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Efficacy and safety of the Chaihuguizhiganjiang-suanzaoren granule on primary insomnia: study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Insomnia is a highly prevalent, often debilitating and economically burdensome sleep disorder with limited effective therapies. Few data are available to understand which of the therapeutic alternatives is the most effective for patients with insomnia, especially for Traditional Chinese Medicine (TCM). Chinese herbal medicine, as a typical TCM, is one of the most popular complementary and alternative therapies for insomnia. We aim to evaluate the efficacy and safety of the Chaihuguizhiganjiang-suanzaoren granule (CSG), a Chinese herbal medicine treatment, in patients with primary insomnia.

Methods and analysis: This is a multicentre, placebo-controlled, double-blinded, randomised controlled clinical trial. A total of 258 participants are randomly allocated to two groups: the intervention group or the placebo group. The intervention group receives CSG and the placebo group receives a placebo granule. The patients receive either CSG or placebo two times daily for 8 weeks. The primary outcome is the Pittsburgh sleep quality index (PSQI). Secondary outcomes include the Insomnia Severity Index (ISI), Total Sleep Time (TST) and the Short-Form Health Survey (SF-36). The assessment is performed at baseline (before randomisation), 4, 8 and 12 weeks after randomisation.

Ethics and dissemination: The protocol has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (reference: 2014BL-003-01). The trial will be helpful in identifying the efficacy and safety of CSG in patients with primary insomnia.

Trial registration number: ISRCTN22001145; Pre-results.

BACKGROUND

Insomnia is a highly prevalent, often debilitating and economically burdensome sleep disorder.[1] The prevalence of at least one type of insomnia was 9.2% in rural and urban regions of Beijing, China; the rates of difficulty initiating sleep, difficulty maintaining sleep and early morning awakening were 7.0%, 8.0% and 4.9%, respectively.[2] The literature suggests that relationships exist between insomnia and major depression, anxiety disorders, substance abuse, suicide, decreased immune functioning and cardiovascular disease.[3] Treatment options for chronic insomnia include pharmacological therapy and non-pharmacological therapy. Pharmacological therapy, particularly benzodiazepines and non-benzodiazepines, is widely prescribed for insomnia, but its role in the management of chronic insomnia is uncertain because of the long-term efficacy and potential for abuse, dependence and adverse effects.[4] Psychological and behavioural therapies of insomnia, including relaxation training, paradoxical intention, stimulus control, sleep restriction and cognitive therapy, are supported by empirical evidence. Among these treatments for insomnia, multicomponent cognitive-behavioural therapy is effective in the short and long terms with few apparent side effects.[4 5] Currently, a proportion of patients with insomnia worldwide resort to various kinds of complementary and alternative medicine. In 2002, a national survey in the USA showed that 4.5% of adults reported using some form of complementary and alternative medicine to treat insomnia or trouble sleeping.[6]

Chinese herbal medicine (CHM), as one of the most popular complementary and alternative therapies of insomnia, either in single herb or in herbal formula, has been commonly used for treating insomnia in Asian countries. Systematic reviews reported that the effects of Chinese herbal medicine were similar to Western medication and

placebo. Owing to the poor methodological quality of the studies and the small number of trials included in meta-analyses, these systematic reviews conclude that the current evidence is insufficient to support the efficacy of CHM for insomnia.[7–9] There is a clear need for further research in this area.

According to the theory of typical Traditional Chinese Medicine (TCM), all the related symptoms and signs in a certain disease phase are generalised to a syndrome ('Zheng' in Chinese medicine), which is the basic unit and a key concept of TCM.[10] Patients with insomnia can be divided into different syndromes (ie, different Zhengs). In the diagnosis of insomnia, the 'spleen deficient and liver heat syndrome' is the main subtype diagnosed from the viewpoint of TCM and our previous clinical practice.[11] Therefore, we consider 'Harmonizing liver and spleen' as the main principle of treatment. Chaihuguizhiganjiang decoctions are a type of Traditional Chinese Medicine chronicled in Shang Han Lun. Suanzaoren decoctions have a long history of use as part of the traditional Chinese pharmacopoeia first documented in the classical Chinese text Jin Gui Yao Lue (essential prescriptions from the golden cabinet) in approximately 210 A.D. by Zhong-Jing Zhang. According to classic theory, Chaihuguizhiganjiang decoctions are beneficial for eliminating liver heat syndrome, while suanzaoren decoctions aid in replenishing the spleen. Together, these two classical compounds cooperate to nourish the spleen and clear liver heat. Tan Y reported that Chaihuguizhiganjiang decoctions plus acupuncture had remarkable effects on improving sleep quality.[11] A population-based study mentioned that suanzaoren decoctions are the most commonly used Chinese herbal products that were coadministered with hypnotic drugs in treating insomnia.[12] However, despite the popular use of Chaihuguizhiganjiang decoctions and suanzaoren decoctions, there is little scientific evidence supporting the efficacy of the clinical use of both. In our preclinical observation, we evaluated 50 patients with primary insomnia with spleen deficiency and liver heat syndrome by sleep diary recording bedtime, rise time, total sleep time and sleep efficiency. Compared with baseline, there were significant differences for total sleep time ($p=0.03$) and sleep efficiency ($p=0.04$) after 8 weeks treatment. We found that Chaihuguizhiganjiang decoctions in combination with suanzaoren decoctions were effective in sleep quality improvement in patients with insomnia with few adverse events (data unpublished). The aim of this multicentre, randomised, double-blind, placebo-controlled study is to evaluate the efficacy and safety of the Chaihuguizhiganjiang-suanzaoren granule (CSG) in patients with primary insomnia.

METHODS/DESIGN

Ethics

The study is performed according to the Declaration of Helsinki, and the International Conference on Harmonisation (ICH)/WHO Good Clinical Practice standards (GCP) including certification by an external audit and has been approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (reference: 2014BL-003-01). This trial has been registered with ISRCTN at Current Controlled Trials (ISRCTN 22001145) on 15 May 2014. At the beginning of the study, we prepared for making case report forms and training the relevant researchers. After all of these preparations were completed, a recruitment poster was displayed outside of clinics in September 2014. Therefore, the first patient was finally recruited on 3 September 2014. Before randomisation, all patients are requested to sign a written informed consent. They are also given enough time to decide whether they are willing to participate in the trial or prefer other treatment options.

Study population

A total of 258 patients are recruited from three centres: the Department of Psychosomatic medicine, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, the Department of Encephalopathy, Dongfang Hospital affiliated to Beijing University of Traditional Chinese Medicine and the Department of Insomnia, Depression, and Anxiety, Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine. The trial is executed from September 2014 to September 2016.

Recruitment of participants

Two strategies are used to recruit patients with primary insomnia. One is to display recruitment posters outside the clinics. The posters contain brief introductions about the population needed, the free Chinese herbal medicine treatments offered to eligible participants, and the contact information of the researcher. The other is to recruit participants in outpatient clinics from the Department of Psychosomatic medicine, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, the Department of Encephalopathy, Dongfang Hospital affiliated to Beijing University of Traditional Chinese Medicine, and the Department of Insomnia, Depression, Anxiety, Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine.

Inclusion criteria

Participants are included if they are aged between 18 and 65 years, of either sex, fulfil the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition criteria for primary insomnia,[13] the TCM syndrome pattern criteria (pattern of spleen deficiency and liver heat syndrome), present with a primary complaint of sleep difficulties for at least 1 month, have sleep difficulties for more than 3 days during the last week, and give written informed consent.

Exclusion criteria

Criteria for exclusion are insomnia caused by drugs, alcohol, pain or physical and mental illness, a self-rating anxiety scale ≥60[14] or self-rating depression scale ≥63,[15] an ongoing alcohol or substance abuse problem, a history of stroke or coronary heart disease, women in pregnancy or lactation or without contraception, an abnormal liver function and heavy somatic disease, or by participating in other clinical trials.

Handling of withdrawal and data management

Participants may withdraw from the study at any time for any reason. If any patients wish to withdraw, clinicians should ask whether they would be willing to complete the assessments according to the study schedule and write down their last time of taking the medicine. Incidences of patient loss to follow-up and withdrawal will be recorded and reported. Patients in the placebo group could withdraw from the study if they are determined as requiring withdrawal based on disease progression, serious complications, or if they voluntarily quit. The data collected in this trial comprises information recorded in case report forms. When every visit is completed at each centre, data will be entered using the double entry method.

Concomitant treatments and forbidden drugs

This trial is not to be combined with any of the following interventions, including other sleep medications (such as zolpidem, zopiclone, alprazolam), antipsychotics, antidepressants, drugs acting on the central nervous system, and any healthcare products or food and beverages that may cause insomnia or hypnotic effects. It is acceptable for patients to have taken other drugs that do not affect the central nervous system before the trial. The dosage, duration and name of any concomitant treatment or medication must be recorded carefully in the CRFs.

Interventions

Study interventions are developed in a consensus process with TCM experts, and performed by three trained and licensed TCM doctors who are qualified for at least 5 years. One researcher (JZ) trains the doctors in the study procedures to monitor compliance with the protocol throughout the study. All patients go through a standardised interview and receive more information about the study and treatments. After obtaining informed consent from each participant and completing a baseline evaluation, patients who meet the inclusion criteria and none of the exclusion criteria are randomised to one of two treatment groups: the intervention group, which receives CSG, or the placebo group, which receives the granule of placebo. The TCM granules are compound preparations of Chinese herbs, and their main components are shown in table 1. The placebo granule is composed by 5% of CSG and 95% starch. The colour is made identical to that of CSG by adding artificial pigment. The placebo granule is similar to the intervention group in the aspects of colour, taste, smell and package.

Table 1 Main components of traditional Chinese medicine treatment

Chinese name	Latin name	Amount (%)
Chaihu	*Bupleurum chinense*	8.0
Guizhi	*Cinnamon Twig*	5.2
Ganjiang	*Dried Ginger*	5.2
Tianhuafen	*Radix Trichosanthis*	5.2
Muli	*Calcined Oyster*	5.2
Huangqin	*Scutellaria*	5.2
Danshen	*Salvia miltiorrhiza*	5.2
Chenpi	*Citrus reticulata Blanco*	5.2
Chaosuanzaoren	*Ziziphus jujuba*	31.5
Fuling	*Poria Cocos*	6.3
Chuanxiong	*Ligusticum chuanxiong*	6.3
Zhimu	*Anemarrhena aspodeloidea*	6.3
Zhigancao	*Glycyrrhiza glabra*	5.2

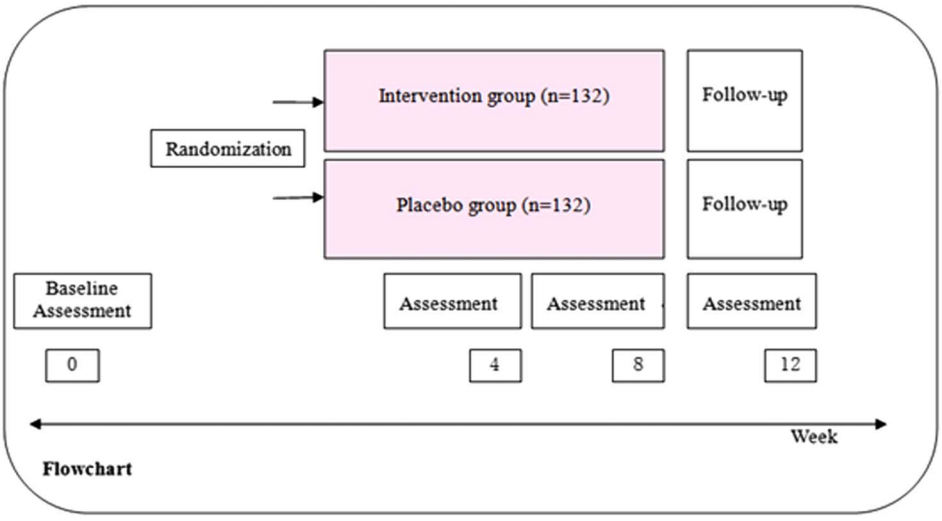
All test drug packages are dispensed and reclaimed by trained research nurses (JY, J-LW, M-MW) in each centre. These nurses are also responsible for storing and keeping records of test drugs. Meanwhile, an investigator (X-QZ) would check each completed questionnaire in the three centres once a month to ensure the quality of the Case Report Form. Patients are administered CSG or placebo in one bag (10.015 g per bag) dissolved in warm water two times daily for 8 weeks. Time points are as shown in figure 1.

The test drugs are manufactured by Kangrentang Pharmaceutical Co Ltd, Beijing, China.

Randomisation and blinding

Randomisation is performed by an independent statistician (HT). The randomisation sequence (blocked, stratified for centres) is generated by use of SAS software (SAS Institute, Inc., Cary, North Carolina, USA). Each centre receives consecutively coded drugs. All of the drugs provided by the pharmaceutical company are numbered with a label according to the randomisation schedule. This trial is a double-blind trial. The first level is for the case number corresponding to groups (group A and group B), and the second level is for the group corresponding to the intervention (the intervention and placebo groups). The numbers are kept in opaque sealed envelopes. The double levels of blinding are sealed separately and given to the leader of the clinical research. Emergency letters are sent to each of the centres, saved with the test drug, and properly preserved until the end of the trial. Treatment assignments are not revealed and are blinded to the patients and investigators (including statisticians) until the entire study is completed.

Figure 1 Flow chart.



Primary outcomes

The Pittsburgh sleep quality index (PSQI) is applied as primary outcome measurements for efficacy evaluation. The global PSQI score is utilised, with a total possible range from 0 (good sleep quality) to 21 (poor sleep quality). In the current sample, PSQI scores comprise 19 self-rated questions and five other questions. The seven component scores are then added to provide a PSQI score.[16] Assessments are measured at baseline (before randomisation) as well as at 4, 8 and 12 weeks after randomisation.

Secondary outcomes

Insomnia Severity Index (ISI) is a self-report questionnaire used to assess the level of insomnia severity.[17] Assessments are measured at baseline (before randomisation) and at 4, 8 and 12 weeks after randomisation. Patients are required to record their sleeping information every day. Participants complete sleep diaries each morning for 1 week prior to starting the experimental therapy and during the study. The sleep diary is a daily patient log that records bedtime, rise time, sleep onset latency, number and duration of night-time awakenings, and sleep quality. Total sleep time and sleep efficiency (total sleep time/time in bed×100) are the primary dependent variables derived from the sleep diary, although sleep quality, sleep onset latency, number of night-time awakenings, and wake after sleep onset are also analysed.

The Short-Form Health Survey (SF-36) is a self-report questionnaire used to assess quality of life.[18] Assessments are measured at baseline (before randomisation) and at 4, 8 and 12 weeks after randomisation.

Safety outcomes

A routine blood test, routine urine test, routine stool test, liver function test, renal function test and an ECG are administered for safety outcomes. These biological indicators are monitored during the period of screening and after 8 weeks treatment.

Adverse events

At every visit, adverse events and vital signs are recorded. The major indicators for vital signs include breath, temperature, systolic blood pressure, diastolic pressure, pulse and so on. Generally, any unexpected symptom, vital sign or sickness, as long as they cause discomfort, shall be recorded as an adverse event. The starting date, ending date, degree, relations with the trial medicine, and whether they drop out of the study will be recorded correspondingly. Severe adverse events are required to be reported to the leader of the trial, ethics committees and sponsors within 24 h, and participants will be provided with every necessary treatment. If the adverse event still exists, the follow-up will continue until the adverse event disappears.

Sample size

The trial aims to detect a difference in quality of sleep between the two study groups. This is deemed a clinically significant difference of an average three-point reduction on the PSQI scores in the intervention group when comparing with the placebo group based on a previously published study.[19] The SD is 4.25 in the intervention group and 3.95 in the placebo group, respectively, as a previous study has suggested.

The following formula is used for a two-group trial:

$$n_1 = n_2 = 2\left[\frac{(\mu\alpha + \mu\beta)s}{\delta}\right]^2$$

On the basis of α=0.05, β=0.2, the required sample size is approximately 112 participants for each group. Allowing for 15% attrition, we should recruit 258 participants, with 129 in each group.

Data analysis

Data analysis will be conducted by statisticians who are independent from the research team. An intent-to-treat analysis (ITT) for the patients, who have received treatment at least once, will be carried out. Missing data will be adjusted using the last observation carried forward method. The per-protocol analysis will be restricted to participants who strictly follow the protocol and complete the study. The mean and SD are applied to the continuous variables, and percentages to the categorical variables. Pearson's χ^2 test or Fisher's exact test will be performed on categorical variables, Student's t test on continuous normally distributed variables and the Wilcoxon rank sum test on non-normal variables. Owing to the multicentre design, the analysis of covariance adjusted for clinical centre and baseline will be used in this study. The statistical significance level will be set at $p<0.05$ and 95% CI will be calculated. 95% CI is used regarding continuous variables. Every analysis is conducted using the SPSS software (SPSS V.16.0 KO for Windows ©).

DISCUSSION

A previous systematic review evaluated 12 RCTs with a total of 1376 adult participants,[8] and found that only three articles reported the method of random sequences generation.[20–22] In addition, none of the included trials described allocation concealment. Blinding is an essential method for preventing research outcomes from being influenced by either the placebo effect or the observer bias. However, only one study reported the blinding of participants.[23] Moreover, no placebo control was used to mask participants and care providers. This multicentre randomised double blind, placebo-controlled study aims to test the efficacy of CHM through comparison between an intervention group and a placebo group. To facilitate appropriate high-quality methodology and strict quality control, this protocol has been developed according to the CONSORT statement[24] and SPIRIT 2013.[25] We describe in detail our method of recruitment, randomisation and allocation concealment, and data collection. In addition, we report the TCM intervention according to Recommendations for Reporting Randomized Controlled Trials of Herbal Interventions.[26] Completion of this trial may highlight evidence on the effectiveness and safety of CHM. The results of this study may generate scientific and rigorous evidence for CSG in patients with primary insomnia.

In TCM theory, different Chinese clinicians possess different ideas on diagnosis and treatment. One or more than one core prescription could therefore possibly be obtained. In this case, the question is raised regarding whether the explored core prescription can be generalised from the current study. The spleen deficiency and liver-qi stagnation transforming into fire is a principal pathogenesis of insomnia based on TCM theory. Some factors such as chronic fatigue, mental stress and emotional tension cause the deficiency of spleen and liver. This leads to metabolic disorders of qi-blood and body fluids and disturbance of Zang fu functions, causing the occurrence of insomnia. Therefore, we propose to treat insomnia according to the principle of harmonic liver and spleen.

Our study has some limitations. One limitation is the absence of polysomnographic sleep parameters. Our study relies only on su+bjective sleep outcomes, which mainly are assessments of patient reports of improved sleep and well-being. Future studies are needed to address these issues. Another limitation is that decoctions are used in preclinical trials, but granule is applied in this study. However, compared with decoctions, granules are more convenient for patients in the study, and patient compliance may be increased. In addition, when we started to design our study protocol, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) had not been published. We decide to use DSM-IV according to prepublished trials. Compared with DSM-IV, DSM-5 shifts towards more data-driven diagnostic criteria, general applicable scope, diagnostic precision improving, emphasising on using biomarkers. In our future studies, DSM-5 will be used to diagnose insomnia disorder.

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