Jinye Baidu granule for wind-warmth lung-heat disease (heat in the lung-wei): protocol for a randomized, double-blind, parallel, controlled trial

Jiang Junjie, Zhang Yin, Xie Yanming, Li Yuan, Sun Shuailing, Zhang Yili, Wang Shuo, Zhu Yong, Qi Wensheng

Objective: To observe the curative effect of Jinye Baidu granule in the treatment of fever and swollen and sore throat caused by wind-warmth lung-heat disease (heat in the lung-wei) to further identify the indications.

Methods: This randomized, double-blind, parallel, controlled trial will include patients with acute upper respiratory infection and wind-warmth lung-heat disease (heat in the lung-wei). Patients with serious bacterial infection (white blood cell count > 12 x 10^9, neutrophils > 80%) will be excluded. Patients will be divided into three categories (blocks) according to their condition: fever only, a swollen and sore throat, and combined fever plus a swollen and sore throat. Patients within each of the three blocks will be further divided into a treatment group and a control group via stratified blocked randomization. The treatment group will be treated with Jinye Baidu granule, and the control group will be treated with Fufang Shuanghua granule. The primary outcome measure will be body temperature recovery time for patients with fever, throat symptom score for patients with a swollen and sore throat, and body temperature recovery time and throat symptom score for patients with combined fever plus a swollen and sore throat. Routine blood testing, urine testing, liver function, kidney function and ECG data of all patients will be collected as safety indices before and after enrollment, and adverse events will be recorded during the whole trial course.

Conclusion: This study protocol will include stratified block analysis according to patients’ symptoms, and identify the accurate clinical indications of Jinye Baidu granule. It will also enable safety evaluation from laboratory indices and adverse events, which will provide reliable evidence for clinical treatment.

Keywords: Syndrome of wind heat invading lung and stomach; Respiratory tract infections; Randomized controlled trial; Clinical protocols; Jinye Baidu granule
INTRODUCTION

In terms of Traditional Chinese Medicine (TCM), wind-warmth lung-heat disease is the name for combined lung-heat disease and wind-warmth disease, which is caused by a wind-heat pathogen invading the lung, heat obstructing lung Qi, and lung Qi failing to purify, with patterns of heat in the lung-wei, phlegm-heat obstructing the lung, heat sinking the pericardium, and dual damage of Qi and Yin. The TCM pattern of heat in the lung-wei is manifested by symptoms including fever, headache, cough, sore throat, thirst, and expectoration of phlegm, which is equivalent to acute upper respiratory infection. Jinye Baidu granule is used to treat wind-warmth lung-heat disease (heat in the lung-wei); it is composed of Jinyinhua (Flos Lonicerae), Yuxingcao (Herba Houttyniae Cordatae), Daqingye (Folium Isatidis), Jinyinhua (Flos Lonicerae) is the chief medicinal ingredient; it affects the lung, heart, and stomach meridians, with the actions of clearing heat, removing toxins and dispersing wind-heat. Yuxingcao (Herba Houttyniae Cordatae) is the deputy medicinal ingredient that affects the lung meridian, and functions to clear heat, remove toxins, disperse abscesses, expel pus, and disinhibit urine and relieve stranguria. Pungongying (Herba Taraxaci Mongolicci) and Dqingye (Folium Isatidis) affect the liver and stomach meridians, with the actions of clearing heat, removing toxins, dispersing swelling, and dissipating binds. Both Pungongying (Herba Taraxaci Mongolicci) and Dqingye (Folium Isatidis) clear heat and remove toxins, which can help Jinyinhua (Flos Lonicerae japonicae) and Yuxingcao (Herba Houttyniae Cordatae) clear and resolve heat-toxin pathogens in lung-wei and the throat. Jinye Baidu granule formula can thus clear heat and remove toxins, with cooling, dissipating, and expelling actions.

Previous clinical studies have indicated that Jinye Baidu granule has a significant effect on wind-warmth lung-heat disease (heat in the lung-wei) with symptoms of fever, sore throat, cough, and expectoration of phlegm, with relatively good safety. Previous study results and the formula composition reveal that the main indications of Jinye Baidu granule are fever and a swollen and sore throat; however, the previous studies were mainly focused on overall curative effect, and lacked more precise identification of indications. It has not yet been determined whether Jinye Baidu granules are more efficient in treating fever and/or a swollen and sore throat. The present proposed study will further evaluate the efficiency and safety of Jinye Baidu granule in treating acute upper respiratory infection (the TCM pattern of heat in the lung-wei of wind-warmth lung heat disease), and then identify the precise indications of Jinye Baidu granule, which will provide a reference and evidence for clinical treatment.

METHODS

Study design

This will be a randomized, double-blind, double-dummy, parallel, controlled, multi-center trial. This trial was registered in the Clinical Trials USA registry in February 2015 (registration No. NCT02539277).

Patients

Identifying the symptom patterns in wind-warmth lung-heat disease (heat in the lung-wei) are as follows. Diagnosis of wind-warmth lung-heat disease (heat in the lung-wei) is referred to in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Patterns in Traditional Chinese Medicine-Standard of Traditional Chinese Medicine Industry of People’s Republic of China. Diagnostic criteria for acute upper respiratory infection are as follows. According to the Regular Higher Education Nationally Planned Textbook of Internal Medicine, the criteria for the diagnosis of acute upper respiratory infection are: (a) acute occurrence and a disease course within 36 h; (b) local symptoms: sneezing, nasal congestion, runny nose, cough, expectoration of phlegm, and a swollen and sore throat; (c) whole body symptoms: usually none, sometimes fever, thirst, or headache.

The included patients will be stratified into three groups according to their symptoms. The diagnosis criteria for each group are: (a) Fever group: body temperature ≥ 37.5 °C. Patients with fever only (no sign of swollen and/or sore throat), but could be combined with other symptoms. (b) Swollen and sore throat group: body temperature < 37.5 °C, including patients without fever, but with a swollen and sore throat, and could be combined with other symptoms. Swollen throat will be graded as I, II, or III degree swelling of the tonsils. Red throat will describe hyperemia and swelling of the pharynx with mucous and a small amount of secretion. Sore throat will describe a sore throat that is affecting swallowing. (c) Combined fever plus a swollen and sore throat group: with both symptoms of fever plus a swollen and sore throat (i.e. body temperature ≥ 37.5 °C plus a swollen and sore throat).

Exclusion criteria are as follows: (a) meeting the diagnostic criteria of wind-warmth lung-heat disease (heat in the lung-wei); (b) meeting the diagnostic criteria of acute upper respiratory infection; (c) disease occurrence is within 36 h; (d) aged 18 to 70 years; (e) patients or responsible caregivers signed written informed consent.

Exclusion criteria are as follows: (a) supplicative tonsillitis; (b) chest radiography showing pulmonary inflammation; (c) white blood cell count > 12 × 10⁹, neutrophils > 80%; (d) ALT, AST, BUN, and/or Cr more than twice the upper limit of normal; (e) patients with body temperature < 37.5 °C and without symptoms of a swollen and sore throat who cannot be assigned to any of the three blocks; (f) body temperature >
38.5 °C; (j) patients who have been treated with antibiotics or other similar medicine; (h) other serious primary lung disease, such as lung tumor, tuberculosis, pneumonia, and other infectious diseases; (i) cardio-cerebrovascular disease, serious primary disease of the hematopoietic system, and/or mental disorder; (j) pregnant or lactating; (k) patients with immunodeficiency who have had organ transplantation, HIV, or long-term application of immunosuppressants; (l) allergy to Jinye Baidu granule; (m) participation in other clinical trials that may influence this study evaluation.

Drop-out and withdrawal criteria are as follows: (a) occurrence of severe adverse reaction; (b) patients who become allergic to Jinye Baidu granule during the trial; (c) intolerance to Jinye Baidu granule; (d) failure to take drugs as instructed, and the dosage taken was > 10%; (e) patients (or their family) with non-compliance that prevents study performance according to the plan, or patients who change medicine randomly; (f) patients lost to follow-up. Criteria for study termination are as follows. The clinical trial will be discontinued for patients who have been included for 72 h and have a body temperature that is still > 38.5 °C or white blood cell count that is > 12 × 10^9/L, and for patients who have the complications of pneumonia and/or myocarditis. These patients will still be given treatment and included as invalid cases. Elimination are as follows: (a) included patients who do not meet the inclusion criteria; (b) except for cases with occurrence of adverse events, patients who did not take the medicine or took an extremely little amount of medicine (≤ 10%); (c) cases without any data. The cases in this study will be collected from outpatient clinics or emergency clinics in the Pneumology Department of 10 grade 3 and first-class hospitals in China, including the Guang’anmen Hospital China Academy of Chinese Medical Sciences, Beijing Hospital of TCM Affiliated to Capital Medical University, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, The Affiliated Hospital to Changchun University of Chinese Medicine, The Second Affiliated Hospital of Liaoning University of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shanghai TCM-Integrated Hospital, Hubei Provincial Hospital of Traditional Chinese Medicine, The Affiliated Hospital of Hunan Province Academy of Traditional Chinese Medicine, and Guangdong Hospital of Traditional Chinese Medicine.

**Interventions**

Fufang Shuanghua granule has been selected as the active control medicine. The formula is composed of Jinyinhua (*Flos Lonicerae*), Lianqiao (*Fructus Forsythiae Suspensae*), Chuanxilin (*Herba Andrographis Paniculatae*), and Banlangen (*Radix Iatridii*), and has the actions of clearing heat and removing toxins, soothing the throat, and dispersing swelling. It is effective in treating externally contracted wind-heat pattern with symptoms of fever, slight aversion to wind, headache, nasal congestion, nasal discharge, red and painful throat, or dryness and scorching pain in throat, increased pain when swallowing, and red and swollen tonsils. The indications and functions of Fufang Shuanghua granule are similar to those of Jinye Baidu granule, and it is licensed for clinical use with proven curative effect and safety. The recommended dosage of Fufang Shuanghua granule is one pack four times daily; hence, in order to meet the requirements of blinding, the administration method of this medicine has been designed as described in Table 1.


### Table 1 Administration methods in the treatment and control groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>1 pack of Jinye Baidu granule, 1 pack of Fufang Shuanghua granule simulation agent</td>
<td>1 pack of Fufang Shuanghua granule, 1 pack of Jinye Baidu granule simulation agent</td>
</tr>
<tr>
<td>13:00</td>
<td>1 pack of Jinye Baidu granule, 1 pack of Fufang Shuanghua granule simulation agent</td>
<td>1 pack of Fufang Shuanghua granule, 1 pack of Jinye Baidu granule simulation agent</td>
</tr>
<tr>
<td>17:00</td>
<td>1 pack of Jinye Baidu granule simulation agent, 1 pack of Fufang Shuanghua granule simulation agent</td>
<td>1 pack of Jinye Baidu granule simulation agent, 1 pack of Fufang Shuanghua granule</td>
</tr>
<tr>
<td>20:00</td>
<td>1 pack of Jinye Baidu granule, 1 pack of Fufang Shuanghua granule simulation agent</td>
<td>1 pack of Fufang Shuanghua granule, 1 pack of Jinye Baidu granule simulation agent</td>
</tr>
</tbody>
</table>

Notes: the details of Jinye Baidu granule and its simulation agent, and of Fufang Shuanghua granule and its simulation agent are described below.

**Measurements**

The primary measurement indices for patients with fever are the overall effective rate and the total obvious effective rate of the fever symptom score. Fever symptoms are divided into four levels: recovery (< 37.3 °C), mild (37.3-37.9 °C), moderate (38-38.5 °C), and severe (> 38.5 °C), with assignment of 0, 2, 4, and 6 points, respectively. According to the patients’ symptoms, the scores will be recorded once at baseline (day 0), and on the third day and the fifth day after treatment commencement. The overall curative effect index is used to evaluate the curative effect of two groups. Overall curative effect index = [(TCM pattern score before treatment - TCM pattern score after treatment)/TCM pattern score before treatment] × 100%. The curative effect evaluation standard is as follows: recovery (symptoms largely disappear and the overall curative effect index is ≥ 90%), obviously effective (symptoms markedly improve or partially resolve, and the overall curative effect index is < 90% and ≥ 70%), effective (symptoms partially improve, and the overall curative effect is < 70% and ≥ 30%), and ineffective (no improvement or symptoms worsen after treatment, and the overall curative effect is < 30%). The differences in the overall effective rate and the total obvious effective rate on the third day and the fifth day will be compared in the treatment group versus the control group.

The secondary measurement indices for patients with fever are body temperature recovery time and the overall effective rate and total obvious effective rate of other TCM pattern scores. The contents of the indices, the evaluation methods and standards are the same as for patients with fever.

The primary measurement indices of patients with a swollen and sore throat are the overall effective rate and the total obvious effective rate of score changes of pharyngeal signs. Pharyngeal signs include the degree of tonsillar swelling and the degree of congestion of the throat. These signs will be evaluated into four categories (recovery, mild, moderate, and severe), with assignment of 0, 1, 2, and 3 points, respectively (Table 2). According to the patients’ symptoms, the scores will be recorded once at baseline (day 0), and on the third day and the fifth day after treatment commencement. The evaluation method and standard are the same as for the primary measurement indices.

The primary measurement indices of patients with a swollen and sore throat are the overall effective rate and the total obvious effective rate of score changes of pharyngeal signs. Pharyngeal signs include the degree of tonsillar swelling and the degree of congestion of the throat. These signs will be evaluated into four categories (recovery, mild, moderate, and severe), with assignment of 0, 4, 6, and 8 points, respectively (Table 3). According to the patients’ symptoms, the scores will be recorded once at baseline (day 0), and on the fifth day after treatment commencement. The overall curative effect index is used to evaluate the difference in the curative effect between two groups. The evaluation method and standard will be the same as for patients with fever.

The primary measurement indices of patients with fever are body temperature recovery time and the overall effective rate and total obvious effective rate of other TCM pattern scores. The contents of the indices, the evaluation methods and standards are the same as for patients with fever.

### Table 2 Traditional Chinese Medicine symptom pattern scoring

<table>
<thead>
<tr>
<th>Observation item</th>
<th>Recovery</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>No sign of cough (0)</td>
<td>Occasional cough (1)</td>
<td>Regular cough (2)</td>
<td>Frequent cough (3)</td>
</tr>
<tr>
<td>Expectoration of phlegm</td>
<td>No sign of expectoration of phlegm (0)</td>
<td>Clear phlegm and easy to expectorate (1)</td>
<td>Sticky phlegm and not easy to expectorate (2)</td>
<td>Yellow thick phlegm and difficult to expectorate (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>No sign of headache (0)</td>
<td>Slight headache (1)</td>
<td>Relatively heavy headache (2)</td>
<td>Heavy headache that influences work and rest (3)</td>
</tr>
<tr>
<td>Thirst</td>
<td>No sign of thirst (0)</td>
<td>Slight thirst (1)</td>
<td>Thirst and desire for drink (2)</td>
<td>Thirst and prefer drinking (3)</td>
</tr>
</tbody>
</table>

### Table 3 Scoring of pharyngeal signs

<table>
<thead>
<tr>
<th>Observation item</th>
<th>Recovery</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling tonsil</td>
<td>No sign of swelling tonsil (0)</td>
<td>I° (4)</td>
<td>II° (6)</td>
<td>III° (8)</td>
</tr>
<tr>
<td>Congestion throat</td>
<td>No sign of congestion throat (0)</td>
<td>Hyperaemia and swelling of pharynx mucous (4)</td>
<td>Hyperaemia and swelling of pharynx mucous with small amount of secretion (6)</td>
<td>Hyperaemia and swelling of pharynx mucous with large amount of secretion or herpes (8)</td>
</tr>
</tbody>
</table>

Notes: the secondary measurement indices of patients with a swollen and sore throat are the overall effective rate and the total obvious effective rate of other TCM pattern scores. The contents of the indices, the evaluation methods and standards are the same as for patients with fever.
combined fever and a swollen and sore throat are the overall effective rate and total obvious effective rate of the cumulative scores of fever, tonsillar swelling, and throat congestion. The contents of the indices, evaluation methods and standards are the same as for patients with fever and patients with a swollen and sore throat. The secondary measurement indices are the body temperature recovery time, and the overall effective rate and the total obvious effective rate of other TCM pattern scores.

Safety measurements included laboratory indices and adverse events. All patients will undergo the following laboratory examination before enrollment and at the end of the clinical trial. The changes in the laboratory indices before and after the clinical trial will be compared to conduct a safety analysis. Laboratory indices are: (a) routine blood and urine testing; (b) liver function, kidney function, ALT, AST, Cr, and BUN; (c) ECG. Adverse events experienced by all patients will be recorded during the whole trial process.

Judgment of the degree of severity. Mild: mild discomfort. Patients can bear the symptom, it has no effect on the study treatment without any special treatment, and has no effect on patient recovery. Moderate: moderate discomfort. Patients can hardly tolerate the symptom, and need special treatment, which has a direct influence on patient recovery. Severe: severe discomfort. The symptom jeopardizes the patient’s life, can cause death or disability, and needs urgent treatment.

Judgment of causal relationship with medicine. According to standards set by the National Centre for ADR Monitoring of China, evaluations will be made on possible correlations between adverse events and medicine administered in trials using the six-level classifications of ‘definitely, very likely, likely, might be irrelevant, to be evaluated, and cannot be evaluated’.

Protocol for adverse events. Any occurrence of adverse events, such as subjective discomfort of patients and abnormal laboratory results, will be carefully handled and analyzed. Measures will be immediately taken to protect the safety of patients. The manifestation and processing of adverse events will be recorded in detail on a case report form (CRF), and a tracking investigation will be undertaken until the laboratory result returns to normal, and symptoms and physical signs resolve.

**Observation cycle**
The observation cycle of this trial will be 5 d.

**Sample size planning**
Referring to similar studies, combined with the overall curative outcome of Jinye Baidu granule in treating the TCM patterns of fever, cough, expectoration of phlegm, headache, thirst, and sore throat, and the functions of the ingredients, the curative effects of Jinye Baidu granule in treating fever, or swollen and sore throat, or combined fever plus a swollen and sore throat are 94% total obvious effective rate in the treatment group, and 80% total obvious effective rate in the control group with α set at 0.05, and β at 0.2. The ratio of treatment group to control group is designated as 1:1. According to the formula of estimating sample size for comparison of two sample rates in Clinical Epidemiology, the formula is:

\[
n = \frac{(1 + 1/k)p(1-p)}{(1 + 1/k)[p_e + p - p]} \]

where \(n\) represents the sample size in each group. As the two groups will have the same sample size, \(k\) is 1. \(p_e\) and \(p_c\) are the positive rate of the treatment group and the control group, respectively. The result is 87 cases required in each group. Considering a 15% drop out rate, 100 patients will be recruited for each block, giving a total of 200 patients in the two groups. As a result, there will be 200 cases in each block (200 patients with fever, 200 patients with a swollen and sore throat, and 200 patients with combined fever plus a swollen and sore throat).

**Randomization**
Block randomization will be used for patient allocation. Firstly, according to stratification factors, there will be 200 patients in each of the three blocks (fever, a swollen and sore throat, and combined fever plus a swollen and sore throat). Each block will be subdivided among the 10 centers, with 20 cases at each center. The random block method will be used to randomly assign patients with a block size of four and a center number of 10. Using the SAS 9.2 statistical software PROC PLAN procedure statement, a seed number will be given, and randomized grouping tables will be generated for the 600 patients receiving treatment (with the trial drug or the control drug). On-site drug blinding will be carried out, and emergency unblinding procedures will be created. Blinded materials will be kept by a full-time investigator who will not participate in any part of the trial. During the course of the trial, the investigator will be able to obtain the randomized number and drug number of each patient from the designated central randomized platform.

**Blinding**
This is a double-blind and double-dummy study. If an adverse reaction occurs or a patient needs emergency treatment, it is necessary to know what kind of treatment the patient has undergone. So when the blinding needs to be broken, the investigators can log on to the central platform of this study, and fill in the reason and drug number to apply for unblinding. Once the blinding is broken, the patient with this number will be withdrawn from the trial, and the investigators will record the reasons in the CRF.

**Informed consent**
Before enrolling patients in the trial, the investigating
In this study, statistical analysis will be conducted for the treatment group and control group. The difference in survivorship curves between the Kaplan-Meier method and Log-Rank test will be compared. Survival analysis will be performed using the Kaplan-Meier method and Log-Rank test. For normally distributed data, the independent t-test will be adopted for the continuous variables with multiple indices. Analysis of Variance for repeated measurement will be conducted for the skewed variables. The \( \chi^2 \) test will be used for hypothesis testing of the counted indices. Analysis of Variance for repeated measurement will be adopted for the continuous variables with multiple observed values. Survival analysis will be done using the Kaplan-Meier method and Log-Rank test to compare the difference in survivorship curves between the treatment group and control group. In this study, statistical analysis will be conducted for three data sets: the full data set, per-protocol set, and safety data set. The full data set refers to patients who are randomly allocated into a group and receive at least one administration of a tested drug and one follow-up visit; an intention analysis will be conducted for curative effect. The per-protocol set refers to all cases that meet the trial protocol with good compliance, do not take prohibited drugs during the trial, and complete the content required by the CRF, or patients who take 80% to 120% of the recommended amount of the tested drugs per-protocol set analysis will be conducted for curative effect. The safety data set refers to the randomized cases that take a tested drug at least once with safety evaluation data after treatment, which constitutes the safety population in this study. Data analysis will be performed with SPSS 22.0 (IBM Corp. 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA).

**Flow chart of the study protocol**

The flow chart of this study is shown in Figure 1.

**DISCUSSION**

Stratified block analysis will be conducted according to patients’ symptoms to identify the accurate clinical indications of Jinye Baidu granule. With the actions of clearing heat and removing toxins, Jinye Baidu granule can treat wind-warmth lung-heat disease (heat in the lung-wei) manifested by fever, sore throat, and tonsillitis. The main symptoms of wind-warmth lung-heat disease (heat in the lung-wei) are body fever, a swollen and sore throat, cough, and expectoration of phlegm. The struggle between healthy Qi and pathogenic Qi manifests fever. The throat is the gateway of the lung and the stomach, so swelling and soreness occur in the throat when a heat pathogen invades the lung. Clinically, the symptoms of fever and a swollen and sore throat can occur simultaneously, or singly. Previous studies have shown that Jinye Baidu granule has definite therapeutic effects in treating wind-warmth lung-heat disease, but it is unclear whether it is effective in treating wind-warmth lung-heat disease of simple fever, or simple sore throat, or a combination of these two symptoms, or whether it is superior in treating certain symptoms. As a result, stratified blocked randomization will be used in this study protocol. Statistical analysis will be conducted for curative effect in each block to identify the accurate clinical indications of Jinye Baidu granule.

**Patients with severe bacterial infection will be excluded**

Wind-warmth lung-heat disease (heat in the lung-wei) is equivalent to acute upper respiratory infection in modern medicine. Patients with acute upper respiratory infection including severe bacterial infection usually have white blood cell count > 12 x 10^9, neutrophils >
80%, and body temperature > 38.5 °C. Numerous experts recommend that such patients should not receive TCM treatment to clear heat and remove toxins; they must be treated with antibiotics. Hence, such patients will be excluded from this study.

**Body temperature changes will be recorded in detail to further identity the appropriate time window for treatment**

For patients with fever, a body temperature table will be contained in the patients’ log cards. The timing of temperature assessment is described above. Analysis of body temperature recovery time in the treatment group and the control group, combined with analysis of the average body temperature change curve of the two groups, will indicate the best time window for lowering body temperature by treatment with Jinye Baidu granule to provide reference for clinical medication.

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