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Efficacy of acupuncture treatment for chronic spontaneous urticaria: study protocol for a randomised controlled trial

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Abstract

Introduction Chronic spontaneous urticaria (CSU) is a troublesome dermatological problem that can have a significant impact on quality of life. Previous studies have indicated that acupuncture may be beneficial for patients with CSU. However, well-designed studies determine the effects of acupuncture on CSU are rare. The aim of this study is to investigate the efficacy and safety of acupuncture treatment for patients with CSU.

Methods and analysis This study is designed as a multicentre, parallel, three-arm, randomised, sham-controlled trial. A total of 330 patients diagnosed as CSU will be randomly allocated into three groups: the verum acupuncture group, the sham acupuncture group, and the waiting-list control group in a 1:1:1 ratio. Patients in the verum and sham acupuncture groups will receive 16 treatment sessions over 4 weeks, while patients in the waiting-list control group will not receive any acupuncture treatment. The primary outcome is the changes of weekly urticaria activity scores (UAS7) at the end of treatment. Secondary outcomes include itching severity measurement, Dermatology Life Quality Index (DLQI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Pittsburgh Sleep Quality Index (PSQI), and serum total immunoglobulin E (IgE) level. Adverse events will be recorded during the study observation period. All patients who are randomised in this study will be included in the intent-to-treat (ITT) analysis.

Ethics and dissemination Ethical approval of this study has been granted by the Sichuan Regional Ethics Review of Committee on Traditional Chinese Medicine (TCM) (ID: 2019kl-006), the Medical Ethic Committee of the First Hospital of Wuhan (ID: [2019] No. 7), and the Medical Ethic Committee of the First Hospital of Hunan University of TCM (ID: HN-LLKY-2019-017-01) in three clinical centres in China, respectively. The results will be disseminated through peer-reviewed journals.

Trial registration: ChiCTR1900022994.

Strengths and limitations of this study

- This is the first study to provide information about the efficacy and safety of acupuncture treatment for patients with chronic spontaneous urticaria (CSU) by comparing verum versus sham acupuncture and waiting-list.
- The risk of bias will be reduced by rigorous methodology, including adequate randomisation, quality control, and the use of blinded outcomes assessors and statisticians.
- Eligible participants will be strictly recruited and screened in three tertiary A hospitals in China, the results may not apply to patients in other countries.
- Because of the nature of acupuncture, unblinded participants and treatment providers are likely to bring bias and be influencing the results.

INTRODUCTION

Chronic urticaria (CU) is a dermatological condition defined as the recurrence of itchy wheals and/or angioedema daily, or almost daily, lasting at least 6 weeks.[1] The estimated prevalence of CU ranges from 0.5% to 1.0% in the general population.[2] Most of the affected patients are between 30 and 50 years old, and there is a significantly higher incidence in women than in men.[3 4]

There are two types of CU: chronic spontaneous (idiopathic) urticaria (CSU) and chronic inducible urticaria (CIU). The main difference between the two is the former type occurs without identifiable triggers.[1 2] Several studies reported that CU has a significant negative impact on patients' quality of life (QoL)[1 5] in terms of sleep and daily activities, such as work, study, recreation and social interaction.[5-8] The decrease in QoL reported by patients with CU was comparable to that of patient with coronary artery disease[9] and psoriasis.[10] The high rates of absenteeism from work and school because of sick leave and medical care,[7] as well as for various autoimmune[11] and psychological[5 12] comorbidities, directly and indirectly increase the economic burden for patients with CU.[8]

According to the consensus on the treatment options for CU, non-sedative H1-antihistamine is the first-line medication, and the doses could increase up to four-fold in refractory cases as the

second-line medication.[1] According to the 2017 version of guideline, omalizumab and cyclosporine A are recommended as the third- and fourth-line therapy, respectively, for who fail to respond to H1-antihistamine.[1] Although omalizumab has been reported effective and safe for CU in recent studies,[13 14] the high cost are burdensome for most patients. Because of the higher incidence of adverse effects, cyclosporin A cannot be recommended as standard treatment.[15]

Acupuncture, which has been used for more than 3000 years, has been widely applied in clinical practice to treat dermatological problems.[16 17] According to the literatures, acupuncture has been applied for a long time in China to treat urticaria. A systematic review included six randomised controlled trials (RCTs) studying the effectiveness and safety of acupuncture treatment for patients with CU.[18] Although the evidence supported that patients with CU may benefit from acupuncture treatment, the poor methodology of the RCTs, particularly in choosing controls and outcomes for assessing the symptoms and QoL, makes the evidence less confirmative.

To counter these deficiencies, a prospective, parallel, three-arm, randomised, sham-controlled trial with a large sample size will be carried out to investigate the efficacy and safety of acupuncture treatment for patients with CSU, comparing them with sham acupuncture and waiting-list control groups. We hope the findings from this study will provide solid evidence for the efficacy of acupuncture treatment for CSU.

METHODS

Study design

This is a multicentre, parallel, three-arm, randomised, sham-controlled trial to testify the efficacy of acupuncture treatment for patient with CSU. This trial will be performed at three settings in China: the First Teaching Hospital of Chengdu University of Traditional Chinese Medicine (TCM), Wuhan Hospital of Traditional Chinese and Western Medicine, the First Hospital of Hunan University of Chinese Medicine. Eligible patients with CSU will be included in our study and randomly allocated into three groups: the verum acupuncture group, the sham acupuncture group, and the waiting-list group (no treatment) in a 1:1:1 ratio. The total observation period is 9 weeks, including a 1-week baseline, 4-week treatment phase, and 4-week follow-up phase. The protocol of this study has been approved by the Sichuan Regional Ethics Review of Committee on TCM (Medical Ethics

Committee of the Affiliated Hospital of Chengdu University of TCM) (Approval ID: 2019kl-006), the Medical Ethics Committee of the First Hospital of Wuhan (Approval ID: [2019] No. 7), and the Medical Ethics Committee of the First Hospital of Hunan University of TCM) (Approval ID: HN-LLKY-2019-017-01). This study will be performed in accordance with Helsinki declaration. Each patient will be required to provide written informed consent. This study has been registered on the Chinese Clinical Trial Registry (CHICTR) platform with the identifier number ChiCTR1900022994. The flowchart of this study is shown in figure 1, and the time points of assessment are shown in table 1.

Participants

Diagnostic criteria

According to the diagnostic criteria from the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA^{2}LEN/EDF/WAO) Guideline (2017) diagnostic criteria,[1] participant with the following aspects will be diagnosed having CSU:

1. Recurrent appearance of wheals, angioedema, or both;
2. An occurrence of urticaria at least twice per week;
3. Presence of symptoms for over 6 consecutive weeks;
4. Wheals occurring spontaneously with no specific factor involved.

Inclusion criteria

Patients with CSU who meet all the following aspects will be included:

1. Age between 18 and 70 years old;
2. No antihistamine drugs in the past 2 weeks, no steroids (corticosteroid, non-steroidal anti-inflammatory drugs) and immunosuppressive drugs in the past 4 weeks prior to participating in this study;
3. No acupuncture treatment in the past 4 weeks;
4. Not participation in other clinical trials in the past 3 months;
5. Voluntarily agree to participate in this study and sign written informed consent.

Exclusion criteria

Patients will be excluded if they meet any of the following aspects:

1. Diagnosed as acute urticaria, or CIU;

2. Having difficulties in expressing their symptoms clearly, because of any mental disorders;

3. Currently having other serious chronic problems, such as cardiovascular, hepatic, renal, gastrointestinal, hematological, infectious diseases, or malignant tumors;

4. Having contraindications to acupuncture treatment, such as bleeding tendency or local infection at acupoints;

5. Pregnant or breastfeeding.

Recruitment process

Participants will be recruited primarily from the Dermatology Department in the First Teaching Hospital of Chengdu University of TCM, Wuhan Hospital of Traditional Chinese and Western Medicine, and the First Hospital of Hunan University of Chinese Medicine in China. Research assistants will be sent to help screen participants in these hospitals. In addition, potential participants will be recruited through advertisements and survey questionnaires to the public in the hospitals, communities and campuses.

Written informed consent

In the written informed consent, all participants will be informed that they will be randomly allocated into verum acupuncture, sham acupuncture or waiting-list control groups, with the possible benefits and risks. They will voluntarily sign the informed consent before participating in this study and will be free to withdraw at any time during the study period.

Randomisation, allocation concealment, and blinding

Patients with CSU who meet the eligibility criteria will be randomly assigned to three groups: the verum acupuncture group, the sham acupuncture group, or the waiting-list control group in a ratio of 1:1:1. The randomisation sequence will be generated by a computer system in the clinical

evaluation centre of China Academy of Chinese Medical Science (CEC-CACMS) with a completely randomised design. The clinical research coordinator in each hospital will be responsible for requesting the randomisation sequence and group assignments through the internet system or mobile phone message. The randomisation sequence will be concealed in the server of CEC-CAMS until this study finishes participant enrollment, observation and data collection.

In this study, we will apply a type of sham acupuncture device to mask verum and sham acupuncture between patients from the two acupuncture treatment groups, and each patient will be treated in a separate room. A blinding assessment will be performed between patients in acupuncture groups. However, because of the nature of acupuncture, it is difficult to achieve masking between acupuncture groups and the waiting-list control group. Thus, the outcomes assessors and statisticians who are responsible for statistical analysis will be masked with respect of group assignments in the process of performing this study and data analysis.

Interventions

All participants will receive 16 sessions verum acupuncture treatment or sham acupuncture treatment over 4 weeks, including 5 consecutive sessions for the first 2 weeks with 2 days off, and 3 sessions for the last 2 weeks performed every other day. Participants in the waiting-list control group will not receive any acupuncture treatment during the observation period. If the symptoms cannot be relieved or get worse during the observation period, participants will be allowed to take loratadine tablets (Clarityne, Bayer Co., Ltd., Shanghai, China) 10 mg daily for emergency use, which are second generation antihistamine drugs, but no steroids and immunosuppressive drugs will be prescribed. The details of medication use will be documented in the case report form (CRF). Sterile disposable acupuncture needles 25-40 mm in length and 0.25 mm in diameter (Hwatuo, Suzhou, China), sterile disposable blunt and retractable needles (AcuPrime Co., Ltd., Exeter, UK)[19], and Park Sham Placebo Acupuncture Device (PSD) (Dong-bang Acupuncture Inc., Seoul, Korea)[20] will be utilized in this study for verum and sham acupuncture treatments, as well as blinding the treatments from each other. All acupuncturists participated in three special training classes during March and July, 2019, to learn how to locate the acupoints and non-acupoints, to use the sham acupuncture device, and to insert and manipulate the needles. Acupuncture treatment will be

performed by acupuncturists who passed an examination following this training.

Verum acupuncture group

Patients in the verum acupuncture group will receive treatment with real acupuncture needles inserted at the specific acupoints. In accordance with the textbooks of TCM, literature research and opinions from acupuncture experts, patients in the verum acupuncture group will have real needles inserted at the following points: LI11 (*Quchi*), SP10 (*Xuehai*), ST36 (*Zusanli*), ST25 (*Tianshu*), SP6 (*Sanyinjiao*), HT7 (*Shenmen*) bilaterally, and CV12 (*Zhongwan*). Details of the location of acupoints are shown in table 2 and figure 2. First, the pedestal of PDS will be adhered to the skin at each acupoint. The real acupuncture needles with tips will be inserted into the tube and then penetrate the skin. Then, according to the location of points and the individual's condition, needles will be positioned at the appropriate depth and angle. During the needle retention, the pedestal and tube of devices will not be removed to retain the blinding of the type of needle application. Manipulations of twirling, lifting, and thrusting will be performed on each needle to achieve the Deqi sensation. The treatment will last 30 minutes, and during the needle retention period the needles will be manipulated by manual twirling, lifting, and thrusting every 10 minutes to maintaining the Deqi sensation.

Sham acupuncture group

Patients in the sham acupuncture group will receive non-penetrating sham acupuncture at non-acupoints. In this group, non-penetrating sham acupuncture and non-acupoints will serve as controls for manual puncturing stimulation and specific acupoints, respectively. Sham acupuncture will be administrated by PSD with blunt and retractable needles at non-acupoints. Details of the location of non-acupoints, which are different than the conventional acupoints located along the meridians are shown in table 3 and figure 2. After the acupuncturist inserts the needle into the tube, the needle will retract into the handle when the blunt tip touches the skin. There will be no Deqi sensation. The manipulation techniques will be the same as in the verum acupuncture group with 30 minutes' duration without needle penetration. In China, most people have experienced an acupuncture treatment. Although we will exclude patients who have received acupuncture treatment 4 weeks

prior to the study and use the sham device, there is still high possibility that patients will distinguish the sham from verum acupuncture. Therefore, patients in the different acupuncture groups will be placed in separate room for receiving treatment and be asked to guess which type of acupuncture they receive after treatment to assess the blinding effects.

Waiting-list control group

Patients in the waiting-list control group will not receive any acupuncture treatment in the 9-week observation period. After the end of follow-up period, they will be offered 10 free sessions of acupuncture treatment with the same treatment protocol applied as the patients in verum acupuncture group as compensation.

Outcome measures

Primary outcome measurement

The primary outcome is the changes of weekly urticaria activity scores (UAS7), which will be utilized for patient self-evaluation of the severity of urticaria once daily for 7 consecutive days. UAS have been widely used to measure the symptoms of urticaria. It scores the number of wheals and the severity of pruritus on a 4-point scale of 0 to 3. Patients in this study will be trained to use this scale for self-evaluation and required to assess their symptoms in every 24 hours for 7 days a week before each clinic visit. They will be required to fill in a 7-day urticaria diary and give it to assessors when coming to the clinic. The scores of UAS7 are the sum of daily UAS scores, ranging from 0 to 42. The higher the scores the worse the condition. UAS7 is a unified and simple scoring system that has recommended by the guidelines and has been validated.[1 21-23] UAS7 will be measured at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8). The schedule of measurement and visit points are shown in table 1. The end point of this study is the change from baseline in UAS7 scores at the end of treatment (visit point 4).

Secondary outcome measurement

The secondary outcomes of this study include itching severity measurement, Dermatology Life Quality Index (DLQI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA),

Pittsburgh Sleep Quality Index (PSQI), and serum total immunoglobulin E (IgE) level. The schedule of measurements and visits for each outcome are shown in table 1. All patients are required to fill in a 7-day urticaria diary. Patients will be reminded to fill these diaries by short message, phone-calls, e-mails, and other social software, such as WeChat.

1. Itch-severity measurement

Itching is one of the troublesome symptoms that has a negative influence on CSU patients' QoL and worsening patents' well-being.[24 25] In this study, a 0-10 cm visual analogue scale (VAS) will be used to assess itching severity of CSU (0 for no itching to 10 for intolerable itching). Itching severity will be measured daily by patients themselves at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8). The total scores are the sum scores of daily scores for 7 consecutive days.

2. Quality of Life

Available data indicate that CSU markedly affects patients' QoL.[5 8] A related questionnaire evaluating QoL of patients is recommended by the guideline.[1] The Dermatology Life Quality Index (DLQI) is a professional questionnaire for evaluating the QoL impacted by dermatological problems, which has been validated for CSU patients.[23 26] It consists of 10 items in 6 subscales: symptoms and feelings, daily activities, leisure, personal relationships, work and school, and treatment.[27] Each item is scored as 0, 1, 2 or 3 according to the different degrees that QoL is impaired. The total scores of DLQI vary between 0 and 30. The higher scores the patients' scores, the more QoL is impaired. We will use the Chinese simplified version downloaded from official website (www.dermatology.org.uk.). DLQI will be measured at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8).

3. Psychological condition

Psychological disorders, such as anxiety and depression, are commonly found in CU patient group.[28] A positive correlation between the severity of urticaria and depression or anxiety has been reported.[29] Additionally, the severity of psychiatric disease indicated a worse QoL in CSU patients.[30 31] Therefore, the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) will be used to assess patients' psychological status in this study. HAMD and HAMA will be measured at baseline, at the end of treatment, week 6 and week 8 in the follow-up phase (visit

points 2, 4, 6 and 8).

4. Sleep quality

Patients with CSU commonly report sleep disturbances or insomnia because of hives, itching or both.[28 32] Sleep problems may also be a predisposing factor for CSU.[33] Poor sleep contributed to fatigue and damaged physical and emotional well-being.[2] The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire to assess sleep quality and disturbance that can be utilized both in clinical practice and research studies for patients with psychiatric or sleep problems and even among the general population.[34] It contains 19 items in 7 subdomains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.[34] The sum scores of each item range from 0 to 21. The higher the patients' scores, the worse sleep quality they experience. PSQI will be measured at baseline, at the end of treatment, and week 8 in the follow-up period (visit points 2, 4 and 8).

5. Serum total IgE level

It was reported that the serum IgE level of patients with CU was higher than in healthy controls,[35] and it was decreased with acupuncture treatment.[35 36] Serum IgE will be examined to detect the allergic and immune status of participants. This test will be performed before randomisation and at the end of treatment (visit points 2 and 4).

6. Patients' expectations about acupuncture treatment

Patient will fill out an acupuncture expectancy questionnaire before the first acupuncture treatment, which aims to detect whether a patient's expectations will impact acupuncture outcomes. This questionnaire includes 7 items. Each of them is rated on a 4-point Likert scale.

7. Treatment effects self-assessment

Overall treatment satisfaction will be assessed at the end of treatment (visit point 4) by a 4-point Likert scale. Patients will be asked "How were your symptoms of urticaria during the past week in comparison with the baseline period?" The answers will include "cured", "improved", "not changed" and "aggravated".

8. Blinding assessment

When we recruit and screen eligible participants, patients will be informed that they will have an equal chance of receiving traditional acupuncture, acupuncture-like stimulation treatment or no

acupuncture treatment. Patients in verum or sham acupuncture groups will be asked to guess what type of acupuncture they receive after the first and the last session of acupuncture treatment to test the patient-blinding effects. The question is "Which style acupuncture do you think you have received?" The patients will be provided with three options to answer this question: traditional acupuncture, acupuncture-like stimulation, or uncertain.

9. Patients' compliance assessment

Patients' compliance will be recorded at the end of the treatment (visit point 4). The drop-outs and reasons will be recorded in the 9-week observation period.

10. Use of medication

Self-reported use of additional medication or healthcare resources to control CSU in the observation period will be required to be recorded in the CSU diary.

Safety assessments

Safety will be assessed by routine blood tests, renal function as well as liver function tests. These indicators will be measured in the screening period and at the end of treatment (visit point 4). Adverse events (AEs) caused by acupuncture treatment, such as bleeding, pain, hematoma, fainting, local infection and so on are to be recorded. Serious AEs related to the interventions will be reported to the principal investigator and documented in the CRF. Treatment or rescue applications will be provided in a timely manner. In the assessment period, researchers will assess the possible relationship between AEs and the study, as well as the combined medications.

Sample size

Before undertaking this study, we performed a pilot study with a small sample size to determine the efficacy of acupuncture for CSU. The protocol has been published in a peer-reviewed journal.[37] In this pilot study, the changes of UAS7 scores in verum acupuncture and sham acupuncture were 16 and 12, respectively (the results are still unpublished). The difference of scores between two groups was 4. Therefore, we assume that the verum acupuncture and sham acupuncture will reduce the UAS7 scores as in the preliminary study. We expect the population standard deviation (SD) to be 10 with effect size (Cohen's d) 4. One hundred patients per group would be needed as calculated by

the G power (3.0.10 version) at a two-sided significance level of 5% and power of 80% in a 1:1:1 ratio. Estimating a 10% drop-out rate, a total of 330 patients (110 patients per group) will need to be enrolled in this study.

Data management

All data will be documented by outcome assessors at each site who have been qualified by a special training class before recruitment. The training includes how to fill in the CRF in an accurate and timely manner, how to assess the electronic CRF (eCRF) that is established by the CEC-CAMS and input the data into the eCRF to double-check the accuracy. Standard operation procedures (SOP) have been established and provided to the assessors and researchers in each clinical trial institution. The data for each participant will be stored in the centre server of the CEC-CAMS, and only the data monitor is able to check the data. The researchers are unable to modify and acquire data before all participants' enrollment, observation and data collection are finished.

Statistical analysis

SPSS 21.0 statistical software (IBM Corp., Armonk, New York, USA) will be used for data analysis. An independent statistician who does not know the group assignments will run the statistical analysis. Continuous variables will be described as mean ± SD with a 95% confidence interval (CI) in a normal distribution and median (range) in abnormal distribution, while categorical variables will be represented by numbers (percentages). The level of significance will be established at 0.05 in a two-sided test.

All analysis will be performed according to intention-to-treat (ITT) protocol. Participants who finish the baseline assessment of primary outcome and receive at least one session of either verum or sham acupuncture treatment will be included in ITT population. The missing data of participants who drop out will be handled by multiple imputations with a package "Amelia" from the R software (www.r-project. org). Per-protocol (PP) population analysis will be also performed, for participants who have finished at least 80% of the treatment protocol after randomisation.

The primary outcome will be compared by an analysis of covariance (ANCOVA). The ANCOVA will be adjusted by the patients' characteristics and baseline outcomes if there are possible

covariates. Pairwise comparisons will be performed by the least significant difference (LSD) test in a post-hoc analysis, if the difference is significant in the global test the among three groups (verum acupuncture, sham acupuncture and waiting-list). There are 8 visit points of this study. Therefore, repeated measures ANCOVA will be performed to detect the differences between groups at different visit points, and interactions between groups and time points. The secondary outcomes will be analysed in the same model of ANCOVA. Categorial variables will be compared by chi-square test or Fisher's exact test. A paired *t*-test or Wilcoxon signed-rank test will be used to compare the differences within groups.

Quality control

All staff participated in special training about the study objectives, study protocol on the treatment strategies, and quality control before the study began. Acupuncturists are licensed and have at least 2 years of acupuncture experience in clinical practice. All study documents (such as screening forms, CRFs, treatment records) and treatment material (such as acupuncture needles, PSD, etc.) are in locked storage at study sites with limited access. A specified monitor in each site will check the CRFs and records of the acupuncture treatment every week. Every 3 months, members of the quality monitor group will perform a quality control review at each study site and produce a report on the quality of the entire study process. The principle investigator will hold regular meetings to discuss and solve the problems discovered during the observation period.

Patient and public involvement

Patient priorities, experiences, and preferences were not involved in the development of the research question, outcome measures, study design, recruitment, or conduct of this study. The results will not be disseminated to study participants. The burden of intervention will not be assessed by trial participants

Dissemination

The results of this study will be presented in select conferences and scientific meetings, and will be published in peer-reviewed journals. For transparency of study results, the raw data set will be

available upon request to the research team 3 years after the publication of study results.

DISCUSSION

CSU significantly impairs patients' QoL and leads to a great economic burden for the families as well as society. This multi-centre, parallel, three-arm, randomised, sham-controlled trial will examine the efficacy of acupuncture in treating CSU, and provide solid evidence of acupuncture treatment for patients with CSU.

According to the theory of TCM, the main etiology and pathogenesis of CSU is the disharmony of nutrients and defenses resulting from the wind evil assailing the exterior, accumulated heat in stomach and intestine, blood deficiency and wind-dryness. Therefore, a method of dispelling wind, harmonizing nutrients and relieving itching should be used for treating CSU. In accordance with the literature and consultation with experts, we will choose the acupoints located along the Hand- and Foot-Yangming Meridians as the main acupuncture points (table 2 and figure 2). LI11 and SP10 can disperse wind and clear heat, harmonize the nutrients and defenses, cool blood, and combine with ST36, ST25, CV12, and SP6 to invigorate spleen, drain dampness and harmonize blood. SP10 is an acupoint with importance for cooling, regulating and nourishing blood, which is commonly used for skin disease. The Yellow Emperor' s Inner Canon records that symptoms of pain, itching, sores and ulcers all result from dysfunction of the Heart. Thus, HT7 will be chosen for tranquilizing the spirit and relieving itching. For non-acupoints, we will choose the same number of points located on non-meridians as our sham controls (table 3 and figure 2). These non-acupoints are located near the corresponding traditional Chinese acupoints, which could blind patients from differentiating them from the verum acupoints.

Previous studies reported that acupuncture treatment was beneficial for patients with CU[18 36]. However, results from these studies seem somewhat unreliable because of poor methodology in the following aspects. First, the sample size of previous studies was small,[18] and lacked a rationale for the sample size calculation. Second, to the best of our knowledge, we did not find reports of any RCT applied sham-acupuncture, placebo or waiting-list controls in any study of acupuncture for CU after a systematic literature search in databases, such as PubMed, CNKI, Wangfang, et al. So, the specific effects of acupuncture for CU have not been well identified so far. Several methods of sham

acupuncture controls have been applied in acupuncture studies, but they are controversial. At present, the common types of controls include non-acupoints (stimulation location), different stimulation methods (such as superficial needling, non-penetrating puncturing or sham-laser acupuncture), and a placebo acupuncture device (such as the Streitberger needle[38] or PSD[20]). Real needles at non-acupoints with normal depth or superficial puncturing were reported as having some effects in different diseases.[39 40] Stimulation, such as superficial needling, could trigger cutaneous therapeutic effects to relieve dermatological problems. In this study, we choose non-penetrating needles and non-acupoints as controls for real acupuncture stimulation and specific acupoints in accordance with TCM theory, respectively. An ideal placebo should be inert and unable to be distinguished by patients. Because of the nature of acupuncture, a placebo device is necessary for a blinded study. Therefore, we will apply PSD in this study to ensure blinding in the verum and sham acupuncture groups. Third, several studies chose global symptom scores as outcome measurements that were not the internationally acknowledged outcomes measurements for CSU. Furthermore, most of them applied cut-points or ranking categories, which may decrease the statistical effects compared to analysis of continuous data. In this study, we will apply USA7, which is recommended by the guidelines and has been validated,[1 23] to assess CSU. Fourth, long-term effects of acupuncture have been demonstrated in various disease, such as migraine,[41] chronic neck pain,[42] hot flashes,[43] and tinnitus.[44] Recurrence and persistence are characteristics of CU.[1] A previous study reported that a lower recurrence rate was observed in the acupuncture group after the end of treatment, when compared to drugs in treating CU.[36] Therefore, we are interested in the long-term effects of treatment during the follow-up period on urticaria, psychology, sleeping, QoL and so on. Last, the randomisation sequence is generated by a computer, and only authorized persons have access to information about the randomisation sequence, and group assignment will be concealed in the CEC-CACMS until the end of the study to avoid selection bias.

This study has several limitations. First, because of the nature of acupuncture, blinding the acupuncturists or patients between acupuncture treatment and waiting-list control groups is impossible. Additionally, it is impossible to blind acupuncturists while they are performing verum or sham acupuncture treatment. Therefore, independent outcome assessors and statisticians who are masked from group assignments will carry out outcome assessments and data analysis in this study.

Second, this study is being performed in Chengdu, Wuhan and Changsha, which are the capitals of Sichuan, Hubei and Hunan Provinces in southwestern and central China, respectively. The patients that we include in this study could be not present patients in China with different ethnic nationalities, either the foreigners living in the western countries.

This trial will follow the Consolidated Standards of Reporting Trial (CONSORT) reporting guidelines[45] and Standard for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations.[46] We hope the results of this study will provide high-quality evidence for the use of acupuncture for CSU treatment.

Trial status

The recruitment started in May 2019 and is expected to end in the middle of 2021.

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Contributors YL is a principle investigator and conceived of the study. YL, HZ, SZ and QZ initiated the study design. YL and SZ are monitors of this study. YS, LZ, XX, FZ and CW will carry out the implementation of this study, including participants recruitment, acupuncture procedure conducting and the case report forms filling in. YL contributed in obtaining research fund. ZH was responsible for design of statistical analysis. YL, WZ and LZ sought ethical approval. YH and MC provided professional advice for the study design and will be responsible for screening eligible participants. QZ drafted this manuscript. QZ, HZ, YS and YL were responsible for revising the manuscript. All authors read this manuscript and approved the publication of the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study protocol was approved by Sichuan Regional Ethics Review of Committee of Traditional Chinese Medicine (23 April 2019, Approval No. 2019kl-006), the Medical Ethic Committee of the First Hospital of Wuhan (15 May 2019, Approval No. [2019] No. 7), and the Medical Ethic Committee of the First Hospital of Hunan University of TCM) (12 July 2019, Approval No. HN-LLKY-2019-017-01).

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1 Time points of treatment assessment

Table 2 Acupoints used in the verum acupuncture group

Table 3 Non-acupoints used in the sham acupuncture group

Figure 1 Trial flow chart. DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.

Figure 2 Location of acupoints and non-acupoints.

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Table 1 Time points of treatment assessment

	Enrollment	Baseline	Treatment phase			Follow-up phase		
Time point	**Week -1**	**Week 0**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week7**	**Week 8**
Screening and enrolment								
Clinical interview	×							
Laboratory test	×			×				
Eligibility screen	×							
Informed consent	×							
Randomisation		×						
Interventions								
Acupuncture			16 sessions treatment					
Sham acupuncture			16 sessions treatment					
Waiting-list			No acupuncture treatment					
Assessments								
Primary outcome								
UAS7		×	×	×	×	×	×	×
Secondary outcomes								
VAS for itch-severity		×	×	×	×	×	×	×
DLQI		×	×	×	×	×	×	×
HAMD		×		×		×		×
HAMA		×		×		×		×
PSQI		×		×				×
Serum total IgE		×		×				
Others								
Adverse events			×	×	×	×	×	×
Blinding assessment			×*	×				

Expectancy questionnaire	×						
Treatment effects self-assessment			×				
Patients' compliance			×				
Medicine alliance	×	×	×	×	×	×	×

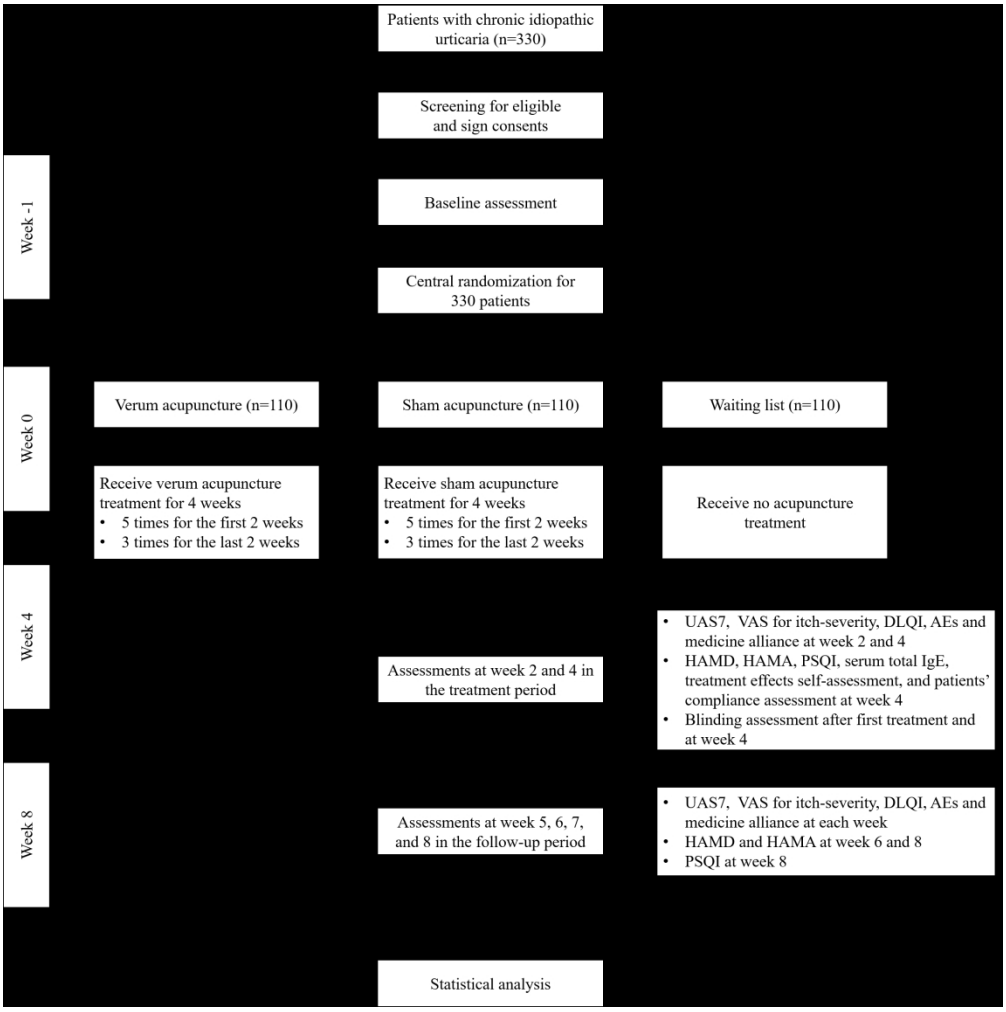
DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.

* Assessed after the first session of acupuncture treatment.

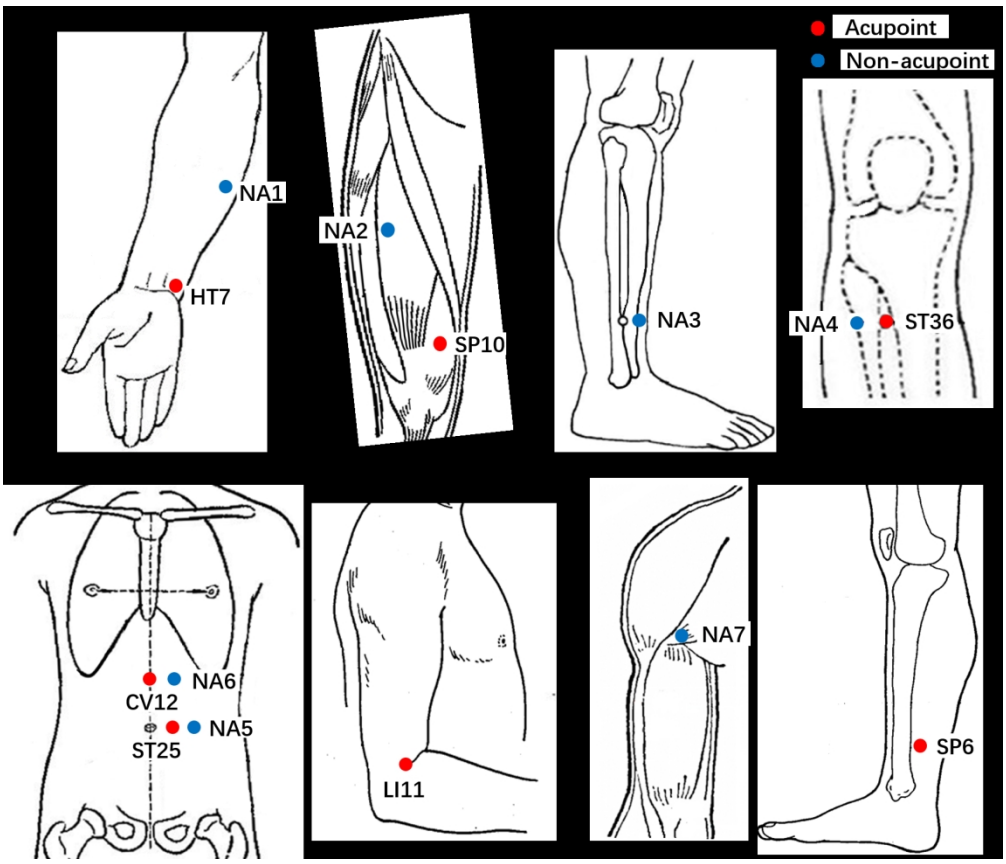
Acupoint	Location
LI11 (*Quchi*)	On the lateral end of the transverse cubital crease, at the midpoint between LU5 (*Chize*) with the lateral epicondyle of humerus (needled bilaterally)
SP10 (*Xuehai*)	On the prominence of the medial head of the quadriceps femoris, 2 cun above the medio-superior border of the base of patella (needled bilaterally)
SP6 (*Sanyinjiao*)	On the medial side of the shank, 3 cun above the medial malleolus, by the posterior border of the tibia (needled bilaterally)
ST36 (*Zusanli*)	On the anterior lateral side of the shank, 3 cun below ST35 (*Dubi*), one horizontally-placed finger distance lateral to the anterior border of the tibia (the middle finger) (needled bilaterally)
ST25 (*Tianshu*)	On the middle portion of the abdomen, 2 cun lateral to the central of the navel (needled bilaterally)
CV12 (*Zhongwan*)	On the anterior media line of the upper abdomen, 4 cun above the navel
HT7 (*Shenmen*)	On the wrist, at the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of the flexor carpi ulnaris (needled bilaterally)

Table 3 Non-acupoints used in the sham acupuncture group

Non-acupoint	Location
Non-acupoint 1	On the radial side, the midpoint between the medial epicondyle of humerus and the styloid process of ulna (needled bilaterally)
Non-acupoint 2	On the thigh, 0.8 cun medial to the midpoint of the line linking the anterior superior iliac spine and the lateral end of the base of patella (needled bilaterally)
Non-acupoint 3	On the lateral side of the lower leg, 3 cun above the tip of external malleolus, between Stomach Meridian of Foot-Yangming and Gallbladder Meridian of Foot-Shaoyang (needled bilaterally)
Non-acupoint 4	On the lateral side of the lower leg, 1 cun lateral to ST36 (*Zusanli*), between Stomach Meridian of Foot-Yangming and Gallbladder Meridian of Foot-Shaoyang (needled bilaterally)
Non-acupoint 5	On the middle of abdomen, 1 cun lateral to ST25 (*Tianshu*), the midpoint between ST25 and SP15 (*Daheng*) (needled bilaterally)
Non-acupoint 6	On the middle of abdomen, 1.2 cun lateral to CV12 (*Zhongwan*) (applied on body side alternatively per each treatment session)
Non-acupoint 7	On the medial anterior border of the upper arm, the junction of the deltoid and the biceps brachii (needled bilaterally)



Trial flow chart. DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.



Location of acupoints and non-acupoints.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4-5, 15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2, 4-5
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2, 16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Efficacy of acupuncture treatment for chronic spontaneous urticaria: study protocol for a randomised controlled trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Dermatology
Keywords:	COMPLEMENTARY MEDICINE, DERMATOLOGY, Clinical trials < THERAPEUTICS

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Efficacy of acupuncture treatment for chronic spontaneous urticaria: study protocol for a randomised controlled trial

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Abstract

Introduction Chronic spontaneous urticaria (CSU) is a troublesome dermatological problem that can have a significant impact on quality of life. Previous studies have indicated that acupuncture may be beneficial for patients with CSU. However, well-designed studies determine the effects of acupuncture on CSU are rare. The aim of this study is to investigate the efficacy and safety of acupuncture treatment for patients with CSU.

Methods and analysis This study is designed as a multicentre, parallel, three-arm, randomised, sham-controlled trial. A total of 330 patients diagnosed as CSU will be randomly allocated into three groups: the verum acupuncture group, the sham acupuncture group, and the waiting-list control group in a 1:1:1 ratio. Patients in the verum and sham acupuncture groups will receive 16 treatment sessions over 4 weeks, while patients in the waiting-list control group will not receive any acupuncture treatment. The primary outcome is the changes of weekly urticaria activity scores (UAS7) at the end of treatment. Secondary outcomes include itching severity measurement, Dermatology Life Quality Index (DLQI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Pittsburgh Sleep Quality Index (PSQI), and serum total immunoglobulin E (IgE) level. Adverse events will be recorded during the study observation period. All patients who are randomised in this study will be included in the intent-to-treat (ITT) analysis.

Ethics and dissemination Ethical approval of this study has been granted by the Sichuan Regional Ethics Review of Committee on Traditional Chinese Medicine (TCM) (ID: 2019kl-006), the Medical Ethic Committee of the First Hospital of Wuhan (ID: [2019] No. 7), and the Medical Ethic Committee of the First Hospital of Hunan University of TCM (ID: HN-LLKY-2019-017-01/03) in three clinical centres in China, respectively. The results will be disseminated through peer-reviewed journals.

Trial registration: ChiCTR1900022994.

Strengths and limitations of this study

- This is the first study to provide information about the efficacy and safety of acupuncture treatment for patients with chronic spontaneous urticaria (CSU) by comparing verum versus sham acupuncture and waiting-list.
- The risk of bias will be reduced by rigorous methodology, including adequate randomisation, quality control, and the use of blinded outcomes assessors and statisticians.
- Eligible participants will be strictly recruited and screened in three tertiary A hospitals in China, the results may not apply to patients in other countries.
- Because of the nature of acupuncture, unblinded participants and treatment providers are likely to bring bias and be influencing the results.

INTRODUCTION

Chronic urticaria (CU) is a dermatological condition defined as the recurrence of itchy wheals and/or angioedema daily, or almost daily, lasting at least 6 weeks.[1] The estimated prevalence of CU ranges from 0.5% to 1.0% in the general population.[2] Most of the affected patients are between 30 and 50 years old, and there is a significantly higher incidence in women than in men.[3 4]

There are two types of CU: chronic spontaneous (idiopathic) urticaria (CSU) and chronic inducible urticaria (CIU). The main difference between the two is the former type occurs without identifiable triggers.[1 2] Several studies reported that CU has a significant negative impact on patients' quality of life (QoL)[1 5] in terms of sleep and daily activities, such as work, study, recreation and social interaction.[5-8] The decrease in QoL reported by patients with CU was comparable to that of patient with coronary artery disease[9] and psoriasis.[10] The high rates of absenteeism from work and school because of sick leave and medical care,[7] as well as for various autoimmune[11] and psychological[5 12] comorbidities, directly and indirectly increase the economic burden for patients with CU.[8]

According to the consensus on the treatment options for CU, non-sedative H1-antihistamine is the first-line medication, and the doses could increase up to four-fold in refractory cases as the

second-line medication.[1] According to the 2017 version of guideline, omalizumab and cyclosporine A are recommended as the third- and fourth-line therapy, respectively, for who fail to respond to H1-antihistamine.[1] Although omalizumab has been reported effective and safe for CU in recent studies,[13 14] the high cost are burdensome for most patients. Because of the higher incidence of adverse effects, cyclosporin A cannot be recommended as standard treatment.[15]

Acupuncture, which has been used for more than 3000 years, has been widely applied in clinical practice to treat dermatological problems.[16 17] According to the literatures, acupuncture has been applied for a long time in China to treat urticaria. A systematic review included six randomised controlled trials (RCTs) studying the effectiveness and safety of acupuncture treatment for patients with CU.[18] Although the evidence supported that patients with CU may benefit from acupuncture treatment, the poor methodology of the RCTs, particularly in choosing controls and outcomes for assessing the symptoms and QoL, makes the evidence less confirmative.

To counter these deficiencies, a prospective, parallel, three-arm, randomised, sham-controlled trial with a large sample size will be carried out to investigate the efficacy and safety of acupuncture treatment for patients with CSU, comparing them with sham acupuncture and waiting-list control groups. We hope the findings from this study will provide solid evidence for the efficacy of acupuncture treatment for CSU.

METHODS

Study design

This is a multicentre, parallel, three-arm, randomised, sham-controlled trial to testify the efficacy of acupuncture treatment for patient with CSU. This trial will be performed at three settings in China: the First Teaching Hospital of Chengdu University of Traditional Chinese Medicine (TCM), Wuhan Hospital of Traditional Chinese and Western Medicine, the First Hospital of Hunan University of Chinese Medicine. Eligible patients with CSU will be included in our study and randomly allocated into three groups: the verum acupuncture group, the sham acupuncture group, and the waiting-list group (no treatment) in a 1:1:1 ratio. The total observation period is 9 weeks, including a 1-week baseline, 4-week treatment phase, and 4-week follow-up phase. The flowchart of this study is shown in figure 1, and the time points of assessment are shown in table 1.

Table 1 Time points of treatment assessment

	Enrollment	Baseline	Treatment phase			Follow-up phase		
Time point	**Week -1**	**Week 0**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week7**	**Week 8**
Screening and enrolment								
Clinical interview	×							
Laboratory test	×			×				
Eligibility screen	×							
Informed consent	×							
Randomisation		×						
Interventions								
Acupuncture			16 sessions treatment					
Sham acupuncture			16 sessions treatment					
Waiting-list			No acupuncture treatment					
Assessments								
Primary outcome								
UAS7		×	×	×	×	×	×	×
Secondary outcomes								
VAS for itch-severity		×	×	×	×	×	×	×
DLQI		×	×	×	×	×	×	×
HAMD		×		×		×		×
HAMA		×		×		×		×
PSQI		×		×				×
Serum total IgE		×		×				
Others								
Adverse events			×	×	×	×	×	×
Blinding assessment			×*	×				

Expectancy questionnaire	×						
Treatment effects self-assessment			×				
Patients' compliance			×				
Medicine alliance	×	×	×	×	×	×	×

DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.

* Assessed after the first session of acupuncture treatment.

Exclusion criteria

Patients will be excluded if they meet any of the following aspects:

1. Diagnosed as acute urticaria, or CIU;

2. Having difficulties in expressing their symptoms clearly, such as severe mental disorders or cognitive impairment;

3. Currently having other serious chronic problems, such as cardiovascular, hepatic, renal, gastrointestinal, hematological, infectious diseases, or malignant tumors;

4. Having contraindications to acupuncture treatment, such as bleeding tendency or local infection at acupoints;

5. Pregnant or breastfeeding.

Recruitment process

Participants will be recruited primarily from the Dermatology Department in the First Teaching Hospital of Chengdu University of TCM, Wuhan Hospital of Traditional Chinese and Western Medicine, and the First Hospital of Hunan University of Chinese Medicine in China. Research assistants will be sent to help screen participants in these hospitals. In addition, potential participants will be recruited through advertisements and survey questionnaires to the public in the hospitals, communities and campuses.

Written informed consent

In the written informed consent, all participants will be informed that they will be randomly allocated into verum acupuncture, sham acupuncture or waiting-list control groups, with the possible benefits and risks. They will voluntarily sign the informed consent before participating in this study and will be free to withdraw at any time during the study period.

Randomisation, allocation concealment, and blinding

Patients with CSU who meet the eligibility criteria will be randomly assigned to three groups: the verum acupuncture group, the sham acupuncture group, or the waiting-list control group in a ratio

of 1:1:1. The randomisation sequence will be generated by a computer system in the clinical evaluation centre of China Academy of Chinese Medical Science (CEC-CACMS) with a completely randomised design. The clinical research coordinator in each hospital will be responsible for requesting the randomisation sequence and group assignments through the internet system or mobile phone message. The randomisation sequence will be concealed in the server of CEC-CAMS until this study finishes participant enrollment, observation and data collection.

In this study, we will apply a type of sham acupuncture device to mask verum and sham acupuncture between patients from the two acupuncture treatment groups, and each patient will be treated in a separate room. A blinding assessment will be performed between patients in acupuncture groups. However, because of the nature of acupuncture, it is difficult to achieve masking between acupuncture groups and the waiting-list control group. Thus, the outcomes assessors and statisticians who are responsible for statistical analysis will be masked with respect of group assignments in the process of performing this study and data analysis.

Interventions

All participants will receive 16 sessions verum acupuncture treatment or sham acupuncture treatment over 4 weeks, including 5 consecutive sessions for the first 2 weeks with 2 days off, and 3 sessions for the last 2 weeks performed every other day. Participants in the waiting-list control group will not receive any acupuncture treatment during the observation period. If the symptoms cannot be relieved or get worse during the observation period, participants will be allowed to take loratadine tablets (Clarityne, Bayer Co., Ltd., Shanghai, China) 10 mg daily for emergency use, which are second generation antihistamine drugs, but no steroids and immunosuppressive drugs will be prescribed. If patients fail to respond to loratadine, Ebastine (Sudi, Lianhuan Pharmacy Co., Ltd., Jiangsu, China) 10 mg daily will be an alternative. The details of medication use will be documented in the case report form (CRF). If a patient use steroids and immunosuppressive drugs during the observation period will be excluded from this study. Sterile disposable acupuncture needles 25-40 mm in length and 0.25 mm in diameter (Hwatuo, Suzhou, China), sterile disposable blunt and retractable needles (AcuPrime Co., Ltd., Exeter, UK)[19], and Park Sham Placebo Acupuncture Device (PSD) (Dong-bang Acupuncture Inc., Seoul, Korea)[20] will be utilized in this study for verum

and sham acupuncture treatments, as well as blinding the treatments from each other. All acupuncturists participated in three special training classes during March and July, 2019, to learn how to locate the acupoints and non-acupoints, to use the sham acupuncture device, and to insert and manipulate the needles. Acupuncture treatment will be performed by acupuncturists who passed an examination following this training.

Verum acupuncture group

Patients in the verum acupuncture group will receive treatment with real acupuncture needles inserted at the specific acupoints. In accordance with the textbooks of TCM, literature research and opinions from acupuncture experts, patients in the verum acupuncture group will have real needles inserted at the following points: LI11 (*Quchi*), SP10 (*Xuehai*), ST36 (*Zusanli*), ST25 (*Tianshu*), SP6 (*Sanyinjiao*), HT7 (*Shenmen*) bilaterally, and CV12 (*Zhongwan*). Details of the location of acupoints are shown in table 2 and figure 2. First, the pedestal of PSD will be adhered to the skin at each acupoint. The real acupuncture needles with tips will be inserted into the tube and then penetrate the skin. Then, according to the location of points and the individual's condition, needles will be positioned at the appropriate depth and angle. During the needle retention, the pedestal and tube of devices will not be removed to retain the blinding of the type of needle application. Manipulations of twirling, lifting, and thrusting will be performed on each needle to achieve the Deqi sensation. The treatment will last 30 minutes, and during the needle retention period the needles will be manipulated by manual twirling, lifting, and thrusting every 10 minutes to maintaining the Deqi sensation.

Table 2 Acupoints used in the verum acupuncture group

Acupoint	Location
LI11 (*Quchi*)	On the lateral end of the transverse cubital crease, at the midpoint between LU5 (*Chize*) with the lateral epicondyle of humerus (needled bilaterally)
SP10 (*Xuehai*)	On the prominence of the medial head of the quadriceps femoris, 2 cun above the medio-superior border of the base of patella (needled bilaterally)
SP6 (*Sanyinjiao*)	On the medial side of the shank, 3 cun above the medial malleolus, by the posterior border of the tibia (needled bilaterally)

ST36 (*Zusanli*)	On the anterior lateral side of the shank, 3 cun below ST35 (*Dubi*), one horizontally-placed finger distance lateral to the anterior border of the tibia (the middle finger) (needled bilaterally)
ST25 (*Tianshu*)	On the middle portion of the abdomen, 2 cun lateral to the central of the navel (needled bilaterally)
CV12 (*Zhongwan*)	On the anterior media line of the upper abdomen, 4 cun above the navel
HT7 (*Shenmen*)	On the wrist, at the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of the flexor carpi ulnaris (needled bilaterally)

Sham acupuncture group

Patients in the sham acupuncture group will receive non-penetrating sham acupuncture at non-acupoints. In this group, non-penetrating sham acupuncture and non-acupoints will serve as controls for manual puncturing stimulation and specific acupoints, respectively. Sham acupuncture will be administrated by PSD with blunt and retractable needles at non-acupoints. Details of the location of non-acupoints, which are different than the conventional acupoints located along the meridians are shown in table 3 and figure 2. After the acupuncturist inserts the needle into the tube, the needle will retract into the handle when the blunt tip touches the skin. There will be no Deqi sensation. The manipulation techniques will be the same as in the verum acupuncture group with 30 minutes' duration without needle penetration. In China, most people have experienced an acupuncture treatment. Although we will exclude patients who have received acupuncture treatment 4 weeks prior to the study and use the sham device, there is still high possibility that patients will distinguish the sham from verum acupuncture. Therefore, patients in the different acupuncture groups will be placed in separate room for receiving treatment and be asked to guess which type of acupuncture they receive after treatment to assess the blinding effects.

Table 3 Non-acupoints used in the sham acupuncture group

Non-acupoint	**Location**
Non-acupoint 1	On the radial side, the midpoint between the medial epicondyle of humerus and the styloid process of ulna (needled bilaterally)
Non-acupoint 2	On the thigh, 0.8 cun medial to the midpoint of the line linking the anterior superior iliac spine and the lateral end of the base of patella (needled bilaterally)

Non-acupoint 3	On the lateral side of the lower leg, 3 cun above the tip of external malleolus, between Stomach Meridian of Foot-Yangming and Gallbladder Meridian of Foot-Shaoyang (needled bilaterally)
Non-acupoint 4	On the lateral side of the lower leg, 1 cun lateral to ST36 (*Zusanli*), between Stomach Meridian of Foot-Yangming and Gallbladder Meridian of Foot-Shaoyang (needled bilaterally)
Non-acupoint 5	On the middle of abdomen, 1 cun lateral to ST25 (*Tianshu*), the midpoint between ST25 and SP15 (*Daheng*) (needled bilaterally)
Non-acupoint 6	On the middle of abdomen, 1.2 cun lateral to CV12 (*Zhongwan*) (applied on body side alternatively per each treatment session)
Non-acupoint 7	On the medial anterior border of the upper arm, the junction of the deltoid and the biceps brachii (needled bilaterally)

Waiting-list control group

Patients in the waiting-list control group will not receive any acupuncture treatment in the 9-week observation period. After the end of follow-up period, they will be offered 10 free sessions of acupuncture treatment with the same treatment protocol applied as the patients in verum acupuncture group as compensation.

Outcome measures

Primary outcome measurement

The primary outcome is the changes of weekly urticaria activity scores (UAS7), which will be utilized for patient self-evaluation of the severity of urticaria once daily for 7 consecutive days. UAS have been widely used to measure the symptoms of urticaria. It scores the number of wheals and the severity of pruritus on a 4-point scale of 0 to 3. Patients in this study will be trained to use this scale for self-evaluation and required to assess their symptoms in every 24 hours for 7 days a week before each clinic visit. They will be required to fill in a 7-day urticaria diary and give it to assessors when coming to the clinic. The scores of UAS7 are the sum of daily UAS scores, ranging from 0 to 42. The higher the scores the worse the condition. UAS7 is a unified and simple scoring system that has recommended by the guidelines and has been validated.[1 21-23] UAS7 will be measured at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8). The schedule of measurement and visit points are shown in table 1. The end point of this study is the change from baseline in UAS7 scores at the end of treatment (visit point 4).

Secondary outcome measurement

The secondary outcomes of this study include itching severity measurement, Dermatology Life Quality Index (DLQI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Pittsburgh Sleep Quality Index (PSQI), and serum total immunoglobulin E (IgE) level. The schedule of measurements and visits for each outcome are shown in table 1. All patients are required to fill in a 7-day urticaria diary. Patients will be reminded to fill these diaries by short message, phone-calls, e-mails, and other social software, such as WeChat.

1. Itch-severity measurement

Itching is one of the troublesome symptoms that has a negative influence on CSU patients' QoL and worsening patents' well-being.[24 25] In this study, a 0-10 cm visual analogue scale (VAS) will be used to assess itching severity of CSU (0 for no itching to 10 for intolerable itching). Itching severity will be measured daily by patients themselves at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8). The total scores are the sum scores of daily scores for 7 consecutive days.

2. Quality of Life

Available data indicate that CSU markedly affects patients' QoL.[5 8] A related questionnaire evaluating QoL of patients is recommended by the guideline.[1] The Dermatology Life Quality Index (DLQI) is a professional questionnaire for evaluating the QoL impacted by dermatological problems, which has been validated for CSU patients.[23 26] It consists of 10 items in 6 subscales: symptoms and feelings, daily activities, leisure, personal relationships, work and school, and treatment.[27] Each item is scored as 0, 1, 2 or 3 according to the different degrees that QoL is impaired. The total scores of DLQI vary between 0 and 30. The higher scores the patients' scores, the more QoL is impaired. We will use the Chinese simplified version downloaded from official website (www.dermatology.org.uk.). DLQI will be measured at baseline, week 2 and week 4 in the treatment phase, and weekly in the follow-up phase (visit points 2-8).

3. Psychological condition

Psychological disorders, such as anxiety and depression, are commonly found in CU patient group.[28] A positive correlation between the severity of urticaria and depression or anxiety has been

reported.[29] Additionally, the severity of psychiatric disease indicated a worse QoL in CSU patients.[30 31] Therefore, the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) will be used to assess patients' psychological status in this study. HAMD and HAMA will be measured at baseline, at the end of treatment, week 6 and week 8 in the follow-up phase (visit points 2, 4, 6 and 8).

4. Sleep quality

Patients with CSU commonly report sleep disturbances or insomnia because of hives, itching or both.[28 32] Sleep problems may also be a predisposing factor for CSU.[33] Poor sleep contributed to fatigue and damaged physical and emotional well-being.[2] The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire to assess sleep quality and disturbance that can be utilized both in clinical practice and research studies for patients with psychiatric or sleep problems and even among the general population.[34] It contains 19 items in 7 subdomains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.[34] The sum scores of each item range from 0 to 21. The higher the patients' scores, the worse sleep quality they experience. PSQI will be measured at baseline, at the end of treatment, and week 8 in the follow-up period (visit points 2, 4 and 8).

5. Serum total IgE level

It was reported that the serum IgE level of patients with CU was higher than in healthy controls,[35] and it was decreased with acupuncture treatment.[35 36] Serum IgE will be examined to detect the allergic and immune status of participants. This test will be performed before randomisation and at the end of treatment (visit points 2 and 4).

6. Patients' expectations about acupuncture treatment

Patient will fill out an acupuncture expectancy questionnaire before the first acupuncture treatment, which aims to detect whether a patient's expectations will impact acupuncture outcomes. This questionnaire includes 7 items. Each of them is rated on a 4-point Likert scale.

7. Treatment effects self-assessment

Overall treatment satisfaction will be assessed at the end of treatment (visit point 4) by a 4-point Likert scale. Patients will be asked "How were your symptoms of urticaria during the past week in comparison with the baseline period?" The answers will include "cured", "improved", "not changed"

and “aggravated”.

8. Blinding assessment

When we recruit and screen eligible participants, patients will be informed that they will have an equal chance of receiving traditional acupuncture, acupuncture-like stimulation treatment or no acupuncture treatment. Patients in verum or sham acupuncture groups will be asked to guess what type of acupuncture they receive after the first and the last session of acupuncture treatment to test the patient-blinding effects. The question is “Which style acupuncture do you think you have received?” The patients will be provided with three options to answer this question: traditional acupuncture, acupuncture-like stimulation, or uncertain.

9. Patients’ compliance assessment

Patients’ compliance will be recorded at the end of the treatment (visit point 4). The drop-outs and reasons will be recorded in the 9-week observation period.

10. Use of medication

Self-reported use of additional medication or healthcare resources to control CSU in the observation period will be required to be recorded in the CSU diary.

Safety assessments

Safety will be assessed by routine blood tests, renal function as well as liver function tests. These indicators will be measured in the screening period and at the end of treatment (visit point 4). Adverse events (AEs) caused by acupuncture treatment, such as bleeding, pain, hematoma, fainting, local infection and so on are to be recorded. Serious AEs related to the interventions will be reported to the principal investigator and documented in the CRF. And the affected participants will be withdrawn from the study. Treatment or rescue applications will be provided in a timely manner. In the assessment period, researchers will assess the possible relationship between AEs and the study, as well as the combined medications.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients

themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

Sample size

Before undertaking this study, we performed a pilot study with a small sample size to determine the efficacy of acupuncture for CSU. The protocol has been published in a peer-reviewed journal.[37] In this pilot study, the changes of UAS7 scores in verum acupuncture and sham acupuncture were 16 and 12, respectively (the results are still unpublished). The difference of scores between two groups was 4. Therefore, we assume that the verum acupuncture and sham acupuncture will reduce the UAS7 scores as in the preliminary study. We expect the population standard deviation (SD) to be 10 with effect size (Cohen's d) 4. One hundred patients per group would be needed as calculated by the G power (3.0.10 version) at a two-sided significance level of 5% and power of 80% in a 1:1:1 ratio. Estimating a 10% drop-out rate, a total of 330 patients (110 patients per group) will need to be enrolled in this study.

Data management

All data will be documented by outcome assessors at each site who have been qualified by a special training class before recruitment. The training includes how to fill in the CRF in an accurate and timely manner, how to assess the electronic CRF (eCRF) that is established by the CEC-CAMS and input the data into the eCRF to double-check the accuracy. Standard operation procedures (SOP) have been established and provided to the assessors and researchers in each clinical trial institution. The data for each participant will be stored in the centre server of the CEC-CAMS, and only the data monitor is able to check the data. The researchers are unable to modify and acquire data before all participants' enrollment, observation and data collection are finished.

Statistical analysis

SPSS 21.0 statistical software (IBM Corp., Armonk, New York, USA) will be used for data analysis. An independent statistician who does not know the group assignments will run the statistical analysis. Continuous variables will be described as mean ± SD with a 95% confidence interval (CI)

in a normal distribution and median (range) in abnormal distribution, while categorical variables will be represented by numbers (percentages). The level of significance will be established at 0.05 in a two-sided test.

All analysis will be performed according to intention-to-treat (ITT) protocol. Participants who finish the baseline assessment of primary outcome and receive at least one session of either verum or sham acupuncture treatment will be included in ITT population. The missing data of participants who drop out will be handled by multiple imputations with a package "Amelia" from the R software (www.r-project. org). Per-protocol (PP) population analysis will be also performed, for participants who have finished at least 80% of the treatment protocol after randomisation.

The primary outcome will be compared by an analysis of covariance (ANCOVA). The ANCOVA will be adjusted by the patients' characteristics and baseline outcomes if there are possible covariates. Pairwise comparisons will be performed by the least significant difference (LSD) test in a post-hoc analysis, if the difference is significant in the global test the among three groups (verum acupuncture, sham acupuncture and waiting-list). There are 8 visit points of this study. Therefore, repeated measures ANCOVA will be performed to detect the differences between groups at different visit points, and interactions between groups and time points. The secondary outcomes will be analysed in the same model of ANCOVA. Categorial variables will be compared by chi-square test or Fisher's exact test. A paired *t*-test or Wilcoxon signed-rank test will be used to compare the differences within groups.

Quality control

All staff participated in special training about the study objectives, study protocol on the treatment strategies, and quality control before the study began. Acupuncturists are licensed and have at least 2 years of acupuncture experience in clinical practice. All study documents (such as screening forms, CRFs, treatment records) and treatment material (such as acupuncture needles, PSD, etc.) are in locked storage at study sites with limited access. A specified monitor in each site will check the CRFs and records of the acupuncture treatment every week. Every 3 months, members of the quality monitor group will perform a quality control review at each study site and produce a report on the quality of the entire study process. The principle investigator will hold regular meetings to discuss

and solve the problems discovered during the observation period.

Patient and public involvement

Patient priorities, experiences, and preferences were not involved in the development of the research question, outcome measures, study design, recruitment, or conduct of this study. The results will not be disseminated to study participants. The burden of intervention will not be assessed by trial participants. The results of this study will be disseminated to study participants via the website of our hospitals.

Ethics and dissemination

The protocol of this study has been approved by the Sichuan Regional Ethics Review of Committee on TCM (Medical Ethics Committee of the Affiliated Hospital of Chengdu University of TCM) (Approval ID: 2019kl-006), the Medical Ethics Committee of the First Hospital of Wuhan (Approval ID: [2019] No. 7), and the Medical Ethics Committee of the First Hospital of Hunan University of TCM) (Approval ID: HN-LLKY-2019-017-01/03). This study will be performed in accordance with Helsinki declaration, and has been registered on the Chinese Clinical Trial Registry (CHICTR) platform with the identifier number ChiCTR1900022994. Each patient will be given full and adequate information about the purpose, possible risks and benefits of the study. Written informed consent are reviewed with the patient by the recruiting physician and signed by patients prior to study entry. Personal information will be removed and replaced with a new, unique and unidentifiable identification number in this study, and there will be no personal details in period of dissemination, thus ensuring the confidentiality of the information. The results of this study will be presented in select conferences and scientific meetings, and will be published in peer-reviewed journals. For transparency of study results, the raw data set will be available upon request to the research team 3 years after the publication of study results.

DISCUSSION

CSU significantly impairs patients' QoL and leads to a great economic burden for the families as well as society. This multi-centre, parallel, three-arm, randomised, sham-controlled trial will

examine the efficacy of acupuncture in treating CSU, and provide solid evidence of acupuncture treatment for patients with CSU.

According to the theory of TCM, the main etiology and pathogenesis of CSU is the disharmony of nutrients and defenses resulting from the wind evil assailing the exterior, accumulated heat in stomach and intestine, blood deficiency and wind-dryness. Therefore, a method of dispelling wind, harmonizing nutrients and relieving itching should be used for treating CSU. In accordance with the literature and consultation with experts, we will choose the acupoints located along the Hand- and Foot-Yangming Meridians as the main acupuncture points (table 2 and figure 2). LI11 and SP10 can disperse wind and clear heat, harmonize the nutrients and defenses, cool blood, and combine with ST36, ST25, CV12, and SP6 to invigorate spleen, drain dampness and harmonize blood. SP10 is an acupoint with importance for cooling, regulating and nourishing blood, which is commonly used for skin disease. The Yellow Emperor' s Inner Canon records that symptoms of pain, itching, sores and ulcers all result from dysfunction of the Heart. Thus, HT7 will be chosen for tranquilizing the spirit and relieving itching. For non-acupoints, we will choose the same number of points located on non-meridians as our sham controls (table 3 and figure 2). These non-acupoints are located near the corresponding traditional Chinese acupoints, which could blind patients from differentiating them from the verum acupoints.

Previous studies reported that acupuncture treatment was beneficial for patients with CU[18 36]. However, results from these studies seem somewhat unreliable because of poor methodology in the following aspects. First, the sample size of previous studies was small,[18] and lacked a rationale for the sample size calculation. Second, to the best of our knowledge, we did not find reports of any RCT applied sham-acupuncture, placebo or waiting-list controls in any study of acupuncture for CU after a systematic literature search in databases, such as PubMed, CNKI, Wangfang, et al. So, the specific effects of acupuncture for CU have not been well identified so far. Several methods of sham acupuncture controls have been applied in acupuncture studies, but they are controversial. At present, the common types of controls include non-acupoints (stimulation location), different stimulation methods (such as superficial needling, non-penetrating puncturing or sham-laser acupuncture), and a placebo acupuncture device (such as the Streitberger needle[38] or PSD[20]). Real needles at non-acupoints with normal depth or superficial puncturing were reported as having some effects in

different diseases.[39 40] Stimulation, such as superficial needling, could trigger cutaneous therapeutic effects to relieve dermatological problems. In this study, we choose non-penetrating needles and non-acupoints as controls for real acupuncture stimulation and specific acupoints in accordance with TCM theory, respectively. An ideal placebo should be inert and unable to be distinguished by patients. Because of the nature of acupuncture, a placebo device is necessary for a blinded study. Therefore, we will apply PSD in this study to ensure blinding in the verum and sham acupuncture groups. Third, several studies chose global symptom scores as outcome measurements that were not the internationally acknowledged outcomes measurements for CSU. Furthermore, most of them applied cut-points or ranking categories, which may decrease the statistical effects compared to analysis of continuous data. In this study, we will apply USA7, which is recommended by the guidelines and has been validated,[1 23] to assess CSU. Fourth, long-term effects of acupuncture have been demonstrated in various disease, such as migraine,[41] chronic neck pain,[42] hot flashes,[43] and tinnitus.[44] Recurrence and persistence are characteristics of CU.[1] A previous study reported that a lower recurrence rate was observed in the acupuncture group after the end of treatment, when compared to drugs in treating CU.[36] Therefore, we are interested in the long-term effects of treatment during the follow-up period on urticaria, psychology, sleeping, QoL and so on. Last, the randomisation sequence is generated by a computer, and only authorized persons have access to information about the randomisation sequence, and group assignment will be concealed in the CEC-CACMS until the end of the study to avoid selection bias.

This study has several limitations. First, because of the nature of acupuncture, blinding the acupuncturists or patients between acupuncture treatment and waiting-list control groups is impossible. Additionally, it is impossible to blind acupuncturists while they are performing verum or sham acupuncture treatment. Therefore, independent outcome assessors and statisticians who are masked from group assignments will carry out outcome assessments and data analysis in this study. Second, this study is being performed in Chengdu, Wuhan and Changsha, which are the capitals of Sichuan, Hubei and Hunan Provinces in southwestern and central China, respectively. The patients that we include in this study could be not present patients in China with different ethnic nationalities, either the foreigners living in the western countries.

This trial will follow the Consolidated Standards of Reporting Trial (CONSORT) reporting

guidelines[45] and Standard for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations.[46] We hope the results of this study will provide high-quality evidence for the use of acupuncture for CSU treatment.

Trial status

This study is currently in the recruitment phase. The first patient was randomised on 27th May 2019, and the study is expected to end in the middle of 2021.

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Contributors YL is a principle investigator and conceived of the study. YL, HZ, SZ and QZ initiated the study design. YL and SZ are monitors of this study. YS, LZ, XX, FZ and CW will carry out the implementation of this study, including participants recruitment, acupuncture procedure conducting and the case report forms filling in. YL contributed in obtaining research fund. HZ was responsible for design of statistical analysis. YL, WZ and LZ sought ethical approval. YH and MC provided professional advice for the study design and will be responsible for screening eligible participants. QZ drafted this manuscript. QZ, HZ, YS and YL were responsible for revising the manuscript. All authors read this manuscript and approved the publication of the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study protocol was approved by Sichuan Regional Ethics Review of Committee of Traditional Chinese Medicine (23 April 2019, Approval No. 2019kl-006), the Medical Ethic Committee of the First Hospital of Wuhan (15 May 2019, Approval No. [2019] No. 7), and the Medical Ethic Committee of the First Hospital of Hunan University of TCM) (12 July 2019, Approval No. HN-LLKY-2019-017-01/03).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement: The submitted manuscript is a study protocol which includes no primary data now. For public purpose or research transparency, the raw data set will be available upon request to the corresponding author.

Author note: 2019.02.10 study protocol (original protocol: V1.0); 2019.03.02 study protocol (first amendment: V2.0); 2019.04.10 study protocol (second amendment: V3.0). Any important protocol modifications and other changes after the publication of this paper will be updated at the trial registration platform.

Table 1 Time points of treatment assessment

Table 2 Acupoints used in the verum acupuncture group

Table 3 Non-acupoints used in the sham acupuncture group

Figure 1 Trial flow chart. DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.

Figure 2 Location of acupoints and non-acupoints.

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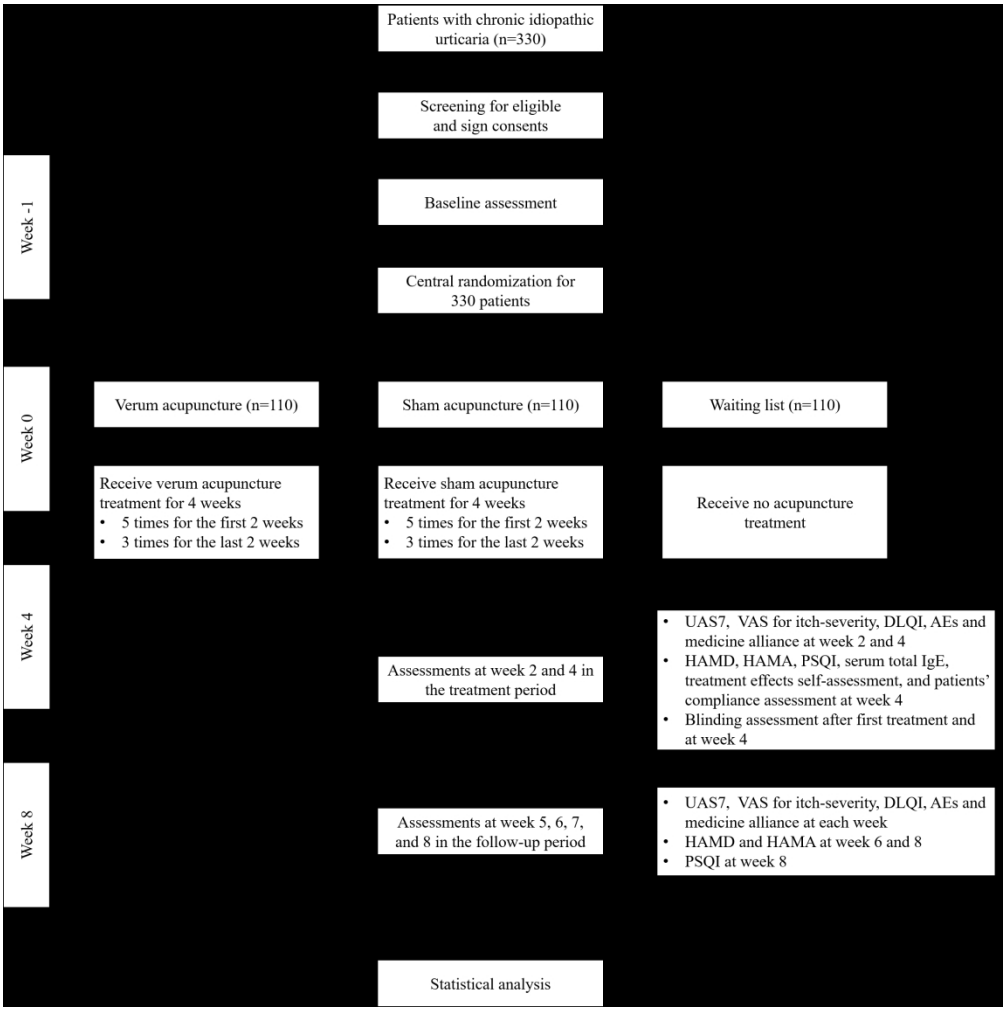
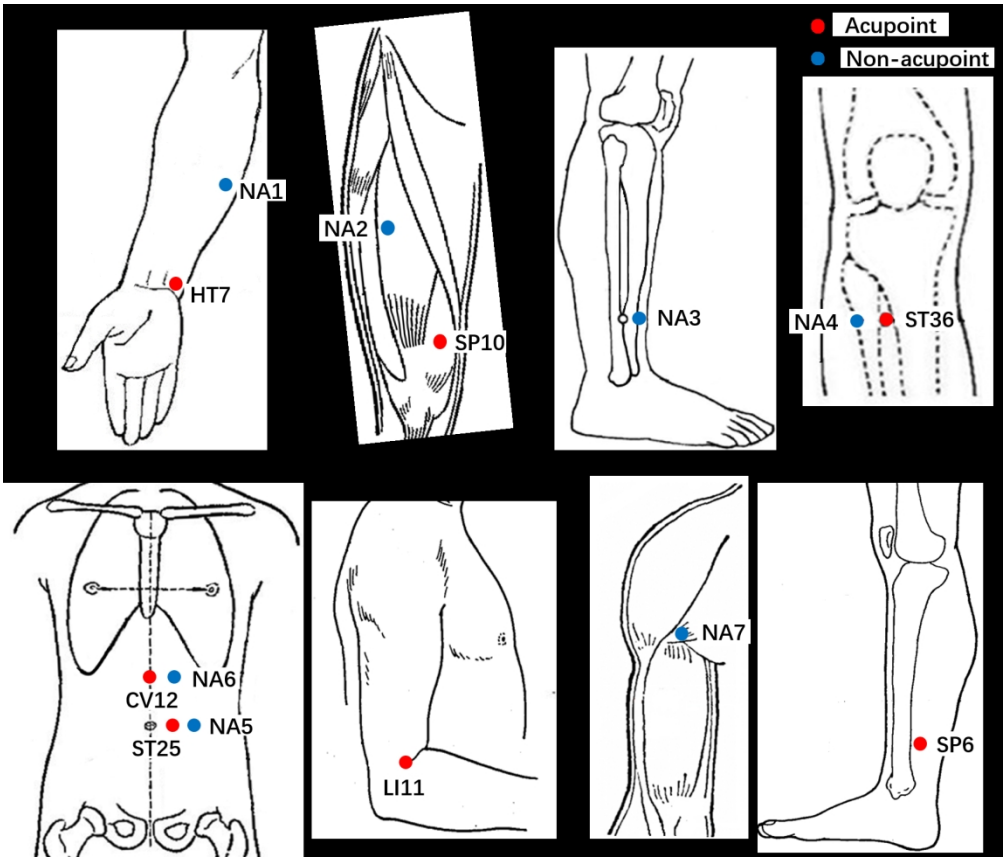


Trial flow chart. DLQI, Dermatology Life Quality Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; IgE, Immunoglobulin E; PSQI, Pittsburgh Sleep Quality Index; UAS7, Urticaria Activity Score for 7 consecutive days; VAS, Visual Analogue Scale.



Location of acupoints and non-acupoints.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 15
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	15-16
Objectives	7	Specific objectives or hypotheses	2, 4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 18
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9, 12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12, 18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.