Evaluation of the safety and efficacy of Chinese medicine in people with asymptomatic hyperuricemia: Protocol for a prospective, double-blinded, randomized, placebo controlled clinical trial.

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Research Article

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Abstract

Background

Hyperuricemia increases the risk of gout and cardiovascular complications. Studies show that Chinese medicine can decrease uric acid through multiple targets, but many of these studies is conducted on animal, because the lack of a consistent prescription and mechanism. So we design this research to study whether Chinese medicine is really effective and which target is essential.

Methods

This study is a prospective, double-blinded, randomized, placebo controlled clinical trial. From March 2020 to December 2021, 30 asymptomatic hyperuricemia people will be recruiting and assigned to either Chinese medicine group or placebo group, each group will have 15 subjects. During the 12-week observation period, there will be 4 times of visits. The decline in the uric acid is the main outcome measure, urinary uric acid, inflammatory biomarkers and other index that may involve in lowering uric acid are the secondary outcome measures.

Discussion

This study will probe the effect of Chinese medicine treatment on hyperuricemia, and explore possible therapeutic mechanisms. By performing this trial, we hoping to provide evidence and data to support further large clinical studies.

Trial registration: ChiCTR2000038575. Registered on September 24, 2020.

Background

As living standards rise and dietary habits changes, the prevalence of hyperuricemia has increased[1], especially in China[2]. It had became the second most common metabolic disease after diabetes mellitus and affects 133 persons per 1000 inhabitants in mainland China (the morbidity of men is 19.4%, women is 7.9%) [3]. Meanwhile, the prevalence rate is higher in cities than in rural areas, statistics show that the incidence of hyperuricemia in Guangzhou and elderly in Beijing is 13.2% and 17.6% respectively[4]. Hyperuricemia may led to GOUT eventually, and accompany augment the risk of hypertension and other cardiovascular disease[5]. Influenced by the Chinese culture of nip in the bud, people with hyperuricemia were seek for early interventions to prevent progressing to GOUT and other disease. Nonetheless, they do not prefer accept uric-acid-lowering drugs, as the hyperuricemia is considered as “not ill”. Thus, many people quest for Chinese medicine treatments.

Some animal studies have shown that Chinese medicine can lower uric acid levels, relief symptoms and reduce the frequency of Gout attacks[6–12]. The mechanism of Chinese medicine is complex and not clear yet. Some study indicates Chinese medicine may promote the uric acid excretion[6–8]; Other researchs has shown that, Chinese medicine can modulate the levels of inflammatory cytokines[9–12];

Evidences also suggest that Chinese medicine inhibit the synthesis of uric acid[13, 14]. So our trial will test subjects' capacity of uric acid excretion and inflammation index. Recently, there are trials support the difference in intestinal microecology between hyperuricemia people and healthy people[15, 16]. Rats experiments showed Chinese medicine has a certain influence on the composition of intestinal flora[17, 18]. Therefore intestinal microecology before or after Chinese medicine treatment is our another interest potential target.

How to evaluate the efficacy of Chinese medicine treatments and develop effective treatment for asymptomatic patients with hyperuricemia is difficult, for Chinese medicine treats patients based on syndrome differentiation rather than disease differentiation, thus the recipes for Chinese medicine for people may vary in composition. So it is essential to establish syndrome standards. Due to the lack of relevant literatures and researchs, we gathered experts of Chinese medicine classic, by consulting Chinese medicine classics and combining their clinical experience, to reach a consensus, that for people with hyperuricemia in Guangdong province, dampness syndrome is the main syndrome.

We designed questionnaires, adopted 11 people with hyperuricemia by electronic questionnaire system. The result showed that all the 11 cases were consistent with the clinical manifestations of dampness syndrome. 8 of which had the manifestations of cold dampness syndrome, 3 showed the manifestations of hot dampness syndrome. The minimum of dampness score is 43, and maximum is 104, the average is 70.09 ± 17.56 . Summarize the performance of the 11 cases, 54.5% of which has superficial syndrome. Based on clinical experience, combined the concept of Chinese medicine that "the beginning of disease is in the grain of skin and the texture of the subcutaneous flesh", guided by the Chinese medicine theory of preventive treatment of diseases, combined with the opinions of many Chinese medicine classic experts, put forward the treatment viewpoint of "treating metabolic diseases at the early stage by skin". Choose the "tuckahoe alisma soup" which is specific to Taiyang YangMing Taiyin combination diseases as the main prescription for the cold dampness population, in the ingredient of the soup, tuckahoe, atractylodes can dissolve the wet inside, cassia twig and ginger work on the surface, treat the disease out and in simultaneously, urge the wet out with alisma; For people with hot dampness, the main prescription is "Scutellaria and ginger pinellia soup".

Methods And Design

Study objective

The objectives of the experiment is to study the efficacy and safety data of Chinese medicine therapy for dampness syndrome of hyperuricemia; And to screen possible related intuitive small molecules/microbial material basis.

Study design

This is a 12 weeks, single-center prospective, double-blinded, randomized, placebo controlled clinical trial. We used the SPIRIT reporting guidelines to perfecting this protocol[19]. From March 2020 to December

2021. Incorporate 30 asymptomatic hyperuricemia subjects, which will be randomly 1:1 assigned to receive Chinese medicine or placebo.

Sample size

This study will enroll 30 subjects. Further large-scale RCT trial will estimate the size of sample according to the results of the main outcome indicators obtained from this study, use the sample content estimation formula for comparing the two means to calculate the sample content, $\alpha=0.025, \beta=0.2$, The sample size ratio of test group and control group is 1, The lost follow-up rate is set according to the pre-experiment lost follow-up rate.

Recruitment

Most asymptomatic patients with hyperuricemia do not seek for medical attention, so we will recruit subjects through recruitment advertisements. The advertisements will be placed in the hospital building, and be broad through the hospital official account.

Study setting

Guangdong provincial hospital of Chinese medicine will be the only study setting.

The study's key problem

Dampness is involved with Hyperuricemia developing. The key of prevent gout, cardiovascular disease and uratic nephropathy is control the serum uric acid level. Whether Chinese medicine can improve the outcomes of hyperuricemia population, access the goal of early prevent disease?

Eligibility criteria

Inclusion criteria:

1. Aged between 18-75 years(including 18 years and 75 years;
2. Meet the diagnosis of asymptomatic hyperuricemia;
3. Meet the dampness syndrome inclusion criteria;
4. Sign the informed consent.

Exclusion criteria:

- 1) Secondary hyperuricemia,for instance,secondary to malignancy,hemopathy,nephropathy,chronic intoxication;
- 2)History of alcoholism without abstinence in recent 3 months;
- 3)Had one or more attacks of gout arthritis in the past;

- 4) Received urate-lowering drugs or drugs that may increase serum uric acid in recent 4 weeks: (1) antituberculous: Pyrazinamide/ethambutol/isoniazid, (2) low dose aspirin, (3) Loop diuretics and thiazide diuretics and blood pressure medications containing diuretics, (4) niacin, (5) large dosage of vitamin C, (6) chemotherapeutic drugs, (7) cyclosporin;
- 5) Pregnancy and lactation population, or has possibility of conception but failure to use effective contraception;
- 6) Alanine aminotransferase or aspartate aminotransferase or creatinine 2 times or more than the normal value;
- 7) Combined with serious organic lesions, mental disorders or other reasons can not cooperate with treatment; 8) Allergic or ineffective to the test drug ingredients.

Randomization and allocation

Adopting simple block group randomization, the allocation ratio will be 1:1. Use SAS9.2 PROC PLAN to carry out procedure coding and random sequence generation by methodology team.

The random distribution results will be released through the "Interactive network response random distribution System for Clinical Research in Guangdong provincial hospital of Chinese medicine. The random assignment table in the random Center will be kept strictly confidential until the end of the study.

After the patients are screened as qualified subjects and given informed consent, the clinicians will log on the Internet to apply for the randomization system to obtain the randomization results. Physicians execute the results according to random grouping, and print and paste them on the corresponding position of CRF.

Blind

Adopt double-blinded, placebo controlled design, both the investigators and the subjects are blinded. All data will be evaluated and statistically processed by a third-party after the clinical research.

The blindness should be broken if there is a serious adverse event that may be related to the experimental drug, so we can know which group the subject was enrolled in to decide the rescue plan. The blindness should be broken in the presence of principal investigator and funders. The time, reason, procedure of the unblinding and the researchers involved in the unblinding should be recorded. After the blindness was broken, the subject will be terminated from the study, and the experimental data will be included in the safety analysis data set, and the subject was given timely treatment and follow-up.

Comparators

Many Chinese medicine studies set Chinese medicine plus western medicine as the experimental group and solely modern medicine as the control group. This may lead to bias. So we use placebo control group

as the comparators.

Chinese medicine syndrome subgroups

All enrolled subjects will be assigned to subgroups: cold-dampness disturbing spleen and damp-heat retention spleen. The definition of which is to draw up with refer to “The guiding Principles for clinical Research of New Chinese medicines (trial)” in 2002, which was edited by Zheng Xiaoyu[20].

Interventions

Subjects will be given therapeutic agent (Chinese medicine) or placebo.

Chinese medicine intervention group: 1) Cold-dampness disturbing spleen: Tuckahoe alisma soup, one dose a day, warm take after meal. 2) Damp-heat retention spleen: Scutellaria and ginger pinellia soup, one dose a day, warm take after meal.

Chinese medicine placebo internal administration: the size, appearance, package and the the administration method are the same as the therapeutic drugs. During the trial, the investigators will monitor dietary and exercise conditions of subjects everyday.

Eliminate and Termination Criteria

Eliminate criteria: 1) Serious violation of exclusion standards after enrollment; 2) Not completing the experimental drug administration during the experimental period as required after enrollment; 3) Incomplete one month follow up, no test records were available for evaluation.

Termination Criteria: 1) Have a gout attack; 2) severe adverse events; 3) Condition deteriorated and required urgent medical attention; 4) The researcher recommended terminate test because of the safety of the subjects. 5) People unwilling to continue to participate in this study for personal reasons.

We will keep in touch with the subjects who drop out to observe any subsequent adverse event and collect subsequent data.

Strategies to improve adherence to interventions

The compliance of investigators and subjects is essential factors of clinical research process and clinical effect. To ensure compliance, investigators or the designated representative must explain the detailed information about the clinical trail to the subjects, and to obtain informed consent after sufficient and detailed explanation.

The compliance evaluation of the subjects is mainly judged from the status recorded by the subject's log card and the status questioned by the researchers.

Plans to promote participant retention and complete follow-up

First, the investigators will keep in touch with the subjects, regular telephone follow-ups and reminders for follow-up visits will be implemented. Second, our research system will prompt the prescription a day in advance. Third, the subjects will receive free tests. Fourth, transportation subsidies will be given after each follow-up visit to encourage subjects to remain engaged and complete follow-up surveys.

Outcome measures

Primary outcome measure

The reduction of serum uric acid.

Secondary outcome measures

1) Chinese syndrome score, measurement of the channels and collaterals, tongue diagnosis evaluation; 2) Glomerular filtration rate, Urinary β_2 microglobulin, uric acid excretion fraction; 3) Incidence rate of complications, such as gout, hyperlipemia, cardiovascular events, diabetes, etc; 4) Ultrasound of double ankles and the first metatarsophalangeal joints[21]; 5) Evaluation index of metabolite: blood, urine metabolite. 6) Inflammation index: hsCRP, TNF- α , IL-6, IL-8; 7) Intestinal microecology(Note: This index is tested by setting a separate subject).

Security indicators

1) Liver function(ALT, AST) , renal function(Urea, Cr); 2) Blood routine, urine routine, stool routine + occult blood; 3) Electrocardiogram, ultrasound of the urinary system.

Data collection and analysis

Within 12 weeks course there will be 4 times of visits: 0 week, 4 weeks $\pm$ 3days, 12 weeks $\pm$ 5days, and the data collection and the filling of the CRF will be performed by two research assistants who have no idea about the subjects grouping. Adopt EPIdata3.1 database software package to establish a database for data entry, use double input data for data entry.

The clinical trial monitors check the quality of data entry regularly. The checked database is then checked by logic inspection and the original laboratory documents of outliers, and the finally checked database is converted into the DATABASE in the format of SPSS statistical software package and locked for statistical analysis.

Statistical analysis

All statistical tests are two-sided, $\alpha=0.05$ will be found statistically.

We will use t-test (or wilcoxon matched-pairs signed-ranks test if the data is non-normal distribution with uneven variances) to compare the decrease in the uric acid between two groups.

For secondary outcomes, the t-test and Wilcoxon test will be conducted to compare the differences in measurement data (such as index's mean and standard deviation, median) between the groups. The Repeated measures analysis of variance will be used to compare multiple measures of the scale and symptom rating among groups. The Chi-square test (or Fisher's Exact test) and 3×C table will be utilized to determine the differences in the proportion, frequency, total effective rate of the indices in Chinese medicine group and placebo group.

To analysis the influence factors of curative effect, the nonconditional logistic regression analysis will be performed. For missing data from long-term follow-up, the last carry-over method (LOCF) will be used.

Safety analysis

Safety data is consist of adverse events and clinical laboratory tests. We will describe specific manifestations of adverse reactions and compare the incidence of adverse events and sever adverse events between two groups. The changes of laboratory test results before and after the test, abnormal changes and their relationship with Chinese medicine will be analysis.

Compliance analysis

A descriptive analysis are will be exploit to analyze compliance among the subgroups included in the study, and between the two groups for baseline of abscission cases.

Adverse events Management

The type, degree, occurrence time, duration, treatment measures, treatment process and follow-up results of adverse events occurred during the trial will be recorded in the case report form, and the correlation between the adverse events and the experimental drugs will be evaluated on the basis of comprehensive consideration of the complications and combined use of drugs, which will also be recorded in detail by the physician.

For non-serious adverse event, the observation physician may decide whether to suspend observation based on the disease condition. Cases that withdrawal drugs due to adverse event will be followed up and reexamine the lab security indicators.

For serious adverse event, drug taking will be stopped immediately. Regardless of whether it is related to the experimental drug, the investigators should report to the Ethics Committee of Guangdong province hospital of Chinese medicine within 24 hours after its occurrence.

If a serious adverse event occurs during the course of the study, the research team and the hospital will be responsible for subsequent treatment and financial compensation.

Protocol amendments

If a protocol change is required, the risk to the subject should be fully assessed and reviewed by the Ethics Committee. Inform all members after the new scheme has been approved by email and face-to-face meeting.

Confidentiality

Subjects have independent codes and only enter codes when uploading test data. Encryption system will be utilized to upload and store data. The final statistical process will be administered by a third-party.

Discussion

Our aim is through carrying out early intervention of Chinese medicine in the stage of asymptomatic hyperuricemia with "not ill", by controlling serum uric acid, thus can decrease the probability of asymptomatic hyperuricemia develop gout and other risk factors of cardiovascular and cerebrovascular disease, prevent and treat disease in early stage.

This research based on previous years of clinical experience and cross-sectional investigation and analysis, plan to carry out pre-research, to proceed study aimed at hyperuricemia people with dampness syndrome in Guangdong, on the basis of the pre-research, the sample size will be expanded and the randomized controlled double-simulation clinical trial will be conducted to obtain high-level evidence-based evidence of Chinese medicine in the treatment of hyperuricemia with dampness syndrome, thus to form an effective early Chinese medicine intervention plan for the population with hyperuricemia with dampness syndrome.

Trial Status

This trial information is available on chictr.org.cn, protocol version 1.4, November 30, 2020. The study was funded on February 25, 2020. Our trial enrolment period is from March to August 2021.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangdong provincial hospital of Chinese medicine (BF2020-172-01).

All the subjects involved in the research will be informed the objectives, duration, treatment, possible risks, rights and interests, etc. Investigators or the designated representative will obtain the written, informed consent to participate from all participants. The study consent process includes permission to collect intestinal flora specimens for additional trials.

Consent for publication

Not applicable.

Availability of data and materials

The data will not be shared, because this is a preliminary experiments. The research unit will have access to the final trial data set.

Competing interests

The authors declare that they do have no competing interests. The study funder has no role in the design, execution, analyses, interpretation of data, or decision to submit results for this study.

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Contributions

HXH, YJY, ZYY, YQW, WJQ received the research funding. HXH conceived the study, designed the study protocol and ethical approval. ZYY drafted the manuscript. YJY, YQW, WJQ participated in the design of the protocol and in charge of clinical case collection and observation. All authors read and approved the final manuscript.

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Dissemination policy

Regardless of the size and direction of the validity of the test results, they will be published.

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Figures

Figure 1

Flow diagram for the study

Timepoint	Study period			
	Visit 0	Visit 1 (0)	Visit 2 (4 weeks $\pm$ 3days)	Visit 3 (12 weeks $\pm$ 5 days)
Activity/assessment	Screening and consent	Allocation	Post-allocation	Close-out
Enroll				
Eligibility screening	√			
Informed consent	√			
Allocation		√		
Intervention				
Chinese medicine intervention group		√	√	
Placebo group		√	√	
Assessment				
Underlying disease	√			
Medication	√	√	√	√
Drinking Status	√	√	√	√
Blood uric acid levels		√	√	√
Chinese syndrome score		√	√	√
Renal excretion index		√	√	√
Complications	√	√	√	√
Joints ultrasound		√	√	√
Metabolite evaluation index		√	√	√
Inflammation index		√	√	√
Intestinal microecology		√	√	√
Security indicators		√	√	√
Diet and exercise	√	√	√	√

Figure 2

Participant timeline

Supplementary Files

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- [SPIRIT.docx](#)