Efficacy and safety of the Qiguiyin formula in severe pneumonia: study protocol for a randomized, double-blind, placebo-controlled clinical trial

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Abstract

OBJECTIVE: To evaluate the clinical efficacy and safety of Qiguiyin (QGY) formula in patients with severe pneumonia in China compared with a placebo.

METHODS: This is a multicenter double-blind, placebo-controlled, randomized clinical trial with two parallel arms. There will be 530 patients enrolled and randomized into either the experimental group (QGY formula) or the control group (placebo). Therapies for patients in the two groups above will be based on the conventional therapy. The primary outcome is 28-day mortality. Secondary outcomes include: (a) duration of hospital stay; (b) duration of time in the intensive care unit (ICU) stays; (c) duration of mechanical ventilation; (d) antibiotic DDD value (which means the doses of antibiotics during the treatment period); (e) serum procalcitonin (PCT) level; (f) serum C-reactive protein (CRP) level; (g) Pneumonia severity index (PSI) score; (h) Sequential Organ Failure Assessment (SOFA) score; (i) sputum culture results; (j) blood routine examination results; (k) routine urine test results; (l) stool routine examination results; (m) electrocardiogram results; (n) alanine aminotransferase levels; (o) aspartate amino transferase levels; (p) total bilirubin; (q) creatinine levels; (r) urea nitrogen levels; and (s) adverse events.

ETHICS AND DISSEMINATION: The protocol has been approved by the Research Ethics Committee of Beijing Hospital of Traditional Chinese Medicine, Affiliated with Capital Medical University (2018BL-053-02). This trial aims to provide evidence for QGY formula combined with conventional therapy in treating patients with severe bacterial pneumonia, and to verify the clinical effectiveness and safety of QGY formula in China compared with placebo. Additionally, this trial will reveal the effect of QGY formula on delaying/reversing the characteristics of drug-resistant bacteria.

Trial registration number: ChiCTR1800019785.

Keywords: Drug resistance; Pneumonia; Pseudomonas aeruginosa; Treatment outcome; Safety; Clinical protocols
INTRODUCTION

Both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) can lead to severe pneumonia (SP), which has high mortality rate. Multiple studies have shown that the SP 30-day mortality rate in intensive care unit (ICU) patients was as high as 23%-47%. Currently, the dominant therapeutic strategy for SP patients comprises initial administration of broad-spectrum drugs followed by narrow-spectrum antibiotics once the diagnostic test results are obtained. However, long-term antibiotic therapy could increase the risk of antibiotic resistance, which is a worldwide issue. Based on the Management of Adults with HAP and Ventilator-associated Pneumonia (VAP): 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society, it is recommended that most patients with HAP and VAP should be treated using a short-term antibiotic treatment that is independent of the pathogenic bacterium. Studies revealed that 36% of the isolated strains in bacterial pneumonia were multi-drug resistant bacteria. The incidence rate was higher in severe bacterial pneumonia, with a proportion was as high as 87%.

The increasing incidence of antibiotic resistant bacteria is a concern for clinicians and patients because of the consequences such as treatment failure, prolonged patient stay in the hospital, and nosocomial infection. Because of the specificity of Chinese herbs, they would be effective formulti drug resistant bacteria infection. Therefore, it is of great significance to exploit antibacterial Chinese herbs, which can help to address the shortage of antibiotics and avoid the adverse events caused by antibiotics. Compared with Western Medicine, Traditional Chinese Medicine (TCM) has been recently shown to have promising results in the treatment of patients with SP, suggesting that, when used in complementary and alternative therapies, TCM may represent a novel therapeutic approach for SP.

The characteristics of drug-resistant infection are similar to incubative pathogenic factors in TCM. From the TCM perspective, the basic pathogenesis of drug-resistant infection includes intermingled deficiency and excess, and the manifestations are blood stasis combined with stagnation of phlegm and heat evil, of which the root causes are a deficiency of Qi and blood combined with stagnation of Qi activity.

Qiguiyin (QGY) formula, a new Chinese herbal compound that was developed by Professor Liu, has acquired a patent for invention in China. This formula is composed of the following five medicinal herbs: Huangqi (Radix Astragali Mongolic) acts as the sovereign drug, tonifying Qi; Danggui (Radix Angelicae Sinensis) and Jinyinhua (Flue Lonicerae) function as the ministerial drugs, activating blood circulation and tonifying blood, clearing heat of yingfen to qifen; and Qianzhao (Herba Artemisiae Annuae) and Huzhanggen (Radix Polygoni Cuspidati) are assistants, which can clear fuming heat that is caused by inner heat and also remove toxicity. Basic research and previous retrospective studies revealed that the QGY formula is beneficial for improving the prognosis of patients who were infected by Pseudomonas aeruginosa and they confirmed that this formula could delay/reverse the characteristics of drug-resistant bacteria (data not published). However, there is no evidence to support the efficacy and safety of this formula in clinical studies. Therefore, a large-scale, multi-center, double-blind, randomized clinical trial (RCT) is required to confirm the clinical efficacy and anti-drug resistance function of QGY formula in the treatment of SP.

METHODS

Objectives
This RCT aims to evaluate the clinical efficacy and anti-drug resistant function of QGY formula in the treatment of SP.

Trial design
This study is a multi-center, double-blind, placebo-controlled, randomized clinical trial with two parallel arms. Patients will be followed for 1 month, including a 2-week intervention period.

Study sites
The hospitals participating in this study are all tertiary referral medical centers, including eight TCM hospitals and one Western Medicine hospital.

Study criteria
The patients enrolled in this study will meet the diagnostic and inclusion criteria for SP and provide written informed consent.

Diagnostic criteria
The diagnostic criteria for SP are based on the Respiratory Society of Chinese Medical Association guideline from 2016 and The Infectious Disease Society of America/American Thoracic Society guideline will also be used.

Primary diagnostic criteria are as follows: (a) endotracheal intubation is needed for ventilation treatment; and (b) septic shock requires vasoactive drug therapy after active fluid resuscitation.

Secondary diagnostic criteria are as follows: (a) respiratory frequency is more than 30 times/min; (b) the oxygenation index is no more than 250 mm Hg; (c) multiple pulmonary infiltration; (d) consciousness and/or of orientation disorders; (e) blood urea nitrogen is more than 7.14 mmol/L; and (f) systolic pressure < 90 mm Hg requires positive fluid resuscitation.

Patients who meet one primary or at least three secondary criteria are diagnosed with SP.
Inclusion criteria
The inclusion criteria are as follows: (a) meet the SP diagnostic criteria; (b) aged 18 to 80 years; and (c) patients or their families are aware of the study content and signed the informed consent voluntarily.

Exclusion criteria
Exclusion criteria for this study are as follows: (a) Pregnancy or planning to become pregnant, or unable to take effective measures to prevent pregnancy; (b) persons with serious mental disorders; (c) the expected survival time of patients resulting from basic diseases is less than 28 d, such as poor control of malignant tumors and cardiac arrest within 30 d in the past; (d) patients in the vegetative state; (e) confirmed or highly suspected acute infectious diseases, such as viral hepatitis active stage or the active stage tuberculosis; (f) allergy to the effective ingredients or auxiliary materials in the test drugs; (g) participated in a clinical intervention trial within the past 3 months; and (h) subjects who are considered unfit to participate in this study by the attending doctor.

Other exclusion criteria
Other exclusion criteria for this study include the use of concomitant drugs such as other TCM formulas or injections. Details of any additional drugs or therapy must be recorded in the case report form (CRF), including the drug name, dose, and treatment duration.

Suspension criteria
Suspension criteria for patients enrolled into the study are as follows: (a) Poor patient compliance; (b) occurrence of serious adverse events, complications, or fatal physiological changes; (c) using concomitant drugs during the trial that might affect analysis of the results; (d) voluntary withdrawal; (e) incomplete data; and/or (f) withdrawal for various reasons, such as failure to attend follow-up visits.

Methods of administration
The treatment group will receive routine medication plus QGY granules (manufactured by Beijing Institute of Traditional Chinese Herbal, Beijing, China; 200 mL of QGY will be administered once orally via a stomach tube, twice a day). The main components of QGY formula are shown as follows, Huangqi (Radix Astragali Mongolici, 54.6%), Danggui (Radix Angelicae Sinensis, 13.6%), Jinyinhua (Flor Lonicerae, 13.6%), Qinghao (Herba Artemisiae Annuae, 9.1%), Huzhanggen (Radix Polygoni Cuspidati, 9.1%). The control group will receive routine medication plus placebo QGY granules (manufactured by Beijing Institute of Traditional Chinese Herbal; placebo granules are composed of asparagine, bitartrate, caramel, and soluble starch, ensuring that the taste and color are consistent with that of the QGY formula). This method is same as that of the treatment group.

Routine medications for SP
Empiric antibiotic therapy should be used before the results of etiology test. Types of antibiotics include a β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either a macrolide (azithromycin, clarithromycin, or erythromycin) or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam). For Pseudomonas infection, a β-lactam (pipercillin/tazobactam, cepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin, or the above β-lactam plus an aminoglycoside and an anti-pneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam) is used. Dosage of hormones was as follows: during the intervention period (5-7 d), low-dose methylprednisolone (1 mg·kg⁻¹·d⁻¹) can be administered if necessary (especially to treat the comorbidity of septic shock).

Sample size
The sample size will be calculated based on the mortality rate. Previous study showed that the mortality of the control group is 23%, assuming that the improvement in the treatment group is 10% lower than that in the control group. The sample size was calculated based on the parameters α = 0.025 (one-sided test) and β = 0.2. Using PASS 11 software (NCSS Statistical Software, Kaysville, UT, USA), we calculated that 228 participants should be recruited into each group. Considering an attrition rate of no more than 15%, there should be at least 263 eligible participants in each group. Thus, we determined that we would need a sample size of 265 in each group (n = 530).

Randomization and blinding
The randomization of this trial will be accomplished using stratified randomization with SAS 9.4 software (Beijing Hospital of TCM Version. Order No. 9C1XJD, Beijing, China), which will generate the random numbers. All of the drugs will be numbered with a label based on the randomization schedule. This trial is double-blind, with the first blinding level corresponding to the case number (groups A and B), and the second blinding level corresponding to the intervention (the intervention and placebo groups). The numbers are kept in opaque sealed envelopes. The information about both levels of blinding is sealed separately and given to the managers who performed the trial. The unblinding letters which need to be opened immediately are sent to each of the center, saved with the test drug, and properly preserved until the end of the trial. Treatment assignments are not revealed and the participants and investigators (including statisticians) will remain blinded to the treatment and group until the entire study is completed.

Emergency unblinding
If knowledge of the patient’s group is required in the
event of an emergency or if it is a requirement for rescue, researchers will first obtain details of the patient’s group from the drug administrators and the reasons for unblinding will be reported to the major investigators within 24 h. The subjects will be withdrawn from the study after unblinding. The details of the unblinding cause, date, treatment, situation, and results will be reported in the CRF and signed by the administrator.

**Primary outcome measures**
The primary outcome of this trial is 28-day mortality.

**Secondary outcome measures**
The secondary outcome measures are as follows: (a) duration of hospital stay; (b) duration of intensive care unit (ICU) stays; (c) duration of mechanical ventilation; (d) antibiotic DDD value (which means the doses of antibiotics during the treatment period); (e) serum procalcitonin (PCT) level; (f) serum C-reactive protein (CRP) level; (g) pneumonia severity index (PSI) score; (h) Sequential Organ Failure Assessment (SOFA) score; (i) sputum culture results; (j) blood routine examination results; (k) routine urine test results; (l) stool routine examination results; (m) electrocardiogram results; (n) alanine aminotransferase levels; (o) aspartic acid amino transferase levels; (p) total bilirubin levels; (q) creatinine levels; (r) urea nitrogen levels; and (s) adverse events.

All of these indicators will be monitored closely throughout the trial.

**Adverse events**
Every adverse event (AE) that occurs during the study must be recorded on the AE form in accordance with the actual circumstances. The following information should be recorded: occurrence time, severity, duration, adopted measure, and AE outcome. The number and rate of AEs and serious AEs in the two groups will be recorded.

**Statistical analysis**
Statistical analysis will be performed using SAS 9.4 Software (Beijing Hospital of TCM Version. Order No. 9C1XJD, produced by SAS Institute Inc., Cary, NC, USA). The rate of 28-day mortality between the groups will be analyzed by performing superiority tests. If the lower limit of the 95% confidence interval is larger than a clinically meaningful difference, therapeutic effects in the experimental group are deemed to be clinically and statistically better than those of the control group. Two-sided tests will be performed for all the other statistical analyses. Cochran Mantel-Haenszel $\chi^2$ tests or Fisher’s exact tests will be used for comparing categorical outcomes. Continuous outcomes will be analyzed using a Student’s $t$-test. $P < 0.05$ are considered to indicate statistical significance.

**Data input**
Two data input media will be applied in this study. Researchers will add patient information to the paper CRF promptly and synchronously with input into the electronic CRF. The occurrence of unexpected problems during this process will be recorded, and the data management center will be informed in a timely manner. The content and points of data capture are shown as Table 1.

**Data verification**
Modifications made by clinical investigators will be checked promptly, and the results will be reported to the researchers and clinical research associates (CRAs). The CRAs are responsible for verifying the consistency and accuracy of the paper and electronic CRFs and for reporting the results to the clinical investigators.

**Data lockup**
Data lockup will be implemented by data management upon completion of the study. Researchers are unable to modify data subsequently, and problems will be modified in the statistical analysis.

**Compliance control**
Before the trial, caution will be used in selecting the participating institutions and investigators. All the participating institutions will be required to have approval from the drug clinical trial agency, and all the investigators will be required to be qualified in the implementation of Good Clinical Practice (GCP) training, in accordance with the State Food and Drug Administration (SFDA). Before the trial, investigators will receive rigorous training and take a comprehensive examination to improve compliance. In the CRF, the investigators will be required to provide authentic and reliable data on combined medications and AE conditions; the subjects will be required to comply with their medication regimen and receive follow-up in accordance with the trial plan; and the drug administrator will ensure accurate recording of the dosage and amount of drug remaining to monitor patient compliance.

**Informed consent form**
The CRF must be signed by the participants or their representatives, and the date must be included. The signed CRF will be preserved by researchers and participants independently. The CRF preserved by the researchers will be made available to project managers for monitoring, auditing, and inspection.

**Ethics statement**
Researchers are responsible for ensuring that the study is conducted in accordance with the principles of the Declaration of Helsinki and GCP. Participants will provide written informed consent voluntarily before any study procedures take place, and they can voluntarily withdraw from the study for any reason. Parents or guardians will be informed of the risks and benefits of the study if the participants have difficulty with decision-making. Each patient will be identified with a
unique random number, and the private data will be preserved by researchers to maintain confidentiality.

**RESULTS**

The results of this study will be published as soon as the patient recruit mentended.

**DISCUSSION**

The aim of this trial is to evaluate the efficacy and safety of the QGY formula in the treatment of patients with SP. Based on the latest guideline, the main therapeutic strategy involves administration of antibiotics, respiratory support, and anti-inflammatory agents. Long-term antibiotic therapy increases the risk of antibiotic resistance and produces liver and kidney toxicity and other side effects. Moreover, a previous study indicated that delayed mechanical ventilation is an independent risk factor for increasing 28-day mortality. Compared with Western Medicine, TCM has been
shown in recent studies to have promising results for the treatment of SP. Thus, as a complementary and alternative therapy, TCM may represent a novel therapeutical approach for SP.

**Research foundation of QGY formula**

As demonstrated above, QGY formula is beneficial for improving the prognosis of patients infected by P. aeruginosa and this formula was shown to delay/reverse the characteristics of drug-resistant bacteria. The effective component of the QGY formula that was analyzed in a previous study using HPLC-ESI-LTQ-Orbitrap demonstrated that most of flavonoids in the QGY formula were excreted via a renal metabolism, which may provide a basis for elucidating the Pharmacology of the QGY formula for delaying drug resistance. In an in vitro test, we found that, using QGY formula containing drug serum, the sensitivity of imipenem-resistant P. aeruginosa to imipenem was restored to some extent, and the hydrolysis rate of β-lactamase was decreased, suggesting that inhibiting β-lactamase hydrolysis might be a mechanism for intervention in imipenem-resistant P. aeruginosa. An in vivo experiment investigated cefazidime’s over-inhibition of the immune response compared with the QGY formula. The QGY formula showed that it could appropriately down-regulate lymphocyte proliferation in rats that were infected with multi-drug resistant P. aeruginosa, and this can balance the immune disorders caused by infection.

**Pharmacological mechanism of QGY formula for treating SP**

Acute respiratory distress syndrome (ARDS) frequently occurs in the later stages of SP. The underlying mechanism of ARDS is an uncontrolled inflammatory response, leading to diffuse lung parenchymal injury and respiratory dysfunction. The main pathological manifestations were vascular endothelial injury and multiple inflammatory cell infiltration. Mechanical ventilation (MV) should be used when ARDS occurs during SP. Although the mechanical ventilation can improve ventilation for SP patients, MV could lead to endothelial activation and inflammation in the lung, especially in those with pre-injury to their lung. Thus, about 24% of patients with MV develop ventilator-induced lung injury (VILI). VILI is characterized by focal lung inflammatory cell infiltration in the lung tissue.

Based on the compatibility of prescriptions, Huangqi (Radix Astragali Mongolici) is the core drug for the QGY formula. Zhao et al. demonstrated that Astragalus membranaceus could alleviate oleic acid-induced acute respiratory distress syndrome in rats, and its pharmacological mechanism of action may be related to an increase in lung SP-A expression, which stimulates alveolar epithelial type II cell proliferation. Yang et al. demonstrated that Astragalus extract attenuates tracheal inflammation by inhibiting expression of the NF-kB signaling pathway. Another study showed that A. membranaceus treatment markedly inhibited airway inflammation and inhibited profound immunoregulatory activities in vitro and in vivo. Moreover, one study suggested that the attenuated accumulation of Treg cells maybe involved in the development of severe ARDS through a reduction in IL-10 synthesis. This result indicates that T cells participate in the process of ARDS, and the QGY formula may have an effect on adjusting the immune imbalance that was demonstrated above.

**Outcome measurement**

Although Wang et al. selected an improvement in the PSI risk rating as the primary outcome, we choose 28-day mortality as the primary outcome because 28-day mortality as the internationally recognized outcome standard that can evaluate the effect of TCM more objectively. Moreover, the serum PCT level was selected based on a study that showed that PCT is appropriate in algorithms for antibiotic de-escalation and discontinuation. Additionally, a systematic review showed that an elevated PCT level was a risk factor for death from CAP, particularly in patients with a low CURB-65 score. Based on our previous study (data were not published), we found that the hydrolysis rate of β-lactamase was decreased following treatment with QGY formula. Here, we will further investigate other mechanisms including the efflux pump and outer membrane poral proteins.

**Strengths and limitations**

This is a large-sample, multi-center, double-blind RCT of a TCM formula and it was designed based on previous studies for SP. Moreover, the therapeutic method is different from previous studies based on its perspective of TCM. The high standards for selection of the participating institutions and researchers, rigorous training of researchers, and the implementation process for inspection and other quality control methods were designed to ensure the quality of this trial. Ethics approval, signed informed consent, and clinical trial insurance coverage fully protect the interests of the subjects. Throughout the trial, safety outcomes will be closely monitored to avoid AEs. Because of the large sample and multiple centers, there will be a long participant recruitment time. It is difficult to control the season and climate change, which may influence the prognosis of this disease. The results of this trial remain to be confirmed by clinical research practice.

**Trial status**

Currently, participant recruitment is ongoing.

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