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Original Research Article

Efficacy and safety of Huzhang Granule, a compound Chinese herbal medicine, for acute gouty arthritis: A double-blind, randomized controlled trial



Hao Wang^{a,b,1}, Si-ting Chen^{c,1}, Xiao-jie Ding^{a,b}, Le Kuai^{a,b}, Liang Hua^{a,b}, Xin Li^{a,b}, Yi-fei Wang^{a,b}, Ming Zhang^{a,b}, Bin Li^{b,d}, Rui-ping Wang^{d,*}, Mi Zhou^{a,b,*}

^a Department of Dermatology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China

^b Institute of Dermatology, Shanghai Academy of Traditional Chinese Medicine, Shanghai 201203, China

^c Department of Dermatology, the Affiliated Hospital of Jiangxi University of Chinese Medicine, Nanchang 330000, Jiangxi Province, China

^d Institute of Dermatology, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai 200443, China

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ABSTRACT

Background: Acute gouty arthritis (AGA) is an inflammatory joint disease with a high prevalence. Typical medical interventions, including nonsteroidal anti-inflammatory drugs, colchicine and glucocorticoids, can have serious adverse reactions. Huzhang Granule (HZG), a compound Chinese herbal medicine, has been used to treat AGA for more than 30 years with satisfactory effects and no significant adverse reactions. However, the efficacy and safety of HZG in AGA patients remains unknown.

Objective: The present investigation was designed to examine the efficacy and safety profile of HZG in managing AGA patients.

Design, setting, participants and interventions: The current study was conducted as a noninferiority, randomized controlled clinical trial on 180 eligible enrolled participants. Participants were randomly assigned into the HZG and etoricoxib groups. Treatments were administered for 5 d, during which the HZG group received HZG and placebo etoricoxib, while the etoricoxib group received etoricoxib and placebo HZG in the same ratio (1:1).

Main outcome measures: The primary outcome was pain experienced by the patient in the gout-afflicted joint from days 2 to 5 of the treatment window. The pain level was measured via a visual analogue scale, ranging from 0 mm to 100 mm. The secondary outcomes comprised joint tenderness and swelling, reduction of inflammatory biomarkers, and the patient's and investigator's global evaluations of therapeutic response.

Results: The mean reduction in pain was -51.22 mm (95% confidence interval [CI], $[-53.42, -49.03]$ mm) for the HZG and -52.00 mm (95% CI, $[-54.06, -49.94]$ mm) for the etoricoxib groups. The mean difference between the two groups was 0.78 mm (95% CI, $[-2.25, 3.81]$ mm). All additional efficacy endpoints, covering decreased inflammation and pain relief, yielded compelling proof of noninferiority. Patients in the HZG group exhibited a comparatively lower rate of adverse events compared to those in the etoricoxib group (4.44% vs 13.33%; $P \leq 0.05$).

Conclusion: HZG and etoricoxib groups demonstrated similar levels of analgesic effectiveness. The safety and efficacy of HZG indicates that it can be used as a potential therapeutic option for treating AGA.

Trial registration: Chinese Clinical Trial Registry (ChiCTR2000036970).

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* Corresponding authors.

E-mail addresses: w19830901@126.com (R.P. Wang), vieky2866@163.com (M. Zhou).

¹ These authors contribute equally to this work.

1. Introduction

Gout, a pathological condition characterized by crystal-associated joint inflammation, arises from the deposition of monosodium urate within the joint. This deposition is closely linked with hyperuricemia [1]. Acute gouty arthritis (AGA) is a common inflammatory joint disorder, predominantly in males over the age of 40 years [2,3]. Recurrent AGA can progress into chronic gout, resulting in the formation of tophi, joint deformities and gouty nephropathy, and drastically affecting the patients' overall quality of life [4]. The global rate and prevalence of gout are rapidly rising [5]. The worldwide prevalence of gout varies from 0.1% to 10%, with an incidence rate from 0.3 to 6 cases per 1000 person per year [3]. The estimated prevalence of gout in the United Kingdom during 2012 was approximately 2.49%. This estimation was derived from an analysis of the health records of 1.2 million Britons [6]. In the Chinese population, the cumulative incidence of gout among adults was 1.1%, indicating a slight increase from the rate of 0.9% reported between 2000 and 2005 [7]. The annual incidence of hospitalizations due to gout has consistently risen among patients with type 2 diabetes, hypertension, coronary atherosclerotic heart disease, and chronic kidney disease. The rates of re-hospitalization, time duration, and mortality exhibited a substantial increase during the designated follow-up period [8–11].

The main focus in treating AGA is the prompt and lasting relief of pain and return of function [12]. The typical medical intervention includes the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and glucocorticoids within 24 h, and has been observed to yield favorable outcomes in anti-inflammatory analgesia and improvement of patient's quality of life [13,14]. However, these drugs carry a risk of severe adverse reactions and drug interactions, particularly among elderly patients, as well as patients with chronic renal insufficiency or diabetes [15]. The therapeutic efficacy of traditional Chinese medicine (TCM) in the treatment of AGA has been found to be satisfactory. Moreover, the use of TCM to treat and manage AGA results in a reduced incidence of adverse events (AEs) and minimal toxicity [16]. Huzhang Granule (HZG) is an herbal prescription comprising 9 ingredients: *Reynoutria japonica* Houtt., *Notopterygium incisum* Ting ex H.T.Chang, *Angelica sinensis* (Oliv.) Diels, *Artemisia capillaris* Thunb., *Phellodendron amurense* Rupr., *Wolfiporia extensa* (Peck) Ginns, *Atractylodes lancea* DC., *Polyporus umbellatus* (Pers.) Fr., and *Alisma plantago-aquatica* L., certified by the National Pharmacopoeia of China 2020 (Supplementary Table 1). The clinical use of HZG has been reported for more than 30 years, and has shown consistently satisfactory outcomes [17]. Previous investigations have developed quality control parameters, and the constituents present in HZG have been documented using liquid chromatography-mass spectrometry [18]. In clinical practice, HZG effectively reduces the symptoms associated with AGA. In a clinical study of AGA patients, the groups treated with HZG and nimesulide showed comparable response rates of 98.4% and 97.1%, respectively [19]. Previously, the efficacy of HZG for reducing inflammatory factors in AGA rats was shown in preclinical trials [20]. However, the study of TCM for the therapeutic management of gout is not without its challenges. These challenges represent limitations in sample size, the absence of widely accepted criteria for evaluating efficacy, and the failure to implement adequate blinding strategies. To investigate the possible therapeutic effects of HZG on pain and inflammation related to AGA, we conducted a randomized clinical trial that evaluated the efficacy and safety of HZG in AGA patients.

2. Materials and methods

2.1. Study design

This study was a randomized, double-blind, double-dummy controlled trial conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine from April 28, 2021 to July 27, 2022. The investigators and sponsor were blinded throughout the study period. The hospital's ethics committee approved the study protocol (2020-123). This trial was prospectively registered with the Chinese Clinical Trial Registry under the registration number ChiCTR2000036970. Informed consent was acquired from all participants before they participated in the study. Reporting of this study strictly follows the guidelines mentioned in the Consolidated Standards of Reporting Trials [21]. The Reporting Standard for Clinical Randomized Controlled Trials of Chinese Medicine Compounds (2017 edition) was also followed.

2.2. Participants

Patients with AGA were enrolled between April 28, 2021 and July 27, 2022, and underwent screening at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. Before the commencement of the study, all participants formally granted written consent. Patients were selected based on the following inclusion criteria: (1) the diagnosis of AGA was determined via gout classification standards established by the American College of Rheumatology/European League Against Rheumatism in 2015 [22]; (2) the study included males or non-pregnant, non-nursing females between the ages of 18 and 70; (3) participants were required to have experienced a gout attack \leq 48 h before the observation. During the week leading up to the observation, participants were instructed to refrain from NSAIDs, analgesic drugs, and drugs that affect uric acid metabolism. The exclusion criteria were defined as follows: (1) patients with uncontrolled concomitant cardiovascular, neurological, hepatic or gastrointestinal disease were only eligible after consultation and agreement with their treating medical team; (2) patients in critical condition that would hinder the clinical observations were omitted; (3) patients with advanced arthritis characterized by severe deformity, stiffness and labor loss were excluded; (4) patients with known drug allergies were also excluded.

2.3. Intervention and comparison

Patients were screened and subsequently randomized on day 1, based on a computer-generated allocation schedule provided by the sponsor (the Data Management Center of Jiangsu Famaisheng Medical Technology). The patients were randomly assigned in a 1:1 ratio to either the HZG or the etoricoxib group and received daily treatment for five days. Each patient was given a pack of HZG or HZG placebo twice daily: one in the morning and one in the evening, approximately 30 min after the meal. Each patient also received a single daily dose of etoricoxib 60 mg or matching etoricoxib placebo. Participants in the HZG group were given HZG and etoricoxib placebo. Participants in the etoricoxib group were given etoricoxib and HZG placebo. HZG and its placebo were provided by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd. HZG was administered as TCM formula granules, and the specific composition of HZG is shown in Supplementary Table 1. HZG placebo was composed of 10% HZG, flavoring agent, dextrin and edible pigment. Etoricoxib tablets were manufactured by Merck East Co., Ltd., contained 60 mg of active ingredient per tablet

(batch No. S041084). The etoricoxib placebo was produced by Nanjing Hengzheng Pharmaceutical Research Institute Co., Ltd.

The study commenced by taking a comprehensive medical history and physical examination of the patient. Baseline laboratory tests were conducted, including complete blood cell count, hepatic and renal functions, inflammatory factors, urinalysis, and electrocardiogram. The patient's pain evaluation and the investigator's observation of swelling, tenderness and erythema were also documented.

The pain assessments were conducted daily for all patients, and patients visited the clinic on days 3 and 5 for examination by the investigator. A post-study visit was scheduled 7 days after the final dose to assess the patient's condition. AEs were also observed and recorded.

2.4. Randomization and masking

After confirming eligibility and obtaining consent, the participants were independently assigned to study groups via a nonstratified permuted block design with varying lengths ($n = 6$ blocks; patient distribution = 1:1). Randomization was done via an internet-based randomization system. The randomization codes were disseminated via a data network platform developed by the Data Management Center of Jiangsu Famaisheng Medical Technology. The packaging and distribution of the test and control drugs were carried out by an independent entity not associated with this trial, under the guidance of the statistician. The authorized personnel accessed the online randomization system interface to verify patient eligibility, and the randomized group allocation was forwarded to the pharmacy. The randomization code was unsealed, and a physician or nurse responsible for the patient's care (outside the study) expressed concerns regarding serious AEs.

2.5. Outcome measurements

The main outcome was the evaluation of joint pain experienced by the patients during 2–5 d following the treatment. The pain was monitored using a visual analogue scale (VAS), from 0 mm (complete absence of pain) to 100 mm (representing the most intense pain ever reported by the patient) [23].

The secondary outcomes comprised the investigator's assessment of tenderness and swelling of the joint, the presence or absence of erythema at baseline and clinic visits, the patient's global examination of response to therapy, the investigator's global evaluation of response to therapy, and the measurement of inflammatory factors in patients on day 5 of treatment. The assessments of response to therapy by both the patient and the investigator, using a scale ranging from 0 (good) to 4 (poor), were performed on days 3 and 5. The joint tenderness and edema were each evaluated using 3-point Likert scales. The investigator evaluated joint tenderness and swelling during the patients' clinic visits. The joint tenderness scale extended from 0, with no pain, to 3, where the patient reported pain with a wincing reaction in response to touch and involuntary withdrawal. The swelling scale extended from 0, with no swelling to 3, with swelling extending beyond the joint boundaries.

2.6. Safety assessment

Safety was assessed throughout the treatment. Physical examinations evaluated vital signs. Samples were collected to perform laboratory tests, including a complete blood count, blood chemistry, and urinalysis at the beginning of the study (baseline) and during follow-up visits. Prespecified AEs refer to any harmful or negative events associated with medication during treatment. These events may include any undesirable symptoms, side effects, complications or reactions that arise as a result of the treatment.

Participants were instructed to promptly report any AEs throughout the course of the study. They were encouraged to seek information regarding AEs during office visits on days 3, 5 and 12. Researchers evaluated the strength, severity, and correlation with the study drug of all AEs while maintaining a state of blindness regarding the treatment administration.

2.7. Statistical analysis

Based on the patient's evaluation of joint pain, we hypothesized that HZG would exhibit a clinical effect comparable to etoricoxib. We focused on the mean change in joint pain from baseline to days 2 and 5, which served as the primary outcome. We aimed to establish a noninferior trial design by ensuring the 95% confidence interval (CI) of the disparity in analgesic effect (pain change) between the two groups within the predetermined clinically significant range of at least -13 mm on a 100-mm VAS. This noninferiority threshold was selected based on previous studies indicating a clinically important disparity in pain scores exceeding 13 mm on a 100-mm VAS [24]. The study population comprised 150 patients, with 75 assigned to each group. The sample size was based on a binary equivalence boundary greater than 13 mm (yes) compared to less than or equal to 13 mm (no). A two-sided significance level of 2.5% was chosen, with a power of 80% and a success rate of 85%. To manage a projected dropout rate of 20%, the aim was to recruit an additional 15 patients per experimental group, resulting in a total patient population of 180, with 90 patients per group. Assuming a continuous resection margin of 13 mm with a standard deviation of 20 mm, a sample size of 100 patients (50 in each group) would yield a statistical power of at least 80% to detect a significant change. The sample size was calculated using PASS15.0 software (LLC, Kaysville, Utah, USA).

The primary and secondary outcomes were assessed using the intention-to-treat (ITT) approach, including all patients who received treatment and had baseline measurements and recorded at least one measurement during the treatment period. A per-protocol analysis was conducted to provide further evidence for the primary approach. The average responses were based on the data, and the last value carried forward method was employed for longitudinal graphs. The ITT approach, which included all patients who were treated and randomly assigned, was employed as the primary and exclusive strategy for analyzing safety endpoints. Rules for inclusion were not applied to patients during the safety analysis.

Data are represented as mean \pm standard deviation or as medians and interquartile ranges for quantitative variables. We employed frequency and proportion (rate) as statistical measures to characterize qualitative variables. The analysis of continuous efficacy variables was carried out with a covariance model that incorporated treatment and baseline response factors. We used Fisher's exact test and Wilson's score method to compare proportions. These analyses comprised the evaluation of prespecified AEs. The continuous outcomes were analyzed using a two-sample *t*-test. The findings were reported as the *P* value and 95% CI. The statistical analysis was conducted using SAS 9.4 software (SAS 9.4, SAS Institute, Cary, North Carolina, USA). A two-tailed *P* value of less than 0.05 was used as the threshold for statistical significance.

3. Results

3.1. Patient characteristics

From 28 April 2021 to 27 July 2022, 185 patients were screened. Following the exclusion of 5 patients, the intention-to-treat

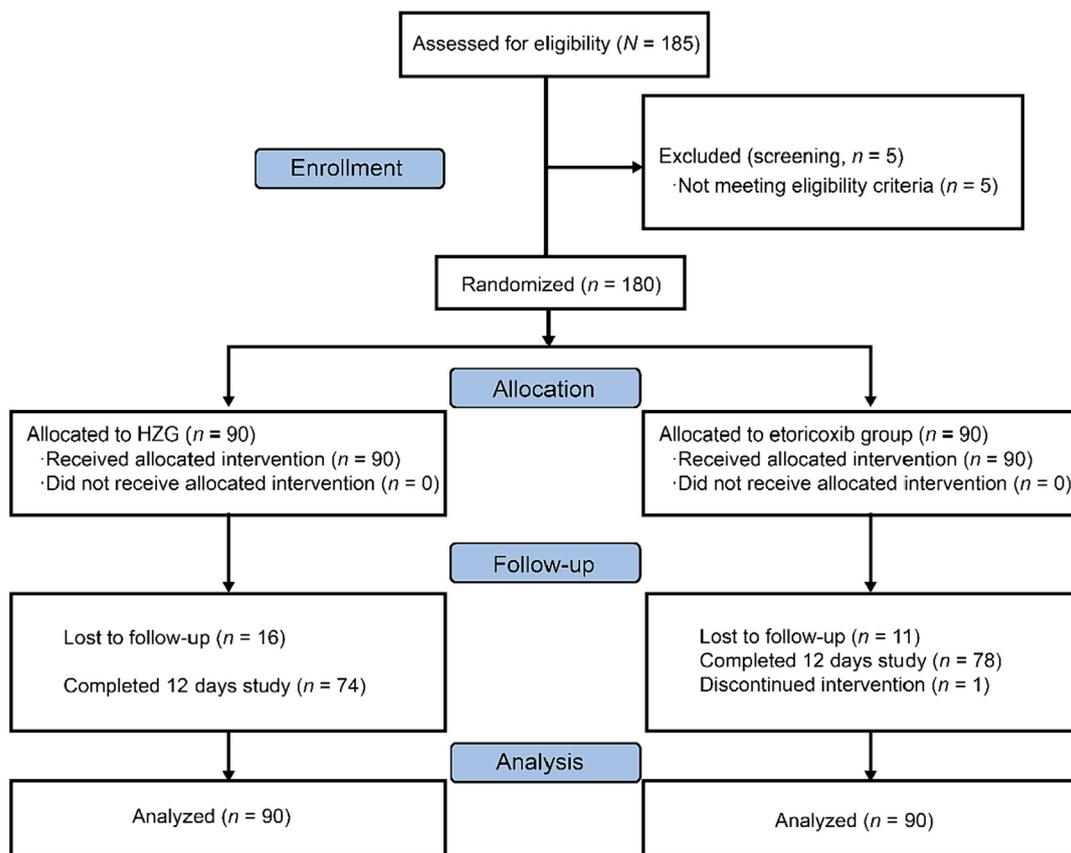


Fig. 1. Study flow diagram. HZG: Huzhang Granule.

analysis comprised 180 patients with AGA (90 in the HZG and 90 in the etoricoxib groups). In this study, 28 patients (15.56%) discontinued their participation. Of these, 16 patients belonged to the HZG group, while 12 patients were from the etoricoxib group (Fig. 1). The baseline characteristics of the patients are presented in Table 1. There were no statistically significant differences in demographic characteristics between the HZG and the etoricoxib groups.

The study participants mainly consisted of males, with a mean age of 53.37 years. Hypertension was the most common comorbidity, with a prevalence rate of 41.67%. Some patients disclosed a medical history of fatty liver (9.44%) or hyperlipidemia (6.11%). Most patients (97.22%) exhibited a history of gout, while a smaller proportion (34.44%) reported a familial predisposition. In the HZG group, 54.44% of patients showed first metatarsophalangeal joint involvement, while in the etoricoxib group this was 50.0% of patients.

3.2. Primary outcome

Fig. 2 depicts the alterations in pain scores between days 2 and 5. The average reduction in pain score was found to be -51.22 mm (95% CI $[-53.42, -49.03]$ mm) for the HZG group and -52.00 mm (95% CI $[-54.06, -49.94]$ mm) for the etoricoxib group. The mean difference was 0.78 mm (95% CI $[-2.25, -3.81]$ mm). No statistically or clinically significant differences were observed between the groups ($P = 0.5772$). During the duration of the study, there was minimal variation in the average pain scores across all experimental groups. In accordance with the noninferiority trial design, the 95% CI related to the disparity in analgesic efficacy declined below -13 mm. During this study, both HZG and etoricoxib lead

to comparable and clinically significant decreases in mean pain scores.

3.3. Secondary outcomes

The efficacy of HZG was comparable to that of etoricoxib across various secondary efficacy endpoints, such as global assessments of response to treatment, joint tenderness, and swelling (Table 2), as well as the levels of inflammatory factors and erythema. There were no cases of treatment discontinuation due to lack of efficacy in either group. Erythema in the affected joint was found to be substantial in both the HZG and etoricoxib groups, with proportions of 93.33% and 94.44%, respectively. In every stage of treatment, these proportions exhibited a similar decline, reaching 8.89% for HZG and 10.0% for etoricoxib by day 5. The observed dissimilarities among the treatments were consistent across all assessed time points (data not shown).

The treatment response evaluations by the patients and investigators were consistent with the primary outcome, confirming the result. The comparison of the patient’s global assessment of treatment response between HZG (0.46, 95% CI $[0.33, 0.58]$) and etoricoxib (0.49, 95% CI $[0.37, 0.61]$) groups over the treatment period (3–5 days) showed a difference of -0.17 , which was not significant (95% CI $[-0.51, 0.16]$, $P = 0.2486$, Table 2). The comparison of the investigator’s global assessment of treatment response between HZG (0.24, 95% CI $[0.15, 0.34]$) and etoricoxib (0.36, 95% CI $[0.26, 0.45]$) groups over the treatment period also showed a non-significant difference of -0.01 (95% CI $[-0.24, 0.22]$, $P = 0.9165$, Table 2). The treatment effect scores showed a consistent improvement in both groups over the 5-day treatment period (Fig. 3). There was significant decrease in levels of inflammatory in both groups

Table 1
Patient demographics and baseline characteristics.

Characteristic	HZG (n = 90)	Etoricoxib (n = 90)	Total (N = 180)
Gender (n, %)			
Male	87 (96.67%)	88 (97.78%)	175 (97.22%)
Female	3 (3.33%)	2 (2.22%)	5 (2.78%)
Age (mean ± SD, year)	53.41 ± 13.33	53.33 ± 12.61	53.37 ± 12.94
Race (n, %)			
Han	90 (100%)	90 (100%)	180 (100%)
Minorities	0	0	0
BMI* (mean ± SD)	26.04 ± 2.45	26.37 ± 3.31	26.21 ± 2.91
Types of comorbidities (n, %)			
Hypertension	40 (44.44%)	35 (38.89%)	75 (41.67%)
Fatty liver	8 (8.89%)	9 (10.00%)	17 (9.44%)
Hyperlipidemia	6 (6.67%)	5 (5.56%)	11 (6.11%)
Diabetes	5 (5.56%)	3 (3.33%)	8 (4.44%)
Disease classification (n, %)			
Monoarticular	87 (96.67%)	88 (97.78%)	175 (97.22%)
Polyarticular	3 (3.33%)	2 (2.22%)	5 (2.78%)
Primary joint affected (n, %)			
First metatarsophalangeal joint	49 (54.44%)	45 (50.00%)	94 (52.22%)
Ankle	14 (15.56%)	18 (20.00%)	32 (17.78%)
Knee	9 (10.00%)	11 (12.22%)	20 (11.11%)
Articulaciones digitorum manus	5 (5.56%)	5 (5.56%)	10 (5.56%)
Other	16 (17.78%)	14 (7.16%)	30 (16.67%)
Time of seizure (mean ± SD, h)	23.07 ± 8.08	22.70 ± 7.36	22.88 ± 7.71
Predisposing factors (n, %)			
High-purine diet	37 (41.11%)	38 (42.22%)	75 (41.67%)
Fatigue	34 (37.78%)	34 (37.78%)	68 (37.78%)
Alcohol drinking	19 (21.11%)	22 (24.44%)	41 (22.78%)
Strenuous exercise	14 (15.56%)	10 (11.11%)	24 (13.33%)
Catching cold	11 (12.22%)	11 (12.22%)	22 (12.22%)
Eating carbohydrates	1 (1.11%)	4 (4.44%)	5 (2.78%)
Trauma and infection	3 (3.33%)	1 (1.11%)	4 (2.22%)
Medicine	0 (0)	2 (2.22%)	2 (1.11%)
Recurrent gout, (n, %)	87 (96.67%)	88 (97.78%)	175 (97.22%)
Attacks per year (mean ± SD)	2.54 ± 3.15	2.30 ± 1.35	2.42 ± 2.41
Family history of gout (n, %)	32 (35.56%)	30 (33.33%)	62 (34.44%)
Smoking history (n, %)	42 (46.67%)	45 (50.00%)	87 (48.33%)
Drinking history (n, %)	26 (28.89%)	28 (31.11%)	54 (30.00%)

BMI: body mass index; HZG: Huzhang Granule; SD: standard deviation. Values in the table are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding. *BMI was calculated as weight in kilograms divided by height in meters squared.

following the initiation of treatment, with a comparable reduction in both groups. C-reactive protein (CRP) changed from baseline to day 5 by -7.45 mg/L (95% CI $[-10.61, -4.29]$ mg/L) in the HZG group and -10.33 mg/L (95% CI $[-15.65, -5.01]$ mg/L) in the etori-

coxib group (group difference: -4.99 mg/L, 95% CI $[-8.69, -1.28]$ mg/L). The concentrations of interleukin (IL)-1 β , IL-6 and IL-8 also decreased significantly in both groups after the intervention. There were no significant differences in the levels of inflammatory factors between groups (Fig. 4).

3.4. Safety

3.4.1. Prespecified AEs

Adverse effects were observed in 4.44% of participants in the HZG and 13.33% in the etoricoxib groups ($P = 0.0361$; Table 3). The incidence of drug-related clinical AEs was investigated and found to be 3.33% in the HZG group and 10.0% in the etoricoxib group ($P = 0.0730$). The HZG group had four AE cases, comprising 1 case of abdominal pain, 1 of vomiting, 1 of nausea, and 1 of headache. The etoricoxib group had 12 cases of AE, including 2 cases of chest tightness, 1 case of stomach pain, 1 case of abdominal pain, 2 cases of abdominal distension, 2 cases of diarrhea, 1 case of elevated blood pressure, 1 case of compromised liver function, 1 case of lower limb edema, and 1 case of headache. All AEs were observed at a mild level. A single patient in the etoricoxib group voluntarily discontinued their involvement in the study due to abdominal discomfort. The clinical trial did not observe any significant AEs. No undesirable cardiovascular events were observed during the treatment in either study group.

3.4.2. Other safety indicators

There were no statistically significant alterations in body temperature, respiration, pulse rate, systolic and diastolic blood pressure, and other vital signs, when comparing the pre-treatment and post-treatment measurements. The biochemical indicators, including alanine transaminase, aspartate transaminase, blood urea nitrogen, serum creatinine and blood uric acid, also exhibited no significant differences over the course of the treatment ($P \geq 0.05$; Fig. 5).

4. Discussion

Previous investigations have demonstrated that selective cyclooxygenase-2 (COX-2) inhibitors have comparable efficacy to non-selective NSAIDs in acute pain management. We have evaluated the effectiveness of etoricoxib, a specific inhibitor of COX-2, compared to indomethacin, the established standard treatment for acute gout [25,26]. Ethical concerns blocked placebo-controlled trials, thus, etomoxir was selected as the control drug in the current study. In the findings, oral HZG exhibited comparable efficacy to etoricoxib for managing pain among patients with AGA. The study participants did not report any significant AEs.

TCM has been used successfully as a therapeutic approach for managing gout over an extended period of time. The primary treat-

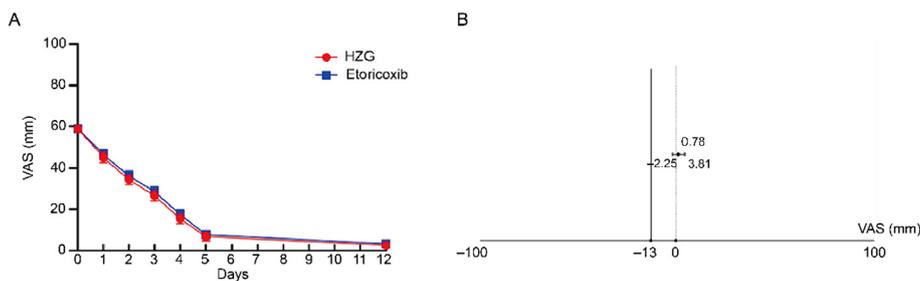


Fig. 2. Mean pain score and 95% CI at each assessment (N = 180). The means and 95% CIs of the coefficients (slopes) of change in pain over unit time for patients in each group were compared using the paired student's *t*-test. Pain scores were from days 1 to 5, and day 12. The mean decrease in pain score was -51.22 mm (95% CI, $[-53.42, -49.03]$ mm) for HZG and -52.00 mm (95% CI, $[-54.06, -49.94]$ mm) for etoricoxib (mean difference, 0.78 mm [95% CI, $[-2.25, 3.81]$ mm). The 95% CI of the difference in analgesic effect was not less than -13 mm. According to the noninferiority trial design, the result was within the prespecified clinically relevant range. CI: confidence interval; HZG: Huzhang Granule; VAS: visual analogue scale.

Table 2
Summary of secondary outcomes for days 1 to 5.

Secondary outcomes	Baseline (mean)	Treatment period (mean)	Least squares mean change from baseline (95% CI)	Least squares mean difference from etoricoxib (95% CI) ^{**}
Tenderness of study joint (0–3 scale)^{*#}				
HZG (n = 90)	1.83	0.26	–1.59 [–1.69, –1.49]	0.10 [–0.05, 0.25]
Etoricoxib (n = 90)	1.87	0.36	–1.50 [–1.60, –1.40]	NA
Swelling of study joint (0–3 scale)^{*△}				
HZG (n = 90)	1.54	0.18	–1.39 [–1.47, –1.31]	0.00 [0.12, 0.12]
Etoricoxib (n = 90)	1.60	0.18	–1.40 [–1.48, –1.32]	NA
Patients' global assessment of response to treatment (0–4 Likert scale)[□]				
HZG (n = 90)	NA	3.44	0.46 [0.33, 0.58]	–0.17 [–0.51, 0.16]
Etoricoxib (n = 90)	NA	3.27	0.49 [0.37, 0.61]	NA
Investigators' global assessment of response to treatment (0–4 Likert scale)[■]				
HZG (n = 90)	NA	4.06	0.24 [0.15, 0.34]	–0.01 [–0.24, 0.22]
Etoricoxib (n = 90)	NA	4.04	0.36 [0.26, 0.45]	NA

^{*} All investigator assessments during the study were performed by the same physician for a given patient. ^{**} Patient and investigator global assessments of response to treatment are least squares mean treatment values. [#]0: no pain; 1: patient states that there is pain; 2: patient states that there is pain and winces; 3: patient states that there is pain, winces and withdraws. [△]0: none; 1: palpable; 2: visible; 3: bulging beyond joint margins. [□]4: poor; 3: fair; 2: good; 1: very good; 0: excellent. [■]4: none (no response, absence of drug effect); 3: poor (minimal response, unacceptable); 2: definite response, but could be better; 1: good (good response, but less than best possible anticipated result); 0: excellent (best possible anticipated response, considering severity of gout attack). CI: confidence interval; HZG: Huzhang Granule; NA: not applicable.

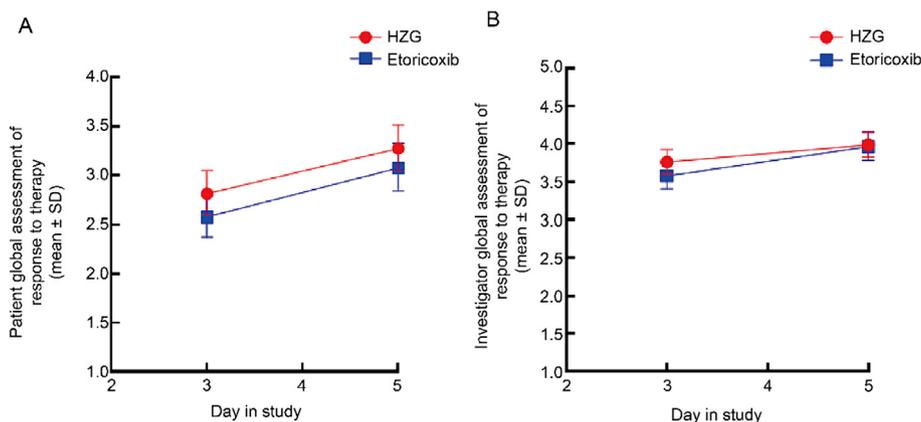


Fig. 3. Patient's (A) and investigator's (B) global assessments of response to therapy. Global assessments were made during clinic visits on days 3 and 5, with the use of a 0–4-point Likert scale. The patient's and investigator's global assessments of response to therapy were secondary efficacy outcomes throughout the treatment period. HZG: Huzhang Granule; SD: standard deviation.

ment modalities in TCM for AGA involve heat clearance and dehumidification, as well as the enhancement of blood circulation and the removal of blood stasis [16]. HZG has the actions of clearing heat, removing dampness and dredging collaterals. Our previous in vitro results revealed that HZG could downregulate IL-1 β , TNF- α and IL-6 to some extent by inhibiting the cysteine-rich 61 expression [27]. However, few clinical trials have been conducted to investigate the efficacy of TCM in the treatment of acute gout. These trials have included a small sample size of patients, thereby offering only preliminary indications of the effectiveness of different interventions.

The present study, characterized by its strong design, represents one of the most extensive controlled trials reported thus far studying TCM interventions for acute gout. The patient selection necessitates a set of well-defined diagnostic criteria for gout attacks. Patients were enrolled within 48 h from the initial onset of the episode. The patients with a mean age of 53 years were more susceptible to developing gastrointestinal complications associated with NSAIDs [28]. In this research, the prevalence of smoking in the patient was 48.33%, and the intake of alcohol was reported in 70.0%. Also, 41.67% of the patients were diagnosed with hypertension, while 34.44% displayed a familial susceptibility to gout. These results were in line with the epidemiological attributes of gout,

indicating that smoking, alcohol consumption, hypertension and familial inheritance participated as risk factors in the onset of gout [29–31]. In our study the first metatarsophalangeal joint was the most common site for symptoms of gout, comprising 52.22% of the cases. This was followed by distal joints, including the ankle (17.78%) and knee (11.11%). These observations may be due to lower temperature in distal joints, differential monosodium urate crystals deposition, and the foot's vulnerability to trauma. The most common factor contributing to the onset of acute gout attacks was diet, accounting for 41.67% of cases. Other commonly observed triggers included fatigue (37.78%), alcohol consumption (22.78%), intense physical exercise (13.33%) and exposure to cold temperatures (12.22%). In light of the self-limiting aspect of acute gout, the research strategy was designed to ensure that efficacy was evaluated within the initial days of the gout attack. The primary evaluation of efficacy was conducted between days 2 and 5, with a follow-up examination on day 12. Previous research on acute gout has relied on endpoint measurements [32]. This study evaluated the effectiveness of HZG in treating the diverse clinical manifestations of AGA. This evaluation included the assessment of pain and inflammation, as well as the measurement of inflammatory factors. The analgesic efficacy of etoricoxib was observed to be fast and long-lasting [33]. The pain reductions reported with

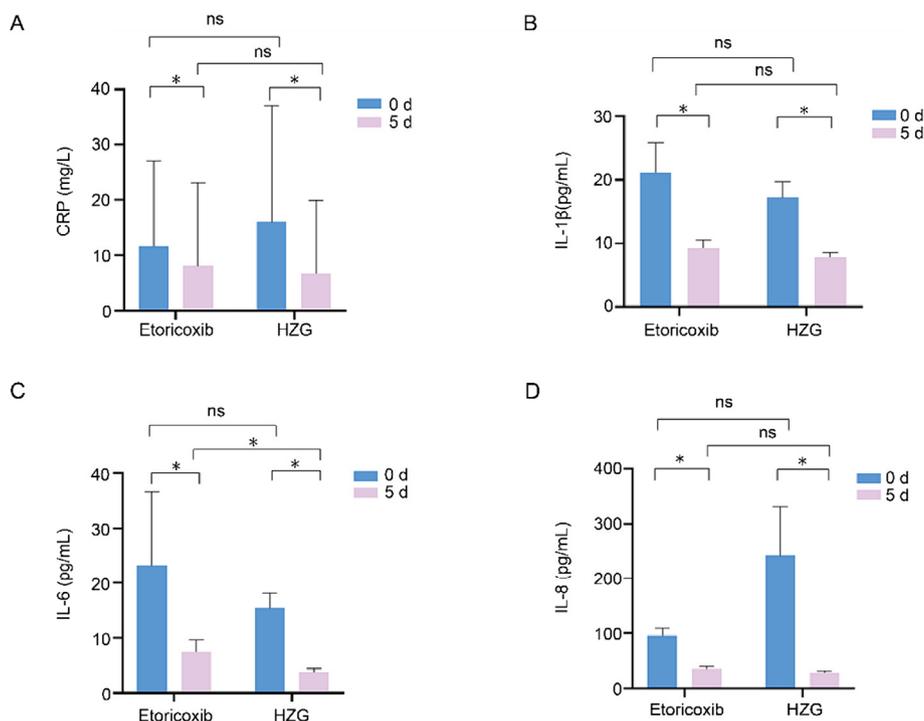


Fig. 4. The expression of CRP, IL-1β, IL-6 and IL-8 in the two groups before and after treatment. These inflammatory factors were significantly decreased after treatment in both groups ($P < 0.05$). CRP: C-reactive protein; HZG: Huzhang Granule; IL: interleukin; ns: not significant.

Table 3
Analysis of prespecified adverse experiences.

Type of adverse experience	HZG (n = 90)	Etoricoxib (n = 90)	P value*
Clinical adverse experience (n, %)	4 (4.44)	12 (13.33)	0.0361
Drug-related clinical adverse experience** (n, %)	3 (3.33)	9 (10)	0.0730
Serious clinical adverse experience (n, %)	0	0	1.000
Discontinued owing to clinical adverse experience (n, %)	0	1 (1.11)	0.3160

* P values were determined by Chi-Square test. **Determined by the investigator to be possibly, probably or definitely drug-related. HZG: Huzhang Granule.

HZG were found to be similar to those observed with etoricoxib. In the current study, HZG exhibited similar time to onset and duration of pain alleviation to etoricoxib administered at 60 mg once a day, as assessed by several measures. The study found that HZG and etoricoxib had similar improvements in levels of inflammation commonly associated with AGA, such as edema and discomfort in the affected joint. Also, both HZG and etoricoxib can decrease the levels of CRP, IL-1β, IL-6 and IL-8.

In this study, both HZG and etoricoxib demonstrated satisfactory safety profiles and were well tolerated by the study participants. Notably, patients taking HZG exhibited fewer AEs that were determined by the investigator to be associated with the drug. The most common AEs reported by patients treated with HZG were gastrointestinal symptoms. In patients receiving etoricoxib treatment, the observed AEs comprised chest tightness, increased blood pressure, edema in the lower limbs, compromised hepatic function, and gastrointestinal symptoms. All patients exhibited complete recovery from the minor AEs experienced during the treatment period, and no participants experienced significant AEs. The present investigation was deemed insufficient in size to conduct a comprehensive assessment of safety measures.

Further investigations are needed to establish conclusive findings regarding the safety of HZG.

The study recruited a patient population that needed therapeutic intervention for AGA. This population was primarily composed of males, with most patients exhibiting clinical symptoms consistent with monoarticular gout and having experienced two or more prior gout attacks. Moreover, the patients exhibited significant levels of pain and inflammation during their initial evaluation. This study also had a few limitations. Initially, the diagnosis of gout was determined via clinical criteria, and the participation of patients without gout is possible, if unlikely. Additionally, the present investigation was conducted as a single-center trial, potentially compromising the objectivity of the outcomes compared to a multicenter study.

Collectively, HZG treatment demonstrated similar efficacy to that of etoricoxib at a daily dose of 60 mg in patients presenting with an acute gout attack. In this study, HZG exhibited a favorable safety profile and was well tolerated by the patients. Also, a reduced rate of AEs related to the intervention was noted. NSAIDs and colchicine have long been established as the primary therapeutic interventions for managing acute gout. Limitations in using these substances exist in the elderly population and patients with comorbidities, including renal insufficiency or gastrointestinal disorders, due to the possibility of facing unfavorable consequences. This study presents compelling evidence promoting the efficacy of HZG as a viable alternative therapeutic intervention for treating acute gout.

5. Conclusion

We have observed that the TCM formula HZG exhibits comparable efficacy to etoricoxib in treating AGA. Thus, it is evident that HZG exhibits potential as a viable therapeutic option for managing AGA. However, further investigation is needed to confirm the findings of this study by an effective research study including a larger population of patients.

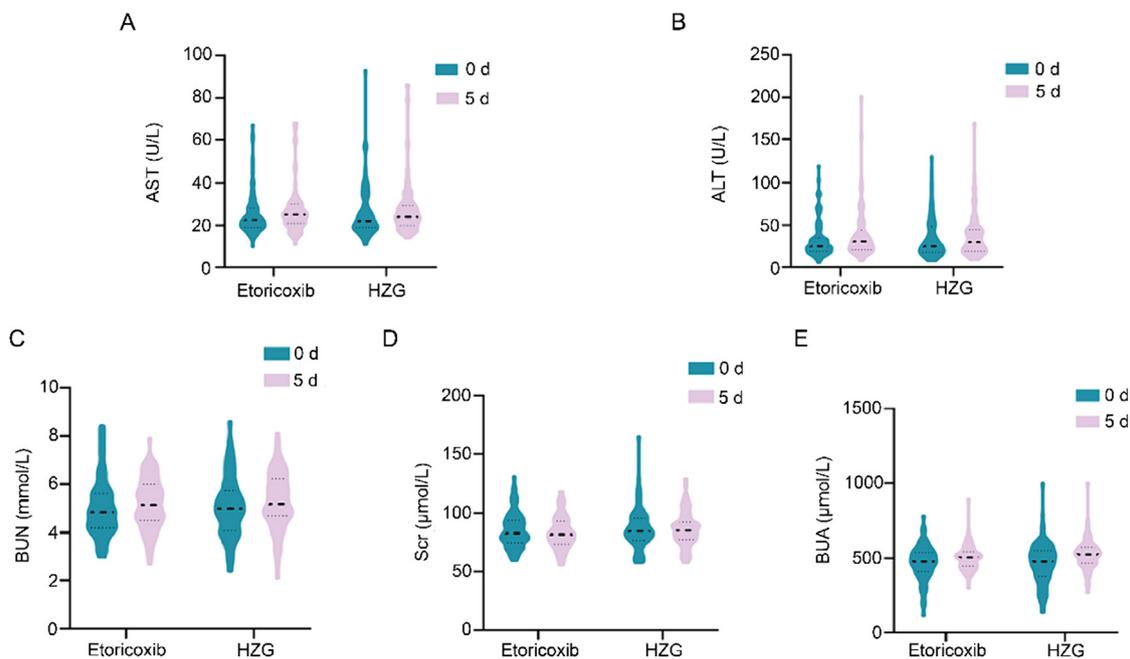


Fig. 5. The expression of AST, ALT, BUN, Scr and BUA in the two groups before and after treatment. There were no significant differences between the two groups ($P > 0.05$). ALT: alanine transaminase; AST: aspartate transaminase; BUA: blood uric acid; BUN: blood urea nitrogen; HZG: Huzhang Granule; Scr: serum creatinine.

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Authors' contributions

MZ and RPW conceived and designed the study; XJD, STC, HW, LK and LH recruited and followed up the patients; RPW and STC analysed and interpreted the data; MZ, BL and YFW were responsible for study monitoring; RPW and XL accessed and were responsible for the raw data associated with the study, and RPW was responsible for data verification; RPW and STC performed the statistical analysis; XJD, HW, STC and MZ drafted the manuscript; XL, BL and MZ critically revised the important intellectual content of

the manuscript. All the authors had full access to the data in this study, gave final approval to the manuscript, and agreed to be responsible for all aspects of the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.joim.2024.03.008>.

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