Efficacy of Rebixiao Chinese herbal tablets and Chinese formula granules in acute gout arthritis patients: a randomized, multicenter, double-blind, controlled trial

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Abstract

OBJECTIVE: To evaluate the clinical efficacy and safety of Rebixiao (RBX) Chinese herbal tablets (CHT) and Chinese formula granules (CFG) in the treatment of acute gout arthritis (AGA).

METHODS: This randomized, multicenter, double-blind, controlled trial included 165 AGA patients with the damp-heat symptom pattern who were randomly divided into an RBX CHT group and an RBX CFG group and treated for 7 d at three centers. The total effective rates of the joint symptom score, Traditional Chinese Medicine (TCM) symptoms score, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were used to evaluate the clinical efficacy. Safety assessments were also performed.

RESULTS: Of the 165 enrolled patients, 147 completed the clinical observation. There was no difference in baseline between the two groups. The total effective rates of the joint symptom score were 94.36% and 97.36%, and the total effective rates of the TCM symptoms score were 95.77% and 97.36% in the CFG group and CHT group, respectively. No statistical difference was found between the two groups (P > 0.05). Additionally, ESR and CRP were similar in both groups (P > 0.05). Furthermore, treatment efficacy regarding TCM and joint symptoms, the ESR, and CRP were consistent within each center and among the different centers (P > 0.05). In addition, the incidence of adverse events was 4.22% and 2.63% in the CFG group and CHT group, respectively, and no difference was observed between the two groups (P > 0.05).

CONCLUSION: RBX CFG and CHT have significant
and similar efficacy in the treatment of AGA, and CFG did not increase adverse side effects.

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Keywords: Gout; Arthritis; Drugs, Chinese herbal; Blood sedimentation; C-reactive protein; Randomized controlled trial

INTRODUCTION

Herbal decoction is the main treatment method in Traditional Chinese Medicine (TCM). With the acceleration of the rhythm of people’s lives, and because decoctions are time-consuming to prepare and inconvenient to carry, new Chinese medicine preparations are urgently needed to meet the needs of patients. In the 1960s and 1970s, Xiaochaihu granules were successfully developed in Japan; they include granules of consistent quality formed by a variety of steps from the mixture of Xiaochaihu decoction. This type of dosage form was named concentrated Chinese medicine and became more popular because of its convenience. Although the curative effect is good, these preparations cannot be flexibly modified according to the patient’s symptoms. To increase the flexibility, researchers developed Chinese formula granules (CFG), which are a new style formula drug made from single-flavored Chinese herbal tablets (CHT) through various production processes. CFG is becoming increasingly popular in clinical applications owing to its ability to be altered to adapt to the patient’s symptoms. However, whether the clinical efficacy of CFG is comparable to CHT remains controversial. Experimental studies have shown that there is a difference in the chemical composition of the two decoctions. One Meta-analysis showed that the clinical efficacy of CFG was better than that of CHT; however, because of various limitations in these studies, evidence-based guidance remains insufficient. Therefore, it is necessary to perform a more rational and rigorous multi-center randomized controlled trial to verify the clinical efficacy and safety of CFG. According to our previous clinical observations, the Chinese herbal compound Rebixiao (RBX) can effectively treat gouty arthritis (AGA) patients with symptoms identified as the damp-heat symptom pattern. RBX is mainly composed of Sishenjian and Simi-aowan. It contains Huangqi (Radix Astragali Mongolici), Yuanzhi (Radix Panaxae), Shihu (Herba Dendrobi Nobilis), Rendongteng (Cu Lonicerae japonicae) honey-suckle stem, Nixii (Radix Achyranthis Bidentatae), Huangbai (Cortex Phellodendri Amurensis), Cangzhu (Rhizoma Atractyloides Lanceae), Yiiren (Semen Coicis), Tufuling (Rhizoma Smilacis Chinae), and Yanhusuo (Rhizoma Corydalis Yanhusuo). In this multi-center, randomized, double-blind, controlled study, we aimed to evaluate the efficacy and safety of RBX CHT and CFG in the treatment of AGA.

METHODS

Ethics approval and consent to participate

The trial protocol was reviewed and approved by the ethical committee of the Chongqing Hospital of TCM (approval No. 2016-ky-LLP) and registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=28039) under number ChiCTR1800016527. There were no major changes in the study protocol after the initiation of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study design

A randomized, double-blind, three-center controlled trial was performed in AGA patients with the damp-heat symptom pattern. The study was conducted from June 2018 to December 2018 at the Chongqing Hospital of Traditional Chinese Medicine (CQ-TCM), Traditional Chinese Medicine Hospital of Dianjiang County Chongqing (TCM-DJ), and Traditional Chinese Medicine Hospital of Yongchuan District Chongqing (TCM-YC). Written informed consent was obtained from all patients prior to their inclusion in the trial, and they were free to withdraw from the study at any time. The study flowchart is shown in Figure 1. The trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

Sample size determination

No clinical trial data existed on the efficacy of Rebixiao CFG in treating AGA, but according to our previous clinical observation, Rebixiao CHT was shown to effectively treat AGA patients with damp-heat syndrome. Based on previous studies, the AGA resolution rates in the two groups were estimated to be 90%, the power of test at 80%, and the shedding rate at 20%. The sample size for each group was calculated to be 83, and thus 166 cases were needed for this study.

Participants

The condition of the patients was diagnosed according to the clinical criteria of the 1977 American College of Rheumatology classification criteria, and TCM symptom pattern judgment was based on the criteria issued by the Department of Medical and Political Affairs of the State Administration of Traditional Chinese Medicine in 1995.

Patients were included in the study if they met the following criteria: (a) age between 18 and 65 years, (b) gout attacks within 48 h and TCM symptom pattern identification as dampness damp-heat symptom pat-
tern, (c) the degree of pain in the most painful joint was at least moderate or greater than 2 points on a Likert scale, and (d) informed consent was obtained. Individuals were excluded if one of the following criteria was met: (a) chronic gouty arthritis stage, (b) clinical suspicion of joint infection or other joint diseases, (c) polyarticular gout involving more than four joints, (d) pregnancy, preparation for pregnancy, or breast-feeding, (e) liver disease activity or abnormal liver function, (f) upper limit of the normal value of blood creatinine, (g) abnormal reduction of white blood cells, hemoglobin, or platelets on routine blood tests or other diseases of the blood system, (h) coronary heart disease, heart failure, gastrointestinal hemorrhage, or a history of peptic ulcers, (i) use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids within 48 h before the baseline assessments, (j) allergic to any of the study drugs, or (k) mental illness or mental disorder.

Patients were removed from the trial when one of the following criteria was met: (a) poor compliance, (b) the clinical data were incomplete so that the efficacy and safety could not be judged correctly, and (c) AGA was aggravated during the trial, resulting in serious problems, such as high fever or acute infection, or other problems that required emergency intervention.

Randomization and blinding
Randomization was performed with SAS 9.2, and the allocation was concealed. The random numbers were sequentially divided into two groups. The group numbers were printed inside envelopes. Patients were assigned a randomization number according to a predetermined list at each center. Clinicians who screened the eligible patients opened the envelopes according to the patients’ screening sequence numbers and then assigned the patients to group A or B in accordance with the group number inside. A total of 166 AGA patients with the damp-heat symptom pattern meeting the eligibility criteria were randomly allocated at a 1:1 ratio to either group. Emergency envelopes containing the randomization code were examined at the end of the trial to ensure that the blinded conditions had been maintained.

A double-blind (with patients and clinicians blinded) trial design was adopted. The evaluation of participants and analysis of results were performed by professionals. Treatment assignments were not revealed until the entire process was complete. If patients had severe adverse events, clinicians were able to reveal the treatment allocation as an emergency and provide relevant treatment. To achieve blinding, RBX CFG and RBX CHT mixtures were prepared by non-blinded personnel in the Chongqing Hospital of TCM in 100 mL bottles with the same taste, smell, and outer packaging. RBX CFG was made by brewing each component granule with boiling water and marked as RBX A drug. RBX CHT was made using a decoction machine to decoct Chinese herbal tablets and marked as RBX B drug. The two drugs can be preserved for 2 years by adding preservatives. CFG and CHT both came from the same batch of herbs from Shenzhen China Resources Sanjiu Medical & Pharmaceutical Co., Ltd. (Shenzhen, China)

Intervention
Participants in the RBX A group received the RBX A drug orally three times a day for 7 d. Participants in the RBX B group received the RBX B drug orally three times a day for 7 d. Patient visits were required after 1 week of treatment. For the duration of the trial, patients were not allowed to take any concomitant medications associated with the treatment of AGA.

Outcome measurements
All outcome measurements were assessed at baseline and on the 8th day. If the disease was cured and the treatment ended prematurely, then the investigation was advanced accordingly.

Primary outcomes
Efficacy evaluation: efficacy was evaluated according to the Nimodipine calculation formula: efficacy index = (score after treatment - score before treatment) / score before treatment × 100%. With reference to the Guiding principles of clinical research on new drugs of TCM, the efficacy criteria for the treatment of gout were classified as clinically cured, markedly effective, effective, and ineffective.16 (a) Clinically cured: clinical symptoms and signs disappeared or almost disappeared, and the score on the symptom pattern efficacy index was ≥ 95%. (b) Markedly effective: significant improvement in clinical symptoms and signs, and the score on the symptom pattern efficacy index was ≥ 60% . (c) Effective: clinical symptoms and signs improved, and the score on the symptom pattern efficacy index was ≥ 30% . (d) Ineffective: the clinical symptoms and signs did not improve significantly or even worsened, and the score on the symptom pattern efficacy index was < 30%. The total effective rate = clinical cured rate + markedly effective rate + effective rate. In this study, the efficacy evaluation included the efficacy measurements of the joint symptom score and TCM symptom score.

Secondary outcomes
Joint symptom score: the joint symptom scale comprises four items (self-assessed pain and the physician’s assessment of swelling, redness, and fever of joints) based on a Likert scale. The degree of pain in the index joint was represented by the Likert scale 0 = none, 2 = mild, 4 = moderate, and 6 = severe; joint swelling on visual examination by the Likert scale 0 = none, 2 = touchable, 4 = visible, and 6 = severe swelling; joint redness by the Likert scale 0 = absent, 2 = a slight redness of the local skin, 4 = present, and 6 = obviously red; and joint fever by the Likert scale 0 = absent, 2 = hot to the touch, 4 = apparent fever on touch and self-heating.
and 6 = obvious fever and conscious burning. The total joint symptom score = the sum of the scores on the four items.

TCM symptom score: the TCM symptom scale comprised seven items: upset, thirst, and scanty dark urine according to the physician’s assessment and the above four joint symptom scales based on a Likert scale. The degree of upset was represented by the Likert scale 0 = none, 1 = occasionally upset, 2 = anxious, and 3 = irritated; the degree of thirst by the Likert scale 0 = none, 1 = occasionally thirsty, 2 = often thirsty, often needing to drink water, and 3 = thirsty with no improvement after drinking water; and the degree of scanty dark urine by the Likert scale 0 = none, 1 = occasionally scanty dark urine, 2 = dark urine and less urine, and 3 = urine stream short and not smooth. The total TCM symptom score = the sum of the scores for the seven items.

Laboratory assessment: the level of C-reactive protein (CRP) was measured using rate nephelometry. The erythrocyte sedimentation rate (ESR) was measured with the Westergren method.

Adverse effects
The following tests were performed to assess the safety at screening and 8 d after the initiation of treatment: routine blood sampling, routine urinalysis, routine fecal analysis, liver function tests, renal function tests, and electrocardiography. Adverse events refer to any adverse medical events that occurred between the initiation of the trial and the final follow-up visit in this clinical trial regardless of whether the incident was due to a causal relationship with the above-mentioned medications. Adverse events were reported and recorded in detail during the entire study. The correlation between adverse events and test drugs was analyzed, and the relationship between adverse events and drugs was recorded as positive, relevant, possibly related, possibly unrelated, definitely unrelated, and indeterminate. The first three and those unable to be judged were included as adverse events. The degree of influence of adverse events on daily life was divided into light, moderate, and severe. Patients with moderate and severe influences were removed from the trial and provided with the appropriate treatment. Patients experiencing severe adverse events were withdrawn for safety reasons, with relevant medical care and monitoring continued until the reaction terminated.

Statistical analysis
SPSS 16.0.1 was produced and released by SPSSInc (Chicago, IL, USA) for statistical analysis. Validity analysis: The t-test method was used to analyze the measurement data, and count data were assessed with the calibrated chi-square χ² test ( \( \bar{x} \pm s \)). Validity analysis: the t-test method was used to analyze the measurement data, and count data were assessed with the calibrated χ² test. Given that this was a multi-center clinical trial, the effect of the center on efficacy indicators was considered in the analysis. The Cochran-Mantel-Haenszel method was used to count the data, and the measurement data were analyzed by variance analysis in the multi-center analysis of the comprehensive curative effect.

Safety analysis: the adverse events were described in a list that included the number of cases of various adverse events with the laboratory index from normal to anomalous and the laboratory conversion rate. The χ² test was used for the statistical analysis of adverse reactions.

Data collection and quality control
The results were recorded in a case report form (CRF) and entered into an electronic database (Epidata 3.0) designed for the trial. Data were entered twice (independently by different persons) and checked by the database software. In addition, an auditor was appointed by the clinical trial unit to ensure that the rights of the participants in the clinical trial were guaranteed and that the test records and reports were accurate and complete. The quality-assured trial followed the approved protocols, drug clinical trial management regulations, and other relevant regulations.

RESULTS

Research population
The trial was initiated on June 10, 2018 and scheduled to be completed on December 31, 2018, but the actual completion time of the test was December 1, 2018. Of the 165 patients enrolled, 147 patients completed the clinical observations. Seventeen patients were lost to follow-up and one patient was excluded because they took NSAIDs during the trial. A total of 82 cases were allocated to the CFG group, but 10 cases were lost to follow-up, and one case excluded, resulting in 71 cases in the final analysis. Eighty-three cases were allocated to the CHT group, but seven cases were lost to follow-up, resulting in 76 cases in accordance with the plan. There were 72 patients recruited by the center of CQ-TCM, among which 61 cases were in accordance with the plan, including 27 cases in the CFG group and 34 cases in the CHT group. Thirty-three patients were recruited by the center of CCM-YC, among which 29 cases were in accordance with the plan, including 14 cases in the CFG group and 15 cases in the CHT group. Sixty patients were recruited by the center of TCM-DJ, among which 57 cases were in accordance with the plan, including 30 cases in the CFG group and 27 cases in the CHT group. The patient flowchart is illustrated in Figure 1.

Characteristics of the patients
According to the χ² test and t-test, the CFG and CHT groups had no statistically significant differences in age, sex, height, or weight (\( P > 0.05 \)). The rank-sum
test showed no difference in disease course between the two groups (\(P > 0.05\)). Statistical analysis also showed that the joint symptom score, TCM symptom score, individual joint symptom score, upset, thirst, scanty dark urine, ESR, and CRP were not significantly different at baseline (\(P > 0.05\)). These indicated that the baseline data for the two groups were balanced and comparable (Table 1).

**Treatment efficacy**
Comparisons were conducted before and after treatment in each group. First, the joint symptoms of pain, swelling, redness, and fever were significantly decreased (\(P < 0.01\), Figure 2A). Second, the changes in the TCM symptom score for upset, thirst, and scanty dark urine showed statistically significant differences (\(P < 0.05\), Figure 2B). Third, the total joint and TCM symptom scores were also evidently reduced (\(P < 0.01\), Figure 2C). Finally, the levels of ESR and CRP were significantly reduced (\(P < 0.01\), Figure 2D).

We also compared the efficacy between the groups. The total effective rates of the joint symptom score

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**Table 1 Patient characteristics at baseline (\(\bar{x} \pm s\))**

<table>
<thead>
<tr>
<th>Item</th>
<th>CFG group ((n = 82))</th>
<th>CHT group ((n = 83))</th>
<th>Statistical quantity</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.4±12.2</td>
<td>46.6±13.0</td>
<td>0.049(^a)</td>
<td>0.961</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.2±6.4</td>
<td>173.1±7.2</td>
<td>0.529(^a)</td>
<td>0.845</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.3±10.3</td>
<td>69.0±8.2</td>
<td>0.124(^b)</td>
<td>0.928</td>
</tr>
<tr>
<td>Sex (n)</td>
<td>12/70(^c)</td>
<td>10/73(^c)</td>
<td>0.239(^a)</td>
<td>0.625</td>
</tr>
<tr>
<td>Course (days)</td>
<td>1.9±2.0</td>
<td>2.4±2.2</td>
<td>0.207(^d)</td>
<td>0.836</td>
</tr>
<tr>
<td>Joint pain (score)</td>
<td>4.0±1.3</td>
<td>4.0±1.4</td>
<td>0.346(^c)</td>
<td>0.729</td>
</tr>
<tr>
<td>Joint swelling (score)</td>
<td>3.6±1.4</td>
<td>3.6±1.4</td>
<td>0.301(^b)</td>
<td>0.764</td>
</tr>
<tr>
<td>Joint redness (score)</td>
<td>3.9±1.5</td>
<td>4.0±1.4</td>
<td>0.316(^b)</td>
<td>0.753</td>
</tr>
<tr>
<td>Joint fever (score)</td>
<td>3.8±1.4</td>
<td>3.7±1.6</td>
<td>0.156(^b)</td>
<td>0.876</td>
</tr>
<tr>
<td>Upset (score)</td>
<td>1.2±1.0</td>
<td>1.0±0.8</td>
<td>1.387(^b)</td>
<td>0.167</td>
</tr>
<tr>
<td>Thirst (score)</td>
<td>1.3±0.9</td>
<td>1.1±0.7</td>
<td>1.087(^b)</td>
<td>0.076</td>
</tr>
<tr>
<td>Scanty dark urine (score)</td>
<td>1.0±0.8</td>
<td>1.0±0.8</td>
<td>0.296(^c)</td>
<td>0.768</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>30.0±21.7</td>
<td>24.5±19.9</td>
<td>1.60(^d)</td>
<td>0.11</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>29.4±22.7</td>
<td>33.0±24.3</td>
<td>0.92(^d)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Notes: CFG: Chinese formula granules; CHT: Chinese herbal tablets; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d. ‘\(t\)-test; \(\chi^2\) value; ‘rank sum test. Baseline comparison between the two groups before treatment. No differences were found at baseline (\(P > 0.05\)).
were 94.36% (67/71) and 97.36% (74/76) in the CFG group and CHT group, respectively. The total effective rates of the TCM symptom score were 95.77% (68/71) and 97.36% (74/76), respectively. Treatment efficacy showed no statistical difference between groups ($P > 0.05$, Table 2). Furthermore, the total scores for TCM symptoms, total scores for joint symptoms, and levels of ESR and CRP were similar, and no difference was

Figure 2 Comparison before and after treatment in each group
A: individual joint symptom scores; B: individual TCM symptom scores; C: total scores of TCM or joint symptoms; D: the ESR and CRP values. TCM: Traditional Chinese Medicine; CFG: Chinese formula granules; CHT: Chinese herbal tablets; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d. Comparing before and after treatment in the same group, $P < 0.01$, $P < 0.05$.

Table 2 Comparison of the total effective rates in the two groups [n (%)]

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>n</th>
<th>Clinical recovery</th>
<th>Remarkable effect</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective</th>
<th>$\chi^2$ value</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint symptom score</td>
<td>CFG</td>
<td>71</td>
<td>20 (28.17)</td>
<td>27 (38.0)</td>
<td>20 (28.17)</td>
<td>4 (5.64)</td>
<td>67 (94.36)</td>
<td>0.47</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>CHT</td>
<td>76</td>
<td>26 (34.21)</td>
<td>25 (32.80)</td>
<td>23 (30.26)</td>
<td>2 (2.64)</td>
<td>74 (97.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCM symptom score</td>
<td>CFG</td>
<td>71</td>
<td>21 (29.50)</td>
<td>31 (43.60)</td>
<td>16 (22.50)</td>
<td>3 (4.20)</td>
<td>68 (95.77)</td>
<td>0.77</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>CHT</td>
<td>76</td>
<td>26 (34.2)</td>
<td>28 (36.80)</td>
<td>20 (26.30)</td>
<td>2 (2.60)</td>
<td>74 (97.36)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: total effective rate = clinical cure rate + remarkable effect rate + effective rate. TCM: Traditional Chinese Medicine; CFG: Chinese formula granules; CHT: Chinese herbal tablets; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d. Comparison of total efficacy between the two groups. No difference was observed between the two groups ($P > 0.05$).

Figure 3 Comparison of the scores for TCM and joint symptoms, ESR, and CRP in the two groups after treatment
A: total scores for TCM and joint symptoms; B: the ESR and CRP values. TCM: Traditional Chinese Medicine; CFG: Chinese formula granules; CHT: Chinese herbal tablets; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d. Comparison of the scores for TCM and joint symptoms, ESR, and CRP in the two groups after treatment. No difference was found between the two groups ($P > 0.05$).
observed between the two groups after treatment ($P > 0.05$, Figure 3A, 3B).

Next, the efficacy between the groups in each center was compared. First, in the CQ-TCM center, the total effective rates of the joint symptom score were 96.29% (26/27) and 100% (34/34) in the CFG group and CHT group, respectively. In the TCM-YC center, the rates were 100% (14/14) and 93.33% (14/15). In the TCM-DJ center, the rates were 90.00% (27/30) and 96.29% (26/27). There were no significant differences in any center between the two groups ($P > 0.05$, Table 3). Second, in the CQ-TCM center, the total effective rates for the TCM symptom score were 96.29% (26/27) and 97.06% (33/34). In the TCM-YC center, the total effective rates were 100.00% (14/14) and 93.33% (14/15). In the TCM-DJ center, the total effective rates were 93.33% (28/30) and 100% (27/27). Similarly, no difference was found between the two groups at each center for these scores ($P > 0.05$, Table 3). Finally, the ability to reduce ESR and CRP was consistent between the two groups in each center ($P > 0.05$, Figure 4A, 4C).

Following the analysis of efficacy in different centers, we found that the CFG total effective rates for the joint symptom score were 96.33% (26/27), 100% (14/14), and 90.00% (27/30) in CQ-TCM, TCM-YC, and TCM-DJ centers, respectively. No difference was found among the three centers ($P > 0.05$, Table 4). The CHT effective rates for the joint symptom score were 100% (34/34), 93.33% (14/15), and 96.29% (26/27) in the three centers, and there was no statistical difference among the three centers ($P > 0.05$, Table 4). Second, the total effective rates for the TCM symptom score were 96.29% (26/27), 100.00% (14/14), and 93.33% (28/30) in the CFG group and 97.06% (33/34), 93.33% (14/15), and 100% (27/27) in the CHT group in the three centers. No significant difference was observed among the different centers ($P > 0.05$, Table 5). Last, the ESR and CRP were consistent among the different centers ($P > 0.05$, Figure 4B, 4D).

**Adverse effects**

There were no significant changes in white blood cells, red blood cells, hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, blood urea nitrogen, blood creatinine, routine urinalysis, routine fecal analysis, or electrocardiography before and after treatment in the two groups. In the CFG group, the adverse events included one case of erythema, one case of diarrhea, and one case of nausea. In the CHT group, one case of abdominal distension and one case of nausea were observed. The adverse events in both groups were mild and transient, and the symptoms could be relieved or eliminated without treatment. No patient was withdrawn from the trial due to adverse events. The incidence of adverse events was 4.22% (3/71) and 2.63% (2/76) in the CFG group and CHT group, respectively, and no difference was observed between the two groups ($P > 0.05$).

**DISCUSSION**

Gouty arthritis is the most common inflammatory joint disease and is caused by the deposition of monosodium urate associated with purine metabolic disorders. The main TCM symptom pattern of AGA is the dampness and heat accumulation pattern characterized by joint pain, swelling, redness, and fever. In addition, it is often accompanied by various TCM symptoms,
Participants in the CHT group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Comparison of the ESR and CRP within each center and among different centers after treatment. No difference was found within each center or among different centers.

**Figure 4** Comparison of the ESR and CRP within each center and among different centers after treatment

A, B: the ESR of the CHT or CFG group in each center or different centers, respectively (P > 0.05). C, D: the CRP of the CHT or CFG group in each center or different centers, respectively (P > 0.05). No difference was found within each center or among different centers.

**Table 4** Comparison of the efficacy of the joint symptom score among different centers [n (%)]

<table>
<thead>
<tr>
<th>Item</th>
<th>Center</th>
<th>n</th>
<th>Clinical recovery</th>
<th>Remarkable effect</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective</th>
<th>χ² value</th>
<th>P value</th>
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<td>CQ-TCM</td>
<td>CQ-TCM</td>
<td>27</td>
<td>12 (44.40)</td>
<td>8 (29.62)</td>
<td>6 (22.22)</td>
<td>1 (3.70)</td>
<td>26 (96.33)</td>
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<td>CQ-TCM</td>
<td>TCM-YC</td>
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<td>1 (3.71)</td>
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Notes: total effective rate = clinical cure rate + remarkable effect rate + effective rate. TCM: Traditional Chinese Medicine; CQ-TCM: Chongqing Traditional Chinese Medicine Hospital; TCM-YC: Traditional Chinese Medicine Hospital Yongchuan Chongqing; TCM-DJ: Traditional Chinese Medicine Hospital Dianjiang Chongqing; CFG: Chinese formula granules; CHT: Chinese herbal tablets; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d.

**Table 5** Comparison of efficacy of the TCM symptom score among different centers [n (%)]

<table>
<thead>
<tr>
<th>Item</th>
<th>Center</th>
<th>n</th>
<th>Clinical recovery</th>
<th>Remarkable effect</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective</th>
<th>χ² value</th>
<th>P value</th>
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<tbody>
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<td>7 (25.92)</td>
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<td>1 (3.71)</td>
<td>26 (96.29)</td>
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<tr>
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<td>13 (38.23)</td>
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</table>

Notes: total effective rate = clinical cure rate + remarkable effect rate + effective rate. TCM: Traditional Chinese Medicine; CQ-TCM: Chongqing Traditional Chinese Medicine Hospital; TCM-YC: Traditional Chinese Medicine Hospital Yongchuan Chongqing; TCM-DJ: Traditional Chinese Medicine Hospital Dianjiang Chongqing; CFG: Chinese formula granules; CHT: Chinese herbal tablets; RBX: Rebixiao. Participants in the CFG group received the RBX A (RBX CFG) drug orally three times a day for 7 d. Participants in the CHT group received the RBX B (RBX CHT) drug orally three times a day for 7 d. P: comparison of the total efficacy rates for the TCM symptom score between the two groups in different centers. No difference was found between the two groups (P > 0.05).
such as upset, thirst, and dark urine, and the inflammatory indicators ESR and CRP are also often elevated. Therefore, we selected these as outcome measurements to evaluate the clinical efficacy before and after treatment. Of the several kinds of medicine used to treat AGA, NSAIDs, prednisolone, and colchicine are the main conventional treatments. In China, the TCM treatment of AGA is very popular because of its remarkable efficacy and low rate of side effects, and TCM has been shown to improve the clinical symptoms of AGA by the therapeutic principles of clearing heat and promoting diuresis. In TCM, the main representative formulas are Simiaowan and Sishenjian, which have confirmed efficacy and are widely used to treat AGA. RBX is a Chinese medicine formula that is mainly composed of Sishenjian and Simiaowan, and its efficacy and safety in the treatment of AGA were confirmed in our clinical studies. Therefore, the disease, TCM symptom pattern, Chinese medicine formula, and observation indicators selected in this study are useful to compare the efficacy of CHT and CFG. Many clinical studies have shown that the clinical efficacy of CFG is greater than that of CHT, but many design limitations were found in these clinical studies, including a lack of randomization and double-blinding, their single-center study design, and an absence of standard assessment criteria. In short, there is a lack of sufficient evidence-based guidance. Therefore, we designed a randomized, double-blind, multicenter, controlled trial to obtain more reliable evidence. To reduce the impact of the trial, homogeneous herbal medicines were first evenly decocted to prepare homogeneous test drugs with identical size, color, shape, taste, smell, and packaging. They were assigned to the test center for double-blind testing to improve the comparability between the two dosage forms. Second, the study strictly implemented random selection, and 147 patients completed the clinical observation period among the 165 enrolled. The rate of loss to follow-up was less than 20% and met the requirements of clinical studies. According to the clinical results and number of completed cases, the effectiveness of this study reached 90% for the equivalence test of rate. Finally, this trial was conducted in three centers to avoid bias due to differences between centers, and we also conducted comparisons among the different centers and within each center. Therefore, our research is rigorous, and the results are credible. Although CFG has been used clinically for many years, its efficacy and safety remain controversial. The lack of high-quality evidence-based trials has led to low credibility. Therefore, a randomized, double-blind, multi-center clinical study was performed to provide evidence regarding the clinical effectiveness of CFG. The current study shows that both agents are consistent in effectively ameliorating joint symptoms, TCM symptoms, ESR, and CRP. No differences were found between the two groups after treatment. Furthermore, the results of the joint symptom score, TCM symptom score, ESR, and CRP were consistent within each center and among different centers. In addition, the incidence of adverse events showed no difference between the two groups. However, there may be some possible limitations. The sample sizes of the three centers were largely uneven; therefore, our conclusions do not fully confirm that CFG and CHT are equally effective, and other prescriptions and diseases need to be verified.

ACKNOWLEDGMENTS

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REFERENCES


