	6 (42.9)		
Female	16 (59.3)	5 (41.7)			6 (60.0)	8 (57.1)		
Age (yr)	46.7±11.9	45.82±9.89	0.22	0.829	30.70±9.63	41.86±13.07	−2.29	0.032
Nationality [n (%)]			NA	NA			NA	NA
Han	27 (100.0)	12 (100.0)			10 (100.0)	14		
Others	0	0			0	0		
Vital signs before enrollment								
Pulse (beats per minute)	91.96±11.41	92.58±8.2	0.17	0.866	95.44±12.75	77±15.95	2.56	0.011
Systolic blood pressure (mmHg)	125.44±10.07	124.42±13.34	0.27	0.792	120.75±11.47	123±14.47	−0.37	0.714
Diastolic blood pressure (mmHg)	85.0 (77.0,88.0)	85.5 (72.5,89.5)	0.21	0.831	78.13±9.69	79±10.8	−0.19	0.854
Medical history [n (%)]								
Suspected or confirmed cases			NA	0.645			NA	0.214
Suspected case	0	0			1 (10.0)	0		
Confirmed cases	22 (81.5)	11 (91.7)			8 (80.0)	11 (100.0)		
Clustering infections	5 (18.5)	1 (8.3)			1 (10.0)	0		
Clinically diagnosed cases	0	0			0	0		
Others	0	0			0	0		
Treatment			NA	1.000			NA	NA
Initial treatment	25 (92.6)	11 (100.0)			10 (100.0)	14 (100.0)		
Re-treatment	2 (7.4)	0			0	0		
Clinical classification			NA	0.131			NA	1.000
Mild	18 (66.7)	11 (91.7)			4 (50.0)	7 (50.0)		
Common	9 (33.3)	1 (8.3)			4 (50.0)	7 (50.0)		
Severe	0	0			0	0		
Allergic history			NA	0.313			NA	1.000
Yes	21 (91.3)	9 (75.0)			9 (100.0)	13 (92.9)		
No	2 (8.7)	3 (25.0)			0	0		
Unknown	0	0			0	1 (7.1)		

Data are presented as the mean±SD, median (Q1, Q3), or number (percentage). NA = not available.

penetrate intact HIV-1 virus particles and inhibit viral replication, reducing HIV-1 infection efficiency by 80%. In addition, before the human cytomegalovirus that enters the cell has undergone DNA replication, emetine can effectively inhibit viral protein expression, thereby inhibiting viral replication.[9] Among more than 290 drugs that were screened against the MERS and SARS coronaviruses, emetine has the lowest EC50.[10] Emetine was found to have an EC50 of less than 0.02 μM, which blocked viral invasion and inhibited viral replication, and emetine could be enriched in lung tissue for more than 12 hours and still retain an effective concentration. Therefore, emetine can be used as a potential treatment for COVID-19.

The single-center randomized controlled clinical trial at Wuhan Fangcang Shelter Hospital showed that low-dose emetine can effectively improve percutaneous blood oxygen saturation and increase the blood oxygen concentration, which is conducive to treating the illness. Additionally, the results of our real-world research conducted at five COVID-19 designated hospitals in Anhui Province also showed that Xiaoer Huatan Zhike Granules containing low-dose emetine can improve percutaneous blood oxygen saturation and breathing difficulties. It is also noteworthy that neither of the two studies found apparent adverse effects and side effects of emetine.

In this study, the use of low-dose emetine combined with basic antiviral drugs to treat COVID-19 showed good safety and effectiveness, suggesting that prophylactic use of emetine may reduce the disease prevalence in adults, reduce the proclivity of mild or moderate cases to become severe cases, and decrease the infectivity of asymptomatic patients. In addition, it is noteworthy that Xiaoer Huatan Zhike Granules contain other herbal ingredients, which may also help to exert the currently observed effects.

Limitations

One of the present study is the small size of the study population. Additionally, patients with severe cases were not included in the analyses because of the limited conditions. In the future, it will be helpful to fully evaluate the clinical efficacy of emetine in terms of the limitations of the research conditions in Fangcang Shelter Hospital by expanding the sample size, adjusting the dose of emetine, including moderate and severe cases, and conducting independent multicenter clinical trials.

Conclusions

The current small-sample study provided promising preliminary results for the use of low-dose emetine in clinical practice; however, a more comprehensive study is still needed to demonstrate that emetine is an effective clinical therapy for COVID-19 for different disease types and populations.

Acknowledgments

None.

Table 2

Comparison of the axillary temperature, respiratory rate, and oxygen saturation at different time points in patients from the two study sites

	Wuhan Fangcang Shelter Hospital				Five designated hospitals in Anhui Province			
Time points	Treatment group (n=27)	Control group (n=12)	t	P	Treatment group (n=10)	Control group (n=14)	t	P
Axillary temperature (°C)								
Before treatment	37.55±0.37	37.39±0.44	1.18	0.244	36.83±0.45	36.72±0.52	0.51	0.613
1 day after treatment	37.35±0.43	37.12±0.49	1.52	0.137	36.74±0.67	36.61±0.37	0.54	0.596
3 days after treatment	36.94±0.37	36.88±0.43	0.43	0.669	36.35±0.17	36.68±0.62	−1.05	0.311
5 days after treatment	36.68±0.32	36.65±0.30	0.27	0.789	36.45±0.37	36.47±0.26	−0.1	0.922
7 days after treatment	36.45±0.31	36.48±0.17	−0.32	0.751	36.30*	36.52±0.24	NA	NA
10 days after treatment	36.36±0.32	36.41±0.18	−0.47	0.643	36.10*	36.51±0.62	NA	NA
The difference in 1 day after treatment	0.20±0.30	0.28±0.38	−0.67	0.510	0.26±0.31	0.12±0.43	0.68	0.509
The difference in 3 days after treatment	0.60±0.36	0.55±0.42	0.33	0.741	0.45±0.29	0.04±0.43	1.79	0.093
The difference in 5 days after treatment	0.89±0.45	0.79±0.45	0.62	0.540	0.25±0.34	0.32±0.38	−0.31	0.760
The difference in 7 days after treatment	1.09±0.48	0.95±0.44	0.82	0.421	0.20*	0.35±0.53	NA	NA
The difference in 10 days after treatment	1.18±0.47	1.03±0.48	0.90	0.373	0.40*	0.38±0.30	NA	NA
Respiratory rate (breaths per minute)								
Before treatment	22.67±2.11	22.25±2.14	0.57	0.574	20.00±1.22	18.38±1.26	2.99	0.007
1 day after treatment	22.04±1.93	21.67±1.72	0.57	0.572	19.40±1.52	18.17±1.59	1.48	0.160
3 days after treatment	20.50±1.24	20.45±1.04	0.11	0.916	19.25±2.22	17.62±1.33	1.85	0.084
5 days after treatment	19.72±1.21	20.00±0.89	−0.69	0.496	18.67±2.31	17.83±0.72	1.15	0.270
7 days after treatment	19.00±1.02	19.18±0.87	−0.52	0.609	17.00*	18.20±1.23	NA	NA
10 days after treatment	18.46±1.56	19.00±1.41	−0.99	0.330	18.00*	17.63±0.92	NA	NA
The difference in 1 day after treatment	0.63±1.11	0.58±1.38	0.11	0.912	0.60±1.34	0.25±2.01	0.36	0.728
The difference in 3 days after treatment	2.08±1.87	1.64±1.91	0.65	0.520	0.25±2.22	0.77±1.88	−0.47	0.648
The difference in 5 days after treatment	2.96±2.47	2.09±2.34	0.99	0.331	0.67±1.53	0.58±1.51	0.09	0.933
The difference in 7 days after treatment	3.58±2.70	2.91±2.66	0.69	0.495	1.00*	0.30±1.42	NA	NA
The difference in 10 days after treatment	4.12±3.34	3.09±3.27	0.86	0.397	1.00*	-0.63±1.19	NA	NA
Oxygen saturation (%)								
Before treatment	97.56±1.28	97.17±0.94	0.94	0.352	98.25±0.50	97.60±0.52	2.14	0.053
1 day after treatment	97.83±1.13	97.00±0.85	2.25	0.031	98.00±1.00	97.50±1.69	0.47	0.648
3 days after treatment	98.23±1.03	97.91±0.54	1.24	0.234	98.00±1.00	97.89±1.36	0.13	0.901
5 days after treatment	98.40±0.71	98.40±0.52	0.00	1.000	98.25±0.50	97.86±1.35	0.55	0.594
7 days after treatment	98.72±0.68	98.70±0.67	0.08	0.938	98.00*	98.25±0.96	NA	NA
10 days after treatment	99.00±0.88	98.80±0.79	0.62	0.541	98.00*	98.67±0.58	NA	NA
The difference in 1 day after treatment	0.25±0.90	-0.17±0.83	1.34	0.188	−0.33±1.53	−0.60±1.34	0.26	0.804
The difference in 3 days after treatment	0.65±1.26	0.73±0.79	−0.18	0.860	0.00±1.00	−0.14±1.46	0.15	0.883
The difference in 5 days after treatment	0.76±1.09	1.30±1.25	−1.27	0.213	0.33±0.58	−0.20±1.64	0.53	0.616
The difference in 7 days after treatment	1.16±1.65	1.60±1.43	−0.74	0.466	0*	1.00±0.00	NA	NA
The difference in 10 days after treatment	1.38±1.66	1.70±1.70	−0.52	0.610	0*	1.00±0.00	NA	NA

* At this time point, data were only collected from one subject. NA=not available. Data are presented as the mean±SD.

Table 3

Results of repeated measures analysis of variance of the axillary temperature, respiration rate, and oxygen saturation

	Wuhan Fangcang shelter hospital				Five designated hospitals in Anhui province			
	Effect	df	F	P	Effect	df	F	P
Axillary temperature	Groups	1	0.64	0.430	Groups	1	0.02	0.893
	Time points	5	43.76	<0.001	Time points	3	4.51	0.014
	Interaction	5	0.96	0.445	Interaction	3	1.16	0.349
Respiratory rate	Groups	1	0.01	0.919	Groups	1	10.35	0.004
	Time points	5	12.8	<0.001	Time points	3	0.94	0.430
	Interaction	5	0.32	0.895	Interaction	3	0.25	0.862
Oxygen saturation	Groups	1	2.3	0.138	Groups	1	2.30	0.1378
	Time points	5	7.04	<0.001	Time points	5	7.04	0.0001
	Interaction	5	1.19	0.332	Interaction	5	1.19	0.3315

In the analyses of patients at Wuhan Fangcang Shelter Hospital, data obtained before treatment and at 1, 3, 5, 7, and 10 days after treatment were used; in the analyses of patients at the five designated hospitals in Anhui province, because the number of cases in the experimental group was small, data obtained before treatment and at 1, 3, and 5 days after treatment were used..

Author contributions

QL and LS had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: QL and LS. Acquisition, analysis, or interpretation of data: QW, HM, CZ, LZ, and BL. Drafting of the manuscript: SF, QZ, CC, and WW. Critical revision of the manuscript for important intellectual content: HG, LY, BL, YY, WC, YM, LS, AW, ZD, HL, JZ, YW, YG, XX, HL, SW, PL, YS, and CL. Statistical analysis: GQ and YS. Obtained funding: QL. Administrative, technical, or material support: WW, ZZ, JC, and LZ. Supervision: MH, QX, and LS. All authors approved the final version of the paper.

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Institutional review board statement

This study was conducted in accordance with the *Declaration of Helsinki* and approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (approval No. PJ2020-03-19) on February 20, 2019.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Conflicts of interest

The authors declare that they have no conflicts of interest.
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