Yiqi Fumai Injection for patients with Septic Shock: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Septic shock is an important problem in critical care medicine and one of the leading causes of death in intensive care units (ICU). In China, Traditional Chinese medicine (TCM) has been widely used as the adjuvant treatment to improve the symptoms and prognosis in patients with septic shock. Yiqi Fumai Injection (YFI) is one of the most important proprietary TCM for septic shock, previous studies have demonstrated its efficacy and safety. However, these conclusions were limited due to the small sample size and low quality of methodologies of these studies. Therefore, we designed this study to evaluate the efficacy and safety of using YFI as an adjunct treatment for septic shock.

Methods/design: This is a double-blind, randomized, parallel, placebo-controlled clinical trial. A total of 800 participants will be randomly assigned to receive either treatment or placebo in a 1:1 ratio. The treatment group will receive YFI combined with conventional treatment, and the control group will receive 0.9% sodium chloride injection combined with conventional treatment for 2 weeks. The primary outcome is the 28-days mortality. Secondary outcomes are blood lactate levels, hemodynamics, blood gas analysis, immune function indicators, inflammatory indicators, acute physiology improvement and chronic health assessment (APACHE) II scores, and sepsis-related organ failure score (SOFA). Adverse events will be observed and recorded at the same time for safety assessment.

Discussion: This randomized controlled trial will help evaluate the efficacy and safety of YFI for the treatment of septic shock. The results of this trial will provide recommendations for the management of septic shock.

Trial registration {2a and 2b}China Clinical Trial Registry, ChiCTR-1900026424.Registered on 15 June 2019.

Introduction

Background and rationale{6a}

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality [1]. Currently, it has been estimated to account for more than 19 million new cases worldwide each year, and 6 million deaths [2].The mortality rate is more than 1/4, and about 3 million of the surviving patients have cognitive dysfunction [3,4].Clinically, approximately 50% of patients with sepsis progress to septic shock, and the mortality rate of septic shock could be as high as 50% or more [5-8].Zhou et al [9] showed that the overall hospital mortality rate of patients with severe sepsis/septic shock in the comprehensive intensive care unit in mainland China was 33.5%. A study in Taiwan, China, found that 28-day mortality rate in patients with severe sepsis/septic shock in the local surgical intensive care unit was 61% [10]. Complex pathogenesis, severe clinical manifestations, and limited treatment made it as one of the leading causes of death in ICU [11-12].Even if survived after treatment, the long-term quality of life is significantly lower

than that of the average person [13-15]. Mortality in septic shock has declined over the decades with the rapid advancement of treatments [16-18] .However, with the acceleration of population aging, and the increase of tumor incidence, immunosuppressive drugs, antibacterial drugs, invasive treatments, antibiotic resistance rates, the incidence of septic shock is increasing year by year and the number of deaths continues to increase [19-22].Studies have shown that the incidence of septic shock increases at a rate of 1.5% to 8.0% per year ,the incidence of septic shock increases by 91.3% in a decade [23-26], and the mortality rate increases with the severity of the disease. Septic shock has led to an increasing economic and public health burden [27-28].

The Surviving Sepsis Campaign 2016 guidelines recommend early resuscitation, antimicrobial therapy, use of vasoactive drugs, glucocorticoid use, anticoagulant therapy, renal replacement therapy, mechanical ventilation, sedation and analgesia, Blood sugar management as conventional treatment for septic shock [29]. Despite such recommendations, the morbidity and mortality rates of septic shock remain high. In addition, adverse reactions and drug tolerance are also ubiquitous. Therefore, there is an urgent need for further efficient and secure management strategies.

In China, traditional Chinese medicine (TCM) has been widely used as an adjuvant therapy for septic shock [30-32]. TCM combined with conventional treatments could relieve symptoms, improve blood gas, and lower blood lactate levels [33-34]. YFI is one of the main proprietary Chinese medicines. A few studies showed that YFI may inhibit inflammation, regulate immune function, and improve patients' Symptoms, reduce the mortality rate [35]. However, these conclusions were limited due to the small sample size and low quality of methodologies of these studies. Therefore, we designed this study to evaluate the efficacy and safety of using YFI as an adjunct treatment for septic shock.

Objectives {7}

The objective of this study is to evaluate the efficacy and safety of YFI in the treatment of patients with septic shock.

Trial design {8}

This is a randomized, placebo-controlled clinical trial (Fig.1). The study was conducted in Guangdong Provincial Hospital of Traditional Chinese Medicine (the Second Affiliated Hospital of Guangzhou University of Chinese Medicine) and will be conducted in accordance with the principles of the Helsinki Declaration (Edinburgh, 2000 EDITION).

The study will continue for three years. Patients who met the diagnostic criteria for septic shock will be assigned to the treatment group or control group in a 1:1 ratio. The researchers will conduct screening based on established criteria and pre standard treatment plans. Data collection will start with basic data collection until the end of follow-up work (Table 1).

Methods

Participants, interventions and outcomes

The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for inter ventional trials (spirit) 2013 checklist: defining standard protocol items for clinical trials (additional file 1). The study has been approved by the ethics committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (approval number BF2019-007-01) and has been registered in the Chinese Clinical Trial Registry (Registration number ChiCTR-1900026424). This study is still in process.

Study setting {9}

This trial will be conducted at the Second Affiliated Hospital of Guangzhou University of Chinese Medicine in Guangzhou, Guangdong Province, China.

The the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, a 3000-bed hospital, is the largest hospital of Chinese Medicine in China. The annual amount of septic shock was more than 500 per year.

Eligibility criteria {10}

Inclusion criteria

Patients who meet all of the following inclusion criteria will be selected as research volunteers:

1.All patients met the diagnostic criteria for sepsis. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score≥2 points consequent to the infection.

2.All patients met the diagnostic criteria for septic shock. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP)≥65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.

3.The age ranged from 18 to 70 years old;

4.They agreed to participate in the study and signed the informed consent.

Exclusion criteria

Patients who meet the following criteria will be excluded.

1.have uncontrollable underlying diseases, such as malignant tumors, active bleeding, definite visceral severe injury, chronic renal failure, chronic liver failure;

2.have a history of stress ulcers or severe head injury within 6 months;

3.use immunosuppressants or hormones in the prior 3 months;

4.age<18 years old or >70 years old;

5.allergic to red ginseng, Ophiopogon japonicus, Schisandra and related injection;

6.Currently pregnant or breast-feeding;

7.Currently participating in another clinical trial;

8.have immunodeficiency diseases.

Discharge criteria

Discharge criteria are as follows:

1.requirement for individuals to withdraw during the test;

2.violation of the test program;

3.occurrence of serious adverse events (AEs).

Withdrawal or dropout criteria

Patients will not be included in the analysis if:

1.The researchers find that subjects were misdiagnosed as septic shock after randomization.

2.The subject did not follow the study plan for medication: (1) The subject receive the study drug treatment for more than 24 hours; (2) The subject do not receive the study drug; (3) subjects receive study drug treatment less than 14 days (excluding discharge from hospital or discharge due to exacerbations or death); (4) The actual dose is less than 80% of the total dose (standard rate <80%).

3.The lack of necessary data affects the assessment of the primary outcome.

4.The use of banned drugs affects the evaluation of efficacy.

5.Experiencing anaphylaxis or serious adverse events during the trial.

6.The patient withdraw.

Discontinuation

Participants who meet any of the following exclusion criteria will be suspended:

1.withdrawal of informed consent.

2.Serious adverse events (AE) or unacceptable adverse reactions associated with the study drug.

3.Serious complications.

4.progression of the disease based on the efficacy evaluation criteria and requires urgent treatment.

5.The regulatory site requires termination of the study.

The reason for the suspension will be recorded on the Case Report Form (CRF), and the last data will be included in the data analysis.

Who will take informed consent? {26a}

The researchers will provide information about the study and obtain oral and written informed consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Additional consent for collection and use of their human biological specimens will be obtained before they are enrolled in the study. Consent for publication Written informed consent will be obtained for use of data for publication from each participant.

Interventions

Explanation for the choice of comparators {6b}

Standard early resuscitation, antimicrobial therapy, use of vasoactive drugs, glucocorticoid use, anticoagulant therapy, renal replacement therapy, mechanical ventilation, sedation and analgesia, and blood sugar management are based on recommended guidelines for septic shock.

Intervention description {11a}

After randomization, eligible participants will be randomized to either the treatment or control group, receiving intravenous injection of either YFI(0.6gmg/bottle, 8 bottles/box) or placebo (0.9% sodium chloride injection, 250mL/bag) once daily for 2 weeks. YFI was manufactured by Tianjin Tianshili Zhijiao Pharmaceutical Company (Tianjin, China) (batch number: 20190033). 0.9% sodium chloride injection is provided by the pharmacy of the Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine. Both groups will receive conventional treatment recommended by the the Surviving Sepsis Campaign 2016 guidelines, including early resuscitation, antimicrobial therapy, use of vasoactive drugs, glucocorticoid use, anticoagulant therapy, renal replacement therapy, mechanical ventilation, sedation and analgesia, and blood sugar management.

The treatment group will receive routine medication combined with intravenous injection of YFI 5.2g + 0.9% sodium chloride injection 250mL for 120 minutes, once daily. The control group will receive routine medication combined with intravenous injection of 0.9% chlorine Sodium injection 250 mL intravenous for 120 minutes. The dose and speed of the two groups were the same. Patients will begin drug

intervention within 24 hours of recruitment with a period of 2 weeks. The disposable photophobic infusion set will be used, so that YFI and placebo have the same appearance and color, all drugs are uniformly packaged and use the same identification label.

Tianjin Tianshili Zhijiao Pharmaceutical Company stated that there is no conflict related to the benefits of this research. The quality of the drug is in compliance with the Chinese Medicine Standards State Food and Drug Administration (SFDA). Any other Chinese herbal medicine soup or proprietary Chinese medicine will be banned in this trial.

Criteria for discontinuing or modifying allocated interventions {11b}

1.Serious AEs occurred with the study drug.

2.The disease worsens and needs urgent treatment.

3.Termination of research by administrative department.

Strategies to improve adherence to interventions {11c}

In order to improve adherence to intervention protocols, we will use pill count□economic compensation, free laboratory examination and free treatment.

Participants will be given USD 100 for completing the 1-month outcome assessment. All treatments, all laboratory tests and echocardiography are free for participants. At enrollment, participants are given a variety of items designed to help promote enthusiasm for the project including nominal gifts such as a thermos cup.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants were prohibited from taking other traditional Chinese medicines.

Provisions for post-trial care {30}

If the patient has an adverse reaction related to the trial drug, he will receive free treatment and financial compensation

Outcomes {12}

Primary outcome

The primary outcome is 28-days mortality. An independent endpoint adjudication committee reviewed and adjudicated the primary outcome.

Secondary outcomes

1.Changes in immune index: T lymphocyte subset typing, neutrophil cd64 percentage.

2.Changes in inflammatory markers: C-reactive protein(CRP), procalcitonin(PCT), interleukin-6(IL-6), interleukin-1(IL-1), tumor necrosis □(TNF-□).

3.Blood gas analysis: oxygenation index (PaO2/FiO2), blood gas, blood lactate.

4.Hemodynamics: heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) and cardiac index (CI).

5.Sepsis-related organ failure score (SOFA).

6.Improve acute physiology and chronic health assessment II (APACHE-II) scores;

7.The name, dose and duration of use of the vasoactive drug.

8.The name, dose and duration of corticosteroid use.

9.The incidence of complications.

10.The duration and cost of ICU.

11.Hospitalization time and expenses.

Safety assessment

The safety assessment will be performed for every participant. The individuals' vital signs and laboratory tests will be examined at every visit. Laboratory tests include routine blood, urine and stool tests, and fecal occult blood tests; electrocardiographic liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma- Glutamyltranspeptidase (GGT) and serum total bilirubin (TBIL); renal function tests (serum creatinine (Cr) and blood urea nitrogen (BUN)); and electrolyte tests (K +, Na +, Cl- and Ca2+).

All AEs should be documented in the case report form including occurrence time, severity, duration, adopted measure, and the outcome of the AE, whether or not they are related to therapy. All AEs will be evaluated for causal relationships.

Participant timeline {13}

For participants randomized to the treatment or control group, study participation will continue for 2 weeks. A total of 6 visits are foreseen: at baseline, 4 interim visits after 24h, 72h, 7 days and 14 days, and a final visit after 28 days (Tab. 1).

Sample size calculation {14}

The sample size was calculated based on the primary endpoint of 28-days mortality. Based on similar previous reports, the 28-days mortality was 36% and 25% for conventional therapy and conventional

therapy combined with YFI, respectively. We expect an effect size of at least 0.1 for primary outcomes. A sample size of 332 participants is required to sufficiently detect a target effect size with a type 1 error of 5% (α=0.05) and 80% power (β=0.20) by using Gpower 3.1.9.2 software. Considering a dropout rate of, a total of 800 participants are necessary, with 400 participants in each group.

Study participants and recruitment {15}

We will recruit 800 patients with septic shock. These participants will be recruited from the Second Affiliated Hospital of Guangzhou University of Chinese Medicine after they meet the inclusion criteria and agree to participate in the study and sign the informed consent form. We have recruited the first patient on November 20, 2019 and recruitment is predicted to end on December 30, 2023. All participants will sign the informed consent form to participate in the clinical trial.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be randomly assigned to the treatment group and the control group at a ratio of 1:1 according to the random number table generated by SPSS 26.0 software package (SPSS Inc. Chicago, Illinois, USA).

Concealment mechanism {16b}

The serial numbers assigned to each patient are kept in a duplicate, sealed, numbered envelopes, which will guarantee that both investigators, enrolling staff and patients do not know the grouping situations.

Implementation {16c}

Randomisation sequences will be generated by a statistician at the Evidence-Based Medicine Center of Guangzhou University of Chinese Medicine, who is not part of the trial statistical team. The principal investigators and enrolling study staff are unaware of the sequence.

Assignment of interventions: Blinding

Who will be blinded {17a}

This is a double-blinded, parallel-group, superiority, single-center, randomized controlled clinical trial. The observers of outcomes and the participants will be blinded. The research nurses dispensing the medication will know the treatment allocation, however, they will not be involved in data collection and statistical analysis. Allocation shall proceed via duplicate, sealed, numbered envelopes, which will be stored by the clinical trial quality control inspectors and the main person in charge of this research group. The blind bottom shall not be opened without reason during the trial. The outcome assessors and the statisticians will not participate in the treatment, they will perform the outcome evaluation and the statistical analysis independently.

Procedure for unblinding if needed {17b}

If patients condition deteriorates or severe adverse reactions occur, emergency unblinding will be allowed.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Statistical professionals are responsible for developing statistical analysis plans through consultation with key researchers. The investigators are responsible for data collection and the data including baseline questionnaires, immune index, inflammatory markers, clinical outcomes, blood gas analysis, hemodynamics, SOFA, APACHE-II, use of the vasoactive drug, use of corticosteroid, complications will be prospectively collected throughout the study period according to the participant timeline (Fig.1).

Plans to promote participant retention and complete follow-up {18b}

Financial compensation, 2 weeks all free treatments and 5 times free examinations will be carried out to promote participant retention and complete follow-up.

Data management {19}

In this trial, we will use two data entry systems. The researcher will fill the information in CRF and enter it into the electronic version of CRF in time, then submit it to research assistant after checking. Time, the person and the reason for the revision will be record when correction is needed. The research assistant is responsible for verifying the consistency and accuracy of the paper and electronic of CRF and providing feedback to the clinical researchers. After the trial is completed and the blind is disclosed, the data will be locked and cannot be modified afterwards. The data manager should document and maintain the CRF. The medical information of subject is confidential and must not be disclosed to a third parties.

Confidentiality {27}

All study data about every participant is confidential and no identifying information will be revealed. The password-protected, validated, encrypted electronic CRF will designed to securely store identifiable information.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This study has no plans for collection or storage of biological specimens for genetic or molecular analysis.

Statistical methods

Statistical methods for primary and secondary outcomes{20a}

All Outcomes will be conducted based on the intention-to-treat (ITT) principle. Missing values will be imputed by the last-observation carried-forward method. The statistical analysis will be performed using the SPSS 21.0(IBM Corp., Armonk, NY, USA). Baseline characteristics will be summarized by means of simple descriptive statistics. The two sample Student's t test will be used for continuous variables and the chi-square test or Wilcoxon test will be used for categorical variables. The primary analysis will be a comparison of 28-days mortality, the chi-squared test or Fisher's exact test will be used.

For secondary outcome measures, repeated measures analysis of variance (ANOVA) will be applied to determine changes at each visit to investigate the effects of treatment and time course. Within-group differences will be assessed with a paired t test for normally distributed data and a Wilcoxon signed-rank test for non-normally distributed data. For AE evaluation, all AEs will be reported including its grade, time of occurrence, duration, treatment, prognosis,and correlation with the intervention drugs. The chi-square test or Fisher exact test will be used to compare the incidence of AEs between the two groups.

Methods for any additional analyses {20b}

No subgroup and adjusted analyses are planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Sensitivity analyses will be conducted to handle protocol non-adherence and statistical methods will be used to adjust for missingness of the data and to smooth the data.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

There are no plans for granting public access to the full protocol, participant-level dataset, and statistical code.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Steering Committee is formed by the chairman and representative(s) from the Clinical Research Organization, whose duty is responsible for all final decisions regarding clinical trial/investigation modifications. The coordinating centre is responsible for non-clinical work, including the establishment and management of the researcher folder, the filling of project-related forms, the communication and coordination of the researcher, the sponsor, ethics, and the organization, the initiation of the project, drug management, and SAE reporting, cooperating with supervision and inspection, and receiving research-related training. The Scientific Research Council will have access to the final test data set. At the end of the study, the original data and results will be submitted to the Scientific Research Council. Endpoint adjudication committee consists of three Critical care specialist responsible for diagnosis of major adverse cardiovascular events. A data safety monitoring board (DSMB) will be composed of three

medical doctors specialized in Pharmacology and Critical care. The DSMB is responsible for making recommendations to the sponsor to continue, modify, suspend or terminate the research.

Composition of the data monitoring committee, its role and reporting structure {5d and 21a}

The Data Monitoring Committee consists of a doctor, a scientific research manager and a statistician. While doctor is responsible for data collection, data classification, storage and statistician for statistical analysis independently.

Description of any interim analyses and stopping guidelines{21b}

If SAEs occurs or the efficacy is not as expected or the quality of the trial drug has problems, the ethics committee, the sponsor or the State Food and Drug Administration have the right to terminate the trial.

Adverse event reporting and harms {22}

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease. All AEs should be documented in the case report form including occurrence time, severity, duration, adopted measure, and the outcome of the AE, whether or not they are related to therapy. All AEs will be evaluated for causal relationships which are graded as not related, probably not related, possibly related, probably related or definitely related. Severe adverse event (SAE) were defined as Grade 3–5.

All AEs and SAEs will be reported to the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, the Data Safety Monitoring Committee (DSMC), the national health authorities and the chief of research.

Frequency and plans for auditing trial conduct {23}

The investigators will conduct a daily audit of screening, enrollment, and data review. Sponsor will perform an audit at any time.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any changes to the research protocol need to be re-approved by the ethics committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine and inform the investigators, participants, data supervision committee.

Dissemination plans {31a}

We plan to share the study results through presentations at scientific meetings.

Results information will be submitted to Chinese Clinical Trial Registry no later than 1 year after the end of this study.

Authorship eligibility guidelines and any intended use of professionalwriters {31b}

No professional writers are planned.

Discussion

There is still a high incidence and mortality in septic shock, which lead to serious economic and social burdens. TCM was first recorded about 2,500 years ago and more and more evidences prove the effect of Chinese and Western medicine for septic shock. Hence, Chinese medicine can be used as an adjuvant treatment of septic shock to obtain better results. YFI has been widely used to treat septic shock in China. The YFI consists of three herbs: red ginseng, Liriope graminifolia and Schisandra chinensis. Previous studies have shown that YFI could improve blood gas, lower lactate levels and improve symptoms. However, these was little . Therefore, we designed this study to evaluate the efficacy and safety of using YFI as an adjunct treatment for septic shock. This study was designed as a randomized, double-blind, parallel, placebo-controlled trial that will provide strong evidence of the efficacy and safety of YFI for the treatment of septic shock. However, this study has certain limitations. First, because the study is being conducted in Guangdong, China, the relative role of uncertain test drugs will be similar in other races. Second, the follow-up time is relatively short.

Trial Status

The study is still ongoing, with first participant enrolled on November 20, 2019 and recruitment is predicted to end on December 30, 2023. The first version was developed in May 14, 2019. Shown above is the second version {3} whose protocol was revised for the following reasons: change of primary outcome, imprecise sample size calculation. To date, 284 participants have been recruited.

Abbreviations

ICU: intensive care units, TCM: Traditional Chinese medicine, YFI: Yiqi Fumai Injection, APACHE-II: acute physiology improvement and chronic health assessment II scores, SOFA: sepsis-related organ failure score, AE: adverse events, CONSORT: Consolidated Standards of Reporting Trials , SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials, MAP: mean arterial pressure, ICH-GCP: institutional policies and the Good Clinical Practice, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: gamma- Glutamyltranspeptidase, TBIL: serum total bilirubin ,Cr: serum creatinine, BUN: blood urea nitrogen, HR: hemodynamics heart rate, CVP: central venous pressure, CI: cardiac index, CRP: C-reactive protein, PCT; procalcitonin, IL-6□interleukin-6, IL-1□ interleukin-1, TNF-□□tumor necrosis □, ECG: Electrocardiogram.

Declarations

Dissemination policy

Results will be published in peer-reviewed journals and presented at national and international scientific meetings regardless of the magnitude or direction of effect.

Ethics approval and consent to participate {24}

The trial is in line with the Helsinki Declaration and China Clinical Trial Quality Management Regulations. This trial has been approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (BF2019-007-01) and has been registered in China Clinical Registration Center (ChiCTR-1900026424). All subjects will receive written informed consent prior to enrollment.

Consent for publication {32}

There is no individual patient data in this manuscript.

Availability of data and materials {29}

All data are fully available without restriction.

Competing interests {28}.

The authors declare that they have no competing interests.

Funding {4 and 5c}

The study was funded by Tianjin Tianshili Zhijiao Pharmaceutical Company. The funder provided research funding but had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Name and contact information for the trial sponsor {5b}

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Authors'contributions {5a}

ZJ and CXG conceived and designed this prospective trial and drafted the manuscript. CHR and LSC helped design the prospective trial, drafted the manuscript and participated in data collection. LSL determined the statistical analysis plan. LZS and ZWZ calculated the sample size and participated in statistical analysis. ZJQ helps with data collection and data management. CBJ is involved in quality control. All authors have read and approved the final manuscript.

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Table 1

Table 1 Measurement items and points of data capture

	Baseline	Treatment period				Follow-up Period
		24h	72h	7 days	14 days	
Enrollment						
Informed consent	×					
Inclusion/exclusion criteria	×					
Medical history	×					
Allocation	×					
Intervention						
Assessments						
Concomitant medication	×	×	×	×	×	
vital signs	×	×	×	×	×	
12-lead ECG	×				×	
liver function and renal function tests	×				×	
Electrolyte tests	×				×	
T lymphocyte subset typing and neutrophil CD64 percentage.	×	×	×	×	×	
CRP, PCT, IL-6, IL-1, TNF-α	×	×	×	×	×	
Pa02/Fi02, blood gas, blood lactate	×	×	×	×	×	
HR, MAP, CVP and CI	×	×	×	×	×	
SOFA	×	×	×	×	×	
APACHE-II	×	×	×	×	×	
The name, dose and duration of use of the vasoactive drug		×	×	×	×	
The name, dose and duration of corticosteroid use		×	×	×	×	
Adverse event evaluation		×	×	×	×	
The duration and cost of ICU					×	
28-days morality						×

Abbreviations: ECG: Electrocardiogram, CRP: C-reactive protein, PCT: procalcitonin, IL-6: interleukin-6, IL-1: interleukin-1, TNF-α: tumor necrosis α, HR: hemodynamics heart rate, CVP: central venous pressure, CI: cardiac index, MAP: mean arterial pressure, APACHE-II: acute physiology improvement and chronic health assessment II scores, SOFA: sepsis-related organ failure score, PaO2/FiO2:Arterial oxygen partial pressure/ Inhaled oxygen concentration.

Figures

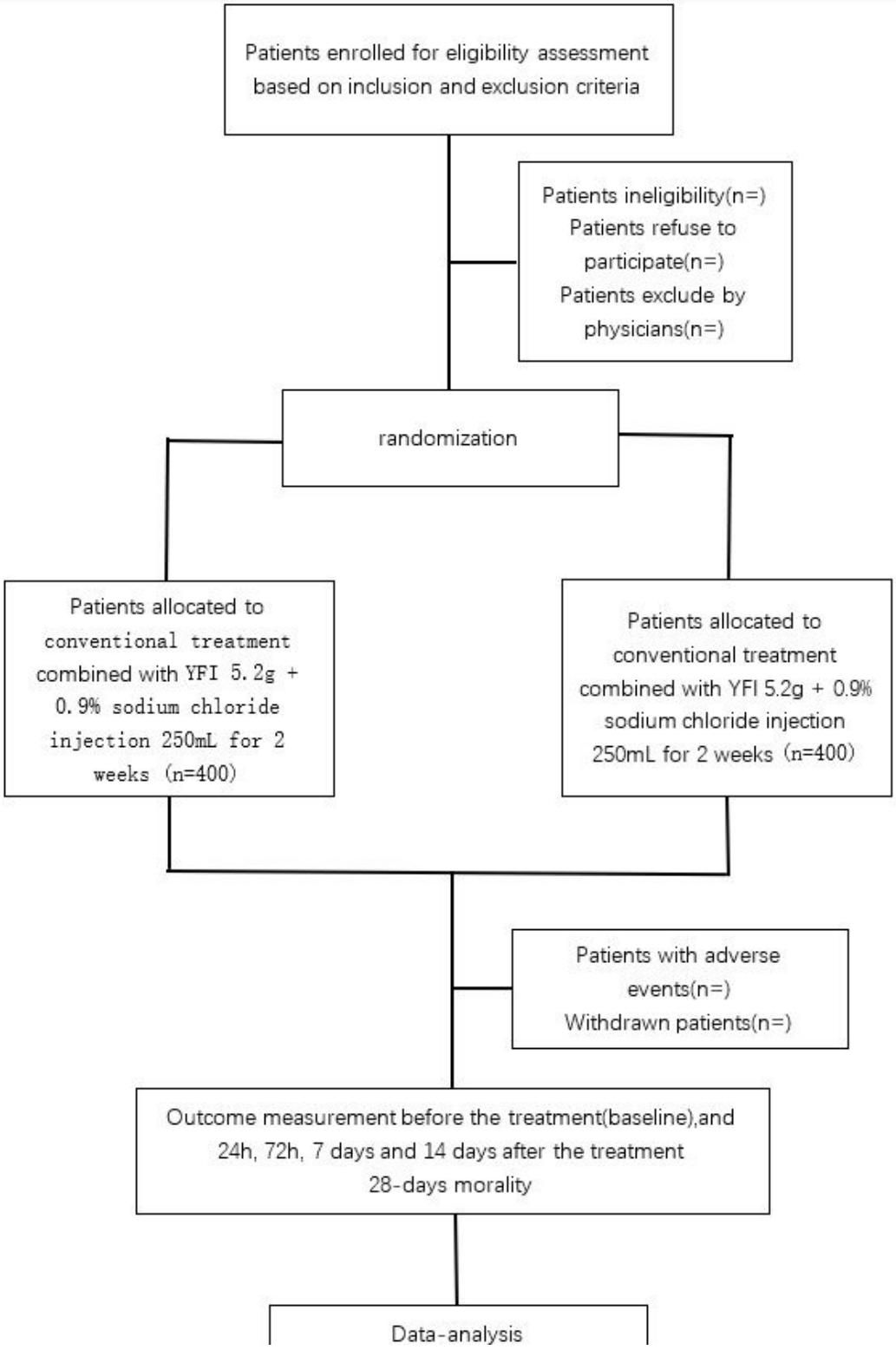

Figure 1

Study flow diagram

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