Baidu Jieduan Granule in the Treatment of Coronavirus Disease-2019 (COVID-19): Study Protocol for an Open-Label Randomized Controlled Clinical Trial

Wen Zhang
LongHua Hospital, Shanghai University of Traditional Chinese Medicine
Qin Xie
Wuhan Mental Health Center, Wuhan
Xiaoming Xu
Medical informatics Department, Wuhan Center Hospital, Tongji Medical College, Huazhong University of Science and Technology
Shuting Sun
Clinical Medicine College of TCM, Hubei University of Chinese Medicine
Tian Fan
Medical Department of Hubei Minzu University
Xinxin Wu
LongHua Hospital, Shanghai University of Traditional Chinese Medicine
Yao Qu
LongHua Hospital, Shanghai University of Traditional Chinese Medicine
Jinhua Che
LongHua Hospital, Shanghai University of Traditional Chinese Medicine
Chao Jiang
The Second Affiliated Hospital of Xi'an Medical University
Bangjiang Fang (fangbji@163.com)
https://orcid.org/0000-0002-4032-6043
Shuang Zhou
Shanghai University of Traditional Chinese Medicine
Ting-rong Huang
Huangshi Hospital of TCM
Hua-cheng Li
Huangshi Hospital of TCM
You Zheng
Huangshi Hospital of TCM

Study protocol

Keywords: COVID-19, Baidu Jieduan Granule, The efficacy and safety, Randomized controlled trial

DOI: https://doi.org/10.21203/rs.3.rs-44542/v1

Abstract

Background: Currently, coronavirus disease-2019 (COVID-19) is continuously and rapidly circulating, resulting in serious and extensive impact on human health. Due to the absence of antiviral medicine for COVID-19 thus far, it is desperately need to develop the effective medicine. Traditional Chinese medicine (TCM) has been widely applied in the treatment of epidemic diseases in China, hoping to produce clinical efficacy and decrease the use of antibiotics and glucocorticoid. The aim of this study is to evaluate the efficacy and safety of Baidu Jieduan Granule in curing COVID-19.

Methods/design: This multicenter, open-label randomized controlled trial is conducted 300 cases with COVID-19. The patients will be randomly (1:1) divided into treatment group or control group. All cases will receive standard therapy at the same time. The experiment group will receive Baidu Jieduan Granule treatment twice a day for 14 days. The outcomes are assessed at baseline and at 3, 5, 7, 14 days after treatment initiation. The primary outcome is the rate of symptom (fever, fatigue, and coughing) recovery. Adverse events will be monitored throughout the trial.

Discussion: The study will provide a high-quality clinical evidence to support the efficacy and safety of Baidu Jieduan Granule in treatment of severe COVID-19, and also enrich the theory and practice of TCM in treating COVID-19.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2000029869. Registered on 15 February 2020

Introduction

An outbreak of coronavirus disease 2019 (COVID-19) in Wuhan city, China, has resulted in a global health emergency, with 2,954,222 confirmed cases, including 202 597 deaths as 28 April, 2020 around the world [1]. Due to asymptomatic individual or cases with milder condition, the number of patients may be underestimated [2]. Now, scientists are sure that COVID-19 is caused by a new virus, named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” [3]. The patients suffer from fever, fatigue, dry cough, and some progress to breathing difficulties, ARDS or sepsis [4]. The disease was diagnosed by clinical characteristics, the epidemiological history and laboratory test according to "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (COVID-19) Infection by the National Health Commission (Trial Version 7)" [5].

Currently, due to the absence of vaccine or specific antiviral drug for COVID-19, meticulous supportive therapies are the cornerstone. Traditional Chinese Medicine (TCM), has a great wealth of clinical experience in preventing and treatment of epidemic diseases [6]. In Ming Dynasty, “Wen Yi Lun”, a famous Medical ancient book, mention that epidemic diseases can be contagious to other people, and be transmitted through the respiratory tract and digestive tract. Modern medical practitioners suggested that the disease should belong to damp-warm pestilence in TCM [7]. Dampness obstructs the Qi mechanism leading to more Dampness and warm. Furthermore, damp-warm may also injure Yin and Qi, and cause

pathogenic toxin and blood-stasis. Based on above TCM pathogenesis of COVID-19, our team put forward “San Tong strategies”[8], which means that integrate three kinds of strategies, including relief exterior syndrome, diarrhea and diuresis, and“Truncation and Reversion” strategy [8, 9], adopting catharsis large intestine rationally to prevent and treat sepsis patients, to timely prevent and treat the disease. On the foundation of the above theories, we developed the Baidu Jieduan Granule, a formula of which consists of *Rheum palmatum L.* stem (*Dahuang*), *Sargentodoxa cuneata (Oliv.) Rehd. et Wils.* (*Hongteng*), *Taraxacum mongolicumHand.-Mazz.* (*Pugongying*), *Raw Gypsum* (*Sheng Shigao*), Herba Ephedra (*Mahuang*),*Talcum* (*Huashi*), *Amygdalus Communis Vas* (*Xingren*), *Radix Glycyrrhizae (Gancao)*, *Verbena officinalis L.*(*Mabiancao*), *Polygonum cuspidatum* (*Huzhang*), *Scutellariae Radix (Huangqin)*, *Bombyx Batryticatus* (Jiangchan), which is evolved from the TCM classical prescription Maxing Shigan decoction and our experiential prescription Jinhong Decoction. TCM has been widely applied to cure patients with COVID-19 attached to the damp-warm syndrome, especially in combination with Western medicine, can reduce antibiotic use, glucocorticoid [10]. Our previous studies have demonstrated that Jinhong Decoction, composed of *Rheum palmatum L.* stem, *Sargentodoxa cuneata*, *Taraxacum mongolicum*, can inhibit the levels of TNF-α, IL-6, IL-8 and other inflammatory cytokines, protect against excessive inflammatory response, maintain organism’s balance between inflammation and anti-inflammatory in infectious diseases [11, 12]. Recent research found that Maxing Shigan decoction were regarded as antipyretic agency, anti-inflammation agency, antiviral agency and antitussive and antiasthmatic agency, and has been used to treat COVID-19 [13]. Therefore, Baidu Jieduan Granule should have a beneficial and curative effects on COVID-19. There is not enough evidence to show the effectiveness of Baidu Jieduan granule in treatment of COVID-19. Hence, we conduct a more designed multi-center, randomized trial, to evaluate the effectiveness and safety of Baidu Jieduan granule on COVID-19. Furthermore, since this TCM decoction is inexpensive and readily available, its efficacy would have immediate and huge implications in treatment of COVID-19 worldwide. This study is expected to develop a new strategy to treat and control the current outbreak of COVID-19.

Methods/design

Study design and settings

The study is a randomized, placebo-controlled, multicenter trial, which will be conducted at four medical centers, including Huangshi Hospital of Traditional Chinese Medicine, Tongji Hospital Tongji Medical College Huazhong University of Science and Technology, LaoHeKou Tradiational Chinese Medicine Hospital and Leishenshan Hospital of Wuhan, that were selected by the expert committee. A total of 300 patients fulfilling the eligibility criteria will be randomized into two groups (Baidu Jieduan Granule group and control group) in a ratio of 1:1. The study flowchart is illustrated in Fig.1. The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) checklist is presented in Additional file 1.

Population

Participant with sepsis will be recruited from 4 study sites in China. Patients with eligibility for inclusion criteria and informed consent, will be screened at the clinical trial period. Subjects Patients with meeting any the exclusion criteria, will be excluded before randomization. The recruitment duration will last for 5 months, from February 2020 to June 2020.

Inclusion criteria

Subjects must meet all of the following requirements:

1. Be 18-85 years of age.
2. Patients with COVID-19 confirmed by SARS-CoV-2 nucleic acid testing of the respiratory specimens showed positive results.
3. Provide signed informed consent form.

Exclusion criteria

The exclusion criteria are as follows:

1. Diagnosis of sepsis for over 48 h.
2. Pregnant and lactating women.
3. Severe primary disease influencing the survival, including malignant tumours, hemorrhagic disease and HIV.
4. Severe liver and kidney dysfunction.
5. Immunosuppressant therapy or an organ transplant within the previous 6 months.
6. Participation in other clinical trials in the last 30 days.
7. Allergy to one or more component in Chinese herbal medicinal ingredient prescription

Patient withdrawal

1. Patients enrollment without meeting inclusion criterion.
2. Not suitable for the trail due to deterioration or recovery of patient condition.
3. Patients with poor complicance.
4. Voluntary withdrawal.

Sample size

A similar clinical trial was conducted, using TCM to decrease the rate of symptom (fever, fatigue, and coughing) in patients with COVID-19 [6]. The rate of recovery of clinical symptoms was 94% in patients received TCM treatment, and 82% in patients received conventional treatments. Considering 90% power with a significance level of 10 %, as well as a rate of withdrawal and loss to follow-up of 10% [7], we plan to recruit at least 150 participants in each group to achieve sufficient precision in a subsequent full trial.

Randomization and blinding

The enrolled participants are randomly assigned to the Baidu Jieduan Granule group or the conventional treatment group, using random numbers. The random sequence of 300 participants from 4 medical centrals will be generated by SPSS 19.0, and stratified according to each center. Two sets of allocation codes are kept opaque envelopes, which should be sent to the lead clinical researcher and each of the centers. Thereafter, the drug administrators arrange the nurse to dispense the study drug, according to a random number. This is an open-label study. The statistical analysis can be carried out by the Professors of Statistics of Shanghai University of Traditional Chinese Medicine, who is blinded to patient allocation.

Interventions

The Baidu Jieduan Granule comprise 15 g of *Rheum palmatum L.* stem (*Dahuang*), 30 g of *Sargentodoxa cuneata (Oliv.) Rehd. et Wils.* (*Hongteng*), 30 g of *Taraxacum mongolicumHand.-Mazz.* (*Pugongying*), 45 g of *Raw Gypsum* (*Sheng Shigao*), 9 g of Herba Ephedra (*Mahuang*)，45 g of *Talcum* (*Huashi*), 12 g of *Amygdalus Communis Vas* (*Xingren*), 9 g of *Radix Glycyrrhizae (Gancao)*, 30 g of *Verbena officinalis L.* (*Mabiancao*), 30 g of *Polygonum cuspidatum* (*Huzhang*), 30 g of *Scutellariae Radix (Huangqin)*，12 g of *Bombyx Batryticatus* (Jiangchan), which were packaged in two bags. The Baidu Jieduan Granule will be administered orally, two times a day for 14 days. The Baidu Jieduan Granules are manufactured by Beijing Tcmages Pharmaceutical Co., LTD (Number: Jing 20180032).

The participants will be categorized into two groups receiving either standard Western medicine therapy alone according to the *The Protocol for Diagnosis and Treatment of Novel Coronarvirus Pneumonia* (7^{th} edition), or the combination of Baidu Jieduan Granule two times a day for 14 days. The routine care includes early fluid resuscitation, antimicrobial anticoagulants, nutritional support and other treatment. Other TCM therapies, including TCM injections and other oral herbal medicine, should be prohibited.

Outcomes and measurements

The primary outcome will be the rate of symptom (fever, fatigue, and coughing) recovery. Symptoms recovery was defined as the complete disappearance of fever, fatigue and coughing symptoms.

Secondary outcomes will be duration of symptom recovery, the proportion of cases with reverting on chest CT, the time of negative of SARS-CoV-2 nucleic acid, and the proportion of cases with clinical cure.

Safety outcomes

All safety-related indexes, including the vital signs, a complete blood count and a general urine analysis, biochemical test, fecal occult blood testing, and electrocardiogram results, will be checked and recorded in CRF at every visit. The biochemical test contains C-reactive protein, hepatic function (alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, and gamma-glutamyltransferase) and renal function (blood urea nitrogen and serum creatinine). Any adverse events will be evaluated by a professional researcher at each visit and recorded on the CRF.

Adverse event reporting

An adverse event (AE) is any undesirable syndrome that connected with the administration of Baidu Jieduan Granule in a patient [14]. Any AEs need be recorded in form immediately, and then evaluated by the physician and the corresponding coordinator. All related information, including occurrence time, severity, duration, the measures adopted and the outcome, can be reported to the sponsors, ethics committees, and drug regulatory authorities in accordance with the provisions. We will follow all subjects with AEs.

Statistical analysis

We will not conduct interim analysis or subgroup analyses for the trial. The independent statistical analysts will be responsible for the data analysis, following the principle of intent-to-treat (ITT) analysis, which contain all subjects with eliminating casas in a minimum and reasonable manner. And then, the statistician timely submits statistical reports to the study director. The statistical analysis is performed in a blinded manner using the SPSS 20.0 software. Continuous variables characterizing each study group will be expressed as means with standard deviations or medians with interquartile ranges. Categorical variables will be reported as frequencies and proportions. The continuous outcomes will be analyzed by unpaired Student's t-test or Wilcoxon nonparametric statistic, while the count data are compared using a chi-square test or Fisher's exact test. Two-sided tests will be performed for all the other statistical analyses. P <0.05 will be considered statistically significant.

Trial oversight

Coordination Center: The membership of Coordination Center consists of clinical experts, statisticians and quality control experts from each center. The center is responsible for the management of clinical research trials, cooperative hospitals, pre-clinical trial training courses, and resolving key issues in whole process of study.

Quality control: All centers and researchers are regular monitored and inspected by Clinical Research Organizations (CRO), following the standard protocol throughout the process.

Data management

Trained research staff collect trial data carefully according to a standard protocol and complete paper case report forms (CRFs) accurately, completely, timely and reliably. The data will be entered into Electronical Data Capture (EDC) system and regularly reviewed by a clinical research associate (CRA). If any changes are conducted by researchers, the feedback will be provided to the researchers and CRA. All modifications and paper CRF transfer between investigators, inspectors, and data managers should be documented and maintained appropriately. The data administrators will lock the data on completion of the study. The medical information on all the study participants will be kept strictly confidential. The

SPIRIT flowchart of the study has been shown in Fig. 2. Data and research findings will be announced via publication.

Quality control

All investigators of the trial should be trained strictly and comprehensively by the State Food and Drug Administration, following Good Clinical Practice (GCP), to profoundly comprehend the detailed contents of the trial and strengthen compliance, and then, improve the quality of the clinical trial. All qualified researchers will collect data and finish the CRF in an accuracy and complete way. After discharge, the subjects will be followed by phone. Regular monitoring and inspecting will be conducted to confirm whether the related research data are correct, and whether the process of the trial complies with the protocol by CRO once a month. They will check details on informed consent, inclusion and exclusion criteria, the original data, management of AEs, the process of storage and distribution of the research drugs, and CRF.

Ethics

This trial will comply with the principles of Declaration of Helsinki and the regulations on quality management of clinical trials in China. The research protocol has been approved by the Ethics Committee of Huangshi Hospital of Traditional Chinese Medicine (approval number HSZY-PJ-2020-002-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2000029869). All the changes in the trial protocol should be maintained as a program addendum and the revised protocol should be submitted to the Ethics Committee for re-review. Study participants or legal representative will receive sufficient explanation and time to sign the informed consent form prior to the study. Any modification on study protocol or AEs attributable to this study will be reported to the research ethics committees.

Discussion

The prevalence of COVID-19 worldwide with the high morbidity implies a high economic and social burden [15]. COVID-19 can cause lung inflammation and infiltration, with inflammatory cytokine storms induced by SARS-CoV-2 infection [16]. The current management is mainly supportive therapies. Other agents, including Lopinavir (LPV)-Ritonavir, Remdesivir, Chloroquine/hydroxychloroquine and Favipiravir, are investigated in clinical researches [15]. TCM was first documented about 2500 years ago and then popularized by world globalization. There are prominent value and extensive applications in the aspect treatment of COVID-19 by Chinese medicine, since no other agents are proved to have efficacy [7, 16]. Additionally, TCM possess the advantages of being simple, convenient, efficient, inexpensive and without serious adverse reactions. Baidu Jieduan Granule, as an experiential prescription of COVID-19 treated, are from Maxing Shigan decoction and our experiential prescription Jinhong Decoction, with the addition *Verbena officinalis L.* (*Mabiancao*), *Polygonum cuspidatum* (*Huzhang*), *Scutellariae Radix (Huangqin)* and *Bombyx Batryticatus* (Jiangchan). *Verbena officinalis L.* and *Polygonum cuspidatum* have the effects of expelling wind and removing dampness, clearing heat and detoxicating, and invigorating the

circulation of blood, relieving coughs and reducing sputum [17, 18]. *Bombyx Batryticatus* can eliminate external wind, resolve phlegm, dissipates nodules, clear heat, and dissipates stagnant heat [19]. *Scutellariae Radix* can clear heat patterns, especially of the upper Jiao, drie dampness, and eliminate toxicity [20]. The traditional medicine theories serve as a powerful guide in prescribing the Chinese herbal formula.

This trial is a well-designed multicenter open-label RCT from the perspective of evidence-based medicine, to assess the efficacy and safety of Baidu Jieduan Granule in management of COVD-19 for the first time. The trial can make a clinical basis for adopting“San Tong” strategy and “Truncation and Reversion” strategy in prevention and treatment of patients with COVID-19, to enrich the theory and practice of treating infectious diseases with TCM. Nevertheless, the design of the trial also has potential limitations. It is not a double-blind placebo controlled clinical trial. Since it’s a deadly infectious disease and the country gives priority to curing diseases and saving lives, no strict randomization stratified and placebo is allowed.

Trial Status

The protocol version is 1.0, 1 Feb 2020. We are currently recruiting participants from February 2020. It is estimated that up to 300 participants will be enrolled by December 30, 2020.

Additional files

Additional file 1: SPIRIT Checklist. (DOCX 417 kb)

Additional file 2: Informed Consent Form (DOC 29.2 kb)

Additional file 3: Inspection Report (DOC 51.3 kb)

Abbreviations

COVID-2019
2019 novel coronavirus; SIRT1:Silent Information Regulator 1; AE:adverse event; AEs:adverse events; CRF:case report form; SPIRIT:Standard Protocol Items Recommendations for Interventional Trials; CT:chest computed tomography; GCP:Good Clinical Practice; TCM:traditional Chinese medicine; CRO:Clinical Research Organization

Declarations

Ethics approval and consent to participate

This trial complies with the principles of Declaration of Helsinki and the regulations of quality management of clinical trials in China. The study has been approved by the Ethics Committee of

Huangshi Hospital of Traditional Chinese Medicine (approval number HSZY-PJ-2020-002-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2000029869). Signed informed consent forms will be obtained from all qualified participants before enrollment.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

The trial is funded by National Key Research and Development Program of China (2018YFC1705900). The study also received funding from research projects of Emergency Committee of the World Federation of Chinese Medicine Societies and Shanghai Society of Traditional Chinese Medicine, Novel Coronavirus Pneumonia Emergency Tackling Key Project (SJZLJZ.N01). Emergency Committee of the World Federation of Chinese Medicine Societies, Shanghai Society of Traditional Chinese Medicine, and National Key Research and Development Program of China play no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Authors' contributions

BJF sponsored the study and designed this protocol. SZ is the primary supervisor and participated in the design of this protocol. WZ drafted the manuscript. QX helped XMX draft and revise the manuscript. STS and TF participated in the design of the protocol and are responsible for trial management. WXX and YQ are involved in the data collection and monitoring of the study. JHC, CJ, TRH, HCL and YZ are supervising this study and

participated in revising the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all the patients who have agreed to participate in our trial and the staff that take part in our trial.

Author details

[1]Department of Emergency, LongHua Hospital, Shanghai University of Traditional Chinese Medicine, NO.725 Wanping South Road, Xuhui District, Shanghai 200032, China; [2]Wuhan Mental Health Center,

Wuhan, 430012, China; [3]Medical Informatics Department, Wuhan Center Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430014, China; [4]Clinical Medical College of TCM, Hubei University of Chinese Medicine, NO.1 Tanhualin, Wuchang District, Wuhan, Hubei, 430065, China; [5]Medical Department of Hubei Minzu University, Enshi, Hubei, 445000, China; [6]The third Department of Neurology, The Second Affiliated Hospital of Xi'an Medical University, NO.167, Textile City East Street, Baqiao District, Xi'an, Shanxi, 710032, China; [7]Shanghai University of Traditional Chinese Medicine, 1200 Cai Lun Road, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai China, Shanghai, 201203, China

References

1. "Coronavirus disease. 2019 (COVID-19) Situation Report – 99". World Health Organization, 28 April 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497–506.
3. Graham Carlos W, Dela Cruz CS, Cao B, et al. Novel Wuhan (2019-nCoV) coronavirus. Am J Respir Crit Care Med. 2020;201(4):P7–8.
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
5. 5.. "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (COVID-19) Infection by the National Health Commission (Trial Version 7)". 2020. National Health Commission of the People's Republic of China. Accessed 3 March 2020. http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml.
6. Hu K, Guan W-J, Bi Y, et al., Efficacy and Safety of Lianhuaqingwen Capsules, a Repurposed Chinese Herb, in Patients With Coronavirus Disease 2019: A Multicenter, Prospective, Randomized Controlled Trial. Phytomedicine 2020:153242. doi:10.1016/j.phymed.2020.153242.
7. Luo E, Zhang D, Luo H, et al. Treatment Efficacy Analysis of Traditional Chinese Medicine for Novel Coronavirus Pneumonia (COVID-19): An Empirical Study From Wuhan, Hubei Province, China. Chin Med. 2020;15:34. doi:10.1186/s13020-020-00317-x.
8. Fang B, Qi W, Huang Y. Handbook of Integrated Traditional Chinese Medicine and Western Medicine in Prevention and Treatment of Novel Coronavirus (COVID-19). Beijing: *People's Medical Publishing House.*; 2020. pp. 25–7.
9. Zhang W, Fang BJ, Wang G, et al. The Basic Theory and Practical Application of Catharsis Large Intestine and Truncating and Reversing in the Prevention and Treatment of Sepsis. CJITWM. 2020;40(01):102–5. DOI: 10. 7661 /j. cjim. 20191009. 224.
10. Liu M, Gao Y, Yuan Y. al. e: Efficacy and Safety of Integrated Traditional Chinese and Western Medicine for Corona Virus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis. Pharmacol Res. 2020;158:104896.

11. Gao J, Zhang JZ, Zhang PT. Clinical research on impact of jinhong decoction on sepsis. Academic Journal of Shanghai University of Traditional Chinese Medicine. 2002; 16(03):43–4. DOI:10.16306/j .1008 -861x.2002.03.014.
12. Zhu PT, Zhang JZ, Gao J, Zhang Xl, Wang ZG, Shen P, et al. Experimental Study on “Jinhong Pill” in Regulating Cytokine and Preventing Intestinal Mucosal Barrier of Acute Biliary Tract Infection in Rats. Shanghai Journal of Traditional Chinese Medicine. 2001(4):39–42. DOI:10.16305/j .1007 -1334.2001.04.020.
13. Wang Z, Sun Y, Qu R, et al. Network pharmacological study on mechanism of Maxing Shigan Decoction in treatment of coronavirus disease 2019 (COVID-19). Chinese Traditional Herbal Drugs. 2020;8(51):1996–2003. DOI:10.7501/j.issn.0253-2670.2020.08.003.
14. Xu X, Liang P. Ethical Review of Unanticipated Adverse Events in Clinical Research. Continuing Medical Education. 2007;30(9):87–8. DOI:10.3969/j.issn.1004-6763.2016.09.049.
15. Wynants L, Calster B, Collins GS, et al. Prediction Models for Diagnosis and Prognosis of covid-19 Infection: Systematic Review and Critical Appraisal. BMJ. 2020;369:m1328. doi:10.1136/bmj.m1328.
16. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. Am J Chin Med. 2020;48(3):737–62.
17. “Polygonum cuspidatum Sieb.et Zucc.”. *China Medical Information Platform*. 2020, Web. n.d. https://www.dayi.org.cn/cmedical/301276#.
18. “Verbena officinalisL” *China Medical Information Platform* 2020, Web. n.d. https://www.dayi.org.cn/cmedical/1114734#.
19. “Beauveria bassiɑna.”. *China Medical Information Platform* 2020, Web. n.d. https://www.dayi.org.cn/cmedical/1155655#.
20. “Scutellaria baicalensis Ceorgi.”. *China Medical Information Platform* 2020, Web. n.d. https://www.dayi.org.cn/cmedical/1006969#.

Figures

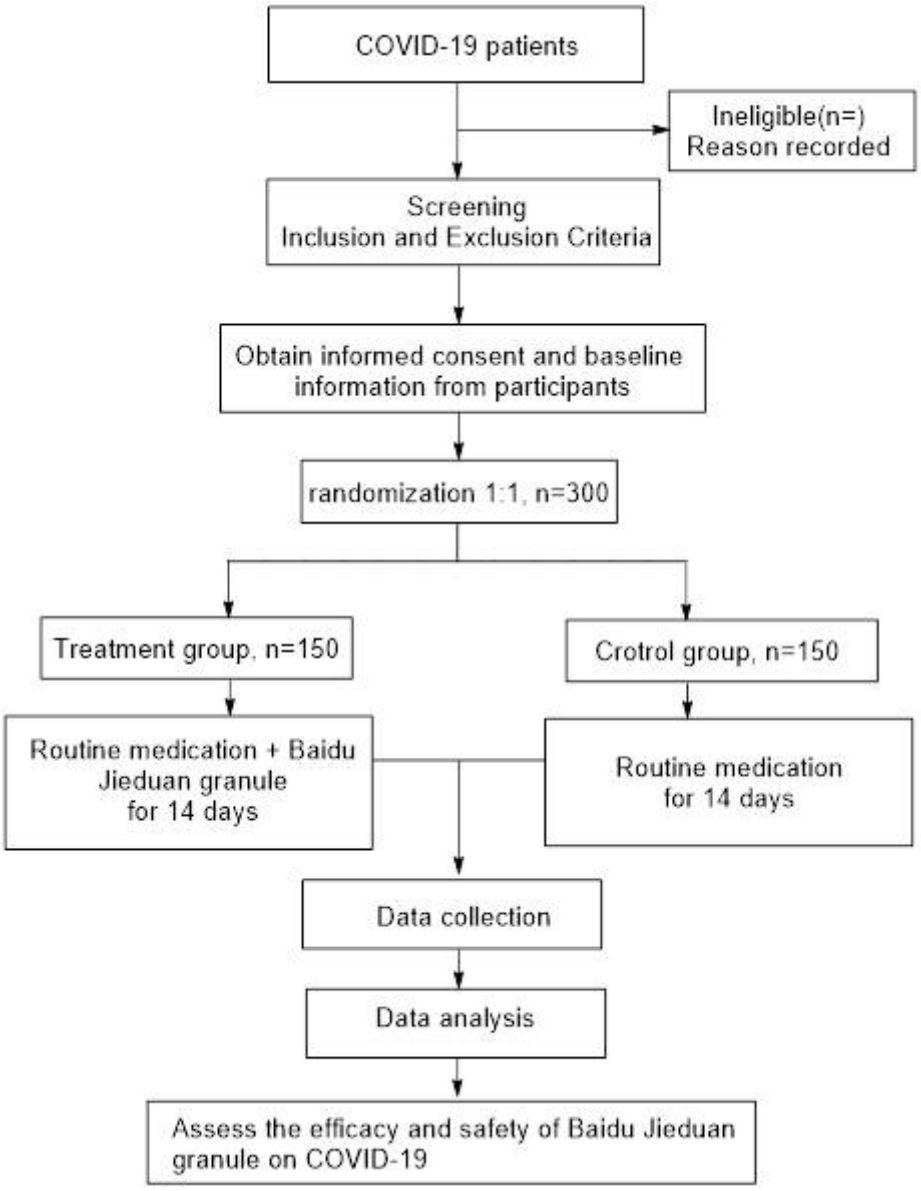

Figure 1

The flow chart of the Efficacy and Safety of Baidu Jieduan granule for COVID-19 study.

	Study Period							
Visit	**Baseline**	**Intervention (14 days)**						
Time point	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D14**
Eligibility screen	X							
Informed consent	X							
Randomization	X							
Demographics	X							
General condition	X							
Primary disease	X							
Comorbidity	X							
Vital signs	X	X	X	X	X	X	X	X
Chest CT	X		X		X		X	X
Symptom (fever, fatigue, and coughing)	X		X		X		X	X
Hepatic function	X		X		X		X	X
Renal function	X		X		X		X	X
Routine blood	X		X		X		X	X
Urine analysis	X		X		X		X	X
Safety	X		X		X		X	X
duration of symptom	X		X		X		X	X
negative of SARS-CoV-2 nucleic acid	X		X		X		X	X
Adverse events record	X	X	X	X	X	X	X	X
Survival condition								X

Figure 2

Study procedures and assessments. CT: computed tomography.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist.doc