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Chinese herbal compound jinji granules for primary premature ejaculation: A study protocol for a randomized, double-blind, double-simulation, multicenter trial

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Abstract

Background: Premature Ejaculation (PE) is one of the common sexual dysfunction. At present, there is a lack of high-quality evidence for Traditional Chinese Medicine (TCM) to treat PE. The trial aims to study the efficacy and safety of Compound Jinji Granules (CJG), a TCM prescription, in treating primary PE, providing evidence-based medical support for PE treatment.

Objective: To assess the efficacy and safety of CJG in treating primary premature ejaculation, pre-intervention and post-intervention evaluations will be compared.

Methods/Design: This study is a multicenter, randomized, double-blind, double-placebo trial. 92 eligible participants who meet the primary PE and diagnostic criteria will be randomly divided into experimental group and control group according to the ratio of 1:1. The experimental group will be given CJG + dapoxetine placebo, and the control group will be given dapoxetine + CJG placebo. Each patient will take the medications for 4 weeks and will be followed-up for additional 4 weeks after withdrawal. The primary efficacy outcome will be the stopwatch-measured average Intravaginal Ejaculatory Latency Time (IELT), while the secondaryoutcomes will include the Premature Ejaculation Profile (PEP), clinical global impression of change (CGI-C), and TCM syndrome score. Safety outcomes will encompass routine tests for hematuria, electrocardiogram readings, and assessments of liver and kidney function.

Results: This study offers a conclusive evaluation of the efficacy of CJG, in halting the progression of primary PE, providing a customizable and cost-effective treatment option.

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Keywords: Primary premature ejaculation; Traditional Chinese medicine; Compound Jinji granule; Randomized controlled trial.

Conclusion: This is the first multicenter, randomized, double-blind, double-placebo, parallel-controlled clinical trial to assess the safety and efficacy of CJG in the treatment of PE. The findings of this study will provide objective clinical evidence for the future use of CJG in treating PE and may also offer an alternative approach for PE treatment. Regardless of whether the results are neutral, negative, or positive, this trial will have a clinical impact on patients with PE.

Introduction

Premature Ejaculation (PE) is the most common male sexual dysfunction, characterized by a brief Intravaginal Ejaculatory Latency Time (IELT), inability to delay or control ejaculation, and negative consequences [1]. The adverse effects of PE extend beyond sexual dysfunction and may also impact confidence and relationships with partners, sometimes leading to psychological distress, anxiety, embarrassment, and depression [2-4]. Based on clinical presentations and characteristics, PE can be classified into two main types: Primary PE and Secondary PE. Primary PE refers to males who have experienced persistent and recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it, over a period of at least 6 months. Key features include the inability to delay ejaculation, negative personal consequences such as distress, worry, frustration, and/or avoidance of sexual intimacy [5].

Dapoxetine is an orally administered short-acting Selective Serotonin Reuptake Inhibitor (SSRI), which acts by modulating serotonin levels in the brain and is currently used as a first-line treatment for PE on an as-needed (prn) basis. This feature distinguishes dapoxetine from other SSRIs, which typically require daily dosing for the effective treatment of conditions such as depression or anxiety. Extensive clinical development programs for dapoxetine's on-demand treatment of PE have confirmed its safety and efficacy, leading to approvals for the treatment of PE in men aged 18-64 by multiple countries. The recommended starting dose of dapoxetine for treating PE is 30 milligrams, with the option to increase the dose to 60 milligrams prn if the desired treatment effect is not achieved and the 30-milligram dose is well-tolerated. Dapoxetine's short-acting nature makes it particularly suitable for on-demand use, allowing it to be taken shortly before anticipated sexual activity.

With its rich historical legacy spanning centuries in China and other Asian nations, TCM presents a compelling array of options for the management of PE [6,7]. In China, a great number of PE patients seek help from TCM, in addition to conventional treatments [8,9]. Besides, clinical trials have shown that TCM and ingredients derived from Chinese herbs are good for patients with PE [10-12]. However, the quality of the studies is low, and high-quality evidence-based evidence cannot be provided [13]. There is a lack of advanced evidence-based medical evidence to confirm its validity and safety.

CJG is an empirical formula for PPE in the andrology department of Xiyuan Hospital. CJG is composed of Radix Astragali seu Hedysari, Rhizoma Acori Graminei, Radix Bupleuri, Radix Paeoniae Alba, Hypericum Perforatum L, Dioscoreae Rhizoma, Morinda officinalis How, Glycyrrhizae Radix et Rhizoma. Our research team had previously conducted small randomized controlled trials, which found that Chinese medicine was safe and effective for PPE [11,12]. However, due to insufficient evidence of its safety and efficacy compared with dapoxetine, CJG have not been widely adopted in clinical practice. Therefore, we propose a multicenter, double-blind, double-placebo, RCT to further compare the efficacy of s with that of dapoxetine hydrochloride in the treatment of PE and to provide high-level clinical evidence for the use of CJG in PPE.

Material and methods

Study design and setting

This study is a double-blind, double-placebo, Randomized Controlled Trial (RCT) conducted across multiple centers, with participants randomized into two parallel groups. Together, we followed the Consolidated Standards of Reporting Trials guidelines Extension for Chinese Herbal Medicine Formulas 2017 (CONSORT CHM Formula) and the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement in designing the study protocol [14,15]. The research protocol obtained approval from the Ethics Committee of Xiyuan Hospital on February 17, 2022 (Approval No. 2021XLA127-4). All researchers are conducting this study in accordance with the Declaration of Helsinki. Informed consent will be obtained from all participants. The study has been registered with the Chinese Clinical Trial Registry in 2022 (Registration No. ChiCTR2200057359).

Our objective is to recruit 92 participants from five research centers in China using a block randomization design, with the allocation ratio set at 1:1. The participating centers include Xiyuan Hospital of China Academy of Chinese Medical Sciences, Jiangsu Provincial Hospital of Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, and Jining Hospital of Integrated Traditional Chinese and Western Medicine. The participant and their sexual partner will undergo an initial screening visit (Visit 1). A research assistant will assist the participant in signing the written informed consent form. Subjects who pass the initial screening evaluation will undergo a 2-week baseline evaluation period, during which subjects must have at least 2 sexual encounters, each separated by a minimum of 24 hours, and record the Intravaginal Ejaculation Latency Time (IELT) for each encounter on a provided diary card. Subjects with an IELT of ≤1 minute for all sexual exposures during the screening period will be eligible to continue in the study, with the average IELT as baseline data. If the subject is eligible for the study, the subject will be randomly assigned to either the treatment or control group in a 1:1 ratio, provided with a new diary card and enough study medication to last until the next clinic visit, and instructed on how to take the medication, with at least 24 hours between sexual encounters during the treatment period. Throughout the trial, subjects will undergo a 4-week treatment period (weekly assessments) and a 4-week follow-up period (every 2 weeks) and will be asked to keep a detailed record of IELT duration and medication in the given diary card. The study's flowchart is depicted in Figure 1, and the schedule for enrollment, intervention, and assessments is outlined in Table 1.

Table 1: Schedule of enrolment, interventions, assessments, and data collection.

Stage	Screening	Enrollment and allocation	Post-allocation				Follow-up	
Time point	**Visit 1**	**Baseline**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	−2w	0 d	1 w ± 2 d	2 w ± 2 d	3 w ± 2 d	4 w ± 2 d	6w ± 3 d	8 w ± 2 d
Information collection								
Demographic information	×							
Clinical examination	×							
Past medical history	×							
Combined medication	×		×	×	×	×	×	×
Informed consent	×							
Enrollment								
Inclusion / exclusion criteria	×							
Allocation		×						
Intervention								
CJG + dapoxetine placebo			×	×	×	×		
Dapoxetine + CJG placebo			×	×	×	×		
Efficacy index								
IELT	×		×	×	×	×	×	×
TCM syndrome score	×		×	×	×	×	×	×
PEP	×		×	×	×	×	×	×
PEDT	×					×		
CGI-C	×		×	×	×	×	×	×
Safety index								
Complete Blood Count	×					×		
Urinalysis	×					×		
Kidney function	×					×		
Liver function	×					×		
Electrocardiogram	×					×		
Adverse event record								
Other content								
Drug distribution		×		×				
Drug recycling and count				×		×		
Distribution of diary cards	×	×						
Collecting Diary Cards	×						×	
Cause analysis of drop-outs	×	×	×	×	×	×	×	

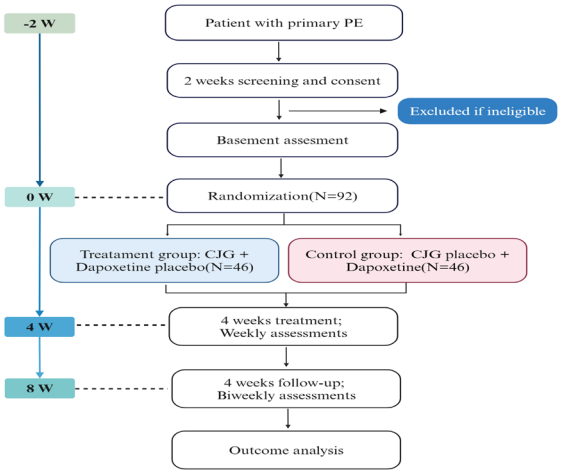

Figure 1: Flow chart of the clinical trial.

Sample calculation

The sample size estimation is based on the average difference in IELT and baseline changes. Previous studies have shown that the efficacy of dapoxetine hydrochloride in treating PE is approximately 2.3±1.3 (minutes) [16]. CJG's efficacy is expected to be similar to dapoxetine. The two-sided significance level is set at 0.025, with a power of 0.8, and the non-inferiority margin is established at 0.8. The trial and control groups are allocated in a 1:1 ratio. Based on these assumptions, the minimum estimated sample size is 84 participants (42 per group). To account for a strict control of study quality and to accommodate a dropout rate of less than 10%, the estimated sample size is increased to 92 participants (46 per group) during the experimental process. This sample size calculation ensures adequate statistical power to detect potential differences in IELT between the trial and control groups while maintaining a reasonable level of confidence in the results. Stringent quality control measures and considerations for potential participant dropout have been taken into account in the sample size estimation.

Randomization and allocation concealment

The allocation sequence will be generated using a block randomization method, stratified by center. Each center will produce corresponding random assignment results, with eligible participants being randomly allocated to the experimental and control groups in a 1:1 ratio. The randomization sequence will be created at Xiyuan Hospital by an independent statistician using SAS 9.4 software. This individual is not involved in participant enrollment, treatment, outcome assessment, data collection, or data analysis. To ensure repeatability, a specific random number seed will be determined. Following stratification based on research center, the resulting random sequence list containing grouping information will be maintained by the Drug Clinical Trial Unit Administrator at Xiyuan Hospital. Details of the randomization process, such as computer-generated random numbers and factors for stratification, will be documented in a separate file to reduce predictability. This document will be inaccessible to those involved in participant enrollment or intervention assignment. In accordance with a random assignment of drug codes, each center will receive drugs with corresponding identification numbers. If the selected cases meet the inclusion criteria, research assistants will sequentially distribute drugs with the respective identification numbers in the order of case inclusion, promptly completing the Drug Dispensing/Recycling Registration Form. The research drugs will be dispensed during medication visits and collected during follow-up visits (or upon returning empty containers). To establish a management system for research drugs, a dedicated counter is designated to store research drugs. These drugs are kept in a well-ventilated, dry, and temperature-appropriate environment, under the unified management of the research drug administrator. Upon completion of the study, the research drug administrator is responsible for centralizing the remaining drugs and returning them to the main research unit or following the prescribed procedures for disposal.

Blinding

During the study, subjects, clinical researchers, and statisticians were blinded to the treatment allocation information. To minimize trial bias, CJG stimulation and Dapoxetine stimulation should comply with relevant pharmaceutical or food standards, exhibit no apparent adverse reactions, and demonstrate no evident therapeutic effects. They should closely resemble the experimental drugs in color, scent, taste, appearance, and texture. Specifications, appearance, packaging, labeling, and identification should be consistent with the experimental drugs. Blinding codes were applied to the investigational drugs (study drug and control drug). Blinded drug kits were prepared by packaging the investigational drugs with an outer covering bearing the blind code number. Emergency letters were prepared for each test code, sealed with disposable, destructible labels to indicate whether they had been opened. An emergency letter has been prepared for each test number, which is sealed and has, among other things, disposable perishable labels to indicate whether or not it has been opened, and is shipped to each clinical research center with the corresponding coded clinical study medication, which is kept in the center's possession, not to be opened except as necessary, and only to be opened to clarify subgrouping information in the event of a medical emergency. If opened, the person responsible, principal investigator, relevant personnel from the drug clinical research institution, opening date, reasons, and other details were documented, and this information was recorded in the Case Report Forms (CRFs). All emergency letters, including those that had been opened, were returned to the Xiyuan Hospital Drug Clinical Trial Institution after the study concluded the leaders of the clinical research unit and the statistician jointly unsealed the emergency letters to perform statistical analysis and processing of the data.

Diagnostic criteria for primary PE

We adopt the definition of primary PE that is developed by the International Society for Sexual Medicine as the first evidence-based definition [17]: (1) The IELT is always less than 1min at the beginning of the first sexual life; (2) The penis always or almost always fails to delay ejaculation after being inserted into the vagina; (3) Rapid ejaculation has negative effects on individuals, such as distress, depression, and fear of sexual life.

Eligibility criteria

Inclusion criteria: (1) Conform to the diagnostic criteria of western medicine for PE; (2) Conform to the TCM syndrome differentiation standard of liver depression and kidney deficiency syndrome; (3) The course of disease exceeds 6 months; (4) 23 ≤50 years old; (5) The frequency of sexual life is ≥1 time/week, and at least 6 times per month; (6) At least in the last three months and in the course of this study, the subject has a stable husband and wife relationship or has a stable adult female sexual partner; (7) Erectile function is normal, International Index of Erectile Function-5 (IIEF-5) score >21; (8) The subject agrees not to use any other premature ejaculation drugs, including SSRIs), Chinese Herbal Medicines (CHMs), or devices used to treat PE during the study period; (9) Subjects (including partners) guarantee that they have no birth plan and voluntarily take appropriate contraceptive measures between the study period and 3 months after the last administration; (10) Subjects voluntarily signed the informed consent form.

Exclusion criteria: (1) Patients with urinary and reproductive tract infections, such as urethritis and prostatitis; (2) Patients with diabetes and nervous system diseases; (3) Patients with cardiovascular disease; (4) Patients with liver and kidney dysfunction; (5) Abuse of psychotropic drugs; (6) Patients with other sexual dysfunction; (7) Patients who are being treated with other drugs.

Discontinuation criteria: Serious Adverse Events (SAEs) caused by the trial drug; poor or even complete ineffectiveness

of the trial drug; discovery of errors in the protocol or significant deviations between the protocol and actual practice; decision to terminate the study for any reason by the drug regulatory authority or the sponsor; concomitant treatments and prohibited drugs.

Comorbidities, prohibited medications, and emergency medications allowed during the trial

Participants will be allowed to receive concurrent treatment for comorbid conditions such as chronic bronchitis, asthma, skin diseases, etc., which will not impact the final results of the trial. However, during the trial, participants are prohibited from using any other medications for the treatment of PE, including but not limited to SSRIs, local anesthetics, and other CHMs that may interact with CJG and dapoxetine or affect their efficacy. Each concurrent treatment should be strictly documented in the CRFs, and if a participant is found to be taking prohibited medications, they will be withdrawn from the study. In clinical trials, investigators should closely observe or follow up with participants for various reactions after medication to promptly detect adverse events or SAEs and provide symptomatic treatment. During the trial, in the event of adverse events or other health risks, the research team has the authority, based on medical judgment, to provide necessary treatment, including discontinuation of the investigational drugs. In emergency medical situations, participants may receive necessary emergency medical interventions, regardless of their association with the investigational drugs.

Recruitment and informed consent

From March 2022 to September 2024, recruitment of PE patients will be conducted through media releases from five hospitals, including promotion on WeChat public accounts and postings on hospital bulletin boards. Prior to randomization, a 2-week baseline assessment will be performed. During the assessment period, recruitment staff will introduce the purpose of the study to eligible and willing participants, obtain informed consent, and initiate the first visit. A research assistant will conduct a preliminary assessment of patient information, and a senior urologis will conduct a final review to identify and invite eligible patients to participate in the study. No further biological samples will be collected for storage or utilization in this study.

Intervention

The CJG used in the treatment group (herbal granules, 13.33 g/packet) and the CJG placebo used in the control group were provided and quality-controlled by Beijing Kangrentang Pharmaceutical Co., Ltd. (Beijing, China). The packaging and labeling of the two medicines were kept consistent. The CJG placebo is composed of 5% original herbs and 95% starch, with the same dosage form, color, appearance, weight, and usage as CJG. The treatment duration is 4 weeks, with a dosage of 1 packet twice daily, taken 30 minutes after breakfast and dinner with warm water. Dapoxetine and dapoxetine placebo are produced by Sichuan Kelun Pharmaceutical Co., Ltd., with consistent packaging and labeling. The placebo is made of starch and is identical to dapoxetine in terms of dosage form, color, appearance, smell, weight, and usage. The treatment duration is 4 weeks, with dapoxetine taken orally 3 hours before sexual activity, at a dose of 30 mg each time. Participants are instructed to engage in sexual activity at least once per week, totaling at least six times per month.

If patients experience any severe illness or SAEs related to the study, the trial will be immediately halted, and appropriate interventions will be administered. Compensation will be provided based on the nature and severity of the harm suffered by the trial participants. Following the completion of the study, clinical practitioners will continue to offer complimentary health advisory services, and they are obligated to propose further treatment options for patients as deemed necessary.

Outcome measurements

The investigators will follow up with the subjects at weeks 1, 2, 3, and 4 of dosing and at weeks 2 and 4 after the end of dosing to assess the therapeutic efficacy and recurrence of PE.

Primary outcome

The primary outcome measure is change in average IELT from baseline to 4 weeks of double-blind treatment. Participants are instructed to have their sexual partners measure IELT using a stopwatch and promptly record the duration in a diary card after each sexual activity. We will document the changes in IELT from baseline levels throughout the 4 weeks after discontinuation.

Secondary outcomes

(1) the degree of improvement in mean IELT from baseline to 4 weeks of double-blind treatment (proportion of subjects with mean IELT >1 minute and proportion of subjects with mean IELT >3 minutes); (2) changes in the dimensions of control of ejaculation, satisfaction with sexual intercourse, personal distress, and interpersonal difficulties at weeks 1, 2, 3, and 4 of the PEP; (3) changes in the dimensions of symptoms on the TCM Symptom Scale at weeks 1, 2, 3 and 4; (4) changes in PEDT scores after 4 weeks of double-blind treatment compared to baseline; (5) evaluation of the treatment effect in the CGI-C during the 4-week double-blind treatment period from baseline (proportion of subjects reporting at least one “better” response and proportion of subjects reporting at least one “slightly better” response). The PEDT is a self-assessment scale used to evaluate the severity of PE, including issues related to ejaculation control ability and penile sensitivity. The total score ranges from 0 to 30, with higher scores indicating more severe PE symptoms. PEDT is typically classified according to the following criteria: 0-7 points suggest the absence of PE or relatively mild symptoms, 8-14 points indicate mild to moderate PE, and 15 points or above suggest potentially severe PE.The PEP is a self-assessment scale used to evaluate PE. It is more concise than the PEDT scale, focusing on assessing patient satisfaction with sexual life. PEP covers four aspects: control of ejaculation, sexual satisfaction, distress caused by PE, and the quality of the partner’s relationship. The total score ranges from 0 to 16, with higher scores indicating less severe PE.CGI-C refers to the overall clinical impression of change, tracking patients’ overall improvement or deterioration during treatment. It assesses seven levels, including very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse.The TCM syndrome scale is a questionnaire used to assess symptoms. It consists of six items, and the total score ranges from 0 to 24. A higher score indicates a more severe manifestation of symptoms. All on-site assessments are conducted in a separate room at the research center’s andrology clinic, and all assessors receive training on how to conduct interviews and measurements before the study.

Assessment of safety

Throughout the entire course of the study, while closely observing therapeutic efficacy, particular attention will be paid to monitoring adverse reactions or unforeseen toxic side effects. This includes symptoms, signs, laboratory examinations (complete blood count, urinalysis, liver function tests including alanine transaminase and aspartate transaminase, and renal function tests including blood urea nitrogen and creatinine, as well as electrocardiograms). For any adverse reactions occurring during the study, the symptoms, severity, onset time, duration, interventions, outcomes, etc., should be documented for each study case. Physicians should refrain from leading questions, assess the relevance to the investigational drug, and record the details, signature, and date. Researchers may decide to discontinue the trial based on the patient's condition. In the event of any SAEs, immediate medical assistance will be sought. The incidence of adverse reactions will be statistically recorded.

Data collection and management

The randomization data will be provided by dedicated statisticians from Xiyuan Hospital. A well-defined data collection plan, including participant intervention data and data on interruptions or deviations, will be implemented and collected by specialized research assistants. Statistical analysis result data will be provided by independent statisticians. The primary and secondary outcomes of this trial will be assessed at baseline and during the 1st, 2nd, 3rd, 4th, and follow-up periods of treatment. Data for each visit must be collected within 2 days before or after the scheduled time, with safety checks conducted at baseline and the 4th week through self-reports and laboratory examinations. To ensure comprehensive data collection, throughout the trial, we will use social media to remind participants of regular medication, encourage them to maintain diligent diaries, and provide free examinations and treatments with flexible appointment times based on participants' schedules. All study personnel will undergo uniform training before the study commences, providing detailed training and explanation of the trial protocol, Standard Operating Procedures (SOPs) for study operations, and the content of CRFs, ensuring adherence to a common protocol by all study personnel. Each research center will designate a well-trained research assistant for data collection, who will record detailed information, including participant compliance, concomitant medication, and primary and secondary outcomes, in the CRFs. Supervisors will regularly check the completeness of CRFs entries. For participants who discontinue, the reasons, timing, and any relevant information will be collected. Researchers will appropriately handle interruptions or deviations as required and assess their potential impact on outcomes. All study-related documents and records, as well as other relevant information, will be used solely for the purpose of the project's research, securely stored in locked file cabinets with limited access, and visible only to the principal investigator. The principal investigator will oversee all procedures, including data collection and analysis, during the study and will have the authority to access the cleaned dataset for further analysis and research.

Statistical analysis

At the conclusion of all measurement data collection, statistical analysis will be conducted by a statistician unaware of the group assignments using SAS software version 9.4. In terms of demographic and baseline characteristics, continuous variables such as age and disease duration will be expressed as mean ± standard deviation (SD) and analyzed using independent sample t-tests, while categorical variables such as education level and marital status will be analyzed using analysis of variance (ANOVA) or Kruskal-Wallis tests. Regarding the primary efficacy endpoint, the changes in the average IELT over each week during the 4-week double-blind treatment period will be described. Between-group comparisons of IELT change values will be analyzed using covariance analysis considering center and baseline as covariates, and the between-group differences will be calculated using the least squares method along with 95% confidence intervals. In terms of secondary efficacy endpoints, the study will describe the changes in weekly scores of PEP, PEDT, and TCM symptom scale scorein each dimension during the 4-week double-blind treatment period. Between-group comparisons of changes in PEP, PEDT, and TCM symptom scale score dimensions will be analyzed using covariance analysis considering center and baseline as covariates. The least squares method will be employed to calculate between-group differences along with 95% confidence intervals. Additionally, the study will summarize the proportion of subjects with average IELT greater than 1 minute and greater than 2 minutes during the 4-week double-blind treatment period. Between-group comparisons of the distribution proportions of average IELT durations will be conducted using the Cochran-Mantel-Haenszel (CMH) chi-square test, considering center factors. For repeated measurements of efficacy endpoints, a repeated measures mixed-effects model analysis will be conducted. Safety analysis will include the description of the number and incidence of adverse events and reactions, as well as clinically significant abnormal laboratory test results. In the double-blind phase, the mean IELT of subjects who dropped out was primarily analyzed based on available measurements, whereas the mean IELT of subjects who did not provide IELT measurements was set as the mean baseline IELT. For the PEP, PEDT, and TCM symptom scale scoredimensions, the primary analyses were conducted using the end-observations carryover to replace missing data. The statistical analysis sets include the Intention-to-Treat (ITT) population, consisting of randomized subjects who received the study drug, for baseline characteristic and efficacy analyses. Additionally, the Per-Protocol Set (PPS) population will be used for the primary efficacy endpoint analysis. Safety analysis will be conducted using the Safety Set (SS). We did not plan to conduct a midterm analysis due to the low risk of both interventions and the short duration of the interventions.

Monitoring compliance

The following committees were established for this experiment. Principal Investigator, Advisory Committee, Methodology Center Staff, Data Monitoring Committee and On-site Auditors. In addition, an independent supervisory committee, with supervisors selected by the GCP Center at Xiyuan Hospital, will be established to examine the data every 1 month and determine whether the trial should be modified or stopped. The monitors are qualified to oversee the progress of clinical research to ensure the protection of subjects' rights, the authenticity, accuracy, and completeness of research records and reports, and adherence to approved protocols and relevant regulations. A formal interim analysis is not planned for this study.

Biological specimens

Blood samples for clinical laboratory testing in this study will be destroyed upon completion of testing.

Protocol amendment

Any modifications to the protocol that may affect the conduct of the study, the potential benefit to patients, or may affect patient safety will require re-review by the Xiyuan Hospital Ethics Committee, and timely updating of the trial registry and protocol after approval.

Quality management

The protocol has undergone multiple reviews by experts in TCM and methodology. Prior to the commencement of the trial, all study personnel will be required to undergo standard operating procedure training to ensure that each member is familiar with the trial protocol. Throughout the trial, the research team will conduct monthly seminars to assess trial progress, clinical feasibility, adverse effects, etc., enabling appropriate adjustments to be made.

Discussion

The aetiology of PE is unknown, with few data to support suggested biological and psychological hypotheses. There is still little consensus about the definition and classification of PE [18]. Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [19,20], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [21].

This is a randomized, double-blind, double-placebo, multicenter trial for PE patients. The classic definition of PE includes the following three aspects: (1) the latent time of vaginal ejaculation is short; (2) Lack of ejaculation control ability; (3) Influence on patients' quality of life. According to this requirement, ISSM's definition of PE quantifies IELT, which is more suitable for clinical and research applications. In this study, IELT is used as the primary efficacy indicator. But IELT anomaly range remains controversial, because there are individual differences. In fact, it is difficult to accurately define exactly how long IELT does not belong to the PE, studies have shown that only on the basis of IELT cannot effectively distinguish between presence of PE, must also be considered clinically patients to control the ejaculation of sexual intercourse ability and whether the two sides can achieve sexual satisfaction [22,23]. This is also the reason why PEP and CGI are used as secondary outcomes in this study.

Dapoxetine is used as a control drug in this study. Dapoxetine, a short-acting SSRIs, is an oral medication indicated for the on-demand (prn) treatment of PE. An extensive clinical development program of the on-demand treatment of PE with dapoxetine has substantiated its safety and efficacy [24,25]. The recommended starting dose is 30 mg prn, with an option in most countries to escalate the dose to 60 mg prn if the treatment effect is insufficient and the 30 mg dose is well tolerated. Dapoxetine has been approved for the treatment of PE in China, however the discontinuation rates of dapoxetine is high, and the main reasons are overexpectation of efficacy and high cost, which means patients need to be fully informed and communicated in the trial [26].

Regardless, several potential limitations of this study should be considered, the design is lacking a CJG + Dapoxetine group, which can be conduct in next studies. Another limitation is that we did not perform a long-term follow-up in terms of observation and surveys at the end of the study period.

In conclusion, this trial will provide high-quality evidence for CJG for PE as a conjunctive therapy. Whether the results are neutral, negative, or positive, this trial will have clinical implications for patients with PE.

Pilot status

The current trial protocol version is 1.0, officially registered on March 9, 2022. Patient recruitment for this study commenced on June 24, 2023, and as of the manuscript submission, the study is actively enrolling participants.

Declarations

Acknowledgement: Not applicable.

Supporting information: S1 Checklist. SPIRIT 2013 checklist.

S1 File. Research protocol.

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Competing interests: The authors declare that they have no conflicts of interest.

Data availability: At this stage, no datasets have been generated. However, upon completion of the study, the data will be made available upon reasonable request. Finally, the results will be disseminated through scientific and academic conferences and published in peer-reviewed journals. The full protocol and model consent form will be available from the corresponding author on reasonable request.

Trial registration: Chinese Clinical Trial Registry (CHICTR): ChiCTR2200057359. Registered on 9 March 2022. (https://www.chictr.org.cn/showproj.html?proj=153220)

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