The effect of Xuanbai Chengqi decoction on patients with pneumonia-derived sepsis: study protocol for a randomized controlled trial

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Abstract

INTRODUCTION We wish to investigate the efficacy of Xuanbai Chengqi decoction (XCD) on management of pneumonia-derived sepsis.

METHODS AND ANALYSIS A single-blind, randomised controlled clinical trial will be conducted involving 90 patients with pneumonia-derived sepsis. Participants will be randomised at a 1:1 ratio to receive XCD (experimental arm) or the same amount of saline treatment (control arm). The intervention will comprise one session/day for 1 week. The primary outcomes will be 28-day mortality, and levels of pro-inflammatory cytokines in bronchoalveolar lavage fluid and serum 1, 3 and 7 days after treatment completion with respect to baseline levels. Secondary outcomes will be the symptom score of traditional Chinese medicine, duration of parenteral nutrition, and prevalence of complications. Measurements will be taken at baseline, 1, 3 and 7 days during the intervention, after 28 days after completing the intervention. Adverse events between arms will be evaluated.

Introduction

Sepsis is a clinical syndrome involving physiological, biological, biochemical abnormalities and life-threatening organ dysfunction caused by a dysregulated inflammatory response to infection. Sepsis and septic shock are major healthcare problems.[1, 2]

The reasons for a possible increased prevalence of sepsis are advancing age, immunosuppression, and multidrug-resistant infection.[3] It may also be due to increased detection of early sepsis from aggressive media campaigns focused on education about and awareness of sepsis (though this hypothesis is unproven).

Pneumonia-derived is one of the important aspects of sepsis. The contribution of various infectious organisms to the burden of sepsis has changed over time.[4, 5]. Gram-positive bacteria are identified most frequently in patients with sepsis (though the number of cases of Gram-negative sepsis is also substantial). The incidence of fungal sepsis has increased over the past decade, but remains lower than that for bacterial sepsis.[1] In approximately half of sepsis cases, an organism is not identified ('culture-negative sepsis').[6] The infection site in patients with sepsis may be an important determinant of outcome, with sepsis from a urinary-tract infection being associated, in general, with the lowest prevalence of mortality [7]. Pneumonia-derived sepsis is also very common.[8]

The theory of traditional Chinese medicine (TCM) dictates that diseases of the lung and those of the large intestine react with each other. The occurrence and development of sepsis is related to complex systemic inflammation, translocation of bacterial/endotoxins to the intestines, and immune dysfunction. [9, 10]

Many studies have been carried out on pro-inflammatory mediators such as tumor necrosis factor (TNF)-, interleukin (IL)−6, IL−8 and high mobility group protein B−1 (HMGB−1). Far fewer studies have been

done on anti-inflammatory mediators, such as IL–10.[11, 12]

Studies have shown that early administration of appropriate antibiotic therapy (i.e., antibiotics to which the pathogen is sensitive) has a beneficial impact on sepsis due to bacterial infection.[13] Another major treatment is restoration of perfusion; failure to restore perfusion aggressively and early (i.e., failure to initiate early goal-directed therapy) may also be associated with death.[14] A severely increased level of lactate (>4 mmol/l) is associated with a poor prognosis in patients with sepsis. Haas and colleagues reported a mortality of 78% in a population of critically ill patients, one-third of whom had sepsis.[15] The main treatments for pneumonia-derived sepsis are liquid resuscitation, early use of antibiotics, and support of organ function.

Scholars have hypothesised that translocation of bacteria and toxins in the gastrointestinal tract caused by intestinal failure is the main driver of severe sepsis and multiple-organ dysfunction syndrome [16 17]. This hypothesis chimes with TCM theory, which states 'the internal organs are used for communication', and the gastrointestinal tract is the main channel to expel turbid harmful material. If gastrointestinal dysfunction, a large number of toxic material will accumulate in the intestinal tract and damage it, thereby providing a new route for toxic material to invade. Therefore, studies on how to purge purulent material and stop sepsis are needed.

Most TCM studies have focused on the role of 'Tongli gongxia' herbs in the treatment of gastrointestinal function in patients suffering from sepsis. Less attention has been paid to the protection and improvement of lung function in sepsis patients. TCM theory states that the 'the lung distributes the nutrients necessary for the metabolism of the human body all over the body', and that 'the disease of lungs and large intestine react with each other'.[18] Xuanbai Chengqi decoction (XCD) is the most common prescription of 'Zang-fu organs combined treatment'.[18] This prescription can be employed with other herbs, and is used for various common diseases of the lungs.[18]

We are planning a trial to aid better understanding of XCD efficacy. We will select patients with pneumonia-derived sepsis, and combine therapy of XCD (using an enema) on the basis of conventional treatment and lung-protective ventilation.

Materials And Methods

Trial design

This will be a two-arm, randomised, single-blind, placebo-controlled clinical trial. The trial will be coordinated at the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China) and all participants will be recruited from this hospital. This trial will be funded through the Guangdong Provincial Bureau of Traditional Chinese Medicine (grant number, 20181117). Ethical approval has been obtained from the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (BF–2018–178–01). This trial has been registered prospectively with the Chinese Clinical Trail Registry (registration number, ChiCTR1900024072). The protocol of our intended trial has been prepared

according to the Standard Protocol Items: Recommendations for Interventional Trials checklist statement (see Online Supplementary Appendix 1).[19]

Participants

Ninety patients who conform to the diagnostic criteria of pneumonia-derived sepsis [1] and admitted to an intensive care unit within the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from August 2019 to August 2021 will be enrolled (*Table 1).*. All patients must provide written informed consent before participating in our trial.

Disease severity will be evaluated according to two criteria: Acute Physiology And Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure/Sepsis Related Organ Failure Assessment (SOFA). Patients will be randomised into two groups: primary disease in the treatment group (45 cases) and primary disease in the control group (45 cases). Comparisons on age, sex, APACHE II scores, SOFA scores, oxygenation index, and positive end-expiratory pressure between patients in the two groups will be collected.

Inclusion criteria

Participants will be recruited from the King Fahd Hospital of Guangzhou University of Chinese Medicine. Individuals will be included in the trial if they fulfil specific criteria: (i) patients who meet the diagnosis of sepsis based on TCM theory, and patients who meet the diagnostic criteria of sepsis in western medicine; (ii) the infection site is the lung; (iii) the baseline APACHE II score is >8; (iv) patients of either sex are aged 18–80 years.

Exclusion criteria

The exclusion criteria are patients: (i) with a malignant tumor and advanced cachexia; (ii) with a severe bleeding tendency or coagulation disorder; (iii) who are pregnant or lactating; (iv) have a mental disability which makes them unable to understand or cooperate with trial investigators; (v) who are currently participating in or participated in other clinical trials within 1 month of our trial starting; (vi) with contraindications to use of enemas or fiberoptic bronchoscopy; (vii) Yin deficiency and Yang deficiency in traditional Chinese medicine.

Criteria for exiting the trial

Participants will be withdrawn from the study if they suffer: (i) septic shock; (ii) severe stenosis/obstruction of the upper respiratory tract or hemoptysis; (iii) active bleeding of the digestive tract, faecal incontinence, intestinal perforation, or mechanical intestinal obstruction.

Sample size

In this trial, α will be 0.05, and β will be 0.10. The formula used for calculation of the trial size will be:

nc = (μ1α/2 + μ1β)2s2(11/k)/(μtμc)2

The mean ± standard deviation of the HMGB1 level in the control group and test group obtained from the literature is (7.12±1.86) and (4.05±1.89), and nc = 45. The total sample size according to this calculation has been determined to be 90 cases.

Randomisation

Eligible participants will be randomised at a 1:1 ratio to receive an XCD enema (experimental arm) or saline therapy of XCD (control arm). Both types of treatment will be conventional (see below). A randomisation list will be generated centrally, in a stratified fashion, using a random permuted-block design of size four and six. A researcher who is not part of the screening, evaluation or treatment in our trial will allocate participants to one of the groups using a sealed, opaque, tamperproof and numbered envelope before recruitment.

Blinding

The trial product will be provided in a blinded manner. All enema fluid will be covered by a cloth. When the enema is prepared, the enema liquids for both groups will be at 37°C. During the trial, patients will be blinded strictly to randomised interventions. The treating physician will know the type of treatment the participant will be given: participants will not have access to such information. The treating physician will be asked not to talk about the treatment groups to other people. Upon completion of the trial, each participant will be interviewed, and asked about the group which they think they were in.

Treatment methods

With regard to primary disease, conventional treatment (e.g., infection prevention; organ-function support; resuscitation after shock; correction of disturbances in water and electrolyte balance; maintenance of acid–base balance) and a lung-protective ventilation strategy (if necessary) will be conducted for patients in both groups. Meanwhile, on that basis, enema therapy using XCD will be added in the treatment group.

For XCD, gypsum, radix et rhizoma rhei, almond powder, and *Trichosanthis pericarpium* will be the basic prescription, with addition or subtraction of components as needed. Then, 200 ml of XCD will be used for strong frying at 37°C. The enema will be given once a day over 1 week of treatment.

Outcomes

The primary outcomes will be: (i) 28-day mortality; (ii) levels of TNF-α, IL−6, HMGB−1 and IL−10 in bronchoalveolar lavage fluid and serum 1, 3 and 7 days after treatment completion with respect to baseline levels; (iii) static lung compliance, dynamic lung compliance, plateau pressure, and peak airway pressure 1, 3 and 7 days after treatment completion with respect to baseline levels.

Secondary outcomes will be the: (i) symptom score of TCM; (ii) duration of parenteral nutrition; (iii) prevalence of complications (e.g., abdominal distension and ventilator-associated pneumonia) after treatment completion.

Measurements will be taken at baseline, 1, 3 and 7 days during the intervention, and 28 days after completing the intervention.

Statistical methods

All randomised patients will be assessed on an intent-to-treat basis. Safety analyses will be undertaken for all patients who received at least one treatment session.

Data will be entered into SPSS v24 (IBM, Armonk, NY, USA) for analyses. Baseline characteristics will be presented according to the treatment group. Binary and categorical variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. If values are missing, the denominator (which will be minus the number of patients assigned to the treatment group) will be reported in the body or as a footnote to the summary table. Continuous variables will be summarised by the mean ± SD as well as by quartiles. Before summarising continuous outcomes, a test of normality will be carried out. If the outcome has a normal distribution, it will be summarised by mean ± SD in each arm, and the difference between arms will be tested using the Student's *t*-test. However, if evidence of a normal distribution is absent, data will be summarised using the median (interquartile range). In such cases, the Wilcoxon rank sum test will be used to test the difference between arms.

The treatment effect for the primary outcome and continuous secondary outcomes will be assessed through analysis of covariance adjusted for the baseline measurement score. The overall treatment effect over time for all continuous outcomes (which will be collected repeatedly over the course of the trial) will be estimated using mixed linear models to take into account the correlation within each individual. The mixed linear model will include a random intercept adjusted with the baseline score, using time as a categorical and the interaction between treatment and time. *P*-values will not be adjusted for multiplicity. However, the outcomes will be categorised clearly according to the degree of importance (primary, main secondary, and other secondary) and a limited number of subgroup analyses will be pre-specified.

Categorical binary efficacy measurements will be assessed primarily using logistic regression. All tests will be two-sided, with $P < 0.05$ considered significant.

Safety measures

XCD has no known side-effects. If side-effects develop or the symptoms of any participants worsen during the trial or follow-up period, appropriate medical care will be given until the situation is resolved. Such participants will be withdrawn from the trial and take the corresponding treatment measures, if necessary. Observed side-effects will be recorded and reported to the Ethics Committee of Guangdong Provinical Hospital of Chinese Medicine.

Privacy and confidentiality

Screening, assessment and treatment will be done in a private area within the Department of Critical Care Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine. Data will be coded, and only one of the researchers will have the key for the codes. All data will be saved in a secured computer protected with a password. Only researchers will have access to data. Upon report writing and publication, data will be presented collectively; the identity of any participant will not be disclosed.

Involvement by participants and the public

Patients or the public were not involved in the development of our trial protocol. The findings of the trial will be disseminated to participants and the community in general through newsletters and presentations in the community.

Ethics and dissemination

The protocol of our trial was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (BF–2018–178–01). Any amendment to the protocol which may impact the conduct of the trial will be approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine before implementation. The trial was registered in the Chinese Clinical Trail Registry (registration number, ChiCTR1900024072) on 24 June 2019. While the trial is being conducted, the Monitoring Office for Research and Research Ethics at the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (where the trial will be conducted) will monitor the various milestones of the trial. The trial will be explained to all participants by one of the researchers. All participants will sign a consent form before beginning any procedures of our trial. The results of our trial will be presented in international conferences and will be published in a peer-reviewed journal.

Discussion

This is the first trial to evaluate the effects of XCD on management of pneumonia-derived sepsis. We will also use 'sham' saline to ensure appropriate control treatment. A rigorous study design with randomized allocation and blinding to assessors and statistical analyzers will be applied to reduce bias. It is expected that this trial will create reliable results.

There are some potential limitations to this study. This will be a single-centre, intervention pilot trial involving 90 patients. Blinding treating physicians to the interventions being administered will not be possible.

Altogether, if the results are as expected, they will provide evidence of XCD in promoting the results in pneumonia-derived sepsis patients.

Declarations

Availability of data and material

Data for the study can be made available upon request. Interested researchers should contact Dr. Huang at firenoodle@163.com.

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Competing interests

The authors declare that they have no competing interests.

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Author contributions

Yu Yi wrote the approved version of the protocol and generated the allocation sequence. The protocol manuscript received input from Zhang Jun and Bojun Zheng, and they will enroll participants. Bojun Zheng designed the trial and directed the project. Huang Jing designed and verified the randomisation schedule and statistical methods, and will assign participants to interventions. Zhang Jun advised on collection of laboratory results and their analyses.

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Competing interests:

None.

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Tables

CONSORT 2010 Flow Diagram