Oral Huzhang Granules For the Treatment of Acute Gouty Arthritis: Protocol For a Double-blind, Randomized, Controlled Trial

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Study protocol

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Abstract

Background: Acute gouty arthritis (GA) is the main clinical manifestation and the most common initial symptom of gout. The treatment of acute GA involves the use of colchicine, non-steroidal anti-inflammatory drugs, and corticosteroids. Because of the side effects of these drugs, their clinical application is limited.The use oftraditional Chinese medicine for the treatment of acute GA is associated with unique advantages.The aim of this trial is to clarify the treatment efficacy, safety, and recurrence control efficacy of Huzhang granules (HZGs) in patients with GA showing dampness-heat syndrome.

Methods/design: This double-blind, randomized, controlled trial was planned to be conducted between July 1, 2020 and December 31, 2022. A sample size of 267 participants (89 per group) with GA will be randomly assigned to three treatment groups in the ratio of 1:1:1: HZG, Etoricoxib, and placebo groups.The study duration will be 13 days, including a one-day screening period, 5-day intervention period, and one-week follow-up period. The primary outcome is analgesic effectiveness, assessed as pain in the worst affected joint, which was measured using the visual analogue scale. Secondary outcomes include the patient's assessment of pain in the primary study joint, patient's global assessment of response to therapy, investigator's global assessment of response to therapy, investigator's assessment of tenderness and swelling of the study joint, and TCM syndromes. Furthermore, the number, nature, and severity of adverse events will be carefully recorded.

Discussion: This study will provide an evidence regarding the clinical efficacy and safety of a Chinese medicine treatment for acute gouty arthritis. The results are worth anticipating.

Trial registration: ClinicalStrials. GovID:NCT04462666, Registered on July 05, 2020(first version).

Background

Gout is a recurrent chronic inflammatory disease caused by monosodium urate (MSU) crystals(1).Acute gouty arthritis (GA) is the most common first symptom of gout. With the progression of the disease, the frequency of acute attacks increases, and joint destruction may occur(2, 3).The pooled prevalence from 2000 to 2014 of hyperuricemia in China was about 13.3%, and the pooled prevalence of gout was 1.1% Repeated attacks of GA seriously affect the quality of life, resulting in huge economic costs and mental stress(4).Because of inadequate prevention and treatment, healing gout is often an unachieved goal(5–7).

Acute GA is the main reason for patients with gout to see a doctor. The main pathological change is the acute inflammation of the joint and its surrounding tissues caused by the precipitation of MSU crystal(8). The treatment of acute GA involves the use of colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or a combination of any two agents among these(9). For severe refractory GA, anti-tumor necrosis factor-α or anti-interleukin-1β monoclonal antibodies can be used(10, 11). However, these agents are associated with severe potential adverse effects (AEs) and risk of drug–drug interactions, especially for elderly patients and those with chronic renal insufficiency or diabetes(12).In addition to these conventional treatments, traditional Chinese medicine (TCM) has attracted abundant attention because of its efficacy and low incidence ratesof side effects(13, 14).

The use of TCM for the treatment of GA has been associated with satisfactory therapeutic effect with less AEs and minimal toxicity(15).In TCM, GA belongs to the category of Bi pattern, and the primary cause is the invasion of wind, cold, dampness, heat, or other pathogenic factors.Among these factors, dampness and heat are the most common external causes of GA.The main TCM treatment for GA includes clearing heat and removing dampness, as well as promoting blood circulation and removing blood stasis(15). The modified Simiao decoction has been proven to be effective in the treatment of GA by eliciting anti-inflammation and lowering urate levels(16).

Huzhang granule (HZG), a Chinese herbal prescription, is a compound preparation with twelve ingredients (*Polygonum cuspidatum, Notopterygium, Angelicaepubescentis, Angelica, Ligusticumwallichii, Rhizomaatractylodis, Cortex phellodendri,Bidentate achyranthes, Capillary wormwood, Stephania tetrandra, Tuckahoe*, and*Cynanchumpaniculatum*) (Table 1). The predecessor of HZG is the HuzhangTongfeng Decoction, which was formulated in the 1980s by Xia Han (a well-known Chinese surgeon) and has been used in the clinical treatment of gout for over 30 years at the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated to Shanghai University of TCM. According to the syndrome differentiation approach in TCM, there are four syndromes of GA: wind-dampness-heat, damp-turbidity, blockage of phlegm and blood stasis, andchronic obstruction owing to deficiency. These four syndrome types correspond to the four stages of GA: acute stage, remission stage, chronic stage, and later stage. The method of clearing heat, removing dampness, and dredging collaterals is generally used for the treatment of acute GA(16, 17). HZG is composed on the basis of this method.

Table 1
Ingredients of HuzhangTongfeng granules (intervention drug) with English translations

Main composition	Latin scientific name	Plant part	Amount (g)
Polygonum cuspidatum	*Reynoutria japonica Houtt.*	rhizome	15
Notopterygium	*Notopterygiumincisum Ting ex H. T. Chang*	rhizome	9
Angelicaepubescentis	*Heracleum hemsleyanum Diels*	rhizome	9
Angelica	*Angelica sinensis (Oliv.) Diels*	root	12
Ligusticumwallichii	*Ligusticum chuanxiong Hort.*	rhizome	10
Rhizomaatractylodis	*Atractylodes Lancea (Thunb.) DC.*	rhizome	12
Cortex phellodendri	*Cortex PhellodendriChinsis*	bark	12
Bidentate achyranthes	*Achyranthes bidentata Blume.*	root	12
Capillary wormwood	*ArtemisiacapillarisThunb.*	stem&foliage	15
Stephania tetrandra	*Stephania tetrandra S. Moore*	root	9
Tuckahoe	*Poria*	sclerotium	15
Cynanchumpaniculatum	*Cynanchumpaniculatum (Bunge) Kitagawa*	root& rhizome	15

Our data from clinical studies confirm the effectiveness of HZG in the treatment of GA, with 87.5% of the patients showing improvement in joint swelling and pain. Moreover, HZG can significantly reduce white blood count, erythrocyte sedimentation rate, and C-reactive protein and interleukin-6 levels in patients with GA(17). However, because of the complex composition of HZG, the mechanism underlying its therapeutic action remains unclear.

The beneficial effects of HZG on acute GA are well known and are considered to be derived from the improvement of wind-dampness-heat syndrome, leading to improvement of joint inflammation. However, no large-scale randomized controlled trials have been conducted on the treatment efficacy, safety, and recurrence control efficacy of HZG. Therefore, we aim to conduct a double-blinded, randomized, controlled clinical trial to evaluate the efficacy of oral HZG for the treatment of patients with acute GA showing wind-dampness-heat syndrome.

Methods

Design

The study is designed as a three-parallel group, double-blind, randomized, controlled clinical trial. The objective is to clarify the clinical efficacy, safety, and recurrence control efficacy in patients with wind-dampness-heat syndrome. The research findings will be applied to establish a clinical standard for the treatment of gout. At the time of the writing of the trial protocol (version 1.0, 09 April 2020), enrollment for the trial was yet to begin. The recruitment is expected to start on July 1, 2020 and end on December 31, 2022.

We aim to recruit from Shanghai region, China. Patients with acute goutrequiring primary and secondary care, including inpatients who develop an acute gout attack, will be recruited. Recruitment will occur in the secondary care setting with treatment occurring on an outpatient basis, or it can occur in secondary care if symptoms warrant admission or if the participant is already an inpatient and develops an acute gout attack. A total of 267 people will participate in this clinical trial, each participant can only be enrolled once.

The study consists of five phases: screening/enrollment, allocation, treatment/intervention, end of intervention, and follow-up. In the enrollment process, participants will be recruited via agout specialist clinicfor physical examination and eligibility assessment. The timebetween the assessment and the intervention should not be longer than one week (week 0). If more than a week has passed since the assessment, assessment of the participant will be repeated before the intervention. If eligible, the participants will be requested to sign the written informed consent regarding participation in the trial (procedures, risks, options for dropping out), the use of laboratory data, and collection, storage, and use of biological specimens. Details of the informed consent will be explained by study investigators or medical staff members with adequate training. Onceinformed consent form is signed and dated by the participant, a participant identification (PID) number will be assigned to facilitate participant identification of the study.

The participants will be randomly allocated to the HZG group,etoricoxib group, or placebo group and undergo corresponding intervention over the course of 5-day treatment period. We will treat the participants in the HZG group withHZG and etoricoxib placebo tablets, those in the etoricoxib group with etoricoxib tablets and HZG placebo, andthose in the placebo group withHZG placebo and etoricoxib placebo tablets (Fig. 1).The participants will receive systemic therapy as per the judgment of their treating physicians. We will record all changes in symptoms, prescriptions, relevant scores, and macroscopic characteristics (based on photographic evidence), as well as any AEs.

The trial protocol was approved by the Shanghai Yueyang Integrated Medicine Hospital ethics committee and registered with the Clinical Trial Registry (NCT04462666).

Eligibility criteria

Inclusion criteria:

i. Diagnosis of acute gout arthritis as defined by the American College of Rheumatology 1977 preliminary criteria.
ii. Male or non-pregnant, non-nursing female.
iii. 18–70 years of age.
iv. Occurrence of gout attack ≤ 48 hours ago.
v. In the week before this observation, non-steroidal anti-inflammatory drugs, analgesic drugs, and drugs affecting uric acid metabolism were not taken.
vi. Subjects capable of giving informed consent.

Exclusion criteria:

(i) Failing to meet the diagnostic criteria.

(ii)Evidence of uncontrolled concomitant cardiovascular, neurological,hepatic, or gastrointestinal disease—potential participants who have active concomitant disease can only be eligible after discussion and agreement with the treating medical team.

(iii) Patients in a critical condition that makes it difficult to evaluate the effectiveness and safety of the clinical observation.

(iv)Severe deformity, stiffness, and labor loss in patients with advanced arthritis.

(v) Known allergy to the drug used in this study.

Interventions

HZG intervention

Participants in the experimental group will receive 10 sacks of HZG granules. They will be instructed to take two sacks per day, one in the morning and one in the evening, approximately 30 minutes after the meal. The major ingredients of HZG are listed in Table 1. The placebo etoricoxib will also be taken daily in the morning for 5 days.

Etoricoxib intervention

Participants in the etoricoxib group will receive 5 etoricoxib capsules. They will be instructed to take one capsule per day in the morning, approximately 30 minutes after the meal. The placeboHZG will also be taken two sacks per day, one in the morning and one in the evening, approximately 30 minutes after the meal.

Placebo intervention

Participants in theplacebogroup will receive 10 sacks of placebo HZG. They will be instructed to take two sacks per day, one sack in the morning and one in the evening, approximately 30 minutes after the meal. Besides, the placebo etoricoxib will also be taken daily in the morning for 5 days.

Outcome measures

Through the implementation of deterministic, double-blind, double-simulated randomized controlled trials, we can provide clear guidance for the safe management of patients with acute gout. Information from the proposed outcome metrics will be collected for further studies with largerstudy populations. Recruitment and retention rates, the proportion of patients who do not meet the criteria, and the willingness of patients to be randomly assigned will be calculated. Compliance and compliance rates as well as qualitative feedback will be checked. Economic data on the use of medical resources and health-related quality of life will be collected and analyzed. Safety outcome measures will be reported in accordance with the requirements of a clinical trial designed to study a drug regimen.

Primary outcome

Proposed primary outcome measures of effectiveness consist of resolution of pain, that is, time to 50% reduction and complete resolution of pain determined asself-assessed pain intensity for the most affected joint at baseline using the visual analogue scale (0–100 mm).The patients were evaluated from baseline to 5 days post-randomization(4 hours, day 1, day 2, day 3, day 4, and day 5) and during the follow-up period after taking the first drug.

Secondary outcome

Proposed secondary outcome measures will consist of Likert scales for the assessment of joint tenderness and swelling.The Likert scale scores of the patients will be assessed during the treatment period (4 hours, day 1, day 2, day 3, day 4, and day 5) and the follow-up period.Besides, symptom relief

time, patient satisfaction, and 36-item Short Form Survey(SF-36)will be collected at the baseline and day 5. C-reactive protein and inflammatory cytokine (IL-1, IL-6, IL-8) levels, vital signs, blood routine, routine urine test, electrocardiogram, and blood biochemical parameters will be assessed at baseline and day 5.

During the treatment period, combined medication, adverse events (including dizziness, drowsiness, nausea, vomiting, abdominal pain, indigestion, rash, xerostomia, and any other symptoms reported by the patient), and serious adverse events (referring to adverse events requiring hospitalization) will be recorded.Patients may be withdrawn or returned to the standard of care at any time if there is a significant clinical indication to do soorparticipants request. Throughout the intraoperative and immediate postoperative period, the study team will be in communication with the clinical team to ensure protocol adherence and safety.

Patient and public involvement

Patients were not involved in the trial design, question research or recruitmentprogram development. At the end of the study, participants will receive the results through a lecture, where the effects found in the studied variables will be introduced. If thesuperiority of one technique is found on the other, it willbe applied in clinical therapy.

Sample size

The required sample size was calculated using an estimation formula on the basis of the differencesamong three sample rates(17–19). A previous clinical study(20) reported that the response rates of the etoricoxib treatment group, traditional Chinese medicine treatment group, and placebo treatment group were 63.89%, 42.5%, and 15.5%.Setting the two-sided significance level (α) at 0.05 and statistical power at 0.8, a minimum sample size of 74 participants per group (222 participants in total) was estimated to provide sufficient statistical power for detecting a between-group difference of approximately 20% in treatment efficiency, defined as the change in analgesic effectiveness. Considering a 20% loss to follow-up, we aim to enroll 89 patients in each arm, that is, a total of 267 patients.

Randomization and allocation

Enrolled patients will undergo randomizationin the ratio of 1:1:1 via sequence generation. Randomization will be conductedusing an internet-based randomization system. Once a patient has consented toparticipate in the trial, the designated staff will log in to the randomization system web page to confirm eligibility; a random allocation will be sent to pharmacy.

Treatment cycles

The treatment was planned for 5days in one cycle. All interventions will be stopped after the 5-day treatment period and one-week of follow-up.

Test drugs and blinding

The study drug and its placebo will be provided by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd. Etoricoxib will be purchased by Merck & Co., Inc.

All trial investigators will be blinded to the intervention. Pharmacy will keep a record of treatments administrated. All trial participants, care providers, and outcome assessors will be blinded to the treatment. Each treatment has its equivalent placebo to ensure that blinding in maintained throughout the study.

All investigators involved with the trial will be blinded to treatment. Patients will not be informed of their assigned treatment during the study. Pharmacy will keep a record of allocated treatment arms in the event of requirement of emergency unblinding.

The treatment code for a participant can be broken by any clinician either directly or via contact of the principal investigator. Allocation lists are made available to the site that will be provided 24-hour cover by the pharmacy. Failing that, the central pharmacy can access allocation list. Where possible the local investigator should aim to discuss the need for unblinding with the coordinating investigator, and attempts to preserve blindingof relevant research staff (data collection, analysis and interpretation) should be made. The coordinating investigator is responsible for pharmacovigilance management and reporting.

Measurements

Demographic data such as age, sex, ethnicity, race, and body mass index will be recorded. Individuals will receive the following instructions during the trial period: No alcohol, low-purine, low-fat diet, and plenty of water (≥ 2000 ml/day);avoid predisposing factors such as joint cold, trauma and excessive fatigue; avoid using diuretics, salicylic acid preparations, glucocorticoids and other drugs that affect uric acid metabolism and excretion.In each allocation and follow-up phase, the electrocardiogram(ECG),erythrocyte sedimentation rate(ESR), C-reactive protein(CRP), interleukin(IL), blood routine(BR), blood biochemistry(BB), routine urine test(RUT) and drug combination(DC) will be measured.In addition, the Tenderness, Redness and swelling of the involved joint, Symptom relief time, Patient satisfaction and 36-Item Short Form Survey values will also be collected.The study team will build and maintain the electronic case report form data and ensure data completeness and quality periodically by means of internal audits. Double data entry will be used to ensure data quality. All efforts will be made to maintain confidentiality of patient data by using multiple means such as de-identification, use of password-protected secure servers, and restriction of access to study team members.

Drug combination

In this study, all drugs will be considered combined drugs. Details including trade name, dosage, indications, and duration of medication will be recorded in the case report form. Whether a participant should withdraw from the trial because of the nature of the combined drugs will be judged by study investigators. The use of diuretics, salicylic acid preparations, glucocorticoids, and other drugs that affect uric acid metabolism and excretionshould be avoided.

Statistical analysis

The statistical analysis plan was developed by professional statisticians upon consultation with the main trial investigators. The data will be stored with the data management center of Jiangsu Famaisheng Medical Technology Co., Ltd., and processed by their in-house statisticians blinded to group allocation. The analyses will be conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and will cover the number of participants enrolled in each group, the number of patients who dropped out of the study and the reason for the drop-out, demographic and other baseline characteristics, compliance, efficacy analysis, and safety analysis.

Descriptive and comparative analyses will be conducted. Qualitative data will be described using frequency tables, percentages, or constituent ratios and compared using the chi-square test, Fisher's exact probability test, Wilcoxon rank-sum test, Cochran–Mantel–Haenszel chi-square test and weighted least squares covariance. Quantitative data will be described using the mean, standard deviation, median, quartile thresholds, minimum & maximum of the range. The t-test will be used for comparative analysis of data showing normal distribution;it will be used with Satterthwaite correction if the variance is uneven. Quantitative data exhibiting non-normal distribution on the Wilcoxon rank-sum test will be analyzed using the Wilcoxon signed-rank sum test and covariance generalized linear models. All hypothesis tests will be two-sided. The test statistics and corresponding *P*-values will be reported. Statistical significance will be established at $P < 0.05$, with high statistical significance established at $P < 0.01$.

Adverse events

The Chinese herbal medicines contained in HZG are all listed in the Pharmacopoeia of the People's Republic of China. The dose used in this study is within the range recommended by the Pharmacopoeia Commission of the Ministry of Health of the People's Republic of China. To date, no adverse reactions have been reported in relation to the clinical application of HZG. Nevertheless, the trial will implement adequate measures to monitor for AEs, including observation of vital signs, laboratory tests, recording of concomitant medications, pregnancy tests, and physical examinations. All AEs will be recorded, regardless of severity, to assess the safety of HZG. The specific implementation of such measures is reflected in Table 2.

Table 2
Schedule for enrollment, intervention, and assessment

	Phase	Screening/Enrolment	Allocation	Treatment/Intervention					End of intervention	Follow-up
Activity	Time points	Day 0		Day 1	Day 2	Day 3	Day 4	Day 5		Week 1
Screening/Enrolment	Eligibility screening	X	X							
	Obtaining informed consent	X								
	Clinicopathological evaluation	X								
	Medical history taking	X								
	Enrolment	X								
	Random allocation		X							
	Biological specimen collection		X						X	X
Treatment/Intervention	HZG + Placebo Etoricoxib			X—	——	——	——	—X		
	Etoricoxib + Placebo granules			X—	——	——	——	—X		
	Placebo granules + Placebo Etoricoxib			●—	——	——	——	—●		
Outcome assessment	VAS score		X					X	X	X
	Tenderness,Redness and swelling of the involved joint		X					X	X	X
	Symptom relief time		X					X	X	X
	Patient satisfaction		X					X	X	X
	36-Item Short Form Survey		X					X	X	X
	CRP		X					X	X	
	IL-1		X					X	X	
	IL-6		X					X	X	
	IL-8		X					X	X	
Safety assessment	Vital signs		X					X	X	
	BR		X					X	X	
	BB		X					X	X	
	RUT		X					X	X	
	DC		X					X	X	
	ECG		X					X		
	PE		X					X	X	
	AEs		X	X	X	X	X	X	X	
	Severe AEs		X	X	X	X	X	X	X	

●Intervention in the Control group; Intervention in the experimentalgroup. HZG, Huzhang granules; VAS, visual analogue scale; ESR,erythrocyte sedimentation rate, CRP,C-reactive protein, IL,interleukin. BR, blood routine; BB, blood biochemistry; RUT, routine urine test; DC, drug combination; ECG,electrocardiogram; PE, physical examination; AE, adverse event

If an AE occurs, the investigators must determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If a severe AE occurs, the study investigators must take immediate action to ensure the safety of the participants. In addition, all severe AEs will be reported to the first responsible staff and to the ethics committee within 24 hours.

Data management and monitoring

Data associated with this study will be collected and maintained in a dedicated database of research medical records that logs outpatient and inpatient data about the participants and must be submitted by the investigators at the end of follow-up (week 2) together with the participant medication records and informed consent forms. The principal investigators at each participating center are responsible for collecting the research medical records from the study investigators, as well as for reviewing and storing these records.

Patient data are entered into electronic case report forms by the responsible staff at each participating center. To ensure the quality and consistency of the source data and of the data entered into the database, two researchers will independently check the source data and compare against the information entered into the corresponding electronic case report forms. Any questions or suspicions arising during the process of checking the source and case report data shall be added to a formal list of queries, which will be addressed by the investigator filling out the data. If a problem is found, it should be processed and recorded in a timely manner. All documentation on quality control will be maintained to objectively assess safety and key outcomes.

Discussion

GA is caused by the deposition of MSU crystals in soft tissue, triggering severe but self-limited bouts of acute arthritis accompanied by intense pain, as well as articular and periarticular inflammation(20).The acute attack of gout not only brings joint pain and dyskinesia, but more importantly, gout is associated with a number of complications, including hypertension, chronic kidney disease, cardiovascular disease, obesity, insulin resistance and diabetes, and hyperlipidemia(21–23).

In the early stage, gout is often only manifested as intermittent acute arthritis.Asingle joint is mainly involved;furthermore, the first metatarsophalangeal joint is the most commonly involved joint.Joint swelling and pain usually last for 7 days, can be spontaneous or relieved by drugs, and do not have any symptoms during the interval(23).With the extension of the course of gout, the number of attacks and the number of joints involved gradually increase, and joint symptoms begin to appear during the interval(24). At the same time, tophus is formed in the joint or skin and soft tissue, and the joint is damaged or even maimed. Although the treatment of gout is effective, the compliance of patients with gout is not satisfactory(25).Poor compliance not only directly affects the therapeutic effect on patients, but also puts a heavy burden on the whole medical and health department(26–29).

TCM has been used for the treatment of gout for a long time, and the curative effect is remarkable.TCM considers that GA is caused by internal and external causes; the external causes mainly include wind, cold, dampness, and heat, while the internal causes mainly include the deficiency of vital qi of the human body, disorder of ascending clear and descending turbid function of spleen and kidney, and deficiency of qi and blood, leading to dampness-heat, turbid phlegm, stagnation of blood stasis, spleen deficiency, and other syndromes(30, 31), among which dampness-heat syndrome is the most commoncause. On the basis of clinical practice, combined with the TCM-based pathogenesis of GA, our research group has formulated the TCM prescription ofHZG, which is used to treat GA on the basis of the treatment principles of clearing heat, removing dampness, and dredging collaterals.

Previous research indicated that HZGhas an anti-inflammatory effect on down-regulating NALP3 and caspase-1 at the protein translation level(32). On the basis of these previous observations, we cultured fibroblast-like synoviocytes (FLSs) stimulated by MSU with serum containing HZG and found that HZG could inhibit the expressions of IL-1β, TNF-α, and IL-6(14) which supports the therapeutic effect of HZG on patients with GA showing dampness-heat syndrome and has motivated us to initiate this trial.

In this trial, we are going to use the granule formulation to minimize deviations associated with the use of herbs from different geographical regions, different varieties, and maintained under different storage conditions. In addition, because of the multicenter design of clinical trials, the results of this study are expected to provide more general clinical evidence. In this study, we aim to clarify the efficacy of HZG treatment twice a day for 5 days.As acute GA is prone to recurrence, we emphasize on a one-week follow-up after the end of treatment.

We will carefully monitor the recurrence after the end of GA treatment. In addition, we will record all AEs and information regarding concomitant medications at each visit. The study results will help clarify the efficacy of HZG, as well as its safety in the treatment of GA in terms of both inflammation regression and rate of recurrence. We expect that this study will provide high-quality evidence that can be used to develop clinical treatment guidelines. Therefore, the results of this study are expected to have an important impact on public health.

Limitation of the study should be mentioned. Only one trial drug regimen will be tested, and the prescription will not be adjusted according to symptoms, which means that the results may be specific to the test regimen. Besides, because of relying on etoricoxib as the control drug in our study, our findings may not apply to the adverse reactions of other NSAIDs. Nevertheless, the findings will still be useful as reference in clinical practice and will help pave the way for future research. Finally, the HZG prescription to be used in this trial was designed for the treatment of GA with dampness-heat syndrome, and thus, the findings may not be applicable to other syndromes.

Declarations

Ethics and dissemination

Ethical approval has been obtained through the Ethics Committee of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (Approval No.2020-024). All participants will be enrolled only after providing written informed consent. No clinical data or bio-samples will be collected without the participant's consent. The trial is conducted in accordance with national laws, Good Clinical Practice guidelines, and the Declaration of Helsinki as revised in 2013. The results will be disseminated to the public through conference presentations and papers in open-access journals.

Blood samples of all participants will be collected at the baseline and the day5. After collection, Peripheral blood mononuclear cells (PBMC) will be isolated within 4 days and stored at -80°C for future analysisof inflammatory biomarkers.

We plan to publish the results of this study in scientific journals.The datasets used or analyzed during the current study will be available from the corresponding author upon reasonable request. We do not intend to separately inform participants about the results of this study.

Trial status

Unique Protocol version :1.0. Protocol version date: 09 April 2020. The recruitment is expected to start on July 1, 2020 and end on December 31, 2022. Study completion is expected to be April 30 2023.The final results will be reported next year.

Authors' Contributions

MZ, LH, and XL drafted the manuscript. BL, XL, MZ, and YFW participated in the design of the study, STC and CMY coordinated the study. All authors read and approved the final manuscript.

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National Key Research and Development Program of China supports the activities of Department of Dermatology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine as trial sponsor. Department of Dermatology is leading the design, analysis, interpretation of data and manuscript writing.

National Key Research and Development Program of China has no role in the design, conduct, analysis, interpretation of data or the decision to write up the manuscript.

Competing interests None declared.

Patient consent Patient recruitment has not started.

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Ethics Committee of Shanghai Yueyang Integrated Medicine Hospital on May 14 2020, with file number 2020-024. This study is designed in accordance with the principles of the Declaration of Helsinki. All participants will provide written informed consent before enrollment.

Consent for publication

Not applicable

References

1. Cabău G, Crișan TO, Klück V, Popp RA, Joosten LA. Urate-induced immune programming: Consequences for gouty arthritis and hyperuricemia. Immunological Reviews. 2020;294(1):92-105.

2. Martinon F, Glimcher LH. Gout: new insights into an old disease. The Journal of clinical investigation. 2006;116(8):2073-5.

3. Terkeltaub R. What makes gouty inflammation so variable? BMC medicine. 2017;15(1):1-10.

4. Khanna PP, Shiozawa A, Walker V, Bancroft T, Essoi B, Akhras KS, et al. Health-related quality of life and treatment satisfaction in patients with gout: results from a cross-sectional study in a managed care setting. Patient preference and adherence. 2015;9:971.

5. Juraschek SP, Kovell LC, Miller III ER, Gelber AC. Gout, urate-lowering therapy, and uric acid levels among adults in the United States. Arthritis care & research. 2015;67(4):588-92.

6. Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nature reviews rheumatology. 2015;11(11):649.

7. Roddy E, Zhang W, Doherty M. The changing epidemiology of gout. Nature Clinical Practice Rheumatology. 2007;3(8):443-9.

8. Towiwat P, Chhana A, Dalbeth N. The anatomical pathology of gout: a systematic literature review. BMC musculoskeletal disorders. 2019;20(1):140.

9. Wilson L, Saseen JJ. Gouty arthritis: a review of acute management and prevention. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2016;36(8):906-22.

10. So A, De Meulemeester M, Pikhlak A, Yücel AE, Richard D, Murphy V, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. Arthritis & Rheumatism. 2010;62(10):3064-76.

11. Tausche A, Richter K, Grässler A, Hänsel S, Roch B, Schröder H. Severe gouty arthritis refractory to anti-inflammatory drugs: treatment with anti-tumour necrosis factor α as a new therapeutic option. Annals of the rheumatic diseases. 2004;63(10):1351-2.

12. Neogi T. Gout. New England Journal of Medicine. 2011;364(5):443-52.

13. Xiao N, Chen H, He S-Y, Xue C-X, Sui H, Chen J, et al. Evaluating the efficacy and adverse effects of clearing heat and removing dampness method of traditional Chinese medicine by comparison with western medicine in patients with gout. Evidence-Based Complementary and Alternative Medicine. 2018;2018:1-18.

14. Zhou M, Ze K, Wang Y, Li X, Hua L, Lu Y, et al. Huzhang Tongfeng Granule Improves Monosodium Urate-Induced Inflammation of Gouty Arthritis Rat Model by Downregulation of Cyr61 and Related Cytokines. Evidence-Based Complementary and Alternative Medicine. 2020;2020:1-13.

15. Chi X, Zhang H, Zhang S, Ma K. Chinese herbal medicine for gout: a review of the clinical evidence and pharmacological mechanisms. Chinese Medicine. 2020;15(1):17.

16. Liu Y-F, Huang Y, Wen C-Y-Z, Zhang J-J, Xing G-L, Tu S-H, et al. The effects of modified simiao decoction in the treatment of gouty arthritis: a systematic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine. 2017;2017:6037037.

17. Zhou M, Ze K, Wang Y, Li X, Hua L, Lu Y, et al. Huzhang Tongfeng Granule Improves Monosodium Urate-Induced Inflammation of Gouty Arthritis Rat Model by Downregulation of Cyr61 and Related Cytokines. Evidence-Based Complementary and Alternative Medicine. 2020;2020:9238797.

18. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett R, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four–hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis & Rheumatism. 2010;62(4):1060-8.

19. Yufei L. Effects of Etoricoxib on primary acute severe gouty arthritis. Medical Journal of Chinese people's health. 2018;30(9):21-3.

20. Gutman AB. Uric acid nephrolithiasis. The American journal of medicine. 1968;45(5):756-79.

21. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007;116(8):894-900.

22. Sun M, Vazquez AI, Reynolds RJ, Singh JA, Reeves M, Merriman TR, et al. Untangling the complex relationships between incident gout risk, serum urate, and its comorbidities. Arthritis research & therapy. 2018;20(1):90.

23. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. The American journal of medicine. 2012;125(7):679-87. e1.

24. Dalbeth N, Choi HK, Joosten LAB, Khanna PP, Matsuo H, Perez-Ruiz F, et al. Gout. Nat Rev Dis Primers. 2019;5(1):69.

25. Scheepers LE, van Onna M, Stehouwer CD, Singh JA, Arts IC, Boonen A, editors. Medication adherence among patients with gout: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism; 2018;47(5):689-702.

26. Chua CK, Cheung PP, Santosa A, Lim AY, Teng GG. Burden and management of gout in a multi-ethnic Asian cohort. Rheumatology International. 2019:1-7.

27. Elfishawi MM, Zleik N, Kvrgic Z, Michet CJ, Crowson CS, Matteson EL, et al. The rising incidence of gout and the increasing burden of comorbidities: a population-based study over 20 years. The Journal of rheumatology. 2018;45(4):574-9.

28. Neves C, Shields G, Beard S. A systematic review of the cost burden of gout. Value in Health. 2015;18(7):A656.

29. Spaetgens B, Boonen A. The importance of 'state-of-the-art' cost-of-illness studies. Comment on: The economic burden of gout: A systematic review. Semin Arthritis Rheum. 2016;45(4):e9.

30. Dang W-t, Xie W-g, Zhou J-g. Expression of PYCARD gene transcript variant mRNA in peripheral blood mononuclear cells of primary gout patients with different Chinese medicine syndromes. Chinese journal of integrative medicine. 2018;24(1):24-31.

31. Shao P, Huang X, Zjang F. Research on relationship of syndrome type and parameters of hemorheology and platelet activation in patients with acute gout arthritis of dampness-heat blockage type and stasis-heat accumulate type. Chinese Journal of Integrated Traditional and Western Medicine. 2006;26(11):992-4.

32. Hua L, Zhou M, He Q-h, Zhao H-b, Tang J-y, Li X, et al. Effects of clearing heat and removing dampness and dredging collateral method on expression of NALP3 inflammasome in model of gouty arthritis rats. China Journal of Traditional Chinese Medicine and Pharmacy. 2018;04(33):1591-4.

Figures

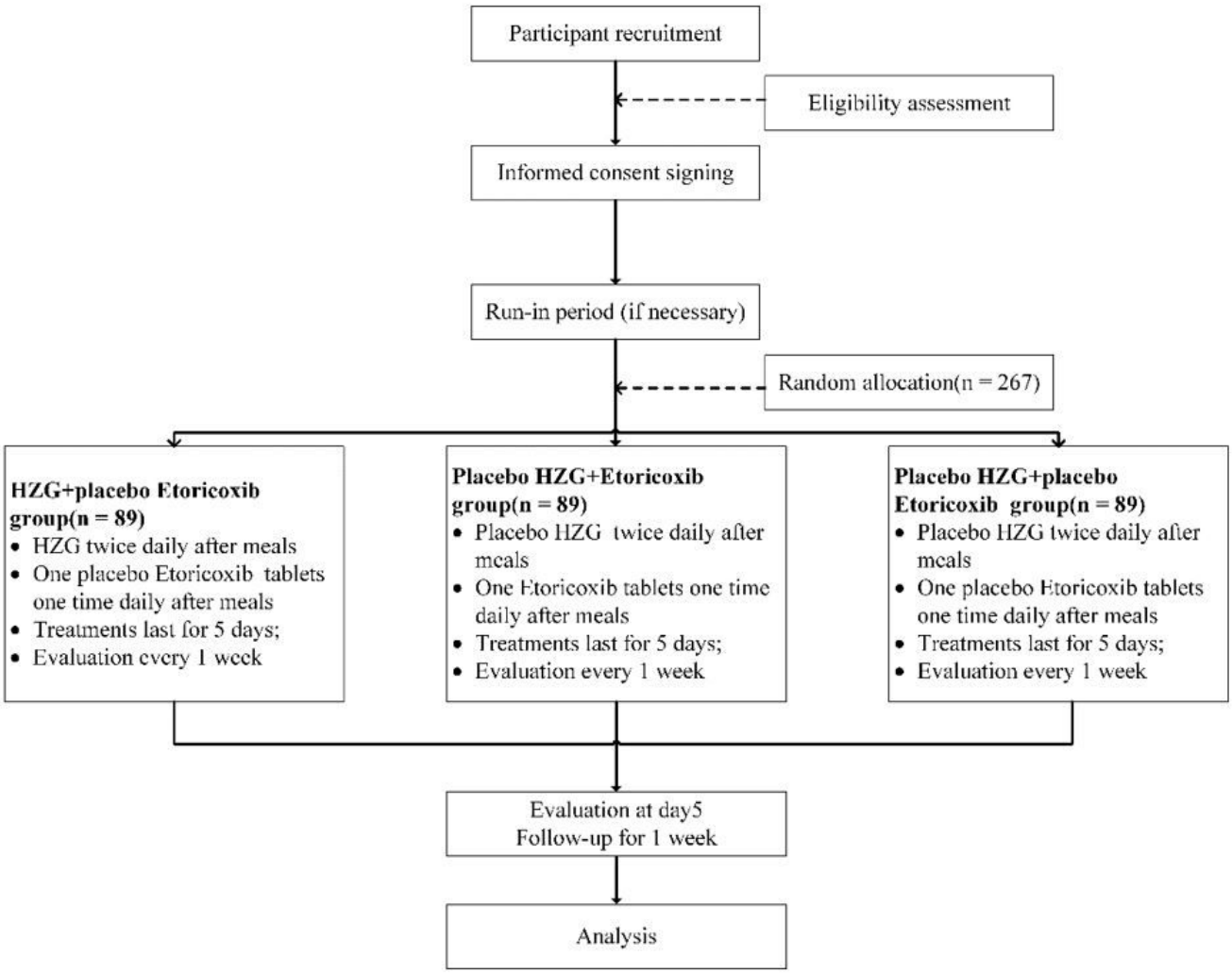

Figure 1

Flow diagram showing progress through the study