# Acupuncture and Moxibustion in the Treatment of Chronic Urticaria: A Case Control Study

**Ye Zhang**
Shandong University of Traditional Chinese Medicine
**Shizhao Zhang**
Shandong University of Traditional Chinese Medicine
**Xiangyu Ping**
Shandong University of Traditional Chinese Medicine
**Zehua Zhang**
Shandong University of Traditional Chinese Medicine
**Liheng Tang**
Shandong University of Traditional Chinese Medicine
**Liyun He**
China Academy of Chinese Medical Sciences
**Xin Zhang** ( doctorzhangxin@163.com )
Shandong University of Traditional Chinese Medicine Affiliated Hospital

**Study Protocol**

**Keywords:** Acupuncture, Chronic urticaria, Randomized controlled trial

**Posted Date:** September 30th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-927180/v1

# Abstract

**Background:** Chronic urticaria is a clinically refractory skin disease with long symptom duration and high recurrence rate. The current research demonstrates that the first-line drugs treated by medicine are the second-generation non-sedation antihistamines. Although the effect is good In the treatment process, the first-line drugs often relapse within a week after withdrawal, which affects the quality of life of patients. Existing studies have shown that acupuncture is safe and effective in the treatment of chronic urticaria. This study is a randomized controlled clinical study designed to provide high-quality evidence for the international use of acupuncture in the treatment of chronic urticaria.

**Methods:** This study is a randomized, double-blind, sham-controlled clinical trial. A total of 60 participants were selected and divided into an acupuncture group and a micro-acupuncture group, with equal numbers in the two groups. The acupuncture group received fixed-point acupuncture treatment, and the micro-acupuncture group received micro-acupuncture treatment (micro-acupuncture at non-acupoints). Patients will receive 4 weeks of treatment, three times per week for a total of 12 treatments. The primary measurement indicator is Urticaria Activity Score (UAS), and the secondary measurement indicators include Visual Analogue Scale (VAS), Dermatology Life Quality Index (DLQI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Pittsburgh Sleep Quality Index (PSQI), adverse events. UAS and VAS were assessed before treatment, during treatment, and 4 weeks, 8 weeks, and 12 weeks after treatment. DLQI was assessed before treatment, in the 4th week of treatment and 4 weeks, 8 weeks, and 12 weeks after treatment. Then HAMD, HAMA and PSQI were measured before treatment and in the 4th week of treatment. Adverse events will be summarized at 1st, 2nd, 3rd, and 4th weeks after randomization.

**Discussion:**This study is a pilot study, and its main purpose is to explore the feasibility and safety of acupuncture in the treatment of chronic urticaria. The research results will help confirm whether acupuncture can improve the quality of life of patients with chronic urticaria, provide evidence that acupuncture can effectively treat chronic urticaria, and provide basic data for further larger-scale experiments.


# Background

Urticaria can be divided into spontaneous urticaria and induced urticaria(1). Spontaneous urticaria is divided into acute urticaria and chronic urticaria. Chronic urticaria refers to the occurrence of temporary inflammatory congestion and intra-organic edema of the skin, mucous membranes, and blood vessels caused by various factors. Hives that are present for at least or greater than 6 weeks are defined as chronic urticaria(2, 3). It clinical manifestations are skin and mucous membrane flushing or wind masses with episodic rashes(4). The wind masses vary in shape and size, and are pale or bright red in color. They fade away from time to time, and leave no traces after they subside. The patients feel severe itching, and a few will be accompanied by systemic symptoms such as fever, joint swelling and pain, headache, nausea, vomiting, abdominal pain, diarrhea, chest tightness, suffocation of breath, dyspnea, and

palpitations(5–8). According to statistics, about 15–20% of the world's total population have urticaria, and 0.5–1% of the population suffers from chronic urticaria(9, 10). Chronic urticaria is a common clinical skin disease, and is difficult to cure. It recurs and persists, which has a serious impact on the patient's life, study, work, and psychology(11).

At present, medicine generally uses antihistamine drugs such as cetirizine and loratadine, glucocorticoids such as prednisone and dexamethasone, and immunosuppressants such as cyclosporine and azathioprine for treatment, but they can only relieve symptoms. The symptoms may relapse easily(12–14). However, Chinese medicine has made great progress in the treatment of chronic urticaria with acupuncture, puncturing and cupping(15–19). It has the advantages of shortening the course of the disease, reducing the recurrence rate, regulating the immune function, and improving the symptoms of the body(20). Traditional Chinese medicine (TCM) treatment of chronic urticaria can be divided into internal treatment and external treatment. TCM internal treatment methods include TCM decoctions, TCM pills, TCM powders, TCM ointments, etc.; TCM external treatment methods include more than 60 methods such as acupuncture, cupping, sticking, and acupoint injection. Acupuncture treatment of chronic urticaria has advantages that other therapies cannot replace. This method adjusts the yin and yang of the viscera according to the different acupuncture points, positions and meridians. It helps to improve immunity, improve the symptoms of patients, reduces the number of relapses, and has a small economic burden and is easy to be accepted by patients.

Although existing studies have shown that acupuncture is safe and effective in the treatment of chronic urticaria, due to the low quality of the research, a rigorously designed and implemented further clinical trial is needed to verify it. This study is a clinical randomized controlled study. In this trial, a practical randomized controlled trial was utilized to compare the effects of acupuncture + conventional treatment, and micro-acupuncture + conventional treatment, and the clinical efficacy of acupuncture-assisted conventional therapy in the treatment of chronic urticaria was observed.Finally, this trial can produce high-quality evidence for the promotion and application of acupuncture in the treatment of chronic urticaria on an international scale.

# Methods And Design

### Study design

This study is a randomized, double-blind, sham-controlled clinical trial experiment. The whole process of this research was carried out in the Treatment Center of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine. Eligible volunteers will be randomly assigned into the experimental group and the control group. The treatment cycle lasts for 4 weeks, with 3 treatments per week. Visits are made in the 4th, 8th, and 12th weeks after the treatment, and the results are recorded. (Fig. 1)

### Recruitment

The 60 volunteers needed for this research will be recruited by, but not limited to, the review and screening of the Dermatology Clinic of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, social media recruitment advertisements, community promotion, recruitment flyers, and online recruitment. Meanwhile, two research assistants will go to the Dermatology Clinic of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine to recruit patients every week. The research assistant will inform patients and their guardians of the details of the study, the benefits, and the potential risks before the start of the study in detail. The recruited patients will get a paper informed consent and sign the informed consent under the witness of the research assistant. If the patient does not recognize words, his guardian will sign on his behalf or reach an informed verbal consent (record audio or video).

## Eligibility

### Inclusion criteria

1. Those who meet the diagnostic criteria of chronic spontaneous urticaria in EAACI/GA2LEN/EDF/WAO urticaria diagnostic guidelines (2017) and China urticaria diagnostic guidelines (2014);
2. Aged between 18 and 70 years;
3. Sign the informed consent form and participate in this study voluntarily.

Note: patients who meet the above three criteria at the same time can be included in this study.

### Exclusion Criteria

1. Patients who are unconscious , unable to express subjective discomfort symptoms, and mentally ill patients;
2. Patients with progressive malignant tumor or other serious wasting diseases, and those prone to co-infection and bleeding;
3. Patients with cardiovascular, liver, kidney, digestive, hematopoietic and other serious primary diseases;
4. Pregnant and lactating women.
5. Patients who have taken antihistamines within 2 weeks, and steroids and immunosuppressive drugs within 1 month before the study;
6. Patients who are currently participating in other ongoing clinical studies.

Note: All patients who meet any of the above items will be excluded.

### Treatment discontinuation criteria

1. Clinical cure,

2. The participants has severe complications or worsening of the condition that cannot continue the treatment during the study;
3. The participants who require to withdraw from the clinical study halfway.

### Follow-up criteria

1. Clinically cured patients;
2. A total of 3 follow-up visits were carried out at the 4th, 8th, and 12th week respectively.
3. Lost to follow-up for 1 month, fill in the lost follow-up record and terminate the follow-up.

### Randomization and allocation concealment

After the baseline assessment of volunteers, 60 participants were randomly divided into two groups: acupuncture group and micro-acupuncture group. According to 1:1 distribution, there were 30 participants in each group. The randomization method adopted was the central randomization. Randomized data and results were managed by an independent research assistant who knew nothing about other parts of this research. The research assistant would contact qualified patients to enter the corresponding group for the research.

### Blinding

This study is a double-blind trial. Due to the nature of acupuncture treatment, the acupuncturists who deliver the treatment to the participants will not be blind to the treatment allocation. All acupuncture therapists will not participate in the process of grouping patients and the final evaluation process. In addition, all volunteers, effect assessors, and statisticians will be unaware of the grouping results. We will evaluate the blinding effect end of study.

### Intervention

### Acupuncture group

The acupuncture group was treated by an acupuncture therapist using sterile needles (Huatuo disposable acupuncture needle, Suzhou Medical Supplies Factory Co. Ltd.) in sizes of 0.25 × 25 mm or 0.25 × 40 mm. Table 1 and Figure 2 are the location of acupuncture points. During the treatment, the acupuncture therapist will pierce the needle into the corresponding acupuncture point, insert the needle to a safe depth, and perform uniform replenishing and reducing techniques(Lift, insert, twist, turn) until each point achieves the Deqi sensation. Needles will be retained for 30 minutes per session, and stimulation of the needles is manipulated every ten minutes.

### Micro-acupuncture group

Volunteers in the micro-acupuncture group would receive 12 micro-acupuncture treatments in 4 weeks. The same acupuncture therapist would use the same specifications of acupuncture needles for non-

acupoint acupuncture. The number of acupunctures was the same, and the depth of acupuncture was 2-3mm. Needles were retained for 30 minutes. During this period, no manipulation was performed to avoid excessive stimulation and prevent the participants achieving the Deqi sensation.

### Process

Urticaria activity score (UAS) and Visual Analogue Scale (VAS) were evaluated after 1 week in the baseline period and 4 weeks in the treatment period. Dermatology Life Quality Index (DLQI) was evaluated after 1 week of the baseline period and the 4th week of the treatment period. During the follow-up, the patients filled in UAS, VAS and DLQI for the corresponding follow-up week. Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and Pittsburgh Sleep Quality Index (PSQI) were evaluated at the entry and the exit point. Adverse events would be summarized at 1st, 2nd, 3rd, and 4th week after randomization. (Table 2)

### Observation indicators

### Demographic

Gender, age, education level, occupation, marital status, etc. Recorded at the time of enrollment.

### Physical examination

1. Vital signs: heart rate (heart Rhythm), respiratory rate, blood pressure. Recorded at each assessment.
2. Basic medical history collection, routine physical examination. Recorded at the time of enrollment.

### Outcomes

### Primary outcome measurement

Urticaria activity score (UAS)(21, 22). Evaluate once a day for 7 consecutive days, and calculate the total score within 7 days.

### Secondary outcome measurements

**Pruritus score:** The degree of itching was evaluated by the Visual Analogue Scale (VAS)(23, 24), which was evaluated once a day for 7 consecutive days. The total score within 7 days was calculated.

**Quality of life score:** The Dermatology Life Quality Index (DLQI)(25-27) was used to evaluate the quality of life of patients

**Psychological assessment:** The Hamilton Depression Scale (HAMD)(28) and Hamilton Anxiety Scale (HAMA) (29)were used for evaluation.

**Sleep assessment:** Pittsburgh Sleep Quality Index (PSQI)(30) was used for evaluation.

### Adverse events and treatment

During the study intervention, any adverse events related to acupuncture would be recorded. Possible adverse events were local hematoma, acupuncture syncope, sticking of the needle, bent needles and broken needles,etc. Timely treatment measures should be taken according to the patient's condition when an adverse reaction occurred. Emergency medical assistance would be sought if any serious adverse effect occurred. Whether the adverse events were related to the treatment in this trial, they would be recorded in detail, including the date of occurrence, time, symptom, degree, duration, laboratory inspection indicators, processing methods and results. Serious adverse events would be immediately reported to the primary investigator to assess whether to proceed with the study.

### Data management

To ensure the successful and smooth study implementation, all researchers would be uniformly required to receive standardized training before the research starts. The collected clinical data would be recorded and managed by two researchers who have received rigorous training on using paper and electronic case report forms (CRFs). In order to avoid data entry errors, data would be proofread by two independent researchers when entering the electronic CRFs, and they would proofread each other before finalizing. Data would be uploaded to **www.amreg.org** and managed by the person in charge.

### Sample size

This study aims to assess the efficacy of acupuncture on the treatment of chronic urticaria and the feasibility of widespread promotion. We did not perform a sample size calculation for this study, but used a convenience sample based on the known availability of study participants in the research base. At the same time, considering that too many volunteers could not be recruited and the dropout rate of 20%, we estimated that we could recruit 60 people for this study(31). There would be 30 people in the acupuncture group and the micro-acupuncture group. The outcomes of this study would facilitate the calculation of the appropriate sample size for other randomized controlled trials in the future.

### Statistical analysis

1. **Case distribution:** Different data set sizes for each group, detailed list of dropped cases, aborted cases and reasons.
2. **Comparability analysis:** Compare demographic data and other basic value indicators to measure the comparability of the two groups.
3. **Compliance analysis:** Compare whether the patients in each group are implemented according to the design plan. To make sure they do not take the drugs and foods prohibited in the plan. Compliance is evaluated based on the records of the Case Report Form (CRF), and calculates the number and percentage of cases <80%, 80%~100%, >100%.
4. **Effectiveness analysis:** Categorical data are described by mean of treatment difference from baseline, standard deviation, median, P25, P75, maximum and minimum. Main indicators and global

indicators were analyzed by PP and ITT.

5. **Analysis of influencing factors:** If there are significant differences in age, gender, disease type, condition, etc. before the test, or there are related factors that significantly affect the efficacy, these factors should be considered as covariates when comparing groups. Covariance analysis or logistic regression analysis is required . Meanwhile, a detailed list of combined medications is required.
6. **Safety evaluation:** First, according to the requirements of the relevance of adverse reactions, the adverse events and adverse reactions of each group(including the number and incidence of various adverse events) should be listed first,and then the reasons and explanations.
7. Data from this clinical trial will be calculated and analyzed using SAS 9.1.3/SPSS 19.0 statistical analysis software. $P<0.05$ will be considered that the difference is statistically significant.

# Discussion

Chronic urticaria is a refractory skin disease with long duration and high recurrence rate. Epidemiology shows that children and adults have the same chance of getting the disease, and it is widely distributed all over the world. Chronic urticaria is not a direct threat to human life, but itching caused by wind mass lesions and pain caused by angioedema can significantly reduce the quality of life. In this study, UAS was the main observation index, and the VAS were selected to evaluate the treatment effect. Meanwhile, DLQI and PSQI were utilized to evaluate the improvement of the patients' living standards. In addition, HAMD and HAMA were utilized to monitor the mental state of patients.

Our research was based on the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, and the patients recruited by dermatology and acupuncture departments were the principal part, which ensures the quality of patients. The treatment protocol for acupuncture was researched and developed by Physician of Dermatology and Acupuncture to assure the reliability of the study. It meets ethical requirements that corresponding drugs are used to treat when the wind mass, itching, and hematoma etc. are more serious. Different methods will be applied to reduce the possible adverse effects on the experiment, for example, micro-acupuncture only pierces the surface of the skin during acupuncture to avoid achieving the Deqi;  patients receive treatment in separate rooms to reduce "Hawthorne effect".

Since this study is only a small-scale clinical trial, it has certain limitations. However, it can provide valuable information and experience for the related research on the treatment of chronic urticaria in the future.

### Trial status

This trial is currently ongoing. The trial started on 10 May 2019. We hope to achieve our research objectives by December 2022.

# Abbreviations

UAS: Urticaria Activity Score, VAS: Visual Analogue Scale; DLQI: Dermatology Life Quality Index, HAMD: Hamilton Depression Scale, HAMA: Hamilton Anxiety Scale, PSQI: Pittsburgh Sleep Quality Index, TCM: Traditional Chinese medicine, CRFs: case report forms.

# Declarations


### Acknowledgements

We would like to express gratitude to A/Prof. Ying ZHAO and Weining LI from the dermatology department of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine for recruiting participants


### Authors' contributions

YZ, ZSZ, LYH and XZ participated in the conception and design of this trial. YZ, ZSZ were responsible for planning the draft and revising the manuscript. XZ are monitors of this study. YZ, XYP, ZHZ and LHT are responsible for the recruitment and/or treatment of patients. ZSZ and LYH are responsible for collecting the data. All authors have read the manuscript and approved the publication of this protocol.


### Funding

The National Key Research and Development Program of the Ministry of Science and Technology of the People's Republic of China-Key Project "Research on Modernization of Traditional Chinese Medicine"–"International Cooperation Research on Evaluation of Acupuncture Advantage Diseases" (2017YFC1703601), this funding body funded the design of this study. Shandong Province Tan Qiwen Famous and Old Traditional Chinese Medicine Expert Inheritance Studio Project (22201906); Shandong University of Traditional Chinese Medicine Prevention and Health Care scientific research and innovation team (220318), These funding bodies funded the collection, analysis, and interpretation of data and in writing the manuscript of this research.


### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

### Ethics approval and consent to participate

The study is approved by the Ethics Committee of Affiliated Hospital of Shandong University of Traditional Chinese Medicine (2019-007-KY) and registered with Clinical Trial Registry, ChiCTR1900022994. The implementation follows the principles of the Declaration of Helsinki. The protocol version is 2019.8.9, F3.0. Only participants who provide written informed consent will be included in this study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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# Tables

Table 1: Acupuncture points and methods of acupuncture group

| Acupoints | Location of acupoints | Manipulation |
| --- | --- | --- |
| Baihui (DU20) | On the middle of the head, 7 cun* directly above the midpoint of the posterior hairline | Penetrate 0.5-0.8 cun at a 15 degree angle to the skin surface |
| Zhongwan (RN12) | On the anterior midline, 4 cun above the umbilicus | Puncture perpendicularly to a depth of 1–1.5 cun |
| Tianshu (ST25)<br>Bilateral | On the same level of the umbilicus,and 2 cun lateral to the anterior midline | Puncture perpendicularly to a depth of 1–1.5 cun |
| Qihai (RN6) | On the anterior midline, 1.5 cun below the umbilicus | Puncture perpendicularly to a depth of 1–1.5 cun |
| Quchi (LI11)<br>Bilateral | In the depression of the radial end of the cubital crease when the elbow is flexed | Puncture perpendicularly to a depth of 1–1.5 cun |
| Hegu (LI4)<br>Bilateral | Between the 1st and 2nd metacarpal bones and in the midpoint of the radial side of the 2nd metacarpal bone | Puncture perpendicularly to a depth of 0.5–1 cunthe hand is half-fisted during acupuncture |
| Fengshi(GB31)<br>Bilateral | On the midline of the outer thigh, 7 cun above the popliteal stripes | Puncture perpendicularly to a depth of 1–1.5 cun |
| Xuehai (SP10)<br>Bilateral | 2 cun above the upper border of the medial patella | Puncture perpendicularly to a depth of 1–1.5 cun |
| Yinglingquan (SP9)<br>Bilateral | Posteroinferior to the medial condyle of the tibia | Puncture perpendicularly to a depth of 1–2 cun |
| Zusanli (ST36)<br>Bilateral | 3 cun directly below Dubi (ST35) and one finger-breadth lateral to the anterior border of the tibia | Puncture perpendicularly to a depth of 1–2 cun |
| Taichong (LR3)<br>Bilateral | In the depression anterior to the junction of 1st and 2nd metatarsal bones On the line joining Daling and Quze, between the tendons of palmaris | Puncture perpendicularly to a depth of 0.5–1 cun |
| Dazhui (DU14) | On the posterior midline,in the depression below the spinous process of the7thcervical vertebra | Sit upright, tilt the head slightly forward, relax the nape, and slowly Puncture 0.5-1 cun in the direction of the jaw |
| Fengchi (GB20)<br>Bilateral | At the level of Fengfu, in the depression between the upper ends of the sternocleidomastoid trapezius muscles | Needle tip slightly down, and Puncture 0.8-1.2 cun at a 45 degree angle to the surface of the skin towards the tip of the nose . |
| Fengfu(GV16) | 1 cun directly above the midpoint of the posterior hairline,in the depression below | Sit upright, tilt the head slightly forward, relax the nape, and slowly |

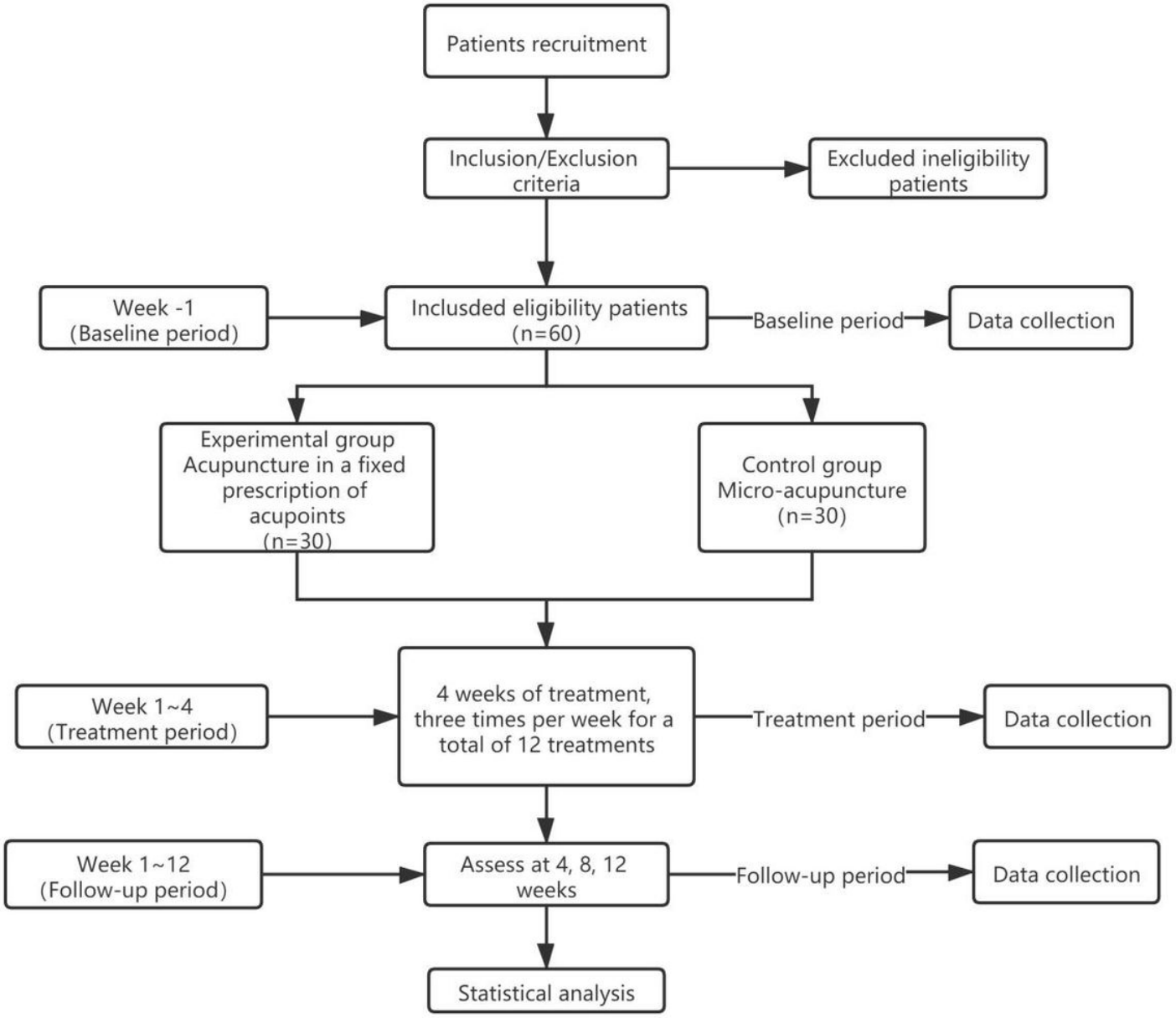
| | | |
|---|---|---|
| | the external occipital protuberance | Puncture 0.5-1 cun in the direction of the jaw |
| Pishu (BL20) （Bilateral） | 1.5 cun lateral to the depression below the spinous process of the 11$^{th}$thoracic vertebra. | Pierce 0.5-0.8 cun at a 45 degree angle to the skin surface |
| Ganshu (BL18) （Bilateral） | 1.5 cun lateral to the depression below the spinous process of the 9$^{th}$thoracic vertebra. | Pierce 0.5-0.8 cun at a 45 degree angle to the skin surface |
| Geshu(BL17) （Bilateral） | 1.5 cun lateral to the depression below the spinous process of the 7$^{th}$thoracic vertebra. | Pierce 0.5-0.8 cun at a 45 degree angle to the skin surface |

*One "cun" is defined as the width of the interphalangeal joint of patient's thumb

Table 2: Timetable of treatment and outcome collection

| Stage | Baseline | Treatment | | | | Follow-up | | |
|---|---|---|---|---|---|---|---|---|
| Time (weeks) | -1~0 | 1 | 2 | 3 | 4 | 4 | 8 | 12 |
| Inclusion criteria/Exclusion Criteria | ● | | | | | | | |
| Sign informed consent | ● | | | | | | | |
| Medical history | ● | | | | | | | |
| Randomization | ● | | | | | | | |
| Demographic | ● | | | | | | | |
| Physical examination | ● | | | | | | | |
| UAS | ● | ● | ● | ● | ● | ● | ● | ● |
| VAS | ● | ● | ● | ● | ● | ● | ● | ● |
| DLQI | ● | | | | ● | ● | ● | ● |
| HAMD | ● | | | | ● | | | |
| HAMA | ● | | | | ● | | | |
| PSQI | ● | | | | ● | | | |
| Adverse events | | ● | ● | ● | ● | | | |
| Blinding effect evaluation | | | | | ● | | | |
| Safety assessment | | | | | ● | | | |

# Figures




## Figure 1

Study flow diagram

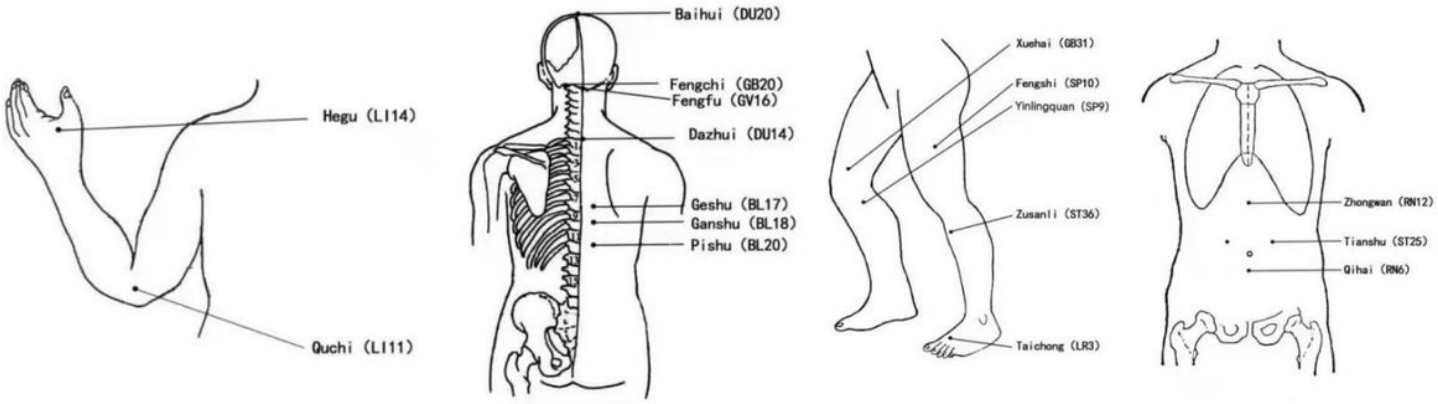



**Figure 2**

Location of acupoints in acupuncture group

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- completedSPIRITchecklist.docx