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Acupuncture for retinitis pigmentosa: study protocol for a randomised, sham-controlled trial

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ABSTRACT

Introduction Primary retinitis pigmentosa (RP) is a common hereditary retinal disease in ophthalmology that has a considerable impact on quality of life, but there are few effective therapeutic strategies. This trial aims to determine the efficacy and safety of acupuncture versus sham acupuncture (SA) for RP.

Methods and analysis This is a study protocol for a randomised, participant-blind, sham-controlled trial. 64 eligible patients with RP will randomly be divided into acupuncture group and SA group. All groups will receive 48 sessions over 3 months. Participants will complete the trial by visiting the research centre in month 6/9 for a follow-up assessment. The primary outcome is visual field mean sensitivity and visual field mean deviation at month 3/6/9 compared with baseline. Secondary outcomes include the best-corrected visual acuity, central macular thickness, subfoveal choroidal thicknes, traditional Chinese medicine syndrome score and the scale of life quality for diseases with visual impairment at month 3/6/9 compared with baseline. Adverse events and safety indexes will be recorded throughout the study. SPSS V.25.0 statistical software was used for analysis, and measurement data were expressed as mean±SD.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of the Chinese Clinical Trial Registry (approval no: ChiECRCT20200460). The results of this study will be published in a peer-reviewed journal, and trial participants will be informed via email and/or phone calls.

Trial registration number ChiCTR2000041090.

Strengths and limitations of this study

- The statistical analysis will be carried out by an independent statistician who is not aware of group allocation.
- The results of this feasibility study will provide data for an adequately powerful pragmatic trial.
- Both the full analysis set and the conforming protocol set were used in the efficacy evaluation, which could enhance the credibility of the test results.
- One of the limitations is that this study is implemented in only one centre in Chinese subjects, without long-term treatment and follow-up.
- Though widely accepted and used, the rationality of sham acupuncture still has been questioned.

BACKGROUND

Primary retinitis pigmentosa (RP) is a group of diseases where a large number of mutations cause the rod type photoreceptors to die. After the rod type dies, the cone type photoreceptors gradually degenerate in a unique pattern.[1]RP is mainly manifested as visual field defects and progressive night blindness,[2] specialty examination showed abnormal electroretinogram (ERG), with typical triple signs of optic nerve waxy atrophy, vascular thinning and osteocellular pigmentation.[3] It is a common hereditary retinal disease in ophthalmology, with an incidence of about 1/4000 of the world.[4] The factors influencing the development of RP have not been fully defined, but it is generally believed that genetics is the most important factor. From the perspective of genetics, there are mainly autosomal dominant RP, autosomal recessive RP and X-linked inheritance RP.[5] There are also a few RP genetic patterns that are mainly inherited by mitochondria and double genes.[6]

Because RP has a high degree of genetic and clinical heterogeneity,[7] as well as a variety of complex clinical subtypes, it has a high rate of blindness and a poor prognosis. Currently, there is no effective method to cure RP, which seriously affects the quality of life of the affected population. At present, the research on the treatment of RP focuses on retinal transplantation and gene therapy,[8] but retinal transplantation has many complications,[9] and gene therapy is mostly still in the experimental stage, which has not been used in clinical practice. No matter what kind of modern medical treatment means can not cure RP, so it is urgent to actively explore and develop a safe and effective treatment for RP. The study has shown that acupuncture has a positive effect on the repair of the function of optic nerve cells in inhibition and partial injury, and the regeneration capacity of the central nervous system is greater than generally believed. If nerve fibres are placed in

a suitable environment, it can accelerate the repair of the optic nerve.[10] Acupuncture can improve the microcirculation of local ocular tissues and shorten the pathological reaction, which plays a good role in RP. Bittner *et al*[11] compared transcorneal electrical stimulation (TES) at 6 weekly half-hour sessions, electroacupuncture or inactive laser acupuncture (sham control) at 10 half-hour sessions over 2 weeks for RP patients by RCT. Both the central retinal artery mean flow velocity of the TES and the electroacupuncture group were significantly improved compared with sham controls. Xu *et al*[12] choose acupuncture treated from 1998 to 2017, a total of 26 patients with primary RP (51 eyes), adopt the method of before-after study in the same patient, and observe the patient's visual acuity and ERG, visual function damage, eye retina patients quality of life scale score index in acupuncture treatment after 3 months, and the change of the acupuncture treatment up to now, and assessed the clinical curative effect, it is concluded that the clinical total effective rate was 69.6%. Xie[13] *et al* observed the effect of traditional Chinese medicine (TCM) combined with acupuncture on RP. The experimental group was treated with TCM combined with acupuncture. After treatment, the indicators of intraocular pressure, vision, visual field mean sensitivity (MS) and visual field mean deviation (MD) of the experimental group were superior to the control group ($p<0.05$), and the total effective rate of the experimental group was higher than that of the control group ($p<0.05$). However, most of the domestic studies are based on the combination of acupuncture and medicine, or single-arm clinical trials, and the main observation indicators are visual acuity and visual field MS and MD. Visual acuity and visual field examination is a subjective examination with many influencing factors. Therefore, central macular thickness (CMT)[14 15] and subfoveal choroidal thickness(SFCT)[16] were added as the indicators in this clinical trial. The non-meridian points were used as the control group, and a strict randomised controlled trial was conducted to evaluate the efficacy and safety of acupuncture alone in the treatment of primary retinal pigment degeneration, in order to provide effective methods and research ideas for the treatment of this disease with TCM.

Objectives

The purpose of this randomised, sham-controlled clinical trial is to evaluate the efficacy and safety of acupuncture in the treatment of RP. Since there is currently no cure for RP, this may provide an additional treatment option for patients with RP.

METHODS

Study design

This randomised, single-blind, sham-controlled trial will be conducted in the Hospital of Chengdu University of Traditional Chinese Medicine, China. The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist[17]: defining standard protocol items for clinical trials (online supplemental file 1 SPIRIT Checklist). The study has been approved by the Ethics Committee of the Chinese Clinical Trial Registry (Ethical approval number: ChiECRCT20200460). A flow diagram of the trial is shown in figure 1. The schedule of enrolment, interventions and assessments are presented in figure 2. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale in each section.

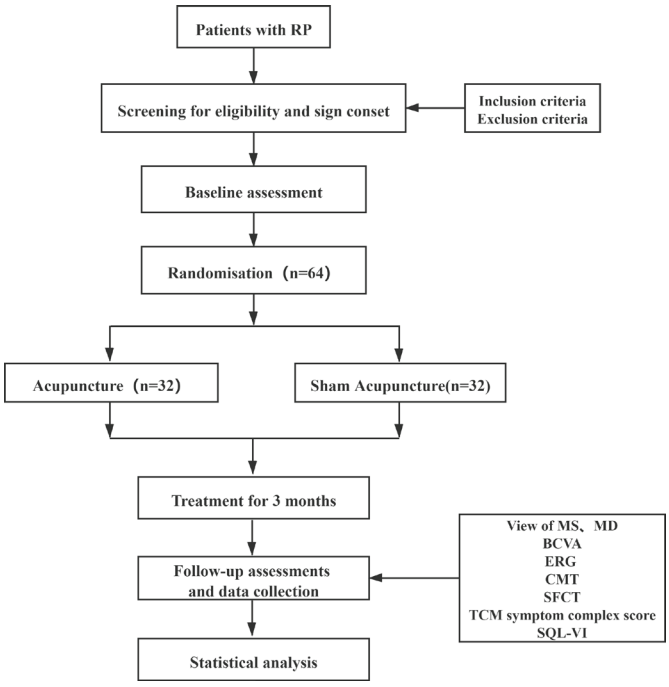

Figure 1 Flow diagram. BCVA, best-corrected visual acuity; CMT, central macular thickness; ERG, electroretinogram; MD, mean deviation; MS, mean sensitivity; RP, retinitis pigmentosa; SFCT, subfoveal choroidal thickness; SQL-VI, scale of life quality for diseases with visual impairment; TCM, traditional Chinese medicine.

Patient recruitment

This study intends to recruit 64 patients with primary RP who meet the diagnostic criteria[18] starting from January 2021, all from the outpatient department of the Hospital of Chengdu University of Traditional Chinese Medicine. The researcher took the initiative to introduce the study, and the subjects volunteered to participate in this study. After the clinician conducted screening according to the inclusion and exclusion criteria, the subjects could be included if they met the criteria. Before randomisation, all patients were required to provide written informed consent (online supplemental file 2 Informed Consent).

Inclusion criteria

- Patients who meet the diagnostic criteria for primary RP.[18]
- Aged 14–80 years (either sex), the course of the disease is not limited.
- Written informed consent. The process of obtaining informed consent conforms to the requirements of clinical trial management standards.

	STUDY PERIOD						
	Enrolment	Allocation	Treatment period (month)			Follow-up period (month)	
TIMEPOINT	-2 days	0	1	2	3	6	9
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Acupuncture group			←	—	→		
Sham acupuncture group			←	—	→		
ASSESSMENTS:							
View of MS,MD		X			X	X	X
BCVA		X			X	X	X
ERG		X			X	X	X
CMT		X			X	X	X
SFCT		X			X	X	X
TCM symptom score		X			X	X	X
SQL-VI		X			X	X	X
ERG		X			X	X	X
Adverse events[1]					X		
Assessment of safety[2]		X			X		

[1] AEs:Treatment-related symptoms include local subcutaneous hematoma, pruritus at the acupuncture site, persistent pain after acupuncture, dizziness, etc.
[2] Assessement of safety include routine blood tests, urine tests, faecal tests, liver function tests, renal function tests, and electrocardiogram.

Figure 2 The schedule of enrolment, interventions and assessments are presented. BCVA, best-corrected visual acuity; CMT, central macular thickness; ERG, electroretinogram; MD, mean deviation; MS, mean sensitivity; SFCT, subfoveal choroidal thickness; SQL-VI, scale of life quality for diseases with visual impairment; TCM, traditional Chinese medicine.

Exclusion criteria

- Best-corrected visual acuity (BCVA) is less than 0.1.
- Patients suffering from ophthalmic diseases such as amblyopia, diabetic retinopathy, glaucoma, severe cataract, etc, which affect vision or other blindness diseases.
- Patients with severe primary diseases such as cardiovascular and cerebrovascular, liver, kidney and haematopoietic system, as well as psychiatric patients.
- Patients who have received other related drugs or treatment for primary RP within 2 weeks.
- Poor compliance or participating in other clinical trials.

Randomisation and allocation concealment

A random sequence is generated by SAS V.9.4 (SAS Institute) and performed by the TCM Good Clinical Practice Centre, Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, China), through the online version of the central randomisation system. Participants will be randomly allocated to an intervention group (acupuncture) or control group (sham acupuncture (SA)) at a ratio of 1:1 with block randomisation. The subject and investigator could not foresee the grouping information of the subjects. The random number is managed by TCM Good Clinical Practice Centre. Until the end of the study, neither the subjects nor the outcome measure knew how the subjects were grouped.

Masking

Due to the nature of acupuncture, masking by acupuncturists is quite difficult to achieve. Patients, outcome assessors and statisticians who perform the statistical analyses will be blinded to group assignment. The treatments subjects received will be not revealed until the statistical analysis is completed. In addition, all patients will be asked to guess which treatment they have received to test the patient-blinding effects at month 3.

Interventions

Treatment will be performed by licensed acupuncturists who have at least 5 years of experience in acupuncture. All the acupuncturists will be trained how to locate acupoints, puncture and manipulate needles before trials. Follow the prescribed treatment regimen four times a week. The baseline time is the day before treatment began. One month is a course of treatment, a total of three courses of treatment. Acupuncture will be discontinued if patients suffer from any serious adverse events (AEs).

Acupuncture

The patients in the acupuncture group were placed in the sitting or supine position. The selected acupoints around the eye were Taiyang (EX-HN5), Cuanzhu (BL2), Yuyao (EX-HN4), Qiuhou (EX-HN7), Jingming (BL1) and the full body acupoints were Baihui (GV20), Hegu (LI4), Taichong (LR3), Sanyinjiao (SP6), Zusanli (ST36). All acupoints are localised according to the WHO Standard Acupuncture Locations and are exhibited in table 1 and figure 3. After the local skin of the patient and the hands of the physician were routinely disinfected with 75% ethanol, both hands were used for needle insertion, and disposable acupuncture needles (0.25 mm×25 mm) were inserted into the acupoint skin except BL1 and EX-HN7 (approximately 10–20 mm depth), and then manipulations of twirling, lifting, and thrusting will be performed on all needles for at least 10 s to reach De qi (a compositional sensation including soreness, numbness, distention, and heaviness), which is believed to be an essential component for acupuncture efficacy. BL1 and EX-HN7 should be the slight twists, do not lift and insert, and press the pinhole after pulling the needle for a moment to prevent bleeding. Needles will be retained in these acupoints for 20–30 min.

The above treatment was performed four times a week. One month is a course of treatment, a total of 3 courses of treatment.

Sham acupuncture

Participants in the SA group will receive the non-meridian and non-acupoint treatment,[19 20] and the selected sham acupoint was at the midpoint of the line between the adjacent meridian acupoints (Xiaguan, Meichong, Touwei,

Table 1 Locations and manipulations of acupoints

	Acupoint	Location	Manipulation
Acupoints around the eye	Taiyang (EX-HN5)	Flat part at each side of the forehead	Puncture perpendicularly to a depth of 0.3–0.5 cun*
	Cuanzhu (BL2)	On the medial end of the eyebrow	Puncture horizontally or obliquely to a depth of 0.5–0.8 cun toward the middle of the eyebrows
	Yuyao (EX-HN4)	Directly above the pupil,in the centre of the eyebrow	Puncture horizontally or obliquely to a depth of 0.3–0.5 cun
	Qiuhou (EX-HN7)	In the face and the outer quarter of the lower orbital margin meets the inner three-quarters	Gently push the eye up,puncture slowly and perpendicularly to a depth of 0.5–1.5 cun toward the orbital rim
	Jingming (BL1)	In the depression and 0.1 cun above the inner canthus	Puncture perpendicularly to a depth of 0.3–0.5 cun close to the orbital rim
Body acupoints	Baihui (GV20)	On the midline of the head, 7 cun directly above the midpoint of the posterior hairline	Puncture horizontally to a depth of 0.5–0.8 cun
	Hegu (LI4)	Between the first and second metacarpal bones,and in the midpoint of the radial side of the second metacarpal bone	Puncture perpendicularly to a depth of 0.5–0.8 cun
	Taichong (LR3)	In the depression anterior to the junction of first and second metatarsal bones	Puncture perpendicularly to a depth of 0.5–1 cun
	Sanyinjiao (SP6)	Three cun superior to the prominence of the medial malleolus, posterior to the medial border of the tibia	Puncture perpendicularly to a depth of 1–1.5 cun
	Zusanli (ST36)	Three cun directly below Dubi†, and one finger-breadth lateral to the anterior border of the tibia	Puncture perpendicularly to a depth of 1–2 cun

*1 cun (≈20 mm) is defined as the width of the interphalangeal joint of patient's thumb.
†Dubi is in the lateral depression of the patellar ligament, when the knee is flexed.

Juliao, Yingxiang, etc). After skin disinfection, disposable acupuncture needles (0.25 mm×25 mm) were inserted into the sham acupoint skin without twist, lift or push all needles to achieve De Qi. This kind of SA with pierce the skin is relatively simple in clinical operation, and participants are not easy to distinguish. and the acupoint. Needles will be retained in these acupoints for 20–30 min.

The above treatment was performed four times a week. One month is a course of treatment, a total of three courses of treatment.

Concurrent treatments

Participants will not receive any other medical treatment for RP other than acupuncture.

Follow-Up

After 3 months of treatment, all participants entered an additional follow-up period. the follow-up time is the third and sixth month after treatment (ie, month 6 and month 9). During this time, they will receive routine healthcare as provided to all other patients with RP. However, acupuncture treatment will not be allowed during follow-up.

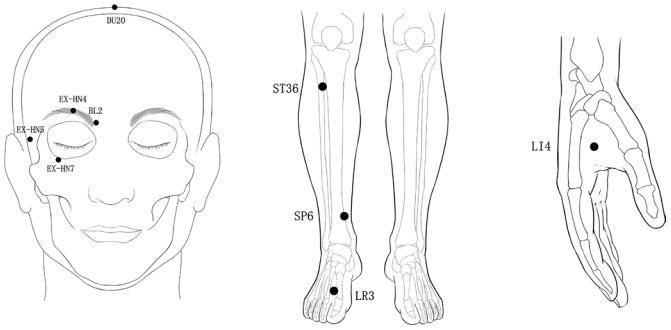

Figure 3 Locations of acupoints.

OUTCOMES

Primary outcome

Visual field MS and visual field MD of the patients. (All main indicators will be measured at each time point). The measurement time points are: the baseline time (month 0), end of treatment (month 3) and the follow-up time (month 6, 9).

Secondary outcomes

The BCVA, ERG waveform changes, CMT, SFCT, TCM syndrome score and the scale of life quality for diseases with visual impairment[21] at the baseline time (month 0), end of treatment (month 3) and the follow-up time(month 6, 9).

Blinding assessment

To test the patient-blinding effects, all patients will be asked to guess their group assignment allocation within 2 min after the last treatment session in the third month as following: 'Which group do you think you are in?' (A) traditional acupuncture; (B) modified acupuncture or (C) not sure.

Adverse events

AEs data will document the occurrence, duration and severity of adverse reactions (symptoms and signs), and how the event was resolved (or not) during the treatment.

Based on their potential association with the acupuncture needling procedure, AEs will be categorised by acupuncturists and related specialists as treatment related or not within 24 hours after the occurrence. Common treatment-related AEs include local subcutaneous haematoma, itching at the sites of needle insertion, continuous postneedling pain, dizziness and so on. For patients with bleeding or severe haematoma, an ice compress or cold compress should be immediately applied to the local swelling area, during which dressing can be replaced several times, which is beneficial to stop bleeding and haematoma subsidence.

All participants will undergo routine blood tests, urine tests, faecal tests, liver function (alanine aminotransferase and aspartate aminotransferase), renal function tests (serum creatinine and blood urea nitrogen) and ECG. These trials will be conducted before treatment and at the end of treatment (3 months). Serious AEs will be reported to Medical Ethics Committee and the participant will be treated with relevant conventional therapy or hospitalisation if necessary (the participant's allocated intervention will be revealed).

Assessment of safety

All participants will undergo routine blood tests, urine tests, faecal tests, liver function (alanine aminotransferase and aspartate aminotransferase), renal function tests (serum creatinine and blood urea nitrogen) and ECG. We will evaluate the safety of the treatment based on the results of these tests.

Sensation during the treatment

Patients will be asked about their sensations during each treatment period as following: 'What sensation do you feel during the treatment? (A) soreness; (B) distention; (C) pain; (D) no feeling; (E) else, please specify___.'

Data collection, management and monitoring

All researchers including acupuncturists, outcome assessors and statisticians will receive training regarding data management. Case report forms will be completed and double entered into the electronic data capture system by two independent investigators to ensure the accuracy of data. All research documents, including both paper files and electronic documents, will be preserved for at least 5 years after publication. If reviewers or readers have any questions regarding our published data, they can contact the corresponding author for access to original data or visit ResMan (http://www.medresman.org/uc/index.aspx). Private information of patients including name, telephone number and ID number will be anonymous to ensure participant confidentiality. The safety of this study will be monitored by a team of independent clinical experts and statisticians.

Statistical methods

Sample size

Sample size estimation for the full-scale trial is based on a clinical trial about acupuncture combined with oral Chinese Medicine for RP.[22] The MS and MD scores were used to calculate the sample size, and a larger sample was used. The assumption is that using oral Chinese Medicine is more effective than SA. Accordingly, the MS and MD scores of control group was refer to baseline data. Sample size was estimated using PASS V.15.0 (NCSS), with a significance level (α=0.05) of a two-sided two-sample t-test and 80% power to detect a difference between the two groups. Allowing for a drop-out of 20% at the end treatment time point, the recruitment goal of RP participants was 64 subjects (32 per group). Prior to formal trial, a pilot study of 10 participants will be conducted to test the feasibility of the trial protocol and adjust the final sample size.

Statistical analysis

Statistical analysis will be performed by an independent statistician who is not aware of group allocation. SPSS V.25.0 statistical software (IBM SPSS Statistics) was used for analysis, and measurement data were expressed as mean±SD. For those with normal distribution, the paired t-test was used for comparison before and after treatment, and the t-test was used for comparison between groups (homogeneity test of variance was performed, with 0.05 as the test standard). If the variance is not uniform or does not conform to a normal distribution, the rank-sum test is used. The χ^2 test was used for counting data, and the rank-sum test was used for grading data. Bilateral tests were used for all tests, with $p<0.05$ indicating a significant difference.

The baseline data were analysed using the full analysis set (including completed cases and exfoliated cases, excluding excluded cases). Both the full analysis set and the conforming protocol set (PP set, including completed cases, excluding exfoliated cases and excluded cases) were used in the efficacy evaluation. When the conclusions of the two analyses were consistent, the credibility of the test results could be enhanced. When there is inconsistency, the differences should be fully discussed and explained. In the analysis of the full analysis set, the missing data is replaced by the method of sequence mean value. In order to investigate the stability of the results, we will conduct sensitivity analysis, including converting data or changing primary outcomes to perform a hypothesis analysis.

Ethics and dissemination

The study protocol which follows the principles of the Declaration of Helsinki has been approved by the Ethics Committee of the Chinese Clinical Trial Registry (Ethical approval number: ChiECRCT20200460). Results will be disseminated through peer-reviewed publications, a master's thesis, or conference presentations. Data will be anonymised before publication to prevent the identification of individual participants.

Availability of data and materials

All unidentified data collected during the trial will be provided to anyone who wishes to access 6 months after publication in accordance with Findable, Accessible, Interoperable, Reusable (FAIR) principles.

DISCUSSION

RP is a serious blinding eye disease, characterised by progressive impairment of photoreceptor cells and pigment epithelial cells that leads to visual dysfunction.[23] Acupuncture has been widely used in the clinical practice of RP treatment in China. However, to date, no properly designed RCT or enough sample size has provided clear evidence for the effectiveness of acupuncture for RP at home and abroad. Most of them were self-controlled single-arm clinical trials, or compared the advantages and disadvantages of two acupuncture methods.[24] In this study, the inclusion criteria ranged from 14 to 80 years old, and were chosen to cover the widest possible age range. During the study period, the subjects will not receive any medical treatment for RP other than acupuncture. We believe that such strategies can reflect real-world practices and better fulfil moral obligations. Standardised treatment regimens will be used to ensure reproducibility. In this trial, the treatment regimen was based on the traditional acupuncture theory and the consensus of ophthalmologists and acupuncturists in the affiliated Hospital of Chengdu University of Traditional Chinese Medicine. Manually stimulate the needle at each acupoint for at least 10 s and keep it in place for 20–30 min. Treatment was given four times a week, with a course of treatment of 1 month, and a total of three courses of treatment.

The right control group is essential to a well-designed clinical trial. This study selected the most commonly used virtual acupuncture device in the clinic.[25 26] Patients who had received related drugs, acupuncture or other treatments for primary RP in the past 2 weeks and were able to distinguish SA from MA were excluded. In addition, all patients will be asked to guess which treatment they received in March to test the blinding effect of the patient.

The severity of RP is assessed depending on the outcome of the patient's visual field examination. visual field MS[27] and visual field MD[28] are relatively valuable indicators to evaluate the pathological status of patients in RP study. Therefore, visual field MS and visual field MD were measured as the main results in this study. The limitation of our trial is that the acupuncturist will not be blind to the nature of the intervention. We hope that the results of this trial will provide more reliable evidence and clarify the value of acupuncture as a treatment for RP.

Even so, there are some limitations of this study. In the first place, the adherence of participants may be poor because the treatment period lasts 3 months. The study size is calculated on the hypothesis of a 20% loss rate, it will be necessary to ascertain that there is no bias between the two intervention groups. In another, due to the lack of accurate efficacy estimation, the calculation of sample size has some deviation. Pilot study before full-scale trial are necessary to help adjust the final sample size. What's more, SA and placebo acupuncture were considered an inappropriate choice for control for several reasons in some studies.[29–31] The ideal method of SA must have the same appearance and feeling as the real acupuncture, but cannot produce specific curative effect. Currently, none of the SA control settings meet the standard requirements of the traditional placebo group. Therefore, in the actual operation process, the implementation conditions of SA should be the same as that of real acupuncture, so as to ensure the minimum non-specific effect (placebo benefit), minimise the bias to the greatest extent, and accurately evaluate the specific effect of treatment acupuncture.

In summary, the trial met the methodological requirements of full randomisation and allocation concealment, patient blindness, outcome evaluator and statistician. The findings of this pilot study will provide a high-quality basis for evaluating the efficacy and safety of acupuncture and moxibustion in the treatment of RP.

Contributors HH, JW and HL contributed equally to this work and are cofirst authors. HH and YZ contributed to the conception of the study. The manuscript protocol was drafted by HH, and was revised by YZ, JW and HL. HH and RL developed the search strategies, and QH and NG will implement them. RL and WZ will extract data of included studies, assess the risk of bias and complete the data synthesis. YZ will arbitrate the disagreements and ensure that no errors are introduced during the study. All authors approved the publication of the protocol.

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Competing interests None declared.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
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	2,4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	2,4
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	14
Roles and responsibilities: committees	#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)	10
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	2-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-4
Objectives	#7	Specific objectives or hypotheses	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, non-inferiority, exploratory)	4-6
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	4-5

		obtained	
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-9
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	8-9
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)	5
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	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11

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
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
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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	8-10

		protocol	
Data collection plan: retention	#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	8
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	6
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	12
Data monitoring: interim analysis	#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	9
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	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if	N/A

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2,4,12
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)	5
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	5
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
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	N/A
Dissemination policy: trial results	#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
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	14

authorship		professional writers	
Dissemination policy: reproducible research	#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	5
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	9

Informed Consent • Information Page

Dear patient:

The doctor has made a definite diagnosis that you have primary retinitis pigmentosa(RP).We will invite you to participate in a clinical study on acupuncture treatment of retinitis pigmentosa. This study was funded by The third Sichuan Ten famous Chinese medicine studio construction (CJJ2019030). The study has been approved by the Ethics Committee of the Chinese Clinical Trail Registry.

Before you decide whether to participate in this study, please read the following as carefully as possible.It can help you understand the study and why it was undertaken, the procedure and duration of the study, and the benefits, risks, and discomfort associated with participating in the study.If you wish, you can also discuss it with your relatives or friends, or ask your doctor for an explanation to help you make a decision.

1. Research background and purpose

1.1. Burden of disease and current status of treatment

Primary retinitis pigmentosa (RP) is a group of diseases where a large number of mutations cause the rod type photoreceptors to die. After the rod type dies, the cone type photoreceptors gradually degenerate in a unique pattern. RP is mainly manifested as visual field defects and progressive night blindness, speciality examination showed abnormal electroretinogram (ERG), with typical triple signs of optic nerve waxy atrophy, vascular thinning and osteocellular pigmentation. It is a common hereditary retinal disease in ophthalmology, with an incidence of about 1/4000 of the world.The factors influencing the development of RP have not been fully defined, but it is generally believed that genetics is the most important factor. From the perspective of genetics, there are mainly autosomal dominant retinitis pigmentosa (ADRP), autosomal recessive retinitis pigmentosa (ARRP), and X-linked inheritance retinitis

pigmentosa (XLRP). There are also a few RP genetic patterns that are mainly inherited by mitochondria and double genes.

The main therapeutic methods for RP are nutrition therapy, neuroprotection therapy, stem cell therapy, gene therapy, etc. 1)Nutritional therapy: Vitamin A is the main nutrient in the treatment of RP, and the usual dose is 15 thousand IU/d. Studies have shown that supplementation of carotenoids can delay the decline of visual function in RP patients treated with vitamin A, and the biological mechanism of supplementation of carotenoids may include blue light filtering and antioxidant. 2)Neuroprotective therapy: neuroprotective therapy can be achieved by delivering neurotrophic growth factors or by inhibiting pro-apoptotic pathways. 3)Stem cell therapy: Stem cell therapy is the application of healthy stem cells to replace the degraded retinal cells, promote cell regeneration and create new intercellular connections, so as to improve the visual function of RP patients.In 2010, the United States, approved by FDA for human retinal disease I / II stem cell clinical trials, the combination of the United States and European countries RPE cells derived from human embryonic stem cell research, domestic also started a similar study in 2015. 4)Gene therapy: the mechanism of gene therapy is through the use of viral or non-viral vectors to transfer therapeutic genes, and the need for genetic modification of eye cells to produce therapeutic effects.

The current research focuses on retinal transplantation, stem cell therapy and gene therapy, but retinal transplantation and stem cell therapy have many complications, and most gene therapy is still in the experimental stage and cannot be used clinically. No matter what kind of modern medical treatment means can not cure RP, so it is urgent to actively explore and develop a safe and effective treatment for RP.

1.2. Purpose of this study

Through randomized single-blind, sham-controlled clinical trials, starting from the foothold of have a scientific basis for the method to assess the curative effect of acupuncture treatment for RP and differences. It provides evidence-based medicine for TCM treatment of RP, and also provides effective and safe methods for delaying

the progression of RP.

1.3. Research institution and the number of participants

1.3.1. All subjects are from the outpatient department of the Hospital of Chengdu University of Traditional Chinese Medicine.

1.3.2. 72 participants will be included, inclusion criteria are as follows:

a. Patients who meet the diagnostic criteria for primary retinitis pigmentosa;

b. Aged 7–80 years (either sex)， the course of disease is not limited;

c. Written informed consent.The process of obtaining informed consent conforms to the requirements of clinical trial management standards.

2. Exclusion criteria

a. Best corrected visual acuity(BCVA) is less than 0.1；

b. Patients with other ophthalmic diseases such as amblyopia, diabetic retinopathy, glaucoma, severe cataract, etc., which affect vision or other blinding eye diseases；

c. Patients with severe primary diseases such as cardiovascular and cerebrovascular, liver, kidney and hematopoietic system, as well as psychiatric patients；

d. Patients receiving other related drugs or treatment for primary retinitis pigmentosa within 2 weeks；

e. Poor compliance, or participating in other clinical trials.

3. What will you need to do if you participate in the study?

3.1. Before you to be included in the study, the doctor will ask and record your medical history. The doctor will arrange some tests for you free of charge, including the best corrected visual acuity(BCVA) , visual field Mean Sensitivity(MS) and visual field Mean Deviation(MD), ERG waveform changes, central macular thickness(CMT), subfoveal choroidal thickness(SFCT), TCM syndrome score, and the scale of life quality for diseases with visual impairment(SQL-VI). In addition, some safety measures that include trauma will also be included, such as blood tests, urine tests,

faecal tests, liver function (alanine aminotransferase and aspartate aminotransferase), renal function tests (serum creatinine and blood urea nitrogen), and electrocardiogram.

You are eligible to participate in the study and sign the informed consent. If you do not wish to participate in the study, we will treat you as you wish.

3.2. If you are willing to participate in the study, you will follow the following steps:

This project is carried out in the Hospital of Chengdu University of Traditional Chinese Medicine. After you participate in this project, you will be randomly assigned to either the acupuncture group or the sham acupuncture group. The specific treatment methods of each group are as follows:

Acupuncture group: the patients were treated with acupuncture, which was as follows: the patients were placed in the sitting or supine position. The selected acupoints around the eye were Taiyang(EX-HN5), Cuanzhu(BL2), Yuyao(EX-HN4), Qiuhou(EX-HN7), Jingming(BL1), and the full body acupoints were Baihui(GV20), Hegu(LI4), Taichong(LR3), Sanyinjiao(SP6), Zusanli(ST36). After the local skin of the patient and the hands of the physician were routinely disinfected with 75% ethanol, both hands were used for needle insertion, and disposable acupuncture needles (0.25mm×25mm) were inserted into the acupoint skin (approximately 10-20 mm depth)，and then manipulations of twirling, lifting, and thrusting will be performed on all needles for at least 10 s to reach De qi (a compositional sensation including soreness, numbness, distention, and heaviness), which is believed to be an essential component for acupuncture efficacy. Needles will be retained in these acupoints for 20-30 min.

Sham acupuncture group: non-meridian and non-acupoint treatment was performed, specifically as follows: the patient was placed in the sitting or supine position, and the selected sham acupoint was at the midpoint of the line between the adjacent meridian acupoints (Sizhukong, Sibai, Touwei, etc.) and the acupoint. After the local skin of the patient and the hands of the physician were routinely disinfected with 75% ethanol, both hands were used for needle insertion, and disposable acupuncture needles (0.25mm×25mm) were inserted into the acupoint skin (approximately 10-20 mm

depth), Do not twist, lift or push all needles to achieve De Qi (a compositional sensation including soreness,numbness, distention, and heaviness). Needles will be retained in these acupoints for 20-30 min.

The above treatment was performed 4 times a week. One month is a course of treatment, a total of 3 courses of treatment.

3.3. Other matters requiring your cooperation

You must come to the hospital with your medical record and personal treatment diary card at the follow-up time agreed by the doctor (during the follow-up period, the doctor may know your situation by phone or by visiting the door).Your follow-up is important because your doctor will determine whether the treatment you are receiving is really working and will guide you in a timely manner.

Please fill in your records of acupuncture treatment in a timely and objective manner.

Please bring any other medications you are taking, including medications you may continue to take if you have other co-existing conditions.

You may not take any other medication for primary retinitis pigmentosa during the study period. If you need additional treatment, please contact your doctor in advance.

4. Possible benefits of participating in the study

Your participation in this study will help increase your understanding of primary retinitis pigmentosa and provide you with relevant health education opportunities. You can receive acupuncture treatment, medical optometry, visual field examination, OCT, blood routine, urine routine, stool routine, liver function, kidney function and electrocardiogram free of charge.

Although evidence has suggested that acupuncture has a satisfactory effect in the treatment of primary retinitis pigmentosa, this does not guarantee that it will be effective for you. Acupuncture in this study is not the only method to treat primary retinitis pigmentosa. If this treatment is not effective for your condition, ask your doctor about possible alternative treatments.

5. Possible adverse reactions, risks and discomfort, inconvenience to participate in the study

Acupuncture therapy is a minimally invasive operation, and some inevitable conditions may occur, as follows:

Fainting during acupuncture treatment: due to the special constitution of the patient, or the fear of acupuncture, or an empty stomach may occur faintng during acupuncture treatment.

Sticking of the needle: due to the patient's mental tension or position changes, there may be sticking of the needle in the process of acupuncture.

Hematoma: As acupuncture is an invasive treatment, local swelling, skin bruising, or local bleeding may occur after acupuncture.

Residual feeling after acupuncture: due to the patient's constitution and the particularity of acupuncture treatment, local pain, swelling pain, numbness and other uncomfortable feelings may occur after acupuncture.

Allergy: Due to the special constitution of the patient, he may be allergic to metal or adhesive tape, local skin pruritus, swelling, ecdysis and other conditions.

If you experience any discomfort during the study period, or if there is a new change in your condition, or if there is any accident, whether or not it is related to the study, you should inform your doctor in a timely manner and he/she will make a judgment and give appropriate medical treatment.

During the study period, you need to go to the hospital for follow-up visits and some examinations on time, which may take up some of your time and cause trouble or inconvenience to you.

6. Correlative charges

Inform patients about what is free and what needs to be paid for during diagnosis and treatment.

When patients are informed of adverse reactions, whether the investigator is

responsible for the costs of the adverse reactions and the possible compensation the patient may receive. Doctors will do their best to prevent and treat any harm that may result from this study. If an adverse event occurs in a clinical trial, a committee of medical experts will determine whether it is associated with acupuncture or an underlying treatment drug. The sponsor will provide the cost of treatment and the corresponding economic compensation for the trial-related damages in accordance with the Provisions of the <Quality Management Standards for Pharmaceutical Clinical Trials> of China.

Treatment and testing for other diseases that you have combined will not be free of charge.

7. Confidentiality of personal information

Your medical records (study records /CRF, laboratory tests, etc.) will be fully preserved at the hospital where you are attending.Your doctor will record the results of your tests and other tests on your medical record.Researchers, ethics committees, and drug regulatory authorities will be allowed access to your medical records.Your identity will not be disclosed in any public report of the results of this study.To the extent permitted by law, we will make every effort to protect the privacy of your personal medical data.

In accordance with medical research ethics, in addition to personal privacy information, trial data will be available for public inquiry and sharing, which will be limited to web-based electronic databases to ensure that no personal privacy information will be disclosed.

8. How to get more information?

You can ask any questions about this study at any time and get answers accordingly.

Your doctor will keep you informed if there is any important new information during the course of the study that could affect your willingness to continue to participate in the study.

9. You can choose to participate in the study or drop out of the study

Participation in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with the doctor or affect your medical treatment or other benefits.

In your best interest, your continued participation in the study may be discontinued at any time during the course of the study by your physician or investigator.

If you withdraw from the study for any reason, you may be asked about your treatment with acupuncture. You may also be required to undergo a laboratory and medical examination if your doctor deems it necessary.

10. What to do now?

It is up to you (and your family) to participate in this study.

Before you make the decision to participate in the study, ask your doctor as much as you can about it.

Thank you for reading the above material.If you decide to participate in this study, please tell your doctor and he or she will arrange for you to participate in the study. Please keep this information.

Informed consent • Consent Signature Page

Name of Clinical Research Project:_____

Project Undertaking Organization:_____

Project Cooperation Organization:_____

Project Assignment No.:_____

Declaration of Consent

I have read the above introduction to this study and have had the opportunity to

discuss and ask questions about this study with my doctor.All my questions have been satisfactorily answered.

I am aware of the possible risks and benefits of participating in this study.I understand that the study is voluntary, I confirm that I have had enough time to consider it, and I understand that:

a. I can always consult my doctor for more information.
b. I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also know that if I withdraw from the study in the middle of the study, especially if I withdraw from the study due to medical reasons, it will be of great benefit to the whole study if I inform my doctor of the change of my condition and complete the corresponding physical examination and physical and chemical examination.

If I need to take any other medication as a result of my disease, I will consult my doctor in advance or tell my doctor truthfully afterwards.

I agree to allow the Ethical Committee of the DRUG regulatory authority or the sponsor's representative to access my research materials.

I will receive a signed and dated copy of the informed consent.

In the end, I decided to agree to participate in the study and promised to follow my doctor's advice as much as possible.

Patient signature:_____ Date:_____

TEL:_____

I confirm that I have explained to the patient the details of the trial, including its rights and potential benefits and risks, and have given him a copy of his signed informed consent.

Doctor signature:_____ Date:_____

TEL:_____