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

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Study protocol

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Abstract

Background: Sepsis and septic shock are major healthcare problems. pneumonia-derived is one of the important aspects of sepsis. The theory of traditional Chinese medicine (TCM) dictates that diseases of the lung and those of the large intestine react with each other. Methods/Design: 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 Xuanbai Chengqi decoction (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 and 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 symptom score of traditional Chinese medicine, duration of parenteral nutrition, prevalence of complications and the course of antibiotic use. 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. Discussion: This is the first trial to evaluate the effects of XCD on management of pneumonia-derived sepsis. If the results are as expected, they will provide evidence of XCD in promoting the results in pneumonia-derived sepsis patients. Trial Registration: Chinese Clinical Trial Registry, ChiCTR1900024072. Registered on 24 June 2019.

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).

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)-a, 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 amount 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 Analysis

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; (v) voluntary participation in the study and give informed consent.

Exclusion criteria

The exclusion criteria are patients: (i) with a malignant tumour 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 fibreoptic 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 haemoptysis; (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:

$$nc = (\mu 1\alpha/2 + \mu 1\beta)2s2(11/k)/(\mu t\mu c)2$$

The mean ± standard deviation of the HMGB1 level in the control group and test group obtained from the historical data from our centre is (7.12±1.86) and (4.05±1.89) respectively, 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-a, 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; and (iv) the course of antibiotic use.

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 Provincial 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 analysers 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

Ethics approval and consent to participate

The protocol of our trial was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (BF-2018-178-01). Signed consent forms will be obtained from all participants prior to their participation in the trial.

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.

Author details

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Competing interests

The authors declare that they have no competing interests.

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The authors are grateful to the research assistants and coordinators at all participating sites.

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 enrol 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.

Funding statement

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Competing interests: None.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	10
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2/10
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	3-5
Trial design	#8	Description of trial design including type of trial (eg,	5

		parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6
Methods: Assignment of			

interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A Not applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	10
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A Temporarily in a period of confidentiality
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A Routine examination items

Tables

CONSORT 2010 Flow Diagram